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Institutional Review Board (IRB)

Policies & Procedures for the Protection of Human Subjects in Research

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Introduction

This Manual details the policies and procedures governing human subjects' research and the requirements for the review and approval of research by the Dana-Farber Cancer Institute (DFCI) Institutional Review Boards (IRB).

Funded by a grant from the National Cancer Institute, seven Harvard-affiliated medical centers have formed the Dana-Farber/Harvard Cancer Center (DF/HCC). The DF/HCC institutions include Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), Boston Children's Hospital (BCH), Dana-Farber Cancer Institute (DFCI), Harvard Medical School (HMS), Harvard School of Public Health (HSPH), and Massachusetts General Hospital (MGH).

IMPORTANT NOTE: For the purposes of this Manual, the term "DF/HCC" encompasses the Dana-Farber Cancer Institute and the other four DF/HCC institutions that conduct clinical research, as well as their satellites and any affiliates that have designated the DFCI IRB as their IRB of record. Appendix A describes the DF/HCC institution's relationships to their parent and affiliate organizations.

The full ethics documents, applicable regulations and standards referenced in this Manual are available at the Office for Human Research Studies' (OHRS) website at: www.dfhcc.harvard.edu/ohrs or by contacting OHRS at (617) 632-3029.

IRB members are also encouraged to become familiar with the DF/HCC *Guide to Human Research Activities,* which outlines the course of the clinical and non-clinical trial process from beginning to end and identifies the procedures for the various steps in the process.

For additional reference materials and resources, IRB members are always welcome to contact OHRS.

Chapter 1
Ethical & Regulatory Mandate for Protecting Human Subjects

Human subject research associated with the DF/HCC must be consistent with the basic ethical principles recognized as governing research involving human subjects. It must also comply with all applicable laws and regulations of the United States and the State in which the research is conducted. The documents discussed in this chapter represent important milestones in the evolving worldwide acceptance of ethical principles for the conduct of human subject research and in the development of protections for human research subjects.[1]

a. Ethical Foundations: The Nuremberg Code. The modern history of human subject protections begins with the post World War II discovery of numerous atrocities committed by Nazi doctors in war-related research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their "research" practices, known as *The Nuremberg Code* (see Table 1.1). The *Code* is significant because it established the necessity for requiring the voluntary consent of the human subject and placed personal culpability for ensuring the quality of consent on any individual "who initiates, directs, or engages in the experiment."

Table 1.1
The Nuremberg Code Summarized

1. The voluntary consent of the human subject is absolutely essential.
2. The experiment should yield fruitful results for the good of society, unprocurable by other means.
3. The experiment should be designed and based on previous animal experimentation and knowledge of the disease such that anticipated results will justify its performance.
4. The experiment should avoid all unnecessary physical and mental suffering and injury.
5. No experiment should be conducted where there is a prior reason to believe that death or disabling injury will occur.
6. The degree of risk should never exceed the humanitarian importance of the problem.
7. The subject should be protected against even remote possibilities of injury, disability, or death.
8. The experiment should be conducted only by scientifically qualified persons.
9. The human subject should be at liberty to end his/her participation in an experiment, if the subject has reached the physical or mental state where continuation of the experiment seems to the subject to be impossible.
10. The scientist in charge must be prepared to terminate the experiment if there is probable cause to believe that continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.

b. Ethical Foundations: The Declaration of Helsinki. *The Nuremberg Code*'s principles were later expanded to further protect subjects. The World Medical Association Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects (1964, latest revision 2000) calls for

[1] The full ethics and regulatory documents are available at the OHRS website www.dfhcc.harvard.edu/ohrs or by contacting OHRS.

prior approval and ongoing monitoring of research by independent ethical review committees (see Table 1.2).

Table 1.2
The Declaration of Helsinki Summarized

Introduction

1. Research involving human subjects includes research on identifiable human material or identifiable data.
2. Considerations related to the well-being of the subject should take precedence over the interests of science and society.
3. Even the best medical methods must be challenged continuously through research on effectiveness, efficiency, accessibility, and quality.
4. Vulnerable research populations need special protection, particularly economically and medically disadvantaged persons and those who cannot consent for themselves, may be subject to duress, have no potential of benefiting personally from the research, and for whom the research is combined with care.

Basic Principles for All Medical Research

1. The life, health, privacy, confidentiality, physical integrity, mental integrity, and dignity of the human subject must be protected.
2. Caution must be exercised in research which may affect the environment, and the welfare of animals used for research must be respected.
3. Research must conform to scientific principles, be formulated in an experimental protocol that is publicly available, and be submitted for ethical review independent of the investigator or sponsor.
4. Research should be preceded by assessment of predictable risks, burdens, and benefits and should be conducted only if its importance outweighs the inherent risks and burdens to the subject.
5. Any investigation should cease if risks are found to outweigh potential benefits or if there is conclusive proof of beneficial results.
6. Research is only justified if there is a reasonable likelihood that the populations in which the research is conducted stand to benefit from it.
7. Research subjects must be volunteers informed about the research aims, methods, funding sources, possible conflicts of interest, institutional affiliations, anticipated benefits, potential risks and discomforts, and the right to abstain or withdraw without reprisal. If written consent cannot be obtained, non-written consent must be formally documented and witnessed.
8. If the subject is in a dependent relationship with the physician or may be under duress, informed consent should be obtained from a qualified research team member who is not engaged in the investigation and is completely independent of this relationship.
9. Informed consent must be obtained from a legally authorized representative if the subject is a minor or is physically or mentally unable to consent. Assent of the subject must also be obtained. These groups should be included only if the research promotes the health of the population they represent and cannot otherwise be carried out.
10. Research should be done on individuals from whom it is not possible to obtain consent only if the condition preventing consent is a necessary characteristic of the research population. Consent to remain in the research should be obtained from the individual or legally authorized surrogate as soon as possible.
11. Authors and publishers have an obligation to publish only research that is in accord with the Declaration of Helsinki's ethical principles.

Additional Principles for Research Combined with Medical Care

The benefits, risks, burdens and effectiveness of a new method should be tested against the best current methods.

At the conclusion of the study, every subject should be assured of access to the best methods identified by the study.

Patients should be fully informed about which aspects of the care are related to the research.

Where proven methods do not exist or have been ineffective in treating a patient, and with the patient's informed consent, the physician may use unproven measures believed to offer hope of saving life, re-establishing health, or alleviating suffering.

c. Ethical Foundations: The Belmont Report. In the early 1970s, a 40-year United States Public Health Service *Study of Untreated Syphilis in the Negro Male at Tuskegee* and other ethically questionable research resulted in legislation in 1974 calling for regulations to protect human subjects and the establishment of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research to examine ethical issues related to human subject research. The Commission's final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research (79 FR 12065, April 17, 1979)*, defines the ethical principles and guidelines for the protection of human subjects. *The Belmont Report's* most important contribution is its elucidation of three basic ethical principles (see Table 1.3):

Table 1.3
The Belmont Principles Summarized

Principle	Application in Research
Respect for Persons ▪ Autonomy ▪ Protection	**Informed Consent** ▪ Information ▪ Comprehension ▪ Voluntariness
Beneficence ▪ Do No Harm ▪ Maximize Benefit/Minimize Harm	**Risks versus Potential Benefits** ▪ Systematic Assessment ▪ Independent Reviewers
Justice ▪ Individual Justice ▪ Social Justice	**Equitable Selection of Subjects** ▪ Individual Fairness ▪ Social Fairness

1. **Respect for Persons** is achieved by obtaining informed consent, providing for privacy, confidentiality, and any other additional protections for vulnerable populations.

2. **Beneficence** is preserved by weighing risks and benefits; and

3. **Justice** is protected by the fair selection of subjects.

The Belmont Report also provides important guidance regarding the boundaries between biomedical research and the practice of medicine.

DF/HCC is guided in its human subject research by the ethical principles set forth in the Belmont Report. All IRB members and all IRB professional and support staff should be thoroughly familiar with these most basic ethical principles.

d. Department of Health and Human Services (DHHS) Regulations. In May 1974, the Department of Health, Education, and Welfare (later divided to form the Department of Health and Human Services (DHHS) and the Department of Education) codified its basic human subject protection regulations at 45 CFR Part 46, Subpart A.

DHHS regulations at 45 CFR Part 46 Subpart A constitute the Federal Policy (Common Rule) for the protection of human subjects. This Common Rule applies to any human subject research supported by any of the agencies of the Federal government that support human subject research (see Table 1.4).

Table 1.4
Federal Common Rule Departments and Agencies

Department / Agency	CFR Citation
Department of Agriculture	7 CFR Part 1c
Department of Energy	10 CFR Part 745
National Aeronautics and Space Administration	14 CFR Part 1230
Department of Commerce	15 CFR Part 27
Consumer Product Safety Commission	16 CFR Part 1028
International Development Cooperation Agency, Agency for International Development	22 CFR Part 225
Department of Housing and Urban Development	24 CFR Part 60
Department of Justice	28 CFR Part 46
Department of Defense	32 CFR Part 219
Department of Education	34 CFR Part 97
Department of Veterans Affairs	38 CFR Part 16
Environmental Protection Agency	40 CFR Part 26
Department of Health and Human Services	45 CFR Part 46
National Science Foundation	45 CFR Part 690
Department of Transportation	49 CFR Part 11
Central Intelligence Agency	Executive Order
Social Security Administration	Authorizing Statute
Nuclear Regulatory Commission	10 CFR 35.6
Department of Homeland Security	Public Law No: 108-458, Sec. 8306

The DHHS regulations presently include additional protections for pregnant women, human fetuses and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D). These regulations are enforced by the DHHS, Office for Human Research Protections (OHRP) (formerly known as the Office for the Protection from Research Risks (OPRR)).

DF/HCC meets the requirements set forth in 45 CFR Part 46 for all DHHS-supported research.

After a lengthy rule making process, the DHHS regulations were significantly revised in 2017 with a required compliance and implementation date of January 21, 2018. The compliance and implementation date of the revised rule were delayed in early 2018 and again in mid-2018. The final revised common rule is effective January 21, 2019. Three burden reducing provisions within the final revised common rule were permitted by DHHS to be implemented as of July 21, 2018, in advance of the 2019 compliance date. The requirement to identify a sIRB for multi-site research under the revised common rule is required as of January 21, 2020.

DF/HCC will not implement the three burden reducing provisions permitted ahead of the January 21, 2019 effective date.

For the purposes of this document and supplemental IRB guidance and policy documents, references to the old rule or common rule may also be considered the Pre-2018 Rule and the revised final common rule may be considered the Post-2018 Rule.

e. Food and Drug Administration (FDA) Regulations. FDA has codified informed consent (21 CFR Part 50), IRB (21 CFR Part 56), and child protection (21 CFR Part 50, Subpart D) regulations that are almost identical to the DHHS regulations. Additional FDA regulations relevant to the protection of human subjects address Investigational New Drug Applications (21 CFR Part 312), Biological Products (21 CFR Part 600), and Investigational Device Exemptions (21 CFR Part 812).

In general, FDA human subject regulations apply to clinical investigations and other research involving products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.

Prospective IRB review and approval is required for all clinical investigations and all other research involving products regulated by FDA for human use, even where an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is not required (see Chapter 12 of this manual for details of FDA requirements).

Chapter 2
Human Subject Research; Non-Research Activities; and Research Not Involving Human Subjects

This chapter provides information relating to when an activity is "research involving human subjects". It also describes the type of human subject research that is conducted by DF/HCC institutions.

a. Important Definitions for the Protection of Human Subjects in Research. The following are important definitions relating to human subject protections:

1. Research.

i. **Pre-2018:** DHHS regulations at 45 CFR 46.102(d) and the Common Rule define research as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.".

i. **Post-2018:** DHHS regulations at 45 CFR 46.102(l) and the Common Rule define research (as "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge") and deem the following not to be research[2]:

1. Scholarly and journalistic activities (e.g., oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.
2. Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).
3. Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.
4. Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.

FDA regulations at 21 CFR 56.102(c) define clinical investigation as "any experiment that involves a test article and one or more human subjects." FDA regulations note that "[t]he terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part." Under FDA regulations, activities are "research" when they involve:

Use of a drug other than the use of an approved drug in the course of medical practice (21 CFR 312.3(b)),

[2] 45 CFR 46.102(l)(1-4)

Use of a medical device other than the use of an approved medical device in the course of medical practice (Food, Drug and Cosmetic Act §530(g)(3)(a)(i)), or

Gathering data that will be submitted to, or held for inspection by, FDA in support of a FDA marketing permit for a food, including a dietary supplement that bears a nutrient content claim or a health claim, an infant formula, a food or colour additive, a drug for human use, a medical device for human use, a biological product for human use, or an electronic product (21 CFR 50.1(a); 21 CFR 56.101(a)).

2. Human Subject.

i. **Pre-2018:** DHHS regulations at 45 CFR 46.102(f) and the Common Rule define human subject as "a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information."

ii. **Post-2018:** DHHS regulations at 45 CFR 46.102(e) and the Common Rule define human subject as "a living individual about whom an investigator (whether professional or student) conducting research (1) obtains information or biospecimens through intervention[3] or interaction[4] with the individual, and uses, studies, or analyzes the information or biospecimens; or (2) obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

FDA regulations at 21 CFR 56.102(e) define human subject as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient." If the research involves a medical device, individuals are considered "subjects" when they participate in an investigation, either as an individual on whom or on whose specimen an investigational device is used or as a control (21 CFR 812.3(p)). When medical device research involves in vitro diagnostics and unidentified tissue specimens, the FDA defines the unidentified tissue specimens as human subjects. (See also Chapter 12 for more information on FDA regulated activities such as emergency use of an investigational test article and humanitarian use of a device.)

3. Private Information.

i. **Pre-2018:** Federal regulations at 45 CFR 46.102(f) define private information as any information that an individual can reasonably expect will not be made public, and any information about behavior that an individual can reasonably expect will not be observed or recorded.

ii. **Post-2018:** Federal regulations at 45 CFR 46.102(e)(4) define private information as information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

4. Identifiable.

[3] Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102 (e)(2))

[4] Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102 (e)(3))

i. **Pre-2018:** Federal regulations at 45 CFR 46.102(f) define identifiable to mean that the identity of the individual subject is or may readily be ascertained by the investigator or may be associated with the information.
ii. **Post-2018:** Federal regulations at 45 CFR 46.102(e)(5-6) define identifiable in two manners:
    1. Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information. (45 CFR 46.102 (e)(5))
    2. An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen. (45 CFR 46.102 (e)(6))

5. **Anonymous.** Anonymous means that the information has no identifiers and no codes exist that can link identities to the information.

6. **Minimal Risk.** Federal regulations at 45 CFR 46.102(f) and 21 CFR 56.102(i) define minimal risk to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

7. **Minimal Risk for Prisoners.** In the case of research involving prisoners, federal regulations at 45 CFR 46.303(d) define minimal risk as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

8. **Institutional Review Board (IRB).** An IRB is a committee created under federal regulations to conduct a review of and monitor research involving human subjects. In accordance with the Common Rule and FDA regulations, the IRB recommends protocol approval, requires modification to secure approval, or disapproves research. The IRB also is authorized to suspend or terminate research for continued non-compliance with the Common Rule and FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

b. Independent Verification that Project is Not Human Subject Research. All planned projects involving interaction (direct or indirect) with humans or the use of human specimens or data should be reviewed by OHRS for a determination that the activity does not constitute research involving human subjects. OHRS will issue a determination notification to the investigator.

c. Types of Human Subject Research. The following examples illustrate common types of human subject research conducted under the auspices of the DF/HCC. These are examples only, and are not exhaustive of all human subject research

1. **Biomedical Research.** Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of biomedical research.
2. **Clinical Research.** Clinical research involves the evaluation of biomedical or behavioral interventions related to disease processes or normal physiological functioning. Clinical research often, but not always, includes drugs, devices, or

biological products regulated by the FDA. The term "clinical trials" implies treatment protocols meant for direct application to a subject population.

Phase I. These trials represent the first or early use of the drug in humans. The major objective of a Phase I trial is to determine the maximum tolerated dose (MTD) of the trial agent given in the schedule for humans while identifying the dose-limiting toxicity (DLT). The Phase I design may also be used to evaluate new schedules or combinations of established drugs and/or radiation.

Phase II. Phase II trials are conducted after the MTD has been determined by the Phase I trial. The major objective is to determine the efficacy of an agent for a given disease or group of diseases. Typically, all subjects receive the same dose of drug (e.g., the MTD defined by the Phase I trial) or undergo the same intervention. A number of Phase II trials are often done utilizing different dosing schedules of the same agent. Alternatively, randomized Phase II studies may compare different dosing schedules or regimens to try to determine which is most promising for further evaluation. The most promising regimen, if shown to be sufficiently active, is then used in the subsequent Phase III trial. Phase II trials also collect additional information relating to toxicity.

Phase III. The major objective of Phase III trials is to compare the efficacy of at least two treatments. This is typically the current standard therapy versus one or more experimental treatment groups. Typically, the primary purpose of a Phase III study is to attempt to determine whether a treatment approach provides a survival advantage as compared with the other(s). Alternatively, if they produce equivalent survival, one might be preferred because it is associated with less toxicity.

Phase IV. Called "post-market approval trials," these trials take place after a new agent has been approved for use and marketing by the FDA. Phase IV trials are designed to further evaluate the long-term safety and effectiveness of a treatment. These trials are less common than Phase I, Phase II, and Phase III trials and sometimes are required by the FDA.

Multi-Modality Trials. Combination trials are done when two or more modes of therapy, such as surgery, chemotherapy, and immunotherapy, are used in combination in an attempt to evaluate potential benefits of combined modality treatment of disease.

1. **Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review.

2. **Social and Behavioral Research.** The goal of social and behavioral research is similar to that of biomedical research—to establish a body of knowledge and to evaluate interventions—but the content and procedures often differ. Social and behavioral research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention. (See also, Chapter 13, "Social and Behavioral Research.")

3. **Epidemiology Research.** Epidemiology research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, interventions, or delivery of services to affected populations. Some epidemiology research is conducted through surveillance, monitoring, and reporting programs—such as those employed by the Centers for

Disease Control and Prevention (CDC)—whereas other epidemiology research may employ retrospective review of medical, public health, and/or other records. Because epidemiology research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may quality for exemption or expedited review. In all cases, the IRB, not the individual investigator, will determine when IRB review of the activity is required. (See also, Chapter 15, "IRB Considerations Regarding Study Design.")

4. **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB must review a protocol detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols.

5. **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (e) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion.

   Genetic studies limited to the **collection of family history information and blood drawing are not automatically "minimal risk" studies**. A breach of confidentiality, among other risks, is a major concern in determining if minimal risk is involved.

d. Quality Assurance Activities vs. Human Subject Research. Quality assurance activities attempt to measure the effectiveness of programs or services. Quality assurance activities constitute human subject research, and require IRB review, when they are designed or intended, at least in part, to develop or contribute to generalizable knowledge.

On the other hand, quality assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, usually do not constitute human subject research, and usually do not require IRB review.

For example, suppose a medical department at the DFCI conducts a review of patient records and then contacts patients to identify cases where recommended follow-up did not occur. If the sole intent is to improve the rate of follow-up within DFCI, then the activity is not human subject research and does not require IRB review.

However, if the intent of the activity, at least in part, includes extending the findings to patients at facilities outside of the DFCI, or disseminating the findings in such a way that applicability outside the DFCI is stated or implied, then the activity does constitute human subject research, and does require IRB review.

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal Institutional purposes lead to a desire to generalize and disseminate the results for application outside DFCI), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

Where any disagreement arises about whether a quality assurance activity constitutes human subject research, the DFCI IRB, not the individual investigator, will determine when IRB review of such activities is required.

e. Research Activities vs. Innovative Treatments in Medical Practice. In the course of medical practice, sound clinical judgment sometimes leads physicians to employ "innovative" treatments where more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient's individual needs. Such innovative treatments employed on an occasional basis and solely for clinical purposes do not normally constitute human subject research and do not normally require IRB review.

However, the use of innovative treatments as part of a systematic investigation designed, at least in part, to develop or contribute to generalizable knowledge does constitute human subject research and does require prospective IRB review.

f. Research Activities vs. Medical Case Reports. Generally speaking, a case report is not considered research because it is not usually "a systematic investigation designed to develop or contribute to generalizable knowledge;" therefore, it does not come under the jurisdiction of the IRB.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review and then requires IRB approval. Usually, a non-research case report summarizes one case (or occasionally two, or at most three, cases) to emphasize a discrete instance of disease. However, it is the nature of the report, not the absolute number of cases, which determines whether or not the activity involves human subject research. A non-research case report may not involve a systematic investigation characterized as developing or contributing to generalizable knowledge. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subject to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A non-research case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at least a systematic qualitative analysis, that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

g. Research Activities vs. Commercial Services. DF/HCC facilities and laboratories may occasionally provide tests or other services to non-DF/HCC researchers solely on a non-research basis.

Provision of such services solely on a non-research or commercial basis does not

constitute human subject research at DF/HCC and does not require review by the DFCI IRB, provided that all of the following conditions are met:

- The research is not otherwise conducted at this Institution;
- The research does not otherwise involve employees or agents of this Institution (e.g., as co-investigators, in planning or analysis, or receiving publication credit);
- The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges; and
- The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality.

However, if DF/HCC personnel are involved in any way that is more than merely providing a commercial service as described above, then prospective review and approval of the DFCI IRB is required.

Chapter 3
Commitment to Protecting Human Subjects

DF/HCC is committed to protecting human subjects by meeting all applicable requirements of the human subject protection regulations.

The Common Rule requires that every institution engaged in Federally-supported human subject research file an "Assurance" to formalize its commitment to protect human subjects (45 CFR 46.103(a)). DFCI must provide written assurance to Federal agencies that it will comply with all federal laws and regulations governing the protection of human research subject.[5] DFCI and DF/HCC also comply with the requirements of FDA regulations where applicable.

a. Protection of Human Subjects Paramount Priority. The protection of human subjects in research is a paramount priority.

b. DFCI Federalwide Assurance. DFCI has an approved Federalwide Assurance (FWA00001121) on file with the OHRP. The DFCI Senior Vice President for Research serves as the Human Subject Signatory Official (hereinafter referred to as the "Institutional Official") for the DFCI FWA.

The FWA authorizes DFCI to conduct human subject research that is supported by DHHS or any of the other Federal "Common Rule" agencies.

The DFCI FWA covers all human subject research conducted (i) by any employee of the DFCI; or (ii) in any component of the DFCI. Thus, any investigator who (i) is an employee of any DFCI component, or (ii) conducts research within any DFCI facility or with DFCI equipment or resources is bound by DFCI's human subject protection policies and requirements.

Under the terms of the DFCI FWA, all research involving human subjects reviewed by the DFCI IRBs designated under the FWA is guided by the ethical principles in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research.

c. DFCI Registered IRBs. The DFCI operates at least six IRBs to accommodate the volume of DF/HCC human subject research. The IRBs are registered with OHRP and are designated in the DFCI FWA to conduct reviews of research involving human subjects:

1. IRB Panel A - IRB00000052
2. IRB Panel B - IRB00000753
3. IRB Panel C - IRB00001186
4. IRB Panel D - IRB00003340
5. IRB Panel E – IRB00005504

[5] The terms of the Federalwide Assurance are available by contacting OHRS.

6. IRB Panel F – IRB00006224

7. IRB Panel G – IRB00007493

IRB Panels A, B, C, D, E, F and G may review all DF/HCC research. However, clinical trials involving pediatric populations will generally be reviewed by IRB Panel G. IRB Panel D generally does not review greater than minimal risk treatment protocols where participants are still in active treatment.

The DFCI may designate additional internal or external IRBs as it deems necessary. No DFCI component may operate or designate an IRB without concurrence of the DFCI FWA Institutional Official.

d. DF/HCC Consortium. Funded by a grant from the National Cancer Institute (NCI), seven Harvard-affiliated medical centers have formed the Dana-Farber/Harvard Cancer Center (DF/HCC). The consortium includes Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), Boston Children's Hospital (BCH), Dana-Farber Cancer Institute (DFCI), Harvard Medical School (HMS), Harvard School of Public Health (HSPH), and Massachusetts General Hospital (MGH). Satellite sites are considered an extension of the main DF/HCC site and fall under the main sites' FWA for the purposes of research.

Of these seven institutions, the five that conduct clinical oncology research have designated the DFCI IRB their IRB of record to review their oncology research (i.e., research supported by the DF/HCC grant from NCI).

1. Beth Israel Deaconess Medical Center (BIDMC) – FWA00003245

2. Brigham and Women's Hospital (BWH) – FWA00000484

3. Boston Children's Hospital (BCH) – FWA00002071

4. Dana-Farber Cancer Institute (DFCI) – FWA00001121

5. Massachusetts General Hospital (MGH) – FWA00003136

e. Network Affiliate Agreements. DFCI has entered into a joint venture with Partners Healthcare to form the Dana-Farber/Partners CancerCare (DF/PCC). Under the terms of specific affiliate agreements, certain DF/PCC network affiliates have also designated the DFCI IRBs for the review of selected DF/PCC clinical trials. These institutions are listed on the front sheet document.

The DFCI Affiliate Office maintains the list of current affiliates. This list changes as new institutions are added or removed from the Dana-Farber/Partners CancerCare Network.

Chapter 4
Shared Responsibilities for the Protection of Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust among DF/HCC administrators, investigators and their research staff, the subjects who enroll in research, and the IRB members and staff.[6]

a. Institutional Responsibilities. The DFCI Chief Executive Officer (CEO) has ultimate authority for the oversight and monitoring of the Institutional Policy for the Protection of Human Subjects. The DFCI CEO also serves as the DF/HCC Center Director and DF/HCC Executive Committee Chair. The Director of OHRS and Chairs of the IRB may approach the CEO directly with respect to significant concerns relating to the protection of human subjects in research.

b. FWA Institutional Official. As stated in the preceding chapter, the DFCI Senior Vice President for Research serves as the Institutional Official for assuring Federal Agencies that DFCI complies with all Federal regulations governing the protection of human research subjects. The DFCI Senior Vice President is connected to the DF/HCC by also serving as the DF/HCC Associate Director for Administration.

The Institutional Official is fully responsible for overseeing the protection of human subjects within DFCI, and on behalf of the DF/HCC, including:

Overseeing the development and implementation of Institutional policies governing the DFCI IRB, all human subject research, and all investigators and research personnel at this Institution.

Maintaining open channels of communication among all parties involved in the human subject protection process at this Institution.

Ensuring that the DFCI IRB is provided with sufficient resources, meeting space and staff to support its substantial review and record keeping responsibilities.

Overseeing the operation and administration of the DFCI IRB and determining that the DFCI IRB functions in accordance with the assurances provided in compliance with all Federal, State, and local laws and regulations that govern human subject protection in the conduct of research.

On an ongoing basis, the Institutional Official and the OHRS Director evaluate the performance of the IRB chairs.

Ensuring the existence of policies to ensure that the Institutional Official, Legal Counsel, Officer for Office of Data Quality (ODQ), Director for the Office for Human Research Studies (OHRS), Clinical Investigation Leadership Committee (CLC), IRB Policy Committee, IRB Chairpersons and other DF/HCC institutional officials are promptly notified regarding (i) any unanticipated problem involving risks to subjects or others; (ii) any serious or continuing non-compliance with DFCI IRB

[6] Investigators and research staff must review the DF/HCC *Guide to Human Research Activities* which outlines the course of the clinical trial process from beginning to end and describes what investigators need to know about their responsibilities.

requirements by research investigators; or (iii) any for-cause suspension or termination of IRB approval.

The Director or Associate Directors of OHRS inform the Institutional Official of any issue of concern raised at an IRB meeting, but is not normally provided with copies of the minutes and the actions taken at each specific meeting. The Institutional Official may at any time request and receive copies of minutes from any IRB meeting.

Ensuring notification of OHRP and FDA of such incidents in accordance with applicable Federal regulations. Such notice will be accomplished in coordination with the OHRS Director, the IRB Chairperson, and as appropriate, Legal Counsel and the ODQ Director.

Overseeing implementation of a research compliance monitoring process that provides monitoring reports, as appropriate, to the Institutional Official, OHRS Director, ODQ Director, CLC, and the IRB Chairpersons.

These responsibilities may be delegated to the OHRS Director.

c. Activation. IRB-approved research cannot begin until the research protocol has been activated. The Office of Data Quality (ODQ) oversees activation and ensures all required operational approvals are in place prior to the initiation of the research. The number and type of operational approvals depend on the nature of the research, but typically include budgeting, contracts, nursing and pharmacy feasibility, ODQ feasibility, and study team operational readiness. If required changes to the research are identified during operational review and activation processes, and cannot be incorporated prior to IRB review and approval, the study will be put on hold until an amendment is approved and activated. The ODQ controls research activation by managing the posting of IRB-approved protocol and consent documents, the protocol status, and the status of cohorts/arms/dose levels.

d. Clinical Investigations Leadership Committee (CLC). CLC includes representatives from institutions across the DF/HCC including the Institutional Official, the Medical Director for Clinical Trials Operations, an IRB Chair, an SRC Chair, DF/HCC Research Pharmacy Director, Research Nursing Director, OHRS Director; biostatistics representative; and faculty leaders in clinical trials and administrative representatives from the DF/HCC member institutions.

The 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. The CLC reviews clinical investigations activities, processes, and systems, as well as DF/HCC issues that require senior-level, inter-institutional attention.

e. Clinical Trials Operations Committee (CLINOPS). CLINOPS is an inter-institutional committee comprised to ensure coordination and integration among the centralized DF/HCC offices and institutionally-based clinical trials offices. CLINOPS reviews DF/HCC clinical trials operations, facilitate inter-institutional communication, resolves CLINOPs-identified DF/HCC clinical trial issues, and develops DF/HCC–wide clinical trials operating procedures. Members include representatives from Members include key representatives with clinical trials responsibilities from each DF/HCC institution, including but not limited to such areas as nursing, pharmacy, information services, and data management.

f. IRB Policy Committee. The IRB Policy Committee is responsible for establishing policies that impact the IRB review of research involving human subjects. This includes, but is not limited to, such issues as: assent for pediatric subjects; reporting of adverse events; reporting of deviations and violations, etc. While institutional policies are critical, any IRB may choose to not follow a particular policy because of the requirements of a specific protocol under its review.

The members of the IRB Policy Committee are the chairs and co-chairs of every DFCI IRB. This includes the chairs/co-chairs of the DFCI IRBs A, B, C, D, E, F and G, as well as any DFCI IRBs that may be created in the future. Membership also includes the Director of the Office for Human Research Studies and the Medical Director for Clinical Trial Operations. OHRS maintains the list of members of this committee.

g. Disease & Discipline-Based Program Leaders. The Disease and Discipline-based Program Leaders are best positioned to oversee investigators as well as determine whether resources such as space, personnel, protocol overlap and subject accrual by disease are appropriate to properly conduct the research. All new protocols submitted for SRC and IRB review must be routed through and endorsed by the Disease & Discipline-based Program Leader before submission to OHRS.

h. Director, Office for Human Research Studies (OHRS). The Director of the Office for Human Research Studies (OHRS) serves as the Human Protections Administrator under the DFCI FWA. The Human Protections Administrator is the institutional official to whom the Senior Vice-President for Research (FWA Institutional Official) delegates day-to-day oversight of the human research protection program under the FWA, including the receipt of notification of IRB findings and actions.

The OHRS Associate Directors are charged with conducting the day-to-day oversight of the human research protection program in the absence of the Director of OHRS. The Director and Associate Directors may at any time bring any matter to the attention of the DFCI CEO.

i. Scientific Review Committees. The Scientific Review Committees (SRC) review all cancer trials that are considered to be greater than minimal-risk 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 or the overall investigator's clinic (i.e., adult oncology clinic versus pediatric oncology clinics), 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. A designated SRC member will also review enrolling clinical trials for scientific progress at the time of continuing review and report any scientific concerns to the SRC.

All scientific review committees are comprised of physicians and biostatisticians who serve as the voting members, as well as representatives from radiation safety, biosafety, pharmacy and nursing departments, etc. Scientific review occurs prior to IRB review. Protocols are not forwarded to the IRB until a determination has been made that the investigators have adequately responded to all conditions for scientific review approval.

j. Institutional Review Boards. The 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 DFCI 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. The DFCI 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.

k. Principal Investigators. As the individual responsible for the implementation of research, the principal investigator bears direct responsibility for protecting every research subject. This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits. In addition, the principal investigator and all members of the research team must comply with the findings, determinations, and requirements of the IRB. The principal investigator must also be responsible for the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team actually obtain and document consent.

Principal Investigators must ensure:

- That all human subject research, which they conduct at this Institution or its components, or they conduct as employees of this Institution, has received prospective review and approval by the IRB.

- That continuing IRB review and approval of the research are secured in a timely fashion.

- That the research is conducted at all times in compliance with all applicable Federal, State, and local regulatory requirements and with the determinations of the IRB.

- That the investigator has reviewed this Institution's FWA, the *Guide to Human Research Activities*, DHHS Regulations for Protection of Human Research Subjects, relevant FDA regulations, and the Belmont Report.

- That no changes in approved research are initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period. The electronic protocol library (OncPro) includes the current protocol and informed consent document(s) that investigators are expected to follow. If any changes are made without prior IRB approval or research continues beyond the IRB approval period, the IRB must be notified as required in the Deviation / Violation / Exception and Other Event Reporting Policy.

- That the IRB is notified promptly of (i) any injuries or unanticipated problems involving risks to subjects or others; (ii) any serious adverse events experienced by subjects, (iii) any adverse events reported to the study sponsor; and (iv) any serious or continuing non-compliance with applicable regulatory requirements or determinations of the IRB of which they become aware.

- That a final report is made to the IRB and to the sponsor within three months after the completion or discontinuance of a research project, or of withdrawal of the exemption for a research project.

- That complete and accurate records are maintained regarding all communications with the IRB, the sponsor, and any Federal Agency, and that such records are made available to the Institutional Official, ODQ, or other appropriate DF/HCC offices immediately upon request.

l. Other Members of the Research Team. Every member of the research team is responsible for protecting human subjects. Co-investigators, study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures; adhere rigorously to all protocol requirements; inform investigators of all adverse events or unanticipated problems involving risks to subjects or others; oversee the adequacy of the informed consent process; and take whatever measures are necessary to protect the safety and welfare of subjects.

Researchers at every level are responsible for notifying the IRB promptly of any serious or continuing non-compliance with applicable regulatory requirements or determinations of the IRB of which they become aware, whether or not they themselves are involved in the research. Researchers may also notify the Institutional Official, Compliance Officer, or Legal Counsel directly of any compliance concerns they may have.

m. Research Subjects. Subjects may be viewed as having certain responsibilities as well. They can be expected to make every effort to comprehend the information researchers present to them so that they can make an informed decision about their participation in good faith. While participating, they should also make every reasonable effort to comply with protocol requirements and inform the investigators of unanticipated problems. Subjects always have the right to withdraw from their participation in research at any time and for any reason without penalty or loss of benefits to which they would otherwise be entitled.

n. Additional Institutional Committees. All DF/HCC human subject research must also be reviewed by (i) the Radiation Safety Committee at the participating site if the research involves ionizing radiation exposure; and/or (b) the Biosafety Committee at the participating site if the research involves recombinant DNA. Additionally, Biomedical Engineering inspects all devices not previously in the respective institution's inventory. If the research is initiated by a DF/HCC investigator and is a multi-center study, review and approval by the DF/HCC Multi-Center Coordinating Committee is also required.

o. Clinical Trials Education. DFCI is required under its OHRP-approved FWA to have a plan to provide education about human subject protections for research investigators and IRB members and staff.

As part of the DF/HCC institutions' commitment to the protection of human subjects, investigators and key research study staff are required to complete human subject protection education. The ODQ, in cooperation with the OHRS Director, determines the education requirements needed for DF/HCC personnel to participate in the conduct of and/or review and approval of human subject research. The ODQ is responsible for maintaining accurate records regarding the mandatory training of investigators, research staff, IRB members and staff. ODQ will make these records available to CLC, OHRS and the IRB. (See the DF/HCC SOP on Continuing Human Subject Protection Training for the specific training requirements).

p. HRPP Assessments & Ongoing Improvements. The Institutional Official, the Director of OHRS, the Senior Chair of the IRB and the Chief Medical Office for Clinical Trials for the DF/HCC meet once a year to discuss the state of the human research protection program and any areas of concern. The group assesses the number of IRBs and the membership to determine whether additional IRBs are necessary; the inclusion of community members on the various IRBs; OHRS staffing and space; the accessibility of legal counsel for advice and guidance; the system for identification of conflicts of interest; the education program in place for IRB members, OHRS staff and investigators; as well as internal review of the adequacy of the systems that support the operations of OHRS. In addition, the group reviews the internal auditing process that is done on a continuous basis within OHRS.

Chapter 5
IRB Roles and Authorities

An Institutional Review Board (IRB) is a committee created by and under Federal regulations for the review, approval and monitoring of research involving human subjects.

In accordance with the Common Rule, DHHS regulations, and FDA regulations, the DFCI IRBs have authority and responsibility for approving, requiring modification in (to secure approval), or disapproving human subject research. The IRBs also have the authority to suspend or terminate research for continued non-compliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and requirements. No official or committee of the DF/HCC institutions may permit the conduct of human subject research that has not been approved by the DFCI IRBs.

a. Human Subject Protections under Federal Regulations. 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[7].

The DFCI 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).

b. Oversight of the DFCI IRBs. The Institutional Official is ultimately responsible for oversight of regulatory compliance for all human subject research activities conducted under the auspices of DFCI. The Human Subject Signatory Officials at the institutions, which have designated the DFCI IRB to review their DF/HCC research, also retain responsibility for the oversight of research conducted within their respective institutions.

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 Director, OHRS Associate Directors and the 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.

c. Purpose and Mission of the IRBs. The DFCI IRBs' primary responsibility is to protect the rights and welfare of participants involved in human subject research. In doing so, the DFCI IRB monitors human subject research to determine that it is conducted ethically, and in compliance with applicable Federal regulations, applicable State law, the DFCI Federalwide Assurance, and these policies and procedures for protecting human subjects.

The DFCI IRBs fulfill these responsibilities by conducting prospective and continuing review of human subject research, including review of the protocol and

[7] Revised Common Rule, NRPM, section IV. D: The final rule, as proposed in the NPRM, also eliminates the requirement that appeared in the pre-2018 rule that an institution designate one or more IRBs on its FWA. Federal departments or agencies retain the ability to ask for information about which IRBs review research conducted at an institution as part of the assurance process, even if that requirement is not explicitly mandated in the regulations.

grant applications or proposals (for Federally-supported research), the informed consent process, procedures used to enroll subjects, and any adverse events or unanticipated problems reported to the IRB. Prospective review and approval of research or changes to previously approved research ensures that research is not initiated without IRB review and approval.

In communications to investigators, the DFCI IRBs will make investigators aware of the requirement to submit protocol changes to the IRBs for review and approval before initiation of such changes except where necessary to eliminate apparent immediate hazards to the subject.

d. Scope of the DFCI IRBs' Authority. As indicated above, the DFCI IRBs have authority and responsibility for approving, requiring modification in (to secure approval), or disapproving human subject research. The DFCI IRBs 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 DFCI 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 DFCI IRB.

Research that has been approved by the DFCI IRB remains subject to any additional review deemed appropriate by the Institutional Official at each participating DF/HCC institution. Each DF/HCC institution retains the authority to prohibit conduct of research within its respective facilities or by its respective employees that it deems not to be in its best interests (e.g., research that is not consistent with the mission of the institution; research that would require skills or resources that are not readily available; or research that might result in unacceptable fiscal or reputational risks).

1. **Requirement for Prospective Review and Approval.** Prospective review and approval by the DFCI IRB is required for the following:
   a) Research projects that involve human subjects and that are conducted by students, faculty members, or DFCI staff; and

   b) Cancer related research projects that involve human subjects and that are conducted by students, faculty members, or staff of DF/HCC institutions including:

      - Beth Israel Deaconess Medical Center (BIDMC)
      - Brigham and Women's Hospital (BWH)
      - Boston Children's Hospital (BCH)
      - Dana-Farber Cancer Institute (DFCI)
      - Massachusetts General Hospital (MGH)
      - Dana-Farber/Partners Cancer Care network affiliates that have designated the DFCI IRB as its IRB of record

   Note: *No human subjects research as described in (a) and (b) above may be initiated or continued without prospective approval of a DFCI IRB.*

2. **Adding a New Site to an Existing Approved Protocol.** Any investigator desiring to add a new site to an existing IRB-approved protocol must submit the request with all required materials to the DFCI IRB. This requirement must be satisfied when adding either a DF/HCC institution or another site or center from outside the DF/HCC.

3. **Power to Take Action.** The DFCI IRB is empowered to take any action necessary to protect the rights and welfare of human subjects participating in DF/HCC research. The DFCI IRB has the authority to approve, require modifications in, or disapprove the respective institution's human subject research.

4. **Power to Suspend or Terminate Enrollment.** The DFCI IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects in research as it determines necessary for the protection of those subjects, especially in instances of serious or continuing non-compliance. The DFCI IRB has the authority to observe and/or monitor the respective institution's human subject research to whatever extent it considers necessary to protect human subjects and assure compliance with applicable laws and regulations.

5. **Cases of Serious or Continuing Non-compliance.** In cases of serious or continuing non-compliance, the DFCI IRB may: (i) disqualify an investigator from conducting a particular research project or research altogether at the institution; (ii) require education and training in the ethics and regulations of human subject research; or (iii) any other reasonable measure deemed appropriate to protect the rights and welfare of research subjects.

6. **Access to Regulatory Correspondence.** All persons conducting research subject to review by the DFCI IRB, must promptly provide the IRB with copies of any reports, audit findings, or correspondence to or from any regulatory agency (such as OHRP or FDA) that bear upon the protection of human subjects in research in which they are involved. The DFCI IRB will review such correspondence to determine if action is needed to protect human subjects.

7. **Access to Institutional Officials.** The IRB, any IRB member, or the OHRS Director or Associate Directors may bring any matter (e.g., concerns of undue influence) directly to the attention of the Institutional Official, the DF/HCC Center Director, CLC, or Legal Counsel when warranted. The OHRS Director is responsible for investigating any such matter and taking appropriate corrective action after consulting with the IRB Chair of CLC, or Legal Counsel.

e. DFCI IRB Relationships with Other Committees within DF/HCC. The DFCI IRB may require that human subject research also be reviewed by other committees or departments as appropriate, including the Scientific Review Committee(s), the Biosafety Committee(s), and the Radiation Safety Committee(s), Research Pharmacy, Nursing, Biomedical Engineering, Pathology, etc.

f. Appeal of IRB Determinations.

1. **No Overrule Permitted.** No DF/HCC committee or official may set aside or overrule a determination by a DFCI IRB to disapprove or require modifications in human subject research. No DF/HCC committee or official may permit the conduct of human subject research that has not been approved by the DFCI IRB.

2. **Notice to Investigator of Disapproval.** The DFCI IRBs must provide the research investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the investigator an opportunity to respond in person or in writing.

3. **Investigator Response and Appeal.** The DFCI IRB will evaluate the investigator's response in reaching its final determination.

g. Relationship of DFCI IRB to Other Institutions. The DFCI IRB may be designated for review of research under another institution's (non-DF/HCC or DF/PCC institution) Assurance only with the written agreement of the Institutional Official and in accordance with applicable regulatory requirements. Any such designation must be accompanied by a written agreement specifying the responsibilities of DFCI and the DFCI IRB under the other institution's Assurance. The DFCI IRB has no authority over, or responsibility for, research conducted at other institutions in the absence of such a written agreement.

h. Relationship of the DFCI IRB to IND/IDE Sponsors. Unless specifically required by an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) sponsor or by the IRB, no written notifications of IRB decisions will be provided to IND/IDE Sponsors by the DFCI IRB. The Principal Investigator serves as the communications link between the DFCI IRB and the Sponsor for this purpose. For FDA regulated test articles, such linkage is agreed to by the Sponsor and principal Investigators when they sign the FDA Form 1572, Statement of Investigator.

i. Ongoing Monitoring Initiatives. The DFCI IRB is responsible for reviewing all audit findings or other reports (e.g., medical monitor, DSMB, or DSMC reports) related to any DF/HCC research. In doing so, the DFCI IRB should determine and document in the IRB records whether or not corrective action may be warranted.

j. Privacy Board Functions and Determinations. The DFCI IRBs are the designated Privacy Boards as required by HIPAA, 45 CFR 164.501, 164.508, 164.512(i). Functions include review and determinations of requests for Waiver or Alteration of Authorization to use or disclose Protected Health Information in Research. Please refer to separate policies and procedures on research privacy under HIPAA.

k. IRB Self-Assessments & Monitoring. In coordination with the OHRS Director, the DFCI IRB will conduct regular meetings to identify areas of review and operations which may require further enhancement and strengthening. This includes an evaluation of the membership and composition of the IRBs to ensure appropriate expertise relative to the portfolio of the research conducted under the auspices of the DF/HCC.

Additionally, the IRB Chairs and OHRS Director will provide ongoing feedback as needed to the IRB membership regarding areas of review and operations that require strengthening. This may be done by addressing the committee as a whole or a specific IRB member as appropriate.

Chapter 6
IRB Structure and Membership

The DFCI IRB shall have sufficient expertise in oncology care and other research in which DFCI and DF/HCC researchers commonly become involved, and shall be knowledgeable about all relevant regulatory requirements, and strive to remain impartial and objective in its reviews.

In accordance with DHHS and FDA regulations, this Institution's IRBs are comprised of persons from various disciplines and departments, including non-scientific members, and community representatives not otherwise affiliated with DFCI or a DF/HCC institution.

The DFCI IRB operates independently of all other committees that review DFCI and DF/HCC research.

a. Appointment of IRB Members, Length of Service, and Duties. 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 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 DFCI 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 DFCI IRB will have at least five members;
- DFCI 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;
- DFCI 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;
- DFCI 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;
- DFCI IRBs will consist of qualified persons of both sexes;
- No DFCI IRB will consist entirely of members of one profession;
- Each DFCI IRB will include at least one member whose primary expertise is in a scientific area;
- Each DFCI IRB will have at least one member whose primary concerns are in non-scientific areas; and

- Each DFCI 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 DFCI 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.

All IRB members will be evaluated on an ongoing basis to ensure appropriate participation and performance in the conduct of their research reviews. Criteria by which IRB members may be evaluated include the following:

- Attendance at meetings
- Completion of IRB member orientation and human subject protection training
- Knowledge of how to obtain access to regulatory guidance
- Demonstrated expertise or interest (appropriate to IRB role)

Any member of the IRB may be removed by the Institutional Official, the IRB Chair or OHRS Director (i) for failure to perform the duties of an IRB member, including failure to attend at least two-thirds of the IRB meetings held within any 12-month period; or (ii) for scientific misconduct, conflict of interest, or behavior such that review of research by the DFCI IRB is made difficult or impossible.

b. Appointment of IRB Chairpersons, Length of Service, and Duties. Each DFCI IRB will have a Chairperson who is well informed concerning regulations relevant to the involvement of human subjects in research. There may also be co-chairpersons of an IRB.

The Chairperson of the DFCI IRB is appointed by the DFCI CEO or the Institutional Official in accordance with DHHS and FDA regulatory requirements. There are no term limits placed on length of service as IRB Chairperson.

The IRB Chairperson has the following duties:

- Conduct each meeting in an orderly manner. The Chairperson is responsible for chairing the meeting, conducting business so that each proposal is fairly

and completely reviewed, seeing that the IRB reaches a decision on the disposition of each proposal and ensuring that these decisions are communicated to the individuals who submitted the proposal.

- Review and approve research utilizing expedited review procedures in accordance with DHHS and FDA regulations.

- Review, as needed and as delegated by the IRB in appropriate circumstances, responses from investigators to determine if they responded sufficiently to the IRB's concern to allow approval under expedited review procedures and without being returned to the fully convened IRB.

- Appoint qualified IRB members to review and approve research utilizing expedited procedures in accordance with DHHS and FDA regulations.

- Sign correspondence on behalf of the IRB.

- Designate a senior IRB member to assume the responsibilities of the Chairperson during any period of the Chairperson's absence.

- Review IRB policies and procedures at least annually to confirm current compliance with all Federal, State, and local requirements for the protection of human subjects.

The IRB Chair has delegated the following responsibilities to the OHRS Director, and OHRS Associate Directors:

- Appoint qualified IRB members to review and approve research utilizing expedited procedures in accordance with DHHS and FDA regulations.

- Designate a senior IRB member to assume the responsibilities of the Chairperson during any period of the Chairperson's absence.

The DFCI CEO may relieve an individual as IRB Chairperson for failure to fulfil the duties listed above and for (i) failure to perform the duties an IRB member, including failure to attend at least two-thirds of the IRB meetings held within any 12-month period; or (ii) scientific misconduct, conflict of interest, or argumentative behavior such that review of research by the IRB is made difficult or impossible.

c. Alternate IRB Members. Each DFCI IRB, at its discretion, may recruit alternate members to substitute for regular members of the IRB. Alternate members must be listed on the IRB's official membership roster, which must specify which member (or members) the alternate is qualified to replace. ***Note:*** *Although an alternate may be qualified to replace more than one regular member, only one such member may be represented by the alternate at any convened meeting.*

Alternate members will have voting rights, except that they may not vote at meetings attended by their respective regular members. Alternate members will be included in determining or establishing quorum at meetings when their respective regular members are absent, but not when those regular members are present.

Procedures for appointment, terms of appointment, length of service, and duties are exactly as for regular IRB members.

d. Consultants to the IRB. At its discretion, each DFCI 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.

1. **Continuing Consultants.** Continuing Consultants serve a fixed term and generally attend all DFCI IRB meetings. They may have access to all documents submitted to the IRB, may participate in IRB deliberations, and make recommendations to influence IRB determinations. However, Continuing Consultants may not vote on IRB determinations. Continuing Consultants will not be included in determining or establishing quorum at IRB meetings. Examples of Continuing Consultants to the DFCI IRBs include the Directors of the DF/HCC institutions' cancer protocol offices as well as the DF/PCC Network Affiliate liaison.

2. **Ad Hoc Consultants.** The IRB Chairs, the OHRS Director and the OHRS Associate Directors, or the Primary Reviewer may at any time determine that the nature of a particular protocol requires review by an Ad Hoc Consultant who is not otherwise a member of the IRB. This individual will be contacted by the IRB Chair, OHRS, or the Primary Reviewer of the protocol, as appropriate. The Ad Hoc Consultant will be asked to disclose in writing (e.g., via email) whether he or she has any conflicts of interest with the research as described in Chapter 18. If any conflicts exist another Ad Hoc Consultant will be identified. Ad Hoc Consultants serve on an as-needed basis and generally attend DFCI IRBs meeting only when their special expertise is needed. Ad Hoc Consultants may have access to all documents submitted to the IRB that are pertinent to the research under review, may participate in IRB deliberations, and make recommendations to influence IRB determinations. If the Ad Hoc Consultant submits a written review, all members of the IRB will be provided a copy. In the alternative, the Ad Hoc Consultant may attend the IRB meeting and present his/her review verbally; in such instances the key points of the review will be documented in the IRB meeting minutes. However, Ad Hoc Consultants may not vote on IRB determinations. Ad Hoc Consultants will not be included in determining or establishing quorum at IRB meetings.

3. **Legal Counsel.** 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.

e. Mentored Trainees. The DF/HCC institutions are teaching facilities and consequently will mentor young physicians and fellows, also known referred to as "mentored trainees." These individuals must be enrolled in a formal mentoring/training program recognized by the DF/HCC or one of its institutions. These individuals may serve and participate on the IRB as trainees. Mentored trainees must be under the supervision of a voting medical IRB member. Mentored trainees will be assigned reviews of protocols as tertiary reviewers and their reviews will supplement and cannot replace the reviews of the primary and secondary reviewers. Mentor trainees will not be IRB members and will not have a vote.

f. Conflicts of Interest. No DFCI IRB member or consultant to the IRB may participate in the IRB's initial or continuing review of any project or the review of amendments or other submissions in which the member has a conflicting interest, except to provide information requested by the IRB. DFCI IRB members, including the Chairperson, who have conflicting interests, are required to disclose such interests in accordance with Chapter 18 and to absent themselves from deliberations, quorum counts, and votes on the relevant protocol. Such absences

are recorded in the meeting's minutes.

Similarly, IRB members may not conduct expedited reviews of any protocol submissions where he/she has a conflict of interest. Expedited IRB reviewers who have conflicting interests must disclose such interests to OHRS staff so that the submission can be forwarded to another IRB member for review.

While many IRB members also conduct research and some have ongoing advisory relationships with clinical trial sponsors, it remains their ongoing responsibility to disclose any real or apparent conflicting interests to appropriate Institutional officials and to absent themselves appropriately from any IRB deliberations on which they may be conflicted.

g. Education and Professional Development of IRB Members. All IRB members are required to take Human Subject Protection (HSP) Training as described in the DF/HCC SOP EDU-102 Human Subject Protection Training Requirements. Investigators and research personnel and staff as well as SRC and IRB members are responsible for monitoring the expiration of their HSP training and responsible for notifying OHRS that new training has been taken. Individuals whose training has expired are not permitted to review items as part of their SRC or IRB responsibilities until new valid training is in place. At least twice per year, Senior OHRS meeting coordinators will verify that all SRC and IRB members have completed the required HSP training. In addition, all SRC and IRB members go through a group training session with the Director of OHRS that describes in detail the Dana-Farber/Harvard Cancer review, approval and oversight of human subjects training. This is only required at the initial appointment of an SRC or IRB member. Upon receiving an appointment to the IRB, a member receives comprehensive reference materials (including this Manual) necessary to review research from an ethical and regulatory perspective. All IRB members must complete the initial human subject protection education. New members have the opportunity to observe several IRB meetings before they are assigned studies as primary or secondary reviewers. Members will periodically be provided with continuing education opportunities within DFCI or at neighboring institutions, and resources will be made available each fiscal year for one or more IRB members to attend national or regional human subject protection meetings. Additional continuing education requirements may be established as deemed necessary by the Institutional Official and/or the Clinical Trials Education Office.

In order to comply with Department of Defense (DoD) requirements, all IRB chairs, the OHRS Director and Institutional Official (as they are listed on the Department of the Navy (DON) Addendum to our FWA) will complete and document additional DoD-specific training. This requirement may be satisfied by completing the DON CITI training module or by circulating guidance documents. The DON may also require documentation of the regular human subject protection CITI training that these individuals complete every three years. The IRB is aware that the DoD components involved in the research may evaluate the education policies to ensure the personnel are qualified to perform the research, based on the complexity and risk of the research.

h. Compensation of IRB Members. Due to the extensive time commitment to service on the IRB, OHRS offers a contribution of 15% of the DFCI IRB Chairperson's annual salary.

Neither DFCI nor DF/HCC institutions provide monetary compensation to the DFCI IRB members. However, it is acknowledged that service on the IRB requires a significant investment of time for all IRB members.

i. Liability Coverage. IRB members are volunteers performing official functions on behalf of the DF/HCC and as such the DFCI's general and professional liability policies cover DFCI and non-DFCI IRB members. For additional information, please contact DFCI's Office of the General Counsel.

Chapter 7
IRB Administrative Support

DHHS regulations at 45 CFR 46.103(b)(2) require that DFCI provide its IRBs with sufficient meeting space and staff to support the IRBs' review and responsibilities.

a. Resource Allocation. The Institutional Official has responsibility for establishing and maintaining systems for the protection of human subjects in research conducted within this Institution or by its employees. To this end, the Institutional Official, the Director of OHRS, the Senior Chair of the IRB and the Chief Medical Office for Clinical Trials for the DF/HCC meet once a year to discuss the state of the human research protection program and any areas of concern. The group assesses the number of IRBs and the membership to determine whether additional IRBs are necessary; the inclusion of community members on the various IRBs; OHRS staffing and space; the accessibility of legal counsel for advice and guidance; the system for identification of conflicts of interest; the education program in place for IRB members, OHRS staff and investigators; as well as internal review of the adequacy of the systems that support the operations of OHRS. In addition, the group reviews the internal auditing process that is done on a continuous basis within OHRS.

b. Reporting Lines and Supervision. OHRS Human Research Coordinators, Protocol Administrators and Support Staff report to the OHRS Director and/or OHRS Associate Directors. For administrative purposes, the OHRS Director reports to the Institutional Official. However, at any time, the OHRS Director may bring any matter directly to the attention of CLC or the DFCI CEO.

c. Initial Training and Professional Development of IRB Staff. DFCI is required under its OHRP Assurance (FWA) to have a plan to provide education about human subject protections for OHRS staff supporting the IRB. At a minimum, all OHRS Human Research Coordinators must complete initial human subject protection training, such as the CITI Course. This education must be completed once every three years either through the CITI training module or by attending a Human Subject Protection Training session facilitated by the OHRS Director. Compliance with this requirement is monitored by OHRS Director and Associate Directors at the time of Annual Review. Any staff not in compliance with the training may be put on a performance improvement plan.

OHRS staff, including the Director and Associate Directors, will be provided resources to attend national or regional human subject protection conferences on a periodic basis and are expected to do so.

Additionally, the OHRS Director and/or Associate Directors coordinate regular educational sessions on a variety of topics related to protecting human subjects including, but not limited to, application of applicable regulations including Department of Defense research, hot topics in cancer research, minute taking, protocol review practices. Staff are further informed about such topics via SOPs and other supportive documentation.

OHRS staff is encouraged to take advantage of other educational opportunities as they are made available.

d. Initial Training and Professional Development of IRB Staff. The Operations Manager of OHRS pulls a report twice a year that reports on the expiration dates of Human Subject Protection (HSP) Training for OHRS staff. Staff are required to complete a new training prior to the expiration of their training. Staff who do not

complete the HSP training in a timely fashion will have this noted on their performance evaluation.

e. Duties of OHRS Associate Directors and OHRS Staff. The OHRS Director, with the appropriate assistance of the OHRS Associate Directors and other OHRS staff, is responsible for ensuring that the following IRB functions are accomplished in a professional manner that complies with all relevant regulatory requirements.

Overseeing the development and implementation of Institutional policies governing the DFCI IRB, all human subject research, and all investigators and research personnel at this Institution.

Overseeing the operation and administration of the DFCI IRB and determining that the DFCI IRB functions in accordance with the assurances provided in compliance with all Federal, State, and local laws and regulations that govern human subject protection in the conduct of research.

Ensuring the existence of policies to ensure that the Institutional Official, Legal Counsel, Director for Office of Data Quality (ODQ), Director for the Office for Human Research Studies (OHRS), Clinical Investigations Leadership Committee (CLC), IRB Chairpersons and other DF/HCC institutional officials are promptly notified regarding (i) any unanticipated problem involving risks to subjects or others; (ii) any serious or continuing non-compliance with DFCI IRB requirements by research investigators; or (iii) any for-cause suspension or termination of IRB approval.

Ensuring notification of OHRP and FDA of such incidents in accordance with applicable Federal regulations. Such notice will be accomplished in coordination with the OHRS Director, the IRB Chairperson, and as appropriate, Legal Counsel and the ODQ Director.

Overseeing implementation of a research compliance monitoring process that provides monitoring reports, as appropriate, to the Institutional Official, OHRS Director, ODQ Director, CLC, and the IRB Chairpersons.

Review of new protocols to ensure that the proposed research is compatible with the subject population, cancer patients, seen by particular disease groups at the DF/HCC.

Maintaining the official roster of DFCI IRB members

Scheduling IRB meetings

Distributing pre-meeting materials with sufficient time to allow IRB members an opportunity to review them in preparation for the meeting

Compiling the minutes of IRB meetings in compliance with regulatory requirements

Maintaining all IRB documentation and records in accordance with regulatory requirements

Assisting new IRB members in completing orientation procedures and meeting required education standards

Securely and properly archiving all IRB records

Facilitating communication between investigators and the IRB

Tracking the progress of each research protocol submitted to the IRB

Maintaining a computerized database for tracking purposes and logging incoming information into the database

Serving as a resource for investigators on general regulatory information, and providing guidance about forms and submission procedures

Drafting reports and correspondence to research investigators on behalf of the IRB or IRB Chairperson regarding the status of the research, including conditions for initial or continuing approval of research and responses to reports of adverse events or unanticipated problems

Drafting reports and correspondence directed to research officials, Federal officials, and others on behalf of the IRB, IRB Chairperson, and Institutional Official

Maintaining quality control of IRB support functions

Assisting in evaluation, audit, and monitoring of human subject research as directed by the IRB and the Institutional Official

Conducting a limited pre-review of incoming applications to ensure completeness and as otherwise directed by the IRB

Conducting a limited pre-review of proposed informed consent documents to ensure that they are written at a level that is easily understandable for prospective subjects and/or is written in a language that prospective subjects are likely to understand

Receiving and managing subject inquiries, concerns and complaints regarding conduct of research. Work with investigators, patient and family relation office(s) and legal counsel to take action as appropriate for the situation. If an expressed concern or complaint involves potential non-compliance or may be an unanticipated problem involving risks to participants or others, ensure that it is reviewed in accordance with the policy as described in paragraph i of Chapter 9.

The OHRS Director serves as the Human Protections Administrator under the DFCI FWA.

Under the direction and supervision of the Director, the Human Research Coordinators are responsible for documenting that IRB activities and determinations fully satisfy all regulatory requirements. Thus, Human Research Coordinators must have a detailed, working knowledge of relevant regulatory requirements.

Though OHRS coordinates the review by the scientific review committees as well as the DFCI IRBs for purposes of human subject research, the reviews by each committee are managed by OHRS as two separate functions. Similarly, OHRS also coordinates the activation of IRB-approved research at each of the DF/HCC institutions as a separate function.

Chapter 8
IRB Recordkeeping and Required Documentation

DHHS regulations at 45 CFR 46.108(3-4) require that DFCI implement written policies and procedures to govern the operations and direct the activities of the DFCI IRB (45 CFR 46.108(3-4)).

IRB records will include documentation of all IRB findings and determinations as required under DHHS and FDA human subject protection regulations and as recommended by official (i.e., written) OHRP and FDA guidance.

a. IRB Communications. OHRS functions as the communication tool for the IRB. IRB minutes and decisions are communicated via correspondence from OHRS staff to investigators. IRB approvals are communicated via OHRS staff through approval memoranda.

b. IRB Records Defined. At a minimum, DFCI IRB records must include all information required under DHHS and FDA regulations at 45 CFR 46.115 and 21 CFR 56.115, respectively and as recommended by official OHRP and FDA guidance.

IRB files will be organized such that the following information may be readily accessed:

- Written IRB Operating Procedures
- Current and Past IRB Membership Rosters
- Training Records
- All Correspondence to and from the IRB
- IRB Research (Protocol) Files
- Research (Protocol) Tracking System
- Documentation of Exemptions from DHHS regulations
- Documentation of Exemptions and Exceptions from FDA regulations
- Documentation of Expedited Reviews
- Documentation of IRB Findings and Review Category for the Involvement in Research of Pregnant Women, Fetuses, Neonates, Prisoners, and Children
- Documentation of IRB Findings and Justifications for Waiver of Informed Consent and Waiver of Documentation of Informed Consent
- Information for All Approved Research Addressing Each of the Eight Criteria for Approval under DHHS regulations at 21 CFR 56.111 and 46 CFR 46.111
- Documentation of Convened IRB Meetings – Minutes

- Records pertaining to initial and continuing review[8], if applicable, of the research reviewed by expedited procedure will include documentation of actions taken by the reviewer, including any findings required by laws, regulations, codes, and guidance.

- Documentation of Review by Another Institution's IRB

- Adverse Event Reports

- Reports of Unanticipated Problems involving Risks to Subjects or Others

- Documentation of Non-Compliance

c. Record Retention and Access. In accordance with Federal regulations at 21 CFR 56.115(b) and 45 CFR 46.115(b), DFCI IRB records will be retained for no less than three years, and research records will be retained by DFCI for no less than three years after the completion of the research. This includes research protocols reviewed by the IRB but for which no subjects were enrolled.

All DFCI IRB records will be kept in a permission-restricted, protected electronic database. Ordinarily, access to IRB records is limited to the IRB Chairperson, IRB members, IRB staff, the Institutional Official, Office for Data Quality staff, and officials of Federal and State regulatory agencies, including OHRP and FDA. Research investigators and their staff will be provided reasonable access to the electronic files related to their research. Records maintained that document compliance or non-compliance with Department of Defense (DoD) requirements shall be made accessible for inspection and copying by representatives of the DoD at reasonable times and in a reasonable manner as determined by the supporting DoD component. All other access to IRB records is limited to those who have legitimate need for them, as determined by the IRB Chairperson or the OHRS Director.

d. IRB Membership Rosters. All DFCI IRB membership rosters will include at least the following information:

- Names of IRB members

- Names of alternate members and the corresponding regular member (s) for whom each alternate may serve

- Earned degrees and specialties of each member and alternate, if applicable, sufficient to describe each member's chief anticipated contribution to IRB deliberations

- The representative capacity of each member or alternate

- Status as a scientist or non-scientist

[8] **Note**: Research reviewed and approved prior to January 21, 2019 will follow the Continuing Review schedule (Expiration Date) indicated at the last approval. DFCI IRB will transition applicable studies to the new Continuing Review schedule, per the Revised Common Rule, and issue a study memo indicating the transition along with any additional requirements.

- Any employment or other relationship with this Institution or its components (*e.g.,* full or part time employee, stockholder, member of governing board, paid or unpaid consultant)

- The IRB rosters are not publicly available[9].

e. Education and Training Records. This Institution is required under its OHRP FWA to have a plan to provide education about human subject protections for research investigators and IRB members and staff. The Clinical Trials Education Office will maintain accurate records listing research investigators, IRB members, IRB staff and research staff who have fulfilled the DF/HCC human subject protection training requirements. Such records will be available for review by CLC, the Institutional Official, IRB Chairpersons and OHRS Director as a part of ongoing compliance monitoring activities, and will include documentation of the following:

1. **Research Investigator Education.** At a minimum, all research investigators must complete Human Subject Protection Training (HSPT) and Good Clinical Practice (GCP) training such as the Collaborative IRB Training Initiative (CITI)[10] educational program or other program approved by the ODQ education coordinator. Re-certification is required every three years and is accomplished by completing the CITI Continuing Education or "Refresher" course, or other human subject protection training approved by the ODQ. It is the investigator's responsibility to ensure that all key research personnel have completed the required training. Failure to comply with the requirement will result in the delay of approval or removal of the individuals who have not completed the requirement from the study.

2. **IRB Member Education.** Upon receiving an appointment to the IRB, a member receives comprehensive reference materials (including this Manual) necessary to review research from an ethical and regulatory perspective. All IRB members must also complete the initial Human Subject Protection Training (HSPT) (e.g., CITI educational program) and Good Clinical Practice (GCP) training. Re-certification is required every three years and is accomplished by completing the CITI Continuing Education or "Refresher" course or other human subject protection training approved by the ODQ. New members have the opportunity to observe several IRB meetings before they are assigned studies as primary or secondary reviewer. Members will periodically be provided with continuing education opportunities within this Institution or at neighboring institutions, and resources will be made available each fiscal year for one or more IRB members to attend national or regional human subject protection meetings (e.g. PRIM&R AER, AAHRPP Annual Meeting). Additional continuing education requirements may be established as deemed necessary by the Institutional Official and/or the OHRS Director.

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[9] Revised Common Rule, NRPM, section IV. D: The final rule eliminates the requirement that appeared in the pre- 2018 rule that an up-to-date list of the IRB members and their qualifications be included in an institution's assurance. Instead, 45 CFR 46.108(a)(2) and 46.115(a)(5) in the final rule require that an IRB or the institution prepare and maintain a current list of IRB members. This eliminates the previous requirement that changes in IRB membership be reported to the department or agency head, or to OHRP when the existence of an assurance approved by HHS for federal-wide use is accepted.

[10] IRB members can register to take the CITI course at www.citiprogram.org or can contact the ODQ at ODQ@dfci.harvard.edu for additional details.

f. IRB Research Protocol Files. The IRB will maintain a separate electronic file for each research protocol that it receives for review. Such electronic files will be kept for a period not less than three years after completion.

Each IRB research protocol file will contain at least the following materials:

- The protocol application form
- Copies of all research related activities reviewed (e.g., protocols, research design and methodology statements) and scientific evaluations of the proposed research (e.g., minutes from the scientific review committee), if any
- The IRB-approved informed consent document
- Investigator Brochure, if any
- Applications for Federal support, if any
- Sponsor or cooperative group protocols and sample informed consent documents, if any
- Advertising or recruiting materials, if any
- For FDA-regulated research, where the DF/HCC PI holds the IND or IDE, copies of FDA correspondence containing the IND/IDE number.
- Applications for protocol amendments or modifications
- Continuing review progress reports and related information
- Reports of unanticipated problems involving risks to subjects or others
- Reports of injuries to subjects and adverse events occurring within institutions that have designated the DFCI IRB to review the research, and reported to any regulatory agency
- Reports of external adverse events and/or safety reports received from sponsors or cooperative groups
- Data and Safety Monitoring Board (DSMB) reports or Data Safety Monitoring Committee (DSMC) reports, if any
- Results of internal quality control and monitoring activities, if any
- All IRB correspondence to and from research investigators, government agencies, data monitoring boards, or sponsors
- All other IRB correspondence related to the research, including documentation of non-compliance.
- Documentation of all IRB review and approval actions, including initial and continuing convened (full) or expedited IRB review
- Documentation of all waivers or alteration of informed consent or documentation of informed consent (see Chapter 11 on informed consent)

- Documentation of type of IRB review (e.g., full or expedited review) (see below as well as Chapter 9 on IRB Review)

- Documentation of Project Closeout. (It is the policy of the DFCI IRB to administratively close and return to the principal investigator any new research application when additional information requested by the IRB is not submitted within a 90-day period.)

- Documentation of statements of significant new findings provided to subjects

g. IRB Database. DFCI IRB records are maintained in a centralized research-tracking database.

The database would include at least the following information:

- Title of the Research (Protocol)

- Name of Overall Principal Investigator

- Name of Site Investigators

- Participating DF/HCC Institution(s)

- Funding Source (if any)

- Date of Initial Approval

- Date of Most Recent Continuing Approval

- End of Current Approval Period

- Type of Review (Expedited, Convened Review or determination of Exemption)

- Involvement of children or vulnerable population

- Current Status (Under Review, Approved, Suspended, Closed)

h. Documentation of Exemptions and Exceptions. Identification of research activities that are exempt from the human subject regulations requires a sophisticated level of expertise and is not left to individual investigators.

Other than the emergency use of a test article (see below), all exemptions claimed for research must be verified and determined (i.e., make an authoritative decision about the exempt status) by the IRB Chairperson, a qualified member of the IRB, the OHRS Director or Associate Directors, or another qualified professional designated by the OHRS Director following appropriate training.

In reviewing exemption requests, the reviewer must receive enough information from the investigator to ascertain whether the claimed exemption genuinely applies. Research for which there is a statutory requirement or funding agency requirement for IRB review, or for which there is significant physical invasion or intrusion upon the privacy interest of the subject or for which ethical concerns are raised, cannot be declared exempt.

Documentation of verified exemptions consists of the reviewer's written concurrence

in the IRB Research Protocol File that the activity described in the Investigator's application for exemption from the human subject protection regulations satisfies the conditions of the cited exemption category.

Other than the emergency use of a test article (see below), the exemptions do not apply to research involving prisoners, except for research aimed at involving a broader subject population that only incidentally includes prisoners.[11]

The exemptions do apply to research involving pregnant women, fetuses, and neonates. The categories of exempt research are stipulated in the Federal Policy (Common Rule) and in DHHS regulations at 45 CFR 46.104(d)(1-8).

The exemptions categories (1), (4), (5), (6), (7), and (8) may be applied to research involving children if the conditions of the exemption are met[12].

Determinations of exemptions and exceptions will be communicated in writing by OHRS on behalf of the reviewer.

Exemptions include the following:

1. **Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations in accordance with 45 CFR 46.104(d)(1). This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods. Even if the research is exempt, the investigator has an ethical obligation to respect and safeguard students' rights and welfare.

2. **Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior (including visual or auditory recording) is ordinarily exempt under Federal regulations at 45 CFR 46.104(d)(2) if at least one of the following is met:
   a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly

[11] 45 CFR 46.104(b)(2): (2) Subpart C. The exemptions at this section do not apply to research subject to subpart C, except for research aimed at involving a broader subject population that only incidentally includes prisoners.

[12] 45 CFR 46.104(b)(3)

or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 46.111(a)(7).

Note: *The research is not exempt unless both (a) and (b), or (c) have been met; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.*

3. **Exempt Research Using Benign Behavioral Interventions**[13] If not exempt under the conditions described above, research involving the use of behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection is exempt under 45 CFR 46.104(d)(3) if at least one of the following criteria is met:
   a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 46.111(a)(7).

   Note: *If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research*[14]*.*

4. **Secondary research for which consent is not required.** Secondary research uses of identifiable private information or identifiable biospecimens, may be exempt from DFCI IRB review and informed consent requirements if at least one of the following criteria is met[15]:
   a) The identifiable private information or identifiable biospecimens are publicly available;
   b) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

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[13] Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

[14] 45 CRF 46.104(d)(3)(iii)

[15] 45 CRF 46.104(d)(4)(i-iv)

c) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b); or
d) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

5. Studies using existing materials occasionally entail greater than minimal risks to subjects and require review by the convened DFCI IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer has concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators). **Exempt Research and Demonstration Projects with Approval of Federal Department or Agency Heads[16].** Research and demonstration projects are exempt under 45 CFR 46.104(d)(5) if they 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.

Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

6. Exempt Taste and Food Quality Evaluation and Consumer Acceptance Studies. Taste and food quality evaluation and consumer acceptance studies are exempt from DFCI IRB review under 45 CFR 46.104(d)(6) if: (a) wholesome foods without additives are consumed or (b) a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, (c) or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This also applies to FDA regulated research.

[16] Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

NOTE: Under the Revised Common Rule, Exempt categories 7 (Storage or maintenance for secondary research for which broad consent is required)[17] and 8 (Secondary research for which broad consent is required) [18] require that "Regulatory Broad Consent" (or Broad Consent under the post-2018 rule) must be obtained. **DF/HCC will not utilize "Regulatory Broad Consent" and research reviewed on/or after January 21, 2019 will not be reviewed by the DFCI IRB as Exempt under categories 7 or 8.**

In addition to satisfying the regulatory criteria as outlined in the six categories of exempt above, reviewers should also ensure that the research meets the following ethical standards:

- The research involves no more than minimal risk to subjects.
- Selection of subjects is equitable.
- There are adequate provisions to maintain the confidentiality of data.
- There are adequate protections of the privacy of subjects.
- When there are interactions with subjects, there is a consent process that provides a description of the procedures, that participation is voluntary, and the name and contact information for the researcher.

Exceptions include the following:

1. **Exception from Informed Consent Requirement for Emergency Use of a Test Article.** FDA regulations at 21 CFR 50.23 permit the use of a test article without the informed consent of the subject (or the subject's legally authorized representative) where the clinical investigator and a physician, not otherwise involved in the research, certify in writing that (i) the subject is confronted with a life threatening emergency; (ii) informed consent cannot be obtained because of an inability to communicate; (iii) time is not sufficient to obtain consent from the subject's legally authorized representative; and (iv) there is no alternative approved or generally recognized therapy that provides equal or greater likelihood of saving the life of the subject. This written certification must be submitted to the DFCI IRB within 5 working days of the use of the test article. This reporting must not be construed as an approval for the emergency use by the DFCI IRB.

   Emergency use of investigational drugs requires that the patient become a subject in a research protocol (21 CFR 50.23(g)).

   OHRS staff is responsible for maintaining this documentation in IRB records. The clinical investigator must notify the IRB Chairperson prior to the emergency use where at all possible. Emergency use of test articles is discussed in greater detail in Chapter 12.

[17] 45 CRF 46.104(d)(7)

[18] 45 CRF 46.104(d)(7)

2. **Exemption from IRB Review Requirement for Emergency Use of a Test Article.** FDA regulations at 21 CFR 56.104(c) permit the emergency use of a test article without IRB review. Emergency use is defined as use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is no sufficient time to obtain IRB approval (21 CFR 56.102(d)). All of the following conditions must be met for this type of emergency use: (i) an individual is in a life-threatening situation; (ii) no standard acceptable treatment is available; (iii) there is insufficient time to obtain IRB approval; and (iv) the emergency use must be reported in writing to the IRB within five working days.

   This reporting must not be construed as an approval for the emergency use by the IRB. OHRS staff is responsible for maintaining this documentation in IRB records.

   The clinical investigator must notify the IRB Chairperson prior to the emergency use where at all possible. Emergency use of test articles is discussed in greater detail in Chapter 12.

i. Documentation of Expedited Reviews. Expedited IRB review procedures may be employed for (i) minor changes in previously approved research during the specified approval period; and (ii) research activities that fall within the FDA/DHHS specified categories (63 FR 60353-60356 and 60364-60367, November 9, 1998) and involve no more than minimal risk to subjects. Documentation for expedited reviews will be maintained in DFCI IRB records and will include the actions taken by the reviewer including the category and circumstances that justify using expedited procedures. Such documentation is ordinarily provided through the reviewer's written concurrence in the reviewer determination section of the application form or other reviewer checklist. Expedited reviews may be conducted by the IRB Chairperson or other members of the DFCI IRB with working knowledge of the expedited categories. The expedited categories are explained further in the next chapter on IRB Review.

j. Documentation of IRB Meetings – Minutes of IRB Meetings. OHRS staff will compile the minutes of DFCI IRB meetings. The IRB meeting minutes will be submitted to the members of the IRB for review and approval at the next possible convened meeting.

The OHRS Director will ordinarily implement protocol approvals and other IRB actions immediately following the IRB meeting at which the action took place and need not wait for the approval of the minutes.

Any errors in the finalized IRB meeting minutes will be rectified as soon as possible after they are identified. After the minutes are corrected, they will be saved as a new "-Revised" version and will be re-routed for IRB review and approval at the next possible convened meeting.

A designated OHRS staff member will be responsible for recording attendance, and monitoring quorum requirements as the IRB discusses, deliberates and votes on each agenda item.

The following specific information will be recorded in the meeting minutes:

1. **Attendance at DFCI IRB Meetings.** IRB minutes will list attendance as follows:

   - Names of members present

- Names of absent members
- Names of alternates attending in lieu of specified (named) absent members (alternates may substitute for specific absent members only as designated on the official IRB membership roster)
- Names of non-voting members and consultants present
- Name of investigators present
- Names of guests present

2. **Quorum Requirements and Voting at DFCI IRB Meetings.** IRB minutes will include a statement of Quorum Requirements based on the following standards:

   A majority of the IRB members (or their designated alternates), including at least one member whose primary concerns are in non-scientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting;

   Members may be present in person or audio (telephone) or audio-visual teleconference. Members present via teleconference will be noted as such in the meeting minutes. All members receive all pertinent information prior to the meeting and are able to actively and equally participate in all discussions;

   Members who arrive to the meeting late or who leave the meeting early will not be counted as present or counted among those voting or abstaining for those actions before their arrival or after their departure. The minutes will identify these individuals as not present for each application action.

   DFCI IRB minutes will include documentation of quorum and votes for each IRB action by recording votes as follows: total number voting ( ); number voting for ( ); number voting against ( ); number abstaining ( ); and names of recused members;

   Members absenting themselves due to conflicting interests may not be counted toward quorum requirements (i.e., may not be counted among those voting or abstaining). These members will be counted and identified by name as "recused"; and

   No individual who is not listed on the official DFCI IRB membership roster may vote with the IRB.

3. **Actions Taken by the Convened DFCI IRB.** IRB minutes will include all actions taken by the DFCI IRB on the initial or continuing review of applicable research; review of protocol or informed consent modifications or amendments; unanticipated problems involving risks to subjects or others; adverse event reports; reports from sponsors, cooperative groups, DSMBs, or DSMCs; reports of continuing non-compliance with the human subject regulations or IRB determinations; suspensions or terminations of research; and other actions. These determinations will also be provided in writing to investigators in the form of a memorandum from the IRB which includes, at minimum, the following information (where appropriate): investigator's name, title of study, IRB number, approval date, continuing review interval, and changes to the materials submitted in order to secure approval. The IRB will also determine the level of

risk of the study.

IRB actions for initial or continuing review of research include those listed below.
Approved as submitted. Approved as submitted with no changes (or no additional changes). The research may proceed once the protocol has all applicable sign offs for activation.

Conditionally Approved with Specific Changes. Approvable with changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol approved by an IRB reviewer. OHRS staff who are not voting IRB members and non-voting members of the IRB may not approve these changes.

Deferred. Deferred pending receipt of additional substantive information. If the DFCI IRB determines that it lacks sufficient information about the research to proceed with its review, the research may not proceed until the convened IRB has approved a revised protocol application incorporating all necessary information.

Disapproved. The IRB has determined that the research cannot or should not be conducted at DF/HCC at this time.

4. **Separate votes for other IRB actions.**

5. **The Basis for Requiring Changes in or Disapproving Research.** The minutes of IRB meetings will include the basis for requiring changes in or disapproving research, including the basis for any deletion or substantive modification of information concerning risks or alternative procedures contained in cooperative group (or other DHHS-approved) sample consent documents. This information will also be provided in writing to the investigator, who will be given an opportunity to respond in person or in writing.

6. **Summary of Controverted Issues at Convened Meetings.** The minutes of IRB meetings will include a summary of the discussion of all controverted issues and their resolution.

7. **Required IRB Findings and Determinations.** The following specific IRB findings and determinations will be documented in IRB meeting minutes, including protocol-specific information justifying each finding or determination: The level of risk of the research. When not stated in the minutes, the IRB has determined that the protocol is greater than minimal risk.

   The approval period for the research, including identification of research that warrants review more often than annually.

   Identification of any research for which there is need for verification from sources other than the investigator that no material changes are made in the research.

   Justification for waiver or alteration of informed consent, addressing each of the four criteria at 45 CFR 46.116(f)(3). Briefly, the criteria that the IRB must find, and document are:

1. the research involves no more than minimal risk to subjects;

2. the waiver or alteration will not adversely affect the rights and welfare of subjects;

3. the research could not practicably be carried out without the waiver or alteration;

4. if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; and

5. whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation. When not stated in the minutes, the IRB has concurred with the criteria information provided in the new protocol application.

Justification for waiver of the requirement for written documentation of consent in accordance with the criteria at 45 CFR 46.117(c).

For DHHS-supported research, justification for approval of research involving pregnant women, human fetuses and neonates, addressing each of the criteria specified under Subpart B of the DHHS human subject regulations.

For DHHS-supported research, justification for approval of research involving prisoners, addressing each of the categories and criteria specified under Subpart C of the DHHS human subject regulations. The IRB Chairperson is responsible for providing certification of the IRB's findings to OHRP.

For DHHS-supported research and for FDA-regulated research, justification for approval of research involving children, addressing each of the categories and criteria specified under Subpart D of the DHHS or FDA human subject regulations. The IRB Chairperson is responsible for providing notification to OHRP of the IRB's findings concerning research requiring review by a panel of experts.

Special protections warranted in specific research projects for groups of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, regardless of source of support for the research.

Rationale for the IRB's determination of significant risk or non-significant risk for a medical device, in accordance with FDA requirements.

Justification for approval of research planned for an emergency setting, with specific reference to the criteria specified under the special 45 CFR 46.101(i) DHHS waiver or the FDA exception at 21 CFR 50.24.

Any IRB discussions or determinations regarding (i) unanticipated problems involving risks to subjects or others; (ii) serious adverse events; and (iii) any other items on which the IRB takes formal action.

8. **Report of Expedited Reviews and Exemption Determinations.** A list of research approved since the last meeting utilizing expedited review procedures as well as research determined to be exempt from DFCI IRB review is submitted to the convened IRB for review. The list is maintained with the IRB meeting minutes.
9. **Duration of the Meeting.** IRB minutes will record when the meeting came to order and when the meeting was adjourned.

k. Documentation of Review by Another Institution's (External) IRB. The DF/HCC Consortium clinical sites have agreed to rely on the DFCI IRB as the IRB of Record for all Cancer Center Support Grant relevant research. OHRS maintains documentation of IRB review by the DFCI IRB as well as other external IRBs where the DF/HCC Consortium clinical sites have agreed to rely on an external IRB. An exception to when OHRS maintains documentation of review by another institutions IRB includes:

- Where the DFCI relies on the IRB review of research by a DF/HCC Consortium site under a reciprocal reliance agreement.

As a general matter, the DFCI and collaborating DF/HCC Institutions within the consortium will only rely on the review by another academic institution's IRB using the SMART IRB Reliance Agreement. In exceptional circumstances, such as where an external IRB with particular expertise reviews a large set of related research studies (e.g., NCI CIRB, NMDP IRB) the DFCI and collaborating DF/HCC institutions may enter into a reliance agreement directly with the external IRB.

When DFCI and collaborating DF/HCC Institutions rely on an external IRB, OHRS will maintain a protocol file to include copies of the following:

- Documentation of agreement to rely on an external IRB by any collaborating DF/HCC institutions.
- Documentation of a SMART IRB reliance agreement, copy of the applicable IRB authorization agreement or other written instrument;
- External IRB Approval for the investigator's participation in the research;
- Copy of the External IRB approved protocol, informed consent, other research materials and the reviewing IRB's approval;
- Copy of any external IRB approved changes in the research
- Copy of any reports of non-compliance, unanticipated problems involving subjects or others, suspensions or terminations;
- If available, copy of the final report or other document closing and/or completing the study.

Such documentation will be obtained either directly from the participating investigator or the reviewing external IRB.

l. Dissemination of IRB Minutes. IRB minutes are sent to all identified study staff as well as Clinical Trials Offices as appropriate. All IRB minutes are sent to the Institutional Official.

Chapter 9
Procedures for IRB Review

All human subject research conducted at DF/HCC institutions must be prospectively reviewed and approved by the DFCI IRB. No human subject research may be initiated or continued without prospective approval of the DFCI IRB.

a. Review by the Convened IRB. The Common Rule, DHHS regulations and FDA regulations require that the IRB conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review (as discussed later in this chapter).

Except for unusual circumstances, at least one week prior to the convened meeting, all IRB members will be provided with protocol submission materials to be discussed at the convened meeting. The purpose of this practice is to provide sufficient time for IRB members to review each protocol submission before the meeting, so they can discuss each submission adequately and determine the appropriate action during the convened review. All IRB members will be afforded full opportunity to discuss each research proposal during the convened meeting. IRB members may contact OHRS staff at any time to request any protocol file materials or other assistance. All IRB members should review all provided materials for each protocol on the agenda such that they will be able to discuss the materials at the convened meeting. In addition to the materials provided for discussion at the meetings, IRB members will have access to the entire study file, the electronic database, and the electronic protocol library (OncPro) which includes the current protocol and informed consent document(s). In addition, IRB members are able to post their comments electronically for review by the other members.

A majority of the DFCI IRB members (or their designated alternates), including at least one member whose primary concerns are in non-scientific areas, must be present in order to conduct a convened meeting. In order for research to be approved, it must receive the approval of a majority of those members present at the meeting. If quorum is lost during a meeting, the IRB cannot take votes until the quorum is restored.

When research involves subjects who may be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, fetuses or neonates, etc., the IRB Chairperson, OHRS Director or Associate Directors, shall ensure that at least one individual who is knowledgeable about or experienced in working with such subjects is present at the meeting. If at least one individual with such knowledge or experience is not present, then the protocol will be tabled to the next meeting.

When research involves the Department of Defense (DoD) support, the following shall be promptly (no longer than within 30 days) reported to the DoD human research protection officer:

- When significant changes to the research are approved by the IRB
- The results of the IRB continuing review
- Change of reviewing IRB

- When the organization is notified by any Federal department, agency, or national organizations that any part of the HRPP is under investigation for cause involving a DoD supported research protocol

DFCI IRB members may participate in convened IRB meetings via telephone and/or video conferencing in accordance with applicable guidance from FDA and OHRP. The DFCI IRB meeting schedule is made available to DFCI IRB members.

b. Initial Review by the Convened IRB. Upon receipt of a complete set of IRB application materials, Human Research Coordinators under the supervision of the Director and/or Associate Directors will designate a Primary Reviewer based on area of expertise and a Secondary Reviewer for the proposed research. As discussed later in this chapter, the Primary and Secondary Reviewer will provide an exhaustive review of the applications assigned to them, fill out the appropriate reviewer forms, and lead the discussion of the proposed research at the convened meeting of the IRB.

Except for unusual circumstances, at least one week prior to the convened meeting, all IRB members will be provided detailed initial review materials describing each proposed research project to be discussed at the convened meeting.

The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing initial review by the convened IRB.

1. **Use of Primary and Secondary Reviewers with Convened Reviews.** In accordance with FDA and OHRP guidance, the DFCI IRB utilizes a "primary and secondary reviewer system" to assist in the initial and continuing review of research by the convened IRB.

   When utilized, the Primary and Secondary Reviewers are considered the lead reviewers for research proposals assigned to them. An IRB member, who is assigned as a primary reviewer, may request that the protocol be assigned to another IRB member if he/she feels they do not have enough expertise to present the protocol to the committee. Primary and Secondary Reviewers are responsible for:

   - Being thoroughly versed in all details of the research
   - Conducting an exhaustive review of the research using the IRB reviewer checklists
   - Contacting individual investigators for clarification as needed prior to the convened meeting
   - Leading the discussion of the research at the convened meeting

2. **IRB Member Initial Review Materials.** Initial review materials provided to all IRB members (including alternate members who will attend the meeting) at least one week prior to the meeting (or as soon as possible) will include:

   - The research application forms (which include information about subject recruitment and selection, the research plan, risks and benefits, privacy and confidentiality protections, safety monitoring, informed consent procedures, and protections for vulnerable subjects)
   - The protocol

- The proposed informed consent document
- Any recruitment materials (including advertisements to be seen or heard by potential subjects)
- SRC approval and comments made by the DF/HCC scientific review committee and the investigator's responses
- For DHHS multi-center trials, the DHHS-approved sample informed consent documents and the complete DHHS-approved protocol

3. **Additional Materials for Primary Reviewers.** The Primary Reviewers will be provided with the following additional materials at least one week prior to the meeting:

    - The Investigator's Brochure (if applicable) **Note:** Copies of the Investigator's Brochure are also forwarded to the IRB members who are from Research Pharmacy
    - The full grant application or proposal (without attachments) for any Federally-supported research on which this Institution or any of its components is the direct awardee
    - Any other information relevant to the approval criteria described in the regulations

    IRB members can obtain copies of any information provided to the Primary and Secondary Reviewers or any other individual reviewer by contacting OHRS.

    If Primary and Secondary Reviewers are not appointed, or if both the Primary Reviewer and the Secondary Reviewer are absent from the convened meeting. The proposed research will be tabled to a subsequent meeting, unless another IRB member has in fact reviewed the proposed research in the same manner expected of an assigned primary reviewer.

4. **Use of Subcommittees to Support IRB Activities.** The IRB may utilize subcommittees to support IRB review activities. At the discretion of the IRB Chairperson, subcommittees may be appointed to perform expedited reviews or fulfill the duties of Primary and/or Secondary reviewers. The IRB Chairperson may also appoint subcommittees on an ad hoc basis to perform additional functions as needed. Subcommittees are not IRBs, however, but may perform functions useful to the full IRB.

Continuing Review. For DHHS-supported research and for FDA-regulated research, the DFCI IRB is required to conduct "substantive and meaningful continuing review" of research at intervals appropriate to the degree of risk, but, unless otherwise indicated below, not less than once per year*****. For example, if the research has an IRB approval date of October 2, 2017, the OHRS protocol database will automatically list the protocol as "lapsed" at 12:01 a.m. on October 2, 2018. Accordingly, the IRB must conduct its continuing review on or before October 1, 2018, before research including the enrollment of new subjects may continue.

***Note:** Research reviewed and approved prior to January 21, 2019 will follow the Continuing Review schedule (Expiration Date) indicated at the last approval. DFCI IRB will transition applicable studies to the new Continuing Review schedule, per

the Revised Common Rule, and issue a study memo indicating the transition along with any additional requirements.

The following regulatory criteria is utilized to determine the continuing review period for DFCI IRB reviewed and approved research:

1. Unless otherwise stated below, the DFCI IRB shall conduct a continuing review of all research at intervals appropriate to the degree of risk, not less than once per year.

2. A continuing review of research is not required in the following circumstances[19]:
   a) Research reviewed and approved after January 21, 2019 by the DFCI IRB via expedited review procedures.
   b) Research reviewed and approved after January 21, 2019 by the DFCI IRB in accordance with the limited IRB review procedures.
   c) Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:
      i. Data analysis, including analysis of identifiable private information or identifiable biospecimens, or
      ii. Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

A new study reviewed after January 21, 2019 by the DFCI IRB, or otherwise appropriate review procedure, will contain the approved continuing review period/requirement within the protocol approval memo.

Please note that the determination of the continuing review period can only be made after the research study has proceeded through its appropriate review/approval procedure (e.g. DFCI IRB, expedited review, etc.).

Continuing reviews will be conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review (as discussed later in this chapter). When appropriate, continuing reviews will continue until the study is complete.

Except for unusual circumstances, at least one week prior to the convened meeting, each IRB member will be provided with detailed continuing review materials sufficient to conduct substantive and meaningful reviews. These materials will include the currently approved informed consent document, a protocol summary detailing the entire history of the protocol, and the Continuing Review Application Form. The Primary Reviewer will conduct an in-depth review of the complete protocol file including any protocol modifications previously approved by the IRB. The primary reviewer may request that the protocol be assigned to another IRB member if he/she feels they do not have enough expertise to present the protocol to the committee. The Continuing Review Application Form is comprised of the following:

- A summary of the research providing sufficient information to address the approval criteria found at 45 CFR 46.111 and the FDA regulations. (See next chapter for additional information regarding the approval criteria)

[19] 45 CRF 46.109(f)(1)

- A status report on the progress of the research, including any significant findings
- The number of subjects enrolled and withdrawn
- A description of any unanticipated problems involving risks to subjects or others
- A summary of major amendments
- A summary of adverse events
- Any change in conflicts of interest
- Reasons for withdrawal of subjects, and complaints about research since the last IRB review
- A summary of relevant recent literature
- References to all publications/abstracts/posters
- The consent document is still accurate and complete
- Other information considered relevant by the investigator, especially information about risks

If the IRB determines that the protocol should be conditionally approved or deferred, and it is not anticipated that the protocol will be approved by the expiration date, the IRB should consider whether any interventions and interactions with already enrolled subjects should continue due to over-riding safety or ethical concerns such that it is in their best interest to continue.

For continuing review of research, the IRB determines that the current consent document is still accurate and complete. The IRB may request any changes to the current consent document or protocol based on the information provided at continuing review. Additionally, if there any significant new findings that may relate to a participant's willingness to continue participation, the IRB should require that this information be conveyed to participants.

The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

c. Review More Often Than Annually. The IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. The IRB may consider the following factors in determining which studies require more frequent review:

- The probability and magnitude of anticipated risks to subjects
- The likely medical condition of the proposed subjects
- The overall qualifications of the principal investigator and other members of the research team

- The specific experience of the principal investigator and other members of the research team in conducting similar research
- The nature and frequency of adverse events observed in similar research at this and other institutions
- Any other factors that the IRB deems relevant

In specifying an approval period of less than one year, the IRB may define the period with either a time interval or a maximum number of subjects.

d. Independent Verification from Sources Other than the Investigator. The DFCI IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator, that no material changes or other problematic events have occurred during the IRB-designated approval period.

The IRB may consider the following factors in determining which studies require such independent verification:

- The probability and magnitude of anticipated risks to subjects
- The likely medical condition of the proposed subjects
- The probable nature and frequency of changes that may ordinarily be expected in type of research proposed
- Prior experience with the principal investigator and research team
- Any other factors that the IRB deems relevant

In making determinations about independent verification, the IRB may prospectively require that such verification take place at predetermined intervals during the approval period or may retrospectively require such verification at the time of continuing review.

e. Expedited Review of Research. DHHS regulations, the Federal Policy (Common Rule), and FDA regulations permit the IRB to review research through an expedited procedure if:

a) Some or all of the research appearing on a list of categories[20] of research that may be reviewed by the IRB through an expedited review procedure, unless the reviewer determines that the study involves more than minimal risk;

b) Minor changes in previously approved research during the period for which approval is authorized; or

[20] The Secretary of HHS has established, and published as a Notice in the Federal Register, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The Secretary will evaluate the list at least every 8 years and amend it, as appropriate, after consultation with other federal departments and agencies and after publication in the Federal Register for public comment. A copy of the list is available from the Office for Human Research Protections, HHS, or any successor office

c) Research for which limited IRB review is a condition of exemption under 45 CFR 46.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7) and (8).

The IRB Chair, OHRS Director and/or Associate Directors determine which IRB members have the experience and expertise (i.e., prior experience on the DFCI IRB and training with an OHRS Directors) to conduct expedited reviews on behalf of the IRB.

Under an expedited review procedure, the IRB Chairperson or an experienced DFCI IRB reviewer may review and approve the research on behalf of the IRB, request additional information, or forward the application to the fully convened IRB. The IRB member may also request that the protocol be assigned to another IRB member if he/she feels they do not have enough expertise to review the protocol. When the convened IRB requests substantive clarifications or modifications that are directly relevant to the determinations required by the IRB, the protocol must return to the convened IRB and not be approved by the expedited procedure. The expedited reviewer may not disapprove any research activity. The research activity may be disapproved only after review by the fully convened DFCI IRB.

For initial reviews conducted by expedited review, the IRB reviewer should receive all of the documentation listed in the relevant sections above. The reviewer must ensure that the research undergoing initial review meets all applicable expedited review criteria.

For review of revisions, modifications, and amendments, the IRB reviewer should receive all of the documentation listed in paragraph g below. The standard requirements for informed consent (or its waiver, alteration, or exception) apply regardless of the type of review. Additionally, the standard requirements for review and approval of research reviewed by the convened IRB also apply and must be documented.

Documentation for expedited reviews will be maintained in IRB records and will include the category and circumstances that justify using expedited procedures.

OHRS Human Research Coordinators will keep all DFCI IRB members advised of research that has been approved under expedited procedures by listing reviews of the research in the minutes of the next possible IRB meeting. At the request of any IRB member, the fully convened IRB may re-review any research that has been approved using expedited review procedures. The re-review will be conducted in accordance with the IRB's usual non-expedited procedures.

1. **Review of Minor Changes in Previously Approved Research.** The IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change. Minor changes are those that are no greater than minimal risk and do not substantially alter the aims, design, or conduct of the research. Minor changes include, but are not limited to:

- Adding or removing key study personnel
- Adding or removing an investigative site
- Adding monitoring procedures aimed at enhancing subject safety
- Changes to the consent document that seek to correct grammatical errors or clarify statements

2. **Expedited Review of Research in Specified Categories.** The IRB may utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk and falls within the FDA/DHHS specified expedited review categories (63 FR 60353-60356 and 60364-60367, November 9, 1998). These categories do NOT apply to research involving prisoners.

Expedited Category #1. Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. **Note:** Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labelling.

Expedited Category #2. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

From healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8-week period and collection may not occur more frequently than 2 times per week; ***or***

From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8-week period and collection may not occur more frequently than 2 times per week.

Expedited Category #3. Prospective collection of biological specimens for research purposes by noninvasive means. **Examples**:

- Hair and nail clippings in a nondisfiguring manner
- Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction
- Permanent teeth if routine patient care indicates a need for extraction
- Excreta and external secretions (including sweat and urine)
- Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue
- Placenta removed at delivery
- Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor
- Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth

and the process is accomplished in accordance with accepted prophylactic techniques

- Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings
- Sputum collected after saline mist nebulization
- Vaginal swabs that do not go beyond the cervical os
- Rectal swabs that do not go beyond the rectum
- Nasal swabs that do not go beyond the nares

Expedited Category #4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) **Examples:**

- Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy
- Weighing or testing sensory acuity
- Magnetic resonance imaging
- Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography
- Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual

Expedited Category #5. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). ***Note:*** *Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.104(d)(4). This listing refers only to research that is not exempt.*

The intent of the drafters was to define two categories, each appropriate for expedited review.

Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.

Non-exempt research involving materials that will be collected in the future (i.e., prospectively) for a non-research purpose (see below).

Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to

identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do ***not*** qualify for **exemption** under DHHS regulations at 45 CFR 46.104(d)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

However, the IRB may utilize **expedited procedures** to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

Expedited Category #6. Collection of data from voice, video, digital, or image recordings made for research purposes.

Expedited Category #7. Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. ***Note:*** *Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.104(d)(2) and (d)(3). This listing refers only to research that is not exempt.*

Expedited Category #8. Continuing review of research previously approved by the convened IRB as follows:

Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **or**

Where no subjects have been enrolled and no additional risks have been identified; **or**

Where the remaining research activities are limited to data analysis.

Unless an IRB determines otherwise, continuing review of research is not required in the following circumstances (refer to Continuing Reviews):

- Research that has progressed to the point that it involves only one or both of the following, which are part of the IRB-approved study:

  (i) data analysis, including analysis of identifiable private information or identifiable biospecimens; or

  (ii) accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Expedited Category #9. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

f. Protocol Revisions, Modifications, and Amendments. Revisions, modifications, or amendments to a research protocol must be summarized in the appropriate submission form or system and must be incorporated into the written protocol using the tracked change function. This practice ensures that there is only one complete protocol with the revision dates noted on the first page of the protocol and the revisions are readily apparent to the reviewer and committee. The IRB may accept a protocol with a detailed summary of all changes in lieu of a tracked protocol document, but a tracked protocol document is strongly preferred. This procedure is consistent with the procedure used for revised and approved informed consent documents, which then supersede the previous one.

All revisions, modifications and amendments must be prospectively reviewed and approved by the IRB prior to implementation (except as necessary to eliminate apparent immediate hazard to subjects in which a violation report should be submitted to the IRB as described below). The review of revisions, modifications and amendments will be conducted by the convened IRB unless the change is minor (as discussed above in this chapter, paragraph e.1) or the research falls into one or more of the categories appropriate for expedited review (as discussed above in this chapter, paragraph e.2).

Except for unusual circumstances, at least one week prior to the convened meeting, each IRB member will be provided with the amendment application form, any revised documents such as the protocol or consent form, a copy of the currently approved version of such documents, and a protocol summary detailing the entire history of the protocol. One IRB member will be designated as the Primary Reviewer and will be expected to be thoroughly versed in all details of the research and the proposed modification and leading the discussion of the research at the convened meeting.

The IRB may request any changes to the current consent document or protocol based on the information provided in the amendment submission. Additionally, if there any significant new findings that may relate to a participant's willingness to continue participation, the IRB should require that this information be conveyed to participants.

In order to approve a revision, modification or amendment to already approved research, the IRB must determine that the criteria set forth at 45 CFR 46.111 and the FDA regulations have been satisfied. (See next chapter for additional information regarding the approval criteria.)

The minutes of IRB meetings will document separate deliberations, actions, and votes for each protocol undergoing review by the IRB.

g. Investigators' Duty to Report to the IRB. DHHS regulations at 45 CFR 46.108(a)(4)(i) and FDA regulations at 21 CFR 56.108(b) require that investigators report promptly to the DFCI IRB (i) any unanticipated problems in research involving risks to subjects or others; and (ii) any serious or continuing non-compliance with the human subject regulations or the determinations of the IRB.

These same regulations require that the Institutional Official report promptly to OHRP, to any Federal Agency supporting the research, and/or to the FDA (i) any **unanticipated problems** in research involving risks to subjects or others; (ii) any **serious or continuing non-compliance** with the human subject regulations or the determinations of the IRB; and (iii) any **suspension or termination of IRB approval** of research.

FDA regulations at 21 CFR 812.150 require that investigators report unanticipated

device effects to the IRB, and requires that investigators report adverse drug effects to the IRB.

1. **Investigators' Duty to Report Unanticipated Problems.** Investigators are required to report to the IRB any unanticipated problems involving risks to subjects or others that occur in research conducted under the auspices of the DF/HCC whether the events occurred on site or off site. These reports must be submitted to OHRS using the 'Report of Unanticipated Problem Involving Risks to Subjects or Others' form.

   An **unanticipated problem** is defined as: 1. **Unexpected** (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; 2. **Related or possibly related** to participation in the research (meaning there is a reasonable possibility that the incident, experience, or outcome may have been caused by the research); and 3. Suggests that **the research places subjects or others at a greater risk of harm than was previously known or recognized** (including physical, psychological, economic, or social harm defined as a new or increased risk for which the reviewer or convened IRB requires some action, such as informing participants or modifying the consent document).

2. **Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report to the IRB any **serious adverse event** that occurs in research conducted at DF/HCC institutions **and** is considered reportable per DFCI IRB Adverse Event reporting policy. These reports must be submitted to OHRS using the appropriate submission forms (e.g. 'Adverse Event Reporting Form' or via 'CTEP-AERS Report' form) or system.

   A **serious adverse event** is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect [see 21 CFR 312.32(a) and 21 CFR 812.3(s)].

3. **Investigator's Duty to Report all Protocol Violations.** Investigators are required to report all violations for approved protocols. This includes any change from the protocol that was implemented by the investigator in order to respond to immediate safety concerns. These reports must be submitted to OHRS using the 'Major Deviation/Violation/Exception Form / Other Event Reporting Form' or the 'Minor Deviation/Violation Log'.

4. **Investigator's Duty to Report all Protocol Deviations.** Investigators are required to request IRB review and approval of all anticipated deviations. This includes any change from the protocol that was implemented by the investigator in order to respond to immediate safety concerns, as well as any eligibility exceptions. These reports must be submitted to OHRS using the 'Major Deviation/Violation/Exception Form / Other Event Reporting Form' or the 'Minor Deviation/Violation Log'.

5. **Investigators' Duty to Forward Correspondence or Reports of Monitoring or Auditing.** Investigators are required to forward reports or correspondence concerning the monitoring or auditing of their research activities or research sites by sponsors, cooperative research groups, federal agencies, or other external entities to the DFCI IRB within five working days of receipt only if the findings require a corrective action plan. These reports must be submitted to

OHRS using the 'Major Deviation/Violation/Exception Form / Other Event Reporting Form.'

6. **Investigators' Duty to Forward Sponsor or Cooperative Group Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events e.g. NCI Action Letters) issued by sponsors or cooperative groups to the DFCI IRB within ten working days of receipt. Each report should be accompanied by the completed Amendment form available at the OHRS website.

7. **Investigators' Duty to Forward Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward non-DF/HCC DSMB reports to the IRB at the time of the annual continuing review submission. When DSMBs are employed, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the DFCI IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

   Note: *The DF/HCC DSMB and DSMC copy their reports to the OHRS Director for submission to the DFCI IRB and these reports are routed to the convened IRB for review.*

8. **Investigators' Duty to Notify the IRB of Non-compliance.** Whether involved in the research or not, all DF/HCC employees are required to notify the DFCI IRB if they become aware of any non-compliance with human subject regulatory requirements or with the determinations of the IRB. These reports should be submitted to OHRS using the "Major Deviation/Violation/Exception Form and Other Event Reporting Form."

9. **Reporting Timelines.** The DFCI IRB should receive all reports covered by the relevant reporting form available from the OHRS website within 10 working days of the investigator becoming aware of the event or report. Protocol deviations should be reported as soon as the event is known with sufficient time for an IRB review before the deviation is to occur.

h. Investigators' Duty to notify the Department of Defense. For research funded by the DoD, it is the investigators' duty to report promptly (no longer than within 30 days) the following to the appropriate DoD human research protection officer: significant changes to the research protocol approved by the IRB, the results of the IRB continuing review, a change of reviewing IRB and when the organization is notified by an Federal department agency or national organization that any part of the HRPP is under investigation for cause involving a DoD-supported research protocol.

i. Review of Reports of Unanticipated Problems, Adverse Events, Protocol Deviations and Violations. All of the materials (including the current informed consent and protocol) and reports described above are reviewed by the IRB Chairperson or a qualified member of the DFCI IRB. If the situation or event is determined not to meet the definition of an unanticipated problem involving risks to subjects or others as defined above, the reviewer documents this determination in writing. In the case where a change was implemented without prospective IRB approval to eliminate apparent immediate hazards to participant(s), the IRB will determine whether the change was consistent with ensuring the participants'

continued welfare. The reviewer will also determine whether any events reported under items 1-6 above are unanticipated problems involving risks to subjects or others. The material and/or report with documentation of the reviewer's determination is placed in the Protocol file, communicated to the investigator, and included in the list of expedited actions provided to the IRB at the next convened meeting. The determination will also include whether the reviewer finds that the event/incident is an unanticipated problem involving risks to subjects or others.

When a newly discovered risk is reported to the DFCI IRB, it will be reviewed in accordance with DFCI policies and procedures for the review of unanticipated problems involving risks to participants or others. In the determination of the reviewer, if the newly discovered risk is one that meets the definition of an unanticipated problem involving risk to participants or others, but is in and of itself no more than minimal risk, then the determination that the new risk is an unanticipated problem involving risks to participants or others can be made using the expedited procedure. Accordingly, any modifications to the protocol or consent form needed to reflect the new risk can be approved under the expedited procedure as long as they meet the definition of minor changes in previously approved research as defined in the DFCI policies and procedures above.

When a report of an unanticipated problem, protocol deviation or protocol violation involves an error on the part of OHRS systems or staff, the report will be sent to the Full IRB for review.

1. **Referral for Convened IRB Review.** If, in the judgment of the IRB reviewer, the event constitutes an unanticipated problem involving risks to subjects or others (in accordance with the above definition), the reviewer will refer the situation or event to the convened DFCI IRB for review. In the interim, the IRB Chairperson may require modification or suspension of research activities as deemed necessary by the Chairperson to eliminate apparent immediate hazards to subjects.

   Except for unusual circumstances, at least one week prior to the convened meeting, each IRB member will be provided with the report form, any applicable sponsor correspondence and the Other Event summary report. The current versions of the protocol and consent form are available for all IRB members to review electronically on OncPro. A Primary Reviewer will be assigned and will conduct an in-depth review of the materials and present the report to the convened IRB.

   The convened IRB will review the reported problem and make a final determination about whether it constitutes an unanticipated problem involving risks to subjects or others. If the event is determined not to be an unanticipated problem involving risks to subjects or others, the convened IRB, at its discretion, may choose to take action to manage the problem or communicate any pertinent information to subjects. If the reported problem is determined to be an unanticipated problem involving risks to subjects or others, the IRB also determines whether a consent form revision is required and to what extent re-consenting and/or notification of either current and/or past subjects about new information is warranted. The IRB may also consider modifying the continuing review schedule or research monitoring or informed consent process monitoring. The DFCI IRB has the authority to suspend or terminate its approval of the research if it has significant safety or other concerns. The IRB will also consider whether the event or problem should be referred to other institutional officials or committees for review or action. Responses to the required actions will be forwarded to the convened IRB for review unless the action is a minor

modification, in which case, the review of the response may be eligible for expedited review.

2. **Notice of IRB Determination(s).** Regardless of the type of review (expedited or convened), the investigator is notified in writing of the IRB's determinations, even if no further action is necessary on the part of the investigator.

   It is the responsibility of the IRB Chairperson, in coordination with the OHRS Director, to provide prompt written notification to the Institutional Official, Legal Counsel, Quality Assurance for Clinical Trials, or other relevant DF/HCC institutional officials of (i) any unanticipated problems in research involving **serious** risks to subjects or others and of the resolution of those problems or issues; (ii) any serious or continuing non-compliance with human subject regulatory requirements or with the determinations of the IRB and of the resolution of that non-compliance; and (iii) and suspension or termination of IRB approval of research.

j. Review of Sponsor Adverse Event or Safety Reports. The DFCI IRB review of such reports is handled as amendments and should only be reported to the DFCI IRB if they meet criteria outlined in the DFCI IRB policy on Receipt and Review of IND/IDE Safety Reports. Events which are considered serious and life-threatening, unexpected, related to the research intervention and also have an implication for the conduct of the study must be reported to the DFCI IRB as an amendment including the applicable changes to the protocol document(s) and/or consent form.

k. Review of Non-DF/HCC Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) Reports. When DSMBs or DMCs are employed and the IRB is conducting continuing review of research, the IRB may rely on a current statement from the DSMB or DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

l. Review of Non-Compliance.
Non-compliance is defined as a failure to follow the IRB approved protocol, other requirements and determinations of the IRB, institutional policies or procedures, or relevant state or federal laws. The DFCI IRB policy requires the reporting of all such non-compliance to the DFCI IRB. This includes reporting deviations/violations and eligibility exceptions to the DFCI IRB for review. Any individual within the DF/HCC may contact senior management at OHRS or any IRB chair regarding any matter involving non-compliance that appears to require immediate attention. **Serious non-compliance** is defined as non-compliance that involves greater than minimal risk of harm or discomfort to subjects or others involved in the research**. Continuing non-compliance** is defined as lasting more than five working days or constituting repetitive incidents that impact the risk-benefit ratio. **Non-Serious** and **Non-Continuing non-compliance** involves isolated incidents, e.g. an unintentional mistake, an oversight, or a misunderstanding and the incident is not serious or continuing in nature.

As a general matter, serious non-compliance would include situations involving risks to subjects or significant problems impacting the integrity of the protocol. Continuing non-compliance may include failure to comply with the protocol, IRB requirements, or institutional procedures, or Federal or state laws, as described above but not in a manner that impacts the safety of subjects.

Reports of non-compliance including anonymous allegations of non-compliance should be directed to the OHRS Director or Associate Directors but may also be directed to the IRB Chair who will forward them on to OHRS for processing.

1. **Initial Review of Reports of Non-Compliance.** An IRB member reviews all reports of non-compliance and determines whether the reports are eligible for expedited review or must be reviewed by the convened IRB. Generally, non-serious, non-continuing non-compliance will be eligible for expedited review. The IRB member reviewer refers for full-board review any matter that is more than minor; and/or any matter that warrants review by a full IRB.

2. **Options for Review of Non-Compliance.** When the IRB Member conducts the initial review, the IRB member may:

   - Conduct initial review in coordination with the IRB Chair
   - Request a convened IRB
   - Request advice from legal counsel
   - Recommend an interim suspension of the research to the IRB Chair and the Director of OHRS pending review by a full IRB committee

   The individual(s) or IRBs conducting the investigation process may review any written materials, including but not limited to, investigator research records, relevant patient medical records, IRB records, available audit reports, etc.; may interview knowledgeable individuals; and collect relevant documentation.

   During the fact-finding process, the OHRS Director may communicate with the Principal Investigator or study team representative about the progress of the investigation and review.

   Expedited review of deviations, violations and eligibility exceptions are assumed to constitute reports that are non-serious, non-continuing non-compliance. These reviews are included in the reports of expedited reviews submitted regularly to full IRB committees.

3. **Convened IRB Review of Non-Compliance.** A written report (typically an investigator **report of an Other Event**) is distributed to all members of the reviewing IRB, along with relevant portions of the protocol file.

   The IRB will consider whether other events referred for full board review constitute serious and continuing non-compliance and have to be reported to any government agencies with oversight of the research. This determination will be documented in the minutes.

   An IRB member will present the report to the convened IRB for discussion and determinations as follows:

   Tabled. The IRB determines that it lacks sufficient information about the report to proceed with its review. The IRB requests the OHRS Director or others to obtain the requested information for presentation at a future meeting.

   No Further Action Required. The IRB determines that no further corrective action need be taken.

Corrective Actions as proposed by the investigator must be implemented. The IRB may determine that the IRB member appropriately referred the report for full IRB review and that the corrective actions proposed by the investigator are appropriate and should be implemented.

Action Required. The IRB determines that further information or further corrective actions are required. Responses to the required actions will be forwarded to the convened IRB for review unless the action is a minor modification, in which case, the review of the response may be eligible for expedited review. The IRB will determine whether a reportable determination of serious or continuing non-compliance can be made initially or whether additional information must be obtained for further review.

Forward to Other Officials for Further Action. The IRB determines that there may be a need for possible action or that there are concerns not within the purview of the IRB and refers the relevant part of the matter to the appropriate official. For example, the IRB might determine that it would be appropriate to refer the matter to an official responsible for conflicts of interest or to the research pharmacy.

The IRB discussion, determinations and vote are recorded in the meeting minutes. All determinations are communicated to the principal investigator and involved individuals.

4. **Actions Considered by the IRB for Serious or Continuing Non-Compliance.** In considering actions for serious or continuing non-compliance, the IRB will seek to correct the non-compliance, deter it from occurring again (e.g., hold the relevant individuals accountable for their actions and provide guidance on how to comply), and attempt to mitigate any adverse effects on subjects. The IRB should also consider whether the other event raises systemic issues that might impact other on-going research, and if so, the IRB should ensure that the corrective actions include reference to possible systems changes. If the IRB action will affect subjects enrolled on the protocol, the IRB must consider the impact on their health and safety.

   Possible IRB actions include, but are not limited to, the following:

   - Modification of the research protocol or information disclosed to subjects
   - Notification or reconsenting of subjects
   - Modification to the continuing review schedule
   - Participation by the research team members in additional training or education
   - Suspension or termination of the protocol
   - Disqualification of an investigator from conducting a particular research project
   - Disqualification of one or more research sites
   - Disqualification of certain study staff

- Additional education and training in the ethics and regulations of human subject research
- Application of any corrective action to other protocols
- Any other reasonable measure deemed appropriate to protect the rights and welfare of research subjects on this protocol or other protocols that may be impacted by the "other event"

m. Outcomes of IRB Review. The DFCI IRB will notify investigators in writing of its determinations All IRB actions must be communicated in writing.

DFCI IRB actions for initial and continuing review of research, as well as the review of revisions, modifications and amendments, include the following:

1. **Approved with no changes** (or no additional changes). The research may proceed once all other DF/HCC signatures for activation sign-off have been obtained.
2. **Approvable with specific changes to be reviewed by an IRB member.** Such changes must be clearly delineated by the IRB, so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol is approved by the IRB Chair, assigned IRB primary reviewer, or other experienced IRB member. If the required changes have not been made, then the protocol should be forwarded for review by the convened IRB. Similarly, if there are changes that are beyond those requested by the IRB and are more than minor, the changes must be forwarded for review by the convened IRB.
3. **Deferred pending receipt of additional substantive information.** The DFCI IRB determines that it lacks sufficient information about the research to proceed with its review or the IRB requests substantive non-specific modifications. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
4. **Disapproved.** The DFCI IRB has determined that the research cannot be conducted at this Institution or by its employees.

The communication to the investigator will include, at minimum, the following information (where appropriate): investigator's name, title of the study, DFCI IRB protocol (legacy) number, level of risk as determined by the IRB, approval date or changes needed to secure approval. Institutional officials will have access to the IRB meeting minutes and reports of expedited reviews which document the IRB actions.

n. Expiration of Approval Period. The IRB is required to conduct substantive and meaningful continuing review of applicable research[21] not less than once per year*****. Thus, the IRB approval period for research may extend no more than 365 days after the convened meeting at which the research was last approved.

Note: Research reviewed and approved prior to January 21, 2019 will follow the Continuing Review schedule (Expiration Date) indicated at the last approval. DFCI IRB will transition applicable studies to the new Continuing Review schedule, per the Revised Common Rule, and issue a study memo indicating the transition along with any additional requirements.

[21] Refer to Chapter 9, section c. Continuing Review by the Convened IRB

Research that continues after the approval period expires is research conducted without IRB approval. Consequently, the IRB will automatically suspend the enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated approval period. Previously enrolled subjects may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the subjects.

o. Suspension or Termination of IRB Approval. The DFCI IRB may vote to suspend or terminate approval of research that is not being conducted in accordance with IRB or regulatory requirements or that has been associated with serious unexpected problems or serious harm to subjects. Suspensions and terminations by external institutional committees must be reported to and reviewed as appropriate by the convened IRB. Any suspension or termination of DoD-supported research must be promptly (no longer than within 30 days) reported, by the investigator, to the DoD human research protection officer.

Suspension means a temporary withdrawal of IRB approval of some or all of a protocol or the permanent withdrawal of IRB approval of part of a protocol. With a suspension of IRB approval, continuing review of the research is still required. A sponsor-imposed suspension alone does not constitute such a suspension, as it is not an action by the IRB to withdraw approval of a previously approved protocol. Similarly, an action by the Principal Investigator that halts or materially changes some or all of the research as previously approved by the IRB does not constitute such a suspension (but may need to be submitted to the IRB as a revision to the protocol). **Termination** means a permanent withdrawal of IRB approval of a previously approved protocol. With a termination of IRB approval, continuing review of the research is still required.

When considering a suspension or termination of approval, the IRB shall also determine whether suspension of continued participation of previously enrolled subjects is required and whether subjects should be notified of the suspension and subsequent outcomes. If the IRB determines that suspension of continued participation of previously enrolled subjects is required, the IRB will also determine whether the plan for withdrawal adequately protects subjects' rights and welfare. The IRB shall also determine whether any other actions such as informing current subjects of the suspension or termination should be taken to protect the rights and welfare of currently enrolled subjects. When research is suspended or terminated, the convened IRBs or the person ordering the suspension (IRB Chairs or the OHRS Director) will require that any adverse events or outcomes are reported to the OHRS.

When the IRB Chair determines that such action is necessary to protect the rights and welfare of subjects, he/she may require an immediate, temporary suspension of enrollment of new subjects, or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB. The OHRS Director also has authority to suspend human subject research for similar reasons.

1. **Notification of Determinations to Investigator.** The DFCI IRB will notify the Principal Investigator in writing of such suspensions or terminations and will include a statement of the reasons for the IRB's actions. The DFCI IRB will also advise the investigator of any requirements for notifying currently enrolled subjects. The investigator will be provided with an opportunity to respond in person or in writing.
2. **Notification of Determinations to DF/HCC Institutional Officials and Federal Agencies.** It is the responsibility of the IRB Chairperson, in

collaboration with the OHRS Director, to provide prompt (within fifteen business days) written notification of any for-cause suspensions or terminations of IRB approval to the Institutional Official, Legal Counsel, CLC, Director for Quality Assurance for Clinical Trials and other relevant DF/HCC institutional officials, as well as relevant Federal agencies, including, OHRP (for DHHS-supported research) and FDA (for FDA-regulated research).

3. **Notification of Determination to Department of Defense.** Determinations of serious or continuing non-compliance of DoD-supported research must be promptly (no longer than 30 days) reported by the investigator to the DoD human research protection officer.

   Written notifications will include the following information:

   - Title of the research project and/or grant proposal that was suspended or terminated;
   - Principal investigator name;
   - Protocol number assigned by the IRB that was suspended or terminated and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
   - A detailed description of the reason for the suspension or termination; and
   - The actions taken or planned to address the suspension or termination (e.g., investigate alleged non-compliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)

Note: The term "suspension or termination of IRB approval" does not include the permanent or temporary suspension of subject enrollment or participation in research that results solely from the expiration of the DFCI IRB approval period for the research.

p. DFCI Reporting Requirements to Federal Agencies. As described earlier in this chapter, DHHS regulations at 45 CFR 46.103(b)(5) and FDA regulations at 21 CFR 56.108(b) require that the Senior Vice President for Research, as the Institutional Official, or the OHRS Director as his/her designee, report the following events as determined by the IRB or Institutional Official promptly (within thirty days) and in writing to OHRP, to any Federal Agency supporting the research (e.g. NIH or DOD), and/or to the FDA:

- Any unanticipated problems in research involving greater than minimal risks to subjects or others (except where the IRB has determined and documented in writing that the problem was not related to the research in any way)
- Any unanticipated problems involving risks to subjects or others for any DoD-supported research must be promptly (no longer than within 30 days) reported, by the investigator, to the DoD human research protection officer.
- Any serious or continuing non-compliance with federal human subject protection regulations or requirements, or with the determinations of the IRB
- Any suspension or termination of IRB approval of research

In developing and forwarding such reports, the OHRS Director will consult as appropriate with the Institutional Official, Legal Counsel, any relying institutions Legal Counsel and IRB office, the IRB Chairperson(s), DF/HCC oversight committees including Audit, DSMC and CLC, the DFCI Vice President for Clinical Research Operations, and the Director of the Office of Data Quality. The OHRS Director will approve any report before it is forwarded to any Federal Agency.

When preparing such reports, consideration should be given to whether the funding agency might also need to be informed of serious non-compliance related to research supported under a federal contract or grant. For example, the National Institutes of Health (NIH) expects to be informed when research that it supports is the subject of a serious allegation of non-compliance or other problem that warrants investigation.

q. Research Activities in Emergency Situations. DHHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity, except as required under FDA regulations.

The IRB must be notified in writing within five working days of any activities involving the Emergency Use of a Test Article under an FDA Exemption or Exception (see Chapter 12). The IRB will acknowledge such notification in writing but, in accordance with FDA guidance, will not issue any "approval" of the activity.

DHHS regulations at 45 CFR 46.101(i) and FDA regulations at 21 CFR 50.24 include special provisions for IRB review and approval of planned emergency research with waiver of the usual informed consent requirements. See Chapter 12 for specific requirements of these provisions.

Chapter 10
Criteria for IRB Approval of Research

DHHS regulations at 45 CFR 46.111, FDA regulations at 21 CFR 56.111, and the Federal Policy (Common Rule) delineate specific criteria for the approval of research.

The DFCI IRB will determine that all the following requirements are satisfied before approving proposed research:

1. Risks are minimized through the use of sound research design, and, when appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks are reasonable in relation to anticipated benefits.
3. The selection of subjects is equitable.
4. The informed consent of subjects will be obtained.
5. The informed consent of subjects will be documented.
6. The research includes adequate provisions for monitoring data to ensure the safety of subjects.
7. The research includes adequate provisions to safeguard the confidentiality of data and the privacy of subjects.
8. The research includes adequate additional protections to safeguard the rights and welfare of subjects who may be vulnerable to coercion or undue influence.

a. Risks are Minimized. The DFCI IRB must consider the overall level of risk to subjects in evaluating proposed research. In general, the regulations require that the IRB distinguish research that is "greater than minimal risk" from research that is "no greater than minimal risk." Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under Federal regulations at 45 CFR 46.102(j) and the Common Rule, "minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests."

The definition of minimal risk based on the phrase "ordinarily encountered in daily life or during the performance of routine physical or physiological examination or tests" shall not be interpreted to include the inherent risks certain categories of human subjects face in their everyday life. For example, the risks imposed in research involving human subjects focused on a special population should not be evaluated against the inherent risks encountered in their work environment (e.g., emergency responder, pilot, soldier in a combat zone) or having a medical condition (e.g., frequent medical tests or constant pain.)

In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks. Whenever appropriate, the research should utilize procedures already being performed on the subjects for diagnostic or treatment purposes.

The IRB is expected to consider the research plan, including the research design and methodology, to determine that there are no flaws that would place subjects at unnecessary risk. When the research design presents unnecessary or unacceptable

risks to subjects without commensurate benefits to the subjects or to others, the research cannot ethically proceed and cannot be approved by the IRB.

In order to ascertain whether the research project is adequately designed and thus subjects protected, the IRB reserves the authority to seek opinions from consultants on proposed research and its design. The IRB may determine that proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, or otherwise protect the rights and welfare of human subjects.

The IRB will also consider the qualifications of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Overall, the research team must possess the professional and educational qualifications, as well as the resources, to conduct the research project and to protect the rights and welfare of subjects.

1. **Psychological and Social Harms.** When evaluating research, this Institution carefully examines not only the risk of physical harm but also the risk of psychological and social harms.

   The IRB considers the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm.
   The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial or legal standing, employability, insurability, reputation, stigmatization, and damage to social relationships.

   Collecting any identifiable, private information or identifiable biospecimens from any living individual constitutes human subject research. If information is being collected on living individuals in addition to the primary "target" subjects, the IRB will consider the risk of harm to those "non-target" individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of "non-target" individuals (unless the requirement for informed consent can be waived).

In order to mitigate such harms, the IRB reviews proposed research for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.

b. Risks Are Reasonable Relative to Anticipated Benefits. In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and/or to the importance of the knowledge that may reasonably be expected to result (45 CFR 46.111(a)(2)).

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB will consider only those risks that result from the research, and will not consider long range effects (e.g., public policy implications) of applying the knowledge gained in the research.

c. Selection of Subjects is Equitable. In order to approve research, the IRB must determine that the selection of subjects is equitable. To this end, investigators at this Institution, and especially NIH-supported investigators, must provide details of the proposed involvement of humans in research, including the characteristics of

the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation.

If ethnic, racial, and gender estimates are not provided as background information for initial review, and enrollment statistics are not provided for continuing review, the investigators must provide a clear rationale for exclusion of this information In making the determination that subject selection is equitable, the IRB will evaluate the purposes of the research and the research setting, and will be especially cognizant of issues involving potentially vulnerable subject populations, which may include children, pregnant women, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB will carefully examine inclusion-exclusion criteria and recruitment procedures in order to determine that the burdens and benefits of the research are being distributed equitably.

1. **Inclusion of Females and Minorities.** Females and members of minority groups and their sub-populations will be included in all biomedical and behavioral research projects involving human subjects, **unless** compelling scientific justification is provided that inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

   The IRB will remain mindful of the desirability of including both males and females as research subjects and will not permit the **arbitrary** exclusion of persons of reproductive age. Exclusion of such persons must be justified and based on sound scientific rationale.

2. **Inclusion of Children.** In June 1996, the American Academy of Pediatrics and the NIH held a joint workshop concerning the participation of children in clinical research. There is valid concern that treatment modalities developed based on research conducted on adults, without adequate data from children, are being used to treat children for many diseases or disorders. Participants in the workshop concluded that there is a sound scientific rationale for including children in research.

d. Informed Consent, Parental Permission, and Child Assent Will Be Obtained. In order to approve research involving adults as subjects, the IRB must determine that legally effective **informed consent** will be sought and obtained from each prospective subject or the subject's legally authorized representative (see 45 CFR 46.116 and 21 CFR 50.20), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal and State laws and regulations.

In order to approve research involving children as subjects, the IRB must determine that the permission of the child's parent(s) or guardian(s) and the assent of the child will be sought and obtained (or formally waived or altered) in accordance with Subpart D of the HHS and FDA human subject regulations at 45 CFR 46.408 and 21 CFR 50.55, respectively. Any waiver or alteration of these permission or assent requirements must be consistent with applicable Federal and State laws and regulations. Chapter 16 details the requirements for permission and assent relative to the involvement of children in research.

The informed consent of an adult subject, the informed consent of a subject's legally authorized representative, the permission of the parent(s) or guardian(s) of a child-subject or the assent of a child-subject may only be sought under circumstances

that minimize the possibility of coercion or undue influence and that provide the parent(s), guardian(s), subject, or legally authorized representative with sufficient opportunity to consider whether or not the subject will participate.

Information for informed consent, permission, and assent must be presented in language that is understandable to the subject or legally authorized representative.

No informed consent, permission, or assent process may include any exculpatory language (i) through which the subject is made to waive, or appear to waive, any of the subject's legal rights; or (ii) through which the investigator, the sponsor, this Institution, or its employees are released from liability for negligence, or appear to be so released.

Although it is appropriate for consent, permission or assent documents to state that certain specimens or information may be used for research purposes, using the word "donation" to characterize the future use of specimens or information for research purposes implies abandonment of rights to the "property" donated and will not be approved by the IRB. Whether or not such wording is contained in "the actual informed consent document" is immaterial. All study-related documents must be submitted to the IRB for review. Any separate "donation" agreement for future research use of specimens is regarded to be part of the informed consent documentation and must be in compliance with regulatory requirements.

Informed consent, permission, and assent (as applicable) must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.

Alternatives to obtaining and documenting informed consent, permission, or assent **immediately** before the start of the research include obtaining and documenting consent, permission, or assent during a reasonable interval prior to the start of the research that permits the individual sufficient time to make an informed choice about the requested participation. When other alternatives are proposed, the IRB must determine that the alternative is appropriate under Federal and State law and regulation in the jurisdiction in which the subject will be enrolled and participate. These instances will be handled on a case-by-case basis.

1. **Consent Monitoring.** In considering the adequacy of informed consent, permission, and assent procedures, the OHRS Director or DFCI IRB may require special monitoring of the process in order to reduce the possibility of coercion and undue influence.

   Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

   Monitoring of the consent process may include any number of situations, including observance of the process by a member of the IRB, OHRS staff or auditing committee.

2. **Waiting Periods.** In considering the adequacy of informed consent, permission, and assent procedures, the IRB may require that investigators include a "waiting period" within the process, or employ devices such as audiovisual aids or tests of comprehension.

3. **Advertisements and Recruitment Incentives.** The DFCI IRB will review advertisements and recruitment incentives associated with the research that it oversees. In addition to the information contained in the advertisement, the IRB must also review the mode of their communication, the final copy of the printed or audio/video taped advertisement, email communications and web-based postings. Advertisements and incentives are directly related to the informed consent, permission, and assent process and must be consistent with prohibitions on coercion and undue influence.

   Any advertisement to recruit subjects should be limited to the information the prospective subjects, legally authorized representatives, parents, or guardians need to determine eligibility and interest. When appropriately worded, the following items may be included:

   - The name and address of the clinical investigator and/or research institution.
   - The condition under study and/or the purpose of the research.
   - In summary form, the criteria that will be used to determine eligibility for the study.
   - A brief list of participation benefits, if any.
   - The time or other commitment required of the subjects.
   - The location of the research and the person or office to contact for further information.
   - Recruitment procedures must be designed so that informed consent, permission, and assent are given freely and coercion and undue influence are avoided. In order to evaluate this, the IRB must know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

   The IRB must ensure that advertisements:

   - Do not state or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol
   - Do not include exculpatory language
   - Do not emphasize the payment or the amount to be paid, by such means as larger or bold type
   - Do not promise “free treatment” when the intent is only to say subjects will not be charged for taking part in the investigation

   For FDA-regulated research:

   - Do not make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with FDA labeling.
   - Do not use terms, such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational

- Do not include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

4. **Payments for Research Participation.** The DFCI IRB will review any proposed payments to research subjects (or their parents, guardians, or legally authorized representatives) associated with the research that it oversees. Payments may not be of such an amount as to result in coercion or undue influence on the decision to participate or continue participation. Payments may not be provided on a schedule that results in coercion or undue influence on the decision to participate or continue participation. The DFCI IRB will not approve research that will raffle off prizes to subjects.
   The IRB will review payments to determine that:
   - Credit for payment accrues as the study progresses and not be contingent upon the subject completing the entire study.
   - Any amount paid as a bonus for completion is reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn.
   - All information concerning payment, including the amount and schedule of payments, is set forth in the consent document.

The DFCI IRB will not approve payments in exchange for referral of potential participants (finder's fees or referral fees) or payments designed to accelerate recruitment of participants (bonus payments).

5. **Investigator Incentives.** Investigators may not receive special incentives for enrolling subjects such as airline tickets and hotel expenses.

6. **Indemnity and Liability Provisions (Exculpatory Language).** Subjects in research at this Institution may not be asked to waive, or appear to waive, any of their legal rights. The OHRS Human Research Coordinators will work with investigators to identify and remove any exculpatory language.

7. **Other Requirements.** For FDA regulated research, the consent form must include a statement that the FDA may inspect the subject's research records.

   For research studies that are posted on Clinical Trials.gov the consent form must include the required statement: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time."

   When following Department of Defense (DoD) regulations, the IRB determines that the disclosure includes that provisions for research-related injury follow the requirements of the DoD component.

   For DoD-funded research involving greater than minimal risk, IRB appointment of an independent research monitor is required, unless the study team obtains a waiver of this requirement from the DoD and submits it to the IRB.

   For DoD-funded research involving no more than minimal risk, the IRB may require a research monitor in its discretion.

   The following applies when a research monitor is required:
   - The research monitor is appointed by name and shall be independent of the team conducting the research.

- There may be more than one research monitor (e.g. if different skills or experience are needed).
- The monitor may be an ombudsman or a member of the data safety monitoring board.
- The IRB must approve a written summary of the monitors' duties, authorities, and responsibilities.
- The IRB official shall communicate with research monitors to confirm their duties, authorities, and responsibilities.
- The duties of the research monitor are determined on the basis of specific risks or concerns about the research, such as:
  - Perform oversight functions (e.g. observe recruitment, enrollment procedures, and the consent process, oversee study interventions and interactions, review monitoring plans and unanticipated problems involving risks to subjects or others, oversee data matching, data collection and analysis).
  - Discuss the research protocol with investigators, interview human subjects, and consult with others outside of the study.
  - Report observations and findings to the IRB or a designated official.
- The research monitor has the authority to:
  - Stop a research study in progress.
  - Remove individuals from study.
    Take any steps to protect the safety and well-being of subjects until the IRB can assess.

e. Informed Consent, Permission, and Assent Will Be Documented. In order to approve research, the IRB must determine that informed consent of adult subjects (or the subject's legally authorized representative) and/or the permission of the parent(s) or guardian(s) of child subjects, will be documented in writing, unless documentation can be waived under Federal regulations. Chapter 16 details the requirements for documentation of permission for the involvement of children in research.

The method of documenting the assent of child subjects will be determined by the IRB in accordance with Subpart D of the DHHS and FDA regulations at 45 CFR 46.408 and 21 CFR 50.55, respectively. Chapter 16 details the requirements for documentation of child assent.

1. Long Form vs Short Form Documentation. Federal regulations at 45 CFR 46.117 and 21 CFR 50.27 provide two methods for documenting informed consent and/or permission:

Consent or permission may be documented through use of a written document that embodies all of the required elements of informed consent. The document must be signed by the subject (or the subject's legally authorized representative, parent(s) or guardian(s) in compliance with all regulatory requirements), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated, or

Consent or permission may also be documented through use of a short form document which states that the elements of informed consent[22] have been presented orally to the subject (or the legally authorized representative, parent(s) or guardian(s) in compliance with all regulatory requirements), and that the key

[22] 45 CFR 46.116

information required by 45 CFR 46.116(a)(5)(i)[23] be presented to the subject first, prior to any other information being provided. When this method is used, (i) there must be a witness to the oral presentation; (ii) the IRB must approve a written summary of what is to be presented orally; (iii) only the short form must be signed by the subject, representative, parent(s), or guardian(s); (iv) the witness must sign both the short form and the summary. The summary must embody the basic elements of disclosure, and as applicable, the additional elements of disclosure; (v) the person actually obtaining consent must sign the summary; and (vi) a copy of the signed summary and the signed short form will be given to the subject, the representative, the parent(s) or guardian(s).

2. **Illiterate Subjects.** Illiterate persons may have informed consent or permission information read to them and may "make their mark" in a manner consistent with the laws of the State in which the research is conducted to document their understanding. In this situation, it is also desirable to obtain the signature of a witness to the process and the signature of the person conducting the consent or permission interview.
3. **Witness Signature.** Where it deems warranted, the IRB may require the signature of a witness who has been present during the entire consent or permission interview and who can attest to the accuracy of the presentation and the apparent understanding of the subject, representative, parent(s) or guardian(s), on the informed consent or permission document. Such attestation will be noted in writing on the document. The witness is also present to attest to the validity of the individual's signature.
4. **Date Stamp Required.** All informed consent and permission documents will have a date stamp indicating the beginning and end of the approval period during which the document may be used to obtain consent or permission. Only the IRB-approved informed consent or permission document can be used for the informed consent or permission process. The investigator is responsible for storing signed informed consent and permission documents for at least three years following the completion of the research.
5. **Copy to Decision-Maker is Required.** Once the informed consent or permission information has been presented, the informed consent or permission document is given to the subject, legally authorized representative, parent(s) or guardian(s) for further review. The individual making the participation decision may take the document home to discuss the matter with family, friends, spouses, or other professionals. When the subject, representative, parent(s) or guardian(s) decide(s) that the subject will enter the study, he/she/they sign(s) and date(s) the informed consent or permission document.

f. Safety Monitoring Is Adequate. In order to approve research, the DFCI IRB must determine that, where appropriate, the research plan makes adequate provision for monitoring the data to protect the safety of subjects. For research in which risks are substantial, a detailed description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events.

The IRB has the authority to require a DSMB/DMC as a condition for approval of research where it determines that such monitoring is needed.

[23] 45 CFR 46.116(a)(5)(i): Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

In lieu of requiring that safety monitoring information be submitted directly to the IRB, the IRB may rely on a current statement from a duly constituted DSMB/DMC indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, and has determined that continuation of the research is justified.

g. Privacy and Confidentiality Provisions Are Adequate. In order to approve research, the IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and the confidentiality of data.

It is important to be sure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individual. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research.

It also is important to protect individually identifiable private information and/or identifiable biospecimens once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects. When information linked to individuals will be recorded as part of the research design, the IRB requires that adequate precautions will be taken to safeguard the confidentiality of the information.

Among the available methods for safeguarding confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that likely would result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

1. **Certificates of Confidentiality (CoC).** The CoC protects the privacy of research subjects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

   Where DF/HCC research involves the collection of highly sensitive information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes. In such situations, the IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC).

   NIH Funded Research: Effective October 1, 2017 the National Institutes of Health (NIH) will automatically issue CoCs to all research funded by the NIH as of December 13, 2016 that is collecting or using identifiable, sensitive information. NIH funded researchers are automatically issued a CoC through their award.

   Other Department of Health and Human Services (HHS) funding agencies: CoCs may also be issued to other HHS funded research including CDC, FDA, HRSA, and SAMHSA. If research is funded by one of these agencies, or is operating

under the authority of the FDA, investigators must contact the Certificate Coordinators at the funding agency to determine how to obtain a CoC.

Non-HHS Federal Funded and Non-Federal Funded Research: Research not funded by HHS can apply to NIH, or the FDA as appropriate, to request a CoC for HHS-mission relevant research or for a specific project that involves sensitive, identifiable information.

If a CoC is issued, automatically or otherwise, research subjects must be informed of the CoC in the research consent form.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA for audit purposes. Consequently, the IRB will require that these conditions for release be stated clearly and explicitly in the informed consent document.

2. **Additional Safeguards for Vulnerable Subjects Are Appropriate.** In order to approve research, the IRB must determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, persons with mental disabilities, or economically or educationally disadvantaged persons. Details about protections for vulnerable subjects are provided in Chapters 16 and 17.

   Should the IRB find that they regularly review research involving such vulnerable subjects, the IRB will include among its reviewers persons who are knowledgeable about and experienced in working with these vulnerable subjects.

h. Research Involving Data Sets and Repositories. When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information.

The use of existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the IRB will first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

If this is not the case, then the IRB will consider whether it is permissible to waive the usual informed consent requirements in accordance with 45 CFR 46.116(f)(3). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses “deidentified” data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that the investigator cannot ascertain subjects’ identities.

An alternative to deidentifying data is to maintain the data set as a data repository under the guidelines established by OHRP (see below and refer to Guidance on this topic on the OHRP Website).

1. **Research Utilizing Data or Tissue Repositories.** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes. The IRB strongly encourages banks/repositories to utilize an Honest Broker to oversee the protection and distribution of samples and/or data to recipient investigators.

   Repository activities involve three components: (i) the collectors of data or tissue samples; (ii) the repository storage and data management center; and (iii) the recipient investigators.

   Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is not required. (Refer to Guidance on this topic on the OHRP Website.)

   Typically, these parameters involve formal, written agreements stipulating these conditions:

   - The repository will not release any identifiers to the investigator;
   - The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects;
   - The investigator will use the data only for the purposes and research specified; and
   - The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

2. **Epidemiology Research.** Epidemiology research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiology research may also combine historical research with survey and interview research.

   Epidemiology studies often present significant issues regarding both privacy and confidentiality.

   The IRB will first consider privacy issues, and must be satisfied that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB will seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

   Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB will seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

Because epidemiology research typically requires very large numbers of subjects, epidemiology investigators almost always request that the IRB waive the usual requirements for informed consent. In order to approve such a waiver in epidemiology research, the IRB must find and document that the first three criteria at 45 CFR 46.116(f)(3) for a waiver of informed consent have been met; specifically, that:

(a) the research presents no more than minimal risk to subjects;

(b) the waiver will not adversely affect the rights and welfare of the subjects;

(c) the research could not practicably be carried out without the waiver; and

(d) if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

The fifth requirement ("whenever appropriate, the subjects will be provided with additional pertinent information after participation") usually does not apply.

3. **Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic information can adversely affect an individual's insurability and employability.

   The protection of private information gathered for and resulting from genetic research is a major concern. The IRB will expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

   A more detailed discussion of issues involving genetic research, an area of research that is expanding rapidly, is located on the OHRS website. The DFCI policy regarding the return of research results is particularly relevant to IRB members.

4. **Family History Research.** Family history research is a common technique used in Bio-Social and Bio-Behavioral Research. Family history research typically involves obtaining information from one family member (called a proband) about other family members.
   It is important to recognize the Federal regulations and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information."

   Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information and/or identifiable biospecimens from them.

   The IRB must determine whether family members are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 45 CFR 46.116(f)(3).

i. **Subject Withdrawal from Clinical Research.** When a subject withdraws from a study, the data collected on the subject to the point of withdrawal remains part of the study database and may not be removed. The consent document cannot give the subject the option of having data removed.

An investigator may ask a subject who is withdrawing whether the subject wishes to provide continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the subject distinguishes between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of privacy and confidentiality of the subject's information.

The investigator must obtain the subject's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). The IRB has an approved "Withdrawal of Consent" that maybe be used for this purpose. If the investigator wishes to utilize a study specific withdrawal of consent document, the IRB must approve the consent document.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

j. Compliance with All Applicable Laws. All human subject research conducted at this Institution or by its employees must comply with all applicable laws and regulations of the United States and the State in which the research is conducted, as well as with any local requirements.

Chapter 11
Required Elements of Informed Consent

One overarching requirement of research involving human subjects is that investigators must obtain the legally effective informed consent of prospective subjects before they can be included in research. Research investigators are responsible for obtaining and documenting informed consent in accordance with Federal regulations (45 CFR 46.116 and 46.117 and 21 CFR 50.25 and 50.27) and Institutional-specific policies.

Informed consent presumes two simultaneous concepts: informed decision making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits in order to reach an **informed decision** as to whether they will **voluntarily participate**.

For an effective informed consent process, DHHS regulations at 45 CFR 46.116(b), the Common Rule, and FDA regulations at 21 CFR 50.25(a) mandate the inclusion of nine basic informed consent elements. Nine additional elements may be required, depending on the nature of the research (45 CFR 46.116(c) and 21 CFR 50.25(b)).

The elements of informed consent as outlined in these regulations shall not preempt any other Federal, State, or local regulation which requires additional information to be disclosed for informed consent to be legally effective. Also nothing in the regulations is intended to limit the authority of a physician to provide emergency care to the extent the physician is permitted to do so under applicable Federal, State, or local law. Such emergency care may not be identified as research, however, except as required by FDA reporting requirements.

The Informed Consent Templates are available at the OHRS website and provide specific guidance on how consent documents should be worded and ordered.

a. Key Information[24]. Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension.

1. Informed consent as a whole must present information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or legally authorized representative's understanding of the reasons why one might or might not want to participate.

2. No informed consent may include any exculpatory language through which the subject or the legally authorized representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

[24] 45 CFR 46.116(a)(5-6)

b. Basic Elements of Informed Consent[25]

1. **Research Statement (Required Element #1).** Informed consent information **must** specifically include **each** of the following:

   - A statement that the study involves research
   - An explanation of the purposes of the research
   - An explanation of the expected duration of subjects' participation
   - A description of what procedures will be followed
   - Identification of any procedures that are experimental

2. **Reasonably Foreseeable Risks or Discomforts (Required Element #2).** Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. All risks listed or described in the research protocol must be referenced in the informed consent document.

3. **Reasonably Expected Benefits (Required Element #3).** Informed consent information must describe any benefits to subjects or to others which may reasonably be expected from the research. However, benefits must not be overstated so as to create an undue influence on subjects.

4. **Appropriate Alternatives (Required Element #4).** Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may be advantageous to the subject. **Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives.** It is not sufficient simply to state that "the doctor will discuss alternatives to participating." **Where applicable, informed consent must disclose to subjects when treatments identical to those offered by the research may be obtained outside the research, i.e., "off protocol."**

5. **Extent of Confidentiality (Required Element #5).** Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who otherwise would not be privy to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private information or records.

   Federal officials have the right to inspect research records, including consent forms and individual medical records, to ascertain compliance with the rules and standards of their programs. FDA requires that information regarding this authority be included in the consent information for all research that it regulates. Identifiable information obtained by Federal officials during such

[25] 45 CFR 46.116(b)(1-9)

inspections is subject to both the privacy provisions and the disclosure provisions of the Privacy Act of 1974.

6. **Compensation or Treatment for Injury (Required Element #6).** Informed consent information for research involving more than minimal risk must include explanations regarding:

   - Whether any compensation is available if injury occurs
   - Whether any medical treatments are available if injury occurs and whether there is a charge for such medical treatment
   - A description of any such compensation or treatments or where more information about them is available

7. **Contact Information (Required Element #7).** Informed consent information must include details, including telephone numbers, about whom to contact for **three specific situations:**

   (i) For answers to questions about the research. The principal investigator and other members of the research team are appropriate contacts for this information.

   (ii) For answers to questions about subjects' rights. The Office for Human Research Studies, reviewing IRB Office or Legal Counsel are appropriate contacts for information about subjects' sights.

   (iii) In the event of a research-related injury. Depending upon the nature of the research, the research team, the Office for Human Research Studies, the reviewing IRB Office, or Legal Counsel, are appropriate contacts for research-related injury.

   It is critical that investigators update consent forms when telephone numbers or contact names change.

8. **Voluntary Participation Statement (Required Element #8).** Informed consent information must contain clear statements of the following:

   - Participation in the research is "voluntary;"
   - Refusal to participate will involve "no penalty or loss of benefits to which the subject is otherwise entitled;" and
   - The subject may discontinue participation at any time "without penalty or loss of benefits to which the subject is otherwise entitled."
   - It is particularly important for subjects and prospective subjects to understand and have complete confidence that declining to participate in research will not jeopardize their care.

9. **Collection of Identifiable Private Information or Biospecimens Statement (Required Element #9). One of the following statements must be included:**

   (i) A statement that identifiers might be removed from the identifiable private information or identifiable biospecimens and that, after such

removal, the information or biospecimens could be used for future research studies or distributed to another investigator for future research studies without additional informed consent from the subject or the legally authorized representative, if this might be a possibility; or

(ii) A statement that the subject's information or biospecimens collected as part of the research, even if identifiers are removed, will not be used or distributed for future research studies.

c. Additional Elements Where Appropriate[26]. Where appropriate, the regulations require that one or more of the following six additional elements be included in the informed consent information.

1. **Unforeseeable Risks to Subjects.** Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that there may be risks that are not known or not foreseeable.

2. **Investigator-Initiated Termination of Participation.** There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from direct-benefit research). The informed consent information should specify these circumstances.

3. **Additional Costs.** If subjects must bear any additional costs (costs of procedures or study drugs, etc.), these must be disclosed in the informed consent information.

4. **Early Withdrawal/Procedures for Termination.** Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staff to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.

5. **Significant New Findings.** Subjects will be informed of any new knowledge or findings about the medication or test article and/or the condition under study that may affect the risks or benefits to subjects or subjects' willingness to continue in the research.

6. **Approximate Number of Subjects.** For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.

7. **Biospecimens and Commercial Profit.** The consent should contain a statement that the subject's biospecimens (even if identifiers are removed)

[26] 45 CFR 46.116(c)(1-9)

may be used for commercial profit and whether the subject will or will not share in this commercial profit.

8. **Disclosure of Research Results.** The consent should contain a statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions.

9. **Whole Genome Sequencing.** For research involving biospecimens, the consent form should disclose whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

d. Broad Consent.[27] Broad consent (or "Regulatory Broad Consent") for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted as an alternative to the informed consent requirements (described above).

Note: DF/HCC will not utilize "Regulatory Broad Consent" and research reviewed on/or after January 21, 2019 will not be reviewed by the DFCI IRB as Exempt under categories 7 or 8.

e. Requirement for Authorized Personnel to Obtain Consent. Informed consent may only be obtained by personnel authorized to do so by the IRB. The person who conducts the informed consent interview must be knowledgeable about the study and be able to answer questions. Informed consent information can be presented by any qualified person involved in conducting the study and is not limited to persons with MD's or PhD's if approved by the IRB. Where the person obtaining consent is not a member of the study team, he or she must be a MD or PhD. Only a principal investigator, co-investigator, or study coordinator who have completed their human subject protection training requirements (and in the case of MD's have a current 1572 FDA Form on file with ODQ) can obtain informed consent.

f. Waiver or Alteration of Informed Consent Requirements. DHHS regulations at 45 CFR 46.116(e)(3) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether in only the two circumstances described below.

1. **State or Local Public Benefit Programs**. DHHS regulations at 45 CFR 46.116(e)(3)(i) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

    - The activity constitutes a research or demonstration project that is to be conducted by, or subject to the approval of, State or local government officials, and is designed to study, evaluate, or otherwise

[27] 45 CFR 46.116(d)(1-7)

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; ***and***

- The research could not practicably be carried out without the waiver or alteration.

These findings and their justifications will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

2. **Minimal Risk Research.** DHHS regulations at 45 CFR 46.116(f)(3) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

   - The research involves no more than minimal risk to the subjects;
   - The waiver or alteration will not adversely affect the rights and welfare of the subjects;
   - The research could not practicably be carried out without the waiver or alteration;
   - If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; and
   - Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

   These findings and their justifications will be clearly documented in IRB minutes when the IRB exercises this waiver provision. This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.

3. **Research Involving Deception.** Deception research involves social science research in which the subject is not told, or is misled, about the true purpose of the research, such as in certain studies of group processes, contextual influences on cognition, etc. The IRB reviewing research involving incomplete disclosure or outright deception must apply both common sense and sensitivity to the review.

   Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects will be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a countervailing benefit.) The IRB should also make sure that the proposed subject population is suitable.

   Deception can only be permitted where the IRB documents that waiver of the

usual informed consent requirements is justified under the criteria present at 45 CFR 46.116(f).

In making the determination to approve the use of deception under a waiver of informed consent, the IRB will consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. Note that the regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects.

4. **Waiver of Documentation of Consent.** DHHS regulations at 45 CFR 46.117(c) and the Common Rule permit an IRB to waive the requirement to obtain written documentation of informed consent. In order to approve such a waiver, the IRB must find and document **one or more** of the following conditions:

   (i) The only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern. ***Please note:*** *This waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve such alterations or waivers for FDA-regulated research.*

   (ii) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research. This waiver provision is applicable to research governed by FDA regulations as set forth at 21 CFR 56.109.

   OR

   (iii) If the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained.

   In addition to determining one of the above conditions, the IRB must also find and document that the waiver or alteration will not adversely affect the rights and welfare of the subjects, and that whenever appropriate, the subjects will be provided with additional pertinent information after participation. When reviewing a request for waiver of documentation of consent, the IRB must review a written description of the information to be orally provided to subjects and/or the written information sheet or letter which includes all elements of consent which will be provided to subjects.

   These findings and their justifications will be clearly documented in IRB review record or minutes when the IRB exercises this waiver provision.

5. **Screening, recruiting, or determining eligibility[28].** An IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

   (i) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, ***or***

   (ii) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

6. **Informed Consent from Non-English Speakers.** Federal regulations at 45 CFR 46.116(a)(3) and 21 CFR 50.20 require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative).

   In accordance with these regulations, informed consent discussions must include a reliable interpreter when the prospective subject does not understand the language of the person who is obtaining consent.

   As indicated previously, investigators may document informed consent in either of two ways:

   A full–length informed consent document written in language understandable to the subject; ***or***

   A "short-form" consent document in the language of the subject that states the general elements of informed consent.

   OHRS will provide generic "short form" consent documents to investigators in languages typically encountered among subject populations. Investigators will be responsible for providing documents in languages not typically encountered.

   If investigators use the "short form" to document informed consent, they must also provide subjects with (i) the full-length informed consent document in English, and (ii) an interpreter who can take part in the oral informed consent discussion to ensure subject's understanding and who may serve as the witness. The "short form" consent document written in the subject's language must be signed by the subject (or the subject's legally authorized representative) and the interpreter. The full-length English consent document must be signed by the interpreter and the person obtaining consent. The subject must be given copies of both the "short form" consent document and the English consent document.

   Whether a full-length or a "short form" consent document is utilized,

[28] 45 CFR 46.116(g)

translated documents must be submitted to OHRS for review and approval prior to their use in enrolling subjects.

7. **Participation of Non-English Speakers in Research:** Non-English speaking subjects should not be excluded from research without a sound scientific or ethical reason so as not to violate the requirement for equitable subject selection.

   Selection of subjects should be equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons. (45 C.F.R. 46.111(a)(3) and 21 C.F.R. 56.111(a)(s))

   Examples of reasons when it may be permissible for a research protocol to exclude Non-English Speaking Subjects include:

   (i) A sound scientific reason for exclusion would be that inclusion of non-English speaking people would not promote the aims of the study.

   (ii) A sound ethical reason for excluding non-English speaking people would be to protect them from harm or exploitation.

   (iii) There are insufficient resources to include non-English Speaking people.

   (iv) The proportion of non-English speaking subjects is very low.

   Investigators should be advised to carefully consider the ethical/ legal ramifications and risk/benefit of enrolling subjects when a language barrier exists.

8. **When following Department of Defense Regulations.**

   Research Involving a Human Being as an Experimental Subject: An activity, for research purposes, where there is an intervention or interaction with a human being for the primary purpose of obtaining data regarding the effect of the intervention or interaction [DoD Directive 3216.02 E2.1.3]

   If the research subject meets the definition of “experimental subject,” the regulations prohibit a waiver of the consent process unless a waiver is obtained from the Assistant Secretary of Defense for Research and Engineering. For classified research, waivers of consent are prohibited.

   The Assistant Secretary of Defense for Research and Engineering may waive the requirements for consent when all of the following are met;

   The research is necessary to advance the development of a medical product for the Military Services.

   The research might directly benefit the individual experimental subject.

The research is conducted in compliance with all other applicable laws and regulations.

If the research subject does not meet the definition of "experimental subject", the IRB is allowed to waive the consent process.

Chapter 12
IRB Review of FDA-Regulated Research: Investigational Drugs, Devices, and Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS) that is responsible for implementing and enforcing the Federal Food, Drug, and Cosmetic Act to regulate the safety and efficacy of these products for human use.

The FDA regulates clinical investigations that are conducted on drugs, biologics, and devices. All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review.

Clinical trials involving an investigational drug, device, or biologic that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with both the FDA and the DHHS human subject regulations (including, of course, the Common Rule).

a. FDA vs. Common Rule and DHHS Requirements. The human subject protection requirements found in FDA regulations and DHHS regulations are substantially the same as the Common Rule requirements. There are, however, important differences:

- FDA regulations contain no Assurance requirement;
- Conditions for exemption, exception, and waiver of IRB review and Informed Consent requirements differ;
- FDA regulations require specific determinations for the IRB review of device studies (see below);
- FDA regulations include specific requirements for reporting adverse events that are not found in the Common Rule or DHHS regulations;
- DHHS regulations include specific additional protections for pregnant women, fetuses, and human neonates (Subpart B) and prisoners (Subpart C) that are not contained in the FDA requirements; and
- FDA regulations define "human subject" and "clinical investigation (research)" differently.

b. Investigational Drugs, Devices, and Biologics. Applications are submitted to FDA for approval of research involving investigational drugs, devices, and biologics. IRB approval is conditioned upon the receipt of this documentation.

1. **Investigational New Drug Application (IND).** An IND is submitted so that an investigation can be conducted in support of a potential New Drug Application. Investigators make the initial determination of whether an IND is necessary. The Scientific Review Committee and Institutional Review Board review these determinations and may require investigators to review the FDA requirements for IND independently. Investigators are responsible for ensuring that the information included in the protocol application is accurate.

   IND Exemptions. The research involves the use of a drug other than the use of a marketed drug in the course of medical practice and the protocol meets one of

the FDA exemptions from the requirement to have an IND. Refer to **HRP-306 - WORKSHEET - Drugs and Biologics** for IND Exemptions.

2. **Investigational Device Exemption (IDE).** An IDE supports research to be conducted for a Pre-Market Approval application. Devices that are substantially equivalent to other devices that are legally on the market are called 510(k) devices and can be marketed without clinical testing (see below). Investigators make the initial determination of whether an IDE is necessary. The Scientific Review Committee and Institutional Review Board review these determinations and may require investigators to review the FDA requirements for IND/IDE independently. Investigators are responsible for ensuring that the information in the protocol application is correct.

   Abbreviated IDE. The research is conducted to determine the safety or effectiveness of a device. Refer to **HRP-307 - WORKSHEET – Devices** to determine if the device fulfills the requirements for an abbreviated IDE.

   IDE Exemption. The research is conducted to determine the safety or effectiveness of a device. Refer to **HRP-307 - WORKSHEET – Devices** to determine if the device fulfills the requirements for an IDE Exemption.

3. **Biologics License Application.** A Biologics License Application is submitted to the FDA to receive approval for research on biological products that would support a Biologics License. Biologics include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

   Investigators should submit documentation of the applicable IND/IDE numbers for studies involving investigational drugs, devices and biologics with their protocol applications to OHRS.

c. Clinical Investigator Responsibilities. Under FDA regulations, the **investigator** in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study.

Each clinical investigator must accept specific responsibilities that include the following:

- Ensuring conduct of the research according to the investigator agreement, investigational plan (protocol), and all applicable regulations
- Protecting the rights, safety, and welfare of the research subjects
- Training and supervising all members of the research team
- Controlling access to and use of the test article (drug / biologic / device)
- Monitoring and reporting adverse events
- Maintaining and retaining accurate records

d. Sponsor Responsibilities. The **sponsor** of a clinical investigation initiates and holds the IND or IDE for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be considered a

sponsor for an investigation. An investigator is referred to as the **sponsor-investigator** when the individual investigator is also the initiator of the clinical investigation.

The responsibilities of sponsors and sponsor-investigators include the following:

- Maintaining the IND, IDE, or Biologics License
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information and Training for Investigators
- Monitoring the Investigation
- Controlling the Investigational Agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and Retaining Accurate Records
- Registering the study on clinicaltrials.gov with responsibility for all reporting requirements.

e. IRB Review of Medical Devices. In accordance with FDA requirements, it is the policy of this Institution that a decision of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

1. **Significant Risk (SR) Device Defined.** A SR device study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant, or (2) is used in supporting or sustaining human life, or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full Board approval.

2. **Nonsignificant Risk (NSR) Device Defined.** A NSR device study is one that does not meet the definition of a SR study.

3. **Review Procedures.** The following procedures govern review of investigational devices by the IRB.
   a) If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a SR, then it would be governed by the IDE regulations at 21 CFR 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

      - A description of the device;
      - Reports of prior investigations conducted with the device;
      - The proposed investigational plan;
      - A description of subject selection criteria;

- Monitoring procedures; and
- The sponsor's risk assessment and the rationale used to make the sponsor's risk determination.

  The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment;
- A device study that is deemed to involve a NSR may begin immediately since it would not require the submission of an application to the FDA; and
- It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.

4. **510(k) Devices.** The review requirements for 510(k) devices are somewhat different. If FDA agrees that a new device is substantially equivalent to a device already on the market, it can be marketed without clinical testing. If, however, clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects follow the same requirements (see below).

5. **Radiology Devices and Radioactive Materials.** FDA is responsible for regulating radiology devices and radioactive materials used in health care and research. Oversight in this area is handled by the Radiation Safety Committee.

f. Investigators' Responsibilities for Reporting to the IRB. FDA IND regulations require that the investigator report promptly to the Sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)). FDA IDE regulations require that the investigator notify the sponsor of any unanticipated adverse device effect within ten days [see 21 CFR 812.150(a)(1)].

1. **Investigators' Duty to Report Unanticipated Problems.** Investigators are required to report to the IRB (using the adverse event/unanticipated problem reporting form) **any unanticipated problems involving risks to subjects or others** that occur in research conducted under the auspices of the DF/HCC whether the events occurred on site or off site.

2. **Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report to the IRB (using the adverse event/unanticipated problem reporting form) **any serious adverse event** that occurs in research conducted at facilities of this Institution or by its employees.
   A **serious adverse event** is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect [see 21 CFR 312.32(a) and 21 CFR 812.3(s)].

3. **Investigators' Duty to Report all Protocol Deviations & Violations.** Investigators are required to report all deviations or violations for approved protocols. This includes any change from the protocol that was implemented by the investigator in order to respond to immediate safety concerns**.**

4. **Investigators' Duty to Forward Sponsor or Cooperative Group Safety Reports.** Investigators are required to forward safety reports (or other information concerning adverse events) issued by sponsors or cooperative groups to the IRB within five working days of receipt. Each report should be accompanied by the completed adverse event/unanticipated problem reporting form.
5. **Investigators' Duty to Forward Data and Safety Monitoring Committee (DSMC) and Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward DSMB reports to the IRB within five working days of receipt when they indicate serious and/or continuing non-compliance and/or an unanticipated problem involving risks to subjects or others. Otherwise, routine DSMC and DSMB reports are submitted to the IRB at the time of continuing review.

   Note: *For studies reviewed by the DF/HCC DSMB and DSMC reports are provided by the Office for Data Quality to OHRS for submission to the DFCI IRB.*

   When DSMCs and DSMBs are employed, IRBs conducting continuing review of research may rely on a current statement from the DSMC or DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.

6. **Duty to Notify the IRB of Serious or Continuing Non-compliance.** Whether involved in the research or not, all employees of this Institution are required to notify the IRB if they become aware of any serious or continuing non-compliance with human subject regulatory requirements or with the determinations of the IRB.

   Non-compliance is defined as an action or activity in human subject research at variation with the IRB approved protocol, other requirements and determinations of the IRB, institutional policies or procedures, or relevant state or federal laws. **Serious non-compliance** is defined as non-compliance that involves greater than minimal risk of harm or discomfort to subjects or others involved in the research. **Continuing non-compliance** is defined as lasting more than five working days.

7. **Ten (10) Day Requirement.** The IRB should receive the completed IRB Adverse Event/Unanticipated Problem Reporting Form, Safety Report, DSMB Report, or other report from the investigator within 10 working days of the investigator becoming aware of the event or report.

g. Other Reporting Responsibilities. Investigators and sponsor-investigators have the following additional reporting responsibilities under FDA regulations:

- FDA IND regulations require the clinical investigator to notify the sponsor of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.

- FDA IND regulations require that the Sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of a drug or biologic that is both serious and unexpected as soon as possible but in no event later than fifteen (15) calendar days after the sponsor determines it to

be reportable. The FDA should be notified by telephone, facsimile, or in writing as soon as possible but in no event later than seven (7) calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.

- The Sponsor is required to evaluate the event and report serious, unexpected adverse device effects to the FDA, to all participating investigators, and to the IRB within ten (10) working days of the sponsor's receipt of the information.

h. Off-Label (Unapproved) Use of FDA-Regulated Products in Medical Practice Versus Research. Good medical practice and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

Off-label use of a marketed product in this manner when the intent is solely the **practice of medicine** does not require IRB review or the submission of an IND or IDE.

Off-label use of a marketed product in **research** (i.e., as part of a systematic investigation designed to develop or contribute to generalizable knowledge) does require IRB review.

Off-label use of a marketed product intended to support **a change in labeling** requires both IRB review and submission of an IND or IDE.

i. Treatment INDs and IDEs. The treatment IND is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. Where necessary, this mechanism can be used even for providing such drugs to a single patient-subject. The Treatment IDE is a comparable mechanism for providing investigational devices to such patient-subjects.

The FDA regulations at 21 CFR Part 312, Subpart I, specify the requirements for the expanded access use of an investigational drug to diagnose, monitor, or treat a patient's disease or condition. The FDA regulations at 21 CFR 812.36 specify the requirements that must be satisfied before a Treatment IDE can be issued.

Treatment IND and IDE studies require prospective IRB review and informed consent. Although the sponsor may apply for a waiver of local IRB review under a Treatment IND or IDE, such a waiver does not apply to the informed consent requirement. It is the policy of this Institution that all Treatment IND or IDE studies must be reviewed and prospectively approved by the IRB.

1. **Treatment IND.** During the clinical investigation of a drug, it may be appropriate to use the drug in treatment of patients not in the clinical trials. Such use requires FDA approval under 21 CFR 312.305, as well as IRB review and approval and informed consent.

2. **Single Patient Treatment IND.** The Single-Patient Treatment IND was added to the law under the FDA Modernization Act (FDAMA) in 1997. Investigators must obtain FDA approval as well as satisfy the requirements set forth at 21 CFR 312.305 and 21 CFR 312.310.

3. **Group C Treatment IND.** Group C drugs are Phase 3 study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are distributed by the National Cancer Institute (NCI) with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, this Institution's policy normally requires review and approval by the IRB. Investigators who are considering use of Group C drugs should contact the IRB Chairperson for guidance.

4. **Orphan Drugs.** The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of orphan drugs requires prospective IRB review and approval and informed consent (21 CFR 316.40).

5. **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.

6. **Treatment IDE.** Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use may occur when: (i) the patient has a serious or immediate life-threatening condition; (ii) there is no comparable or satisfactory alternative available; (iii) the device is under investigation in a controlled trial for the same use (or such trials have been complete); (iv) the Sponsor is pursuing marketing approval/clearance; (v) the Sponsor has submitted and the FDA has approved an IDE under 21 CFR 812.36. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required.

j. Gene Transfer Research. Gene transfer research involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the FDA. As of October 1, 2018, RAC review by the NIH Office for Biotechnology Activities (OBA) is no longer required.

FDA regulations require the submission of an IND for human gene transfer research.

DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the Recombinant DNA Advisory Committee (RAC) at NIH; approval of relevant Institutional component-designated Committee(s) has been obtained; component IRB approval has been obtained; and the investigator has obtained all other regulatory authorizations (such as any consents required by regulations) from the subject (65 FR 196, October 10, 2000).

k. Emergency Use of a Test Article without IRB Review. An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval. Subsequent use of the investigational drug, device, or biologic must be prospectively reviewed by the IRB.

The emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a subject, and the FDA may require data from an emergency use to be reported in a marketing application.

- DHHS regulations do not permit data obtained from patients to be classified as human subject's research, nor permit the outcome of such care to be included in any report of a research activity subject to DHHS regulations.
- Informed consent is sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 21 CFR 50 and informed consent is appropriately documented, in accordance with and to the extent required by 21 CFR 50.27.

Refer to the following documents for more information:

- HRP-322 - WORKSHEET - Emergency Use
- HRP-325 - WORKSHEET - Device Compassionate Use
- IS - Single Patient / Emergency Use Information Sheet

1. **Institutional Requirements.** If at all possible, this Institution's policy requires that investigators consult the IRB Chairperson, or medically qualified designee, for guidance when considering the emergency use of drugs or medical devices.

2. **Required Conditions.** Before the use of the test article, must certify in writing that all of the following conditions have been met for this type of emergency use: A human subject is in a life-threatening situation

   - No standard acceptable treatment is available

   - There is insufficient time to obtain IRB approval

   - The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use). The IRB will review the report of the emergency use and will confirm that the circumstances of the emergency use was compliant with the required FDA conditions set forth above.

   - Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below

l. **Emergency Use of a Test Article without Informed Consent.** An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic <u>without informed consent</u> where before the immediate use of the test article both the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all of the specific conditions described below.

1. **Institutional Requirements.** If at all possible, this Institution's policy requires that the investigator consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices. When consulted, the IRB Chairperson shall evaluate and confirm that the required conditions are satisfied.

2. **Required Conditions.** Before the use of the test article, the investigator and another physician, who is not otherwise participating in the clinical investigation, must certify in writing that all of the following conditions have been met for this type of emergency use <u>without informed consent</u>:

- The subject is confronted by a life-threatening situation necessitating the use of the test article and the immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject.

- Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject

- There is not sufficient time to obtain consent from the subject's legally authorized representative

- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life

  Note: If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within five working days from the use of the test article.

- The emergency use must be reported to the IRB within five working days (such reporting must not be construed as IRB approval for the emergency use)

3. **IRB Review of Report of Emergency Use without Informed Consent.** The IRB will review the report of the emergency use and will confirm that the emergency use was compliant with the required conditions set forth above.

m. Expanded Access to Investigational Drugs and Devices. "Compassionate Use" is not a term that appears in the FDA or DHHS regulations or the Common Rule.

For studies involving investigational drugs, "Compassionate Use" is often meant to refer to the emergency use situations discussed above.

For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition who does not qualify for the trial. Such uses require prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior FDA approval for compassionate use should be obtained before the device is used.

On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the following protections as possible: (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chairperson (which does not constitute IRB approval; (iv) an independent assessment of an uninvolved physician; and (v) authorization of the IDE sponsor. Follow-up reports should be provided to the Sponsor. Such use may involve an individual patient or a small group of patients.

1. **Institutional Requirements.** If at all possible, this Institution's policy requires that investigators consult the IRB Chairperson for guidance when considering such "compassionate use."

Note: The above "Compassionate Use" situations should not be confused with the Humanitarian Use Device (HUD) Exemption (see paragraph "n" below).

n. Humanitarian Device Exemptions. A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission of a humanitarian device exemption (HDE) application. Refer to **HRP-323 - WORKSHEET - Criteria for Approval HUD** to determine if the device fulfills the requirements for a HUD Exemption.

o. Right to Try (RTT). Federal RTT law lifts most parts 50, 56 and 312 of title 21 of the Code of Federal Regulations (CFR), which contain rules and regulations for IRB oversight of drug testing, including jurisdiction for expanded access requests and informed consent requirements. The federal RTT law makes no mention of IRB or ethics review or review by any independent third-party (e.g., a local governmental or institutional body).

While the federal RTT law states that patients or their legally authorized representatives must provide "informed consent" to the treating physician for use of the investigational drug, the RTT law explicitly exempts RTT access from the informed consent provisions contained in federal regulations at 21 CFR 50, which are applicable to requests under the FDA's Expanded Access Program. The federal RTT law does not replace these key details with any alternative requirements, including the validity of the information conveyed, the voluntariness of the consent provided, or review of the informed consent procedures by an IRB or other third party.

Under the RTT law, an investigational drug eligible for request must fulfill certain requirements contiguous with current federal law, including:

- that it is the subject of an application filed with the FDA (pursuant to 505(b), or 351(a) of the Public Health Services Act); and
- Investigational drugs are only eligible if they have already completed a Phase I clinical trial; and
- are not FDA approved for any indication; and
- are part of either a pending FDA drug approval application or a current trial whose data will be submitted to FDA as part of an application; and
- have not during development been placed on a clinical hold.

The federal RTT law specifies that clinical outcomes associated with the use of an eligible investigational drug typically cannot be used to adversely affect the review or approval of that drug, though any known serious adverse events (SAEs) must be summarized in an annual report and submitted in conjunction with the new drug application for the drug.

The sponsor, manufacturer, or other "dispenser" of the investigational drug under federal RTT bears no liability for any act or omission with respect to an eligible investigational drug.

p. Note: The DFCI IRB does not conduct IRB review of Federal Right to Try requests. Institutional policy for access to investigational drugs under RTT must be followed.

q. Planned Emergency Research. An exception under FDA regulations at 21 CFR 50.24 permits planned research in an emergency setting without the informed consent of the subjects. This exception applies to a limited class of research involving human subjects who are in need of emergency medical intervention. The DF/HCC does not conduct planned emergency research.

Chapter 13
Social & Behavioral Research

Social and behavioral research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This chapter discusses when exemption and expedited review are appropriate for this type of research and when it requires full board review.

a. Social and Psychological Harms. When evaluating behavioral and social science research, the IRB carefully examines the research to determine the probability of risk of harm to subjects, particularly subjects who are burdened with disease or end of life caregiving. The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm. The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.

If information is being collected on living individuals other than the primary "target" subjects, the IRB should consider the risk of harm to those "non-target" individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of "non-target" individuals (unless the requirement for informed consent can be waived).

To mitigate such risks, the IRB reviews the proposal for appropriate preventative protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

b. Privacy and Confidentiality Concerns. In order to approve research the IRB must determine that the research protocol or plan contains adequate provisions to protect the privacy of subjects and the confidentiality of data. The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances in which certain activities are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements. These have been discussed previously in Chapter 10 and will also be discussed briefly in following sections of this chapter.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information and/or identifiable biospecimens once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

c. Safeguarding Confidentiality. When information linked to individuals will be recorded as part of the research design, the IRB ensures that adequate precautions shall be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with the techniques for protecting confidentiality.

IRBs that review research in which the confidentiality of data is a serious issue

should have at least one member (or consultant) familiar with the strengths and weaknesses of the different mechanisms available to protect subjects' confidentiality.

When reviewing survey and interview research, the IRB will be aware of the regulatory provision at 45 CFR 46.117(c)(1) for waiving documentation of consent when a signed consent form constitutes the only link between the research and the subjects and would itself be a risk to the subjects.

Among the available methods for ensuring confidentiality are the following: coding of records; statistical techniques, and physical or computerized methods for maintaining the security of stored data.

DHHS regulations at 45 CFR 46.116(b)(5), FDA regulations, and the Common Rule require that subjects be informed of the extent to which confidentiality of research records will be maintained.

Federal officials have the right to inspect and copy research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. FDA requires that information regarding this authority be included on the consent information for all research that it regulates. Identifiable information obtained by Federal officials during such inspections is protected by the provisions of the Privacy Act of 1974.

The IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings.

d. Exempt Research. Pre-2018: Some social and behavioral research is exempt from the requirements of the DHHS regulations (45 CFR 46.101(b)) and the Common Rule. However, appropriate application of these exemptions requires a relatively sophisticated level of expertise and should not be left to individual investigators. This Institution's IRB policy requires that the IRB Chairperson or qualified designee review all requests for exemption from IRB Review and must have sufficient information from the investigator to ascertain whether the claimed exemption really applies.

Post-2018: Some social and behavioral research is exempt from the requirements of the DHHS regulations (45 CFR 46.104(d)) and the Common Rule. However, appropriate application of these exemptions requires a relatively sophisticated level of expertise and should not be left to individual investigators. This Institution's IRB policy requires that the IRB Chairperson or qualified designee review all requests for exemption from IRB Review and must have sufficient information from the investigator to ascertain whether the claimed exemption really applies.

The following exemptions are particularly applicable to social and behavioral research. **These exemptions do not apply to FDA-regulated research.**

1. **Exempt Research in Educational Settings. Pre-2018:** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations and the Common Rule in accordance with 45 CFR 46.101(b)(1).

   This exemption does not apply if the setting is not commonly recognized as an

educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected.

When educational institutions become engaged in the actual conduct of research, they are required to file an Assurance in accordance with DHHS regulations at 45 CFR 46.103(a) and the Common Rule.

Post-2018: Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction is exempt from Federal regulations and the Common Rule in accordance with 45 CFR 46.104(d)(1). This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected.

When educational institutions become engaged in the actual conduct of research, they are required to file an Assurance in accordance with DHHS regulations at 45 CFR 46.103(a) and the Common Rule.

2. **Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior. Pre-2018:** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 45 CFR 46.101(b)(2).

   When the subjects are adults, this exemption applies UNLESS: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); AND (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. *Note: The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.*

   This exemption applies to research involving children, EXCEPT that: (a) research involving survey or interview procedures with children is NOT EXEMPT; and (b) research involving observation of the public behavior of children is NOT EXEMPT if the investigator participates in the actions being observed.

   If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) federal statutes require confidentiality without exception. *Note: Condition (b) regarding federal statutes rarely applies. The IRB should consult with OHRP if it receives an exemption request based on absolute confidentiality under a federal statue.*

If not exempt under the conditions described above, the IRB may often utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.
Post-2018: Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) is ordinarily exempt under Federal regulations at 45 CFR 46.104(d)(2) if at least one of the following criteria is met:

(i) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

(ii) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; **or**

(iii) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by 46.111(a)(7).

This exemption applies to research involving children ONLY involving educational tests or the observation of public behavior when the investigator(s) do not participate in the activities being observed. Item (iii), list above, may not be applied to research involving children.

3. **Exempt Research Using Existing Data and Documents. Pre-2018:** Social and behavioral research often relies on analysis of existing data or documents. Such research, which is often exempt, is discussed in Chapter 8.
Post-2018: Exempt Research Using Benign Behavioral Interventions[29] If not exempt under the conditions described above, research involving the use of behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection is exempt under 45 CFR 46.104(d)(3) if at least one of the following criteria is met:
   a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;
   b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or
   c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly

[29] Benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, or having them decide how to allocate a nominal amount of received cash between themselves and someone else.

or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by § 46.111(a)(7).

Note: *If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research*[30].

e. Expedited Review of Behavioral and Social Science Research Pre-2018: that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998, Federal Register FR 60364-60367 and FR 60353-60356 may be reviewed by the IRB utilizing expedited procedures (see Chapter 9).

The categories discussed below are particularly applicable to social and behavioral research, and include research involving children as well as adult subjects.

1. **Expedited Review of Research Involving Existing Data and Documents (Expedited Category #5).** Minimal risk research involving materials, (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures. The intent is to define two categories here, each appropriate for expedited review.
Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.

   Non-exempt research involving materials that will be collected in the future for a non-research purpose.

   Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes (Expedited Category #6). The IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.

   Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies (Expedited Category #7). The IRB may utilize expedited procedures to review the following:

   Research on individual or group characteristics or behavior; or

   Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

   This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identification, language, communication, cultural beliefs or practices.

[30] 45 CRF 46.104(d)(3)(iii)

f. Research Involving Deception or Withholding of Information. IRBs reviewing research involving incomplete disclosure or outright deception must apply both common sense and sensitivity to the review. **Deception research** involves psychology research in which the subject is not told, or is misled, about the true purpose of the research, such as in certain studies of group processes, contextual influences on cognition, etc.

Where deception is involved, the IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in Federal regulations and the Common Rule at 45 CFR 46.116(f). Specifically, the IRB must find and document that all four of the following criteria have been satisfied:

- The research presents no more than minimal risk to subjects.
- The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
- The research could not practicably be carried out without the waiver or alteration.
- If the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.
- Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. ***Note:*** *The regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects.*

g. Community-Based Participatory Research. The DFCI IRB does not review Community-Based Participatory Research.

Chapter 14
Research Combining Biomedical and Social & Behavioral Elements

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. They often use or create tissue, specimen, or data repositories (banks).

a. Prospective Use of Existing Materials.

- **Pre-2018:** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

  Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under Federal regulations at 45 CFR 46.101(b)(4) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated.

  However, IRBs may utilize **expedited procedures** (under expedited category #5) to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

- **Post-2018:** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

  Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under Federal regulations at 45 CFR 46.104(d) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated.

  However, IRBs may utilize **expedited procedures** (under expedited category #5) to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

b. Retrospective Use of Existing Materials.

- **Pre-2018:** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g.. medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

  Such research may be exempt under Federal regulations at 45 CFR 46.101(b)(4) if the information is publicly available or if the information is

recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects. If the data is anonymized or de-identified such that the investigator cannot reasonably ascertain the identity of the individuals from whom the data was obtained and will not have access to the code and the investigator will not have any interaction with the individual, then the research may be deemed not human subjects research. This is applicable for both biological samples and data sets.

If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

- **Post-2018:** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

  Such research may be exempt under Federal regulations at 45 CFR 46.104(4) if the identifiable private information or identifiable biospecimens is (at least one of the following criteria must be met)[31]:

  i. The identifiable private information or identifiable biospecimens are publicly available;

  ii. Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects;

  iii. The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of "health care operations" or "research" as those terms are defined at 45 CFR 164.501 or for "public health activities and purposes" as described under 45 CFR 164.512(b);

OR

  iv. The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the

[31] 45 CRF 46.104(d)(4)(i-iv)

Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 et seq.

If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

c. Research Utilizing Large Existing Data Sets. Biosocial and bio-behavioral research often involves the use of large, existing data sets.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information. Of course, use of data from publicly available data sets would still be exempt or not human subjects research if the information is not sensitive or not identifiable.

The use of large, existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 45 CFR 46.116(b). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities.

An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP). See next section.

d. Research Using Data or Tissue Banks (also called Repositories). Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

Tissue Bank activities involve three components: (a) the **collectors** of data or tissue samples; (b) the **bank/repository** storage and data management center; and (c) the **recipient** investigators. Under a **repository arrangement**, an IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data and/or tissues

with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters involve formal, written agreements stipulating conditions as follows:

- The repository shall not release any identifiers to the investigator.
- The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.

The investigator shall use the data only for the purposes and research specified.

The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects. Additional information about the operation of DF/HCC data or tissue repositories can be found in the OHRS Information Guidance on the OHRS website.

Chapter 15
IRB Considerations Regarding Study Design

a. Epidemiological Research. Epidemiological research often makes use of sensitive, individually identifiable private information and/or identifiable biospecimens (usually obtained from medical or other private records) and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research.

Epidemiological studies often present significant problems regarding both **privacy** and **confidentiality**.

The IRB must first consider privacy issues and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any identifiable private information and/or identifiable biospecimens that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (45 CFR 46.116(f)); specifically that: (a) the research presents no more than minimal risk to subjects; (b) the research could not practicably be carried out without the requested waiver or alteration; (c) if the research involves using identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format; (d) the waiver or alteration will not adversely affect the rights and welfare of the subjects; and (e) whenever appropriate, the subjects or legally authorized representatives will be provided with additional pertinent information after participation.

b. Issues in Genetic Research. Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained. (See Chapter 2.)

c. Family History Research. Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one family member (called a proband) about other family members (third parties).

It is important to recognize that the Federal regulations at 45 CFR 46.102 (e)(1-7) and the Common Rule define a human subject, in part, as a living individual about whom an investigator (whether professional or student) conducting research: (a) obtains information or biospecimens through intervention[32] or interaction[33] with the individual, and uses, studies, or analyzes the information or biospecimens; or (b) Obtains, uses, studies, analyzes, or generates identifiable private information[34] or identifiable biospecimens[35].

Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information and/or identifiable biospecimens from them.

DFCI IRBs must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived (see Chapter 11) under the conditions specified at 45 CFR 46.116(f).There is not total consensus in the available guidance on this issue. OHRP representatives have advised that "third parties" about whom identifiable private information and/or identifiable biospecimens is collected in the course of research are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRBs can consider if informed consent from third parties can be waived in accordance with Section 116 and if so, document that in the IRB minutes. In most cases, waiver of consent may be appropriate.

d. Research Involving Potentially Addictive Substances. Research involving potentially addictive substances often involves the use of what may be termed "abuse-liable" substances. Abuse-liable substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-liable substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:

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[32] 45 CFR 46.102 (e)(2): Intervention includes both physical procedures by which information or biospecimens are gathered (e.g., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

[33] 45 CFR 46.102 (e)(3): Interaction includes communication or interpersonal contact between investigator and subject.

[34] 45 CFR 46.102 (e)(4-5): Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (e.g., a medical record).

Identifiable private information is private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

[35] 45 CFR 46.102 (e)(6): An identifiable biospecimen is a biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.

If such research involves subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.

The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.

The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.

It is critical that the IRB focus on the considerations of risk and benefit of such research.

Chapter 16
IRB Review of Research Involving Children

DHHS regulations at 45 CFR Part 46, Subpart D and FDA Regulations at 21 CFR 50 Subpart D require special protections for research involving children. Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

There are several important issues for the IRB to consider when reviewing research involving children, particularly including: (i) the risk-benefit analysis to determine permitted regulatory categories; (ii) assent of the child; and (iii) permission of one or both parents/legally authorized representative, depending upon the level of risk.

a. Risk-Benefit Analysis and Permitted Categories. The IRB will make the specific findings and determinations required under federal regulations when reviewing research involving children. IRB records will reflect the IRB's understanding and justification for the risks and benefits posed by approved research involving children.

Based in part on its risk-benefit analysis, the IRB must find and document that the proposed research falls within one of the following four categories:

Research not involving greater than minimal risk;

Research involving greater than minimal risk, but presenting the prospect of direct benefit to the individual subjects;

Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition; or

Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

Each category stipulates specific criteria that must be found and documented by the IRB to have been satisfied before the proposed research can be approved (see Table 16.1). As appropriate, the IRB will also consult with continuing and/or ad hoc consultants as described in Chapter 6.

When following Department of Defense regulations, research involving children cannot be exempt.

In accordance with OHRP guidance (OHRP Compliance Oversight Activities: Determinations of Noncompliance, 02/04/2009), the IRB will document these required findings in IRB records and/or the minutes of the IRB meeting in such a manner as to include *protocol-specific* information justifying each IRB finding.

b. Reasonable Expectation of Benefit. The IRB requires particularly strong justification for the involvement of children in greater than minimal risk research that holds out little reasonable prospect of direct therapeutic benefit to the individual child. The strength of the child's assent or dissent will generally be given greater weight as the age of the child more closely approaches the age of majority.

Table 16.1
Category Requirements for Research Involving Children

Regulatory Category	Requirements
No Greater Than Minimal Risk	▪ Assent of child and permission of at least one parent/legally authorized representative
Greater Than Minimal Risk and Prospect of Direct Benefit to the Individual Subjects and	▪ Assent of child and permission of at least one parent/legally authorized representative ▪ Anticipated benefit justifies the risk ▪ Anticipated benefit is at least as favorable as that of alternative approaches
Greater Than Minimal Risk and No Prospect of Direct Benefit to Individual Subjects	▪ Assent of child and permission of both parents/legally authorized representative ▪ Only a minor increase over minimal risk ▪ Likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition ▪ The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child's actual or expected medical, dental, psychological, social, or educational situations
Not Otherwise Approvable But Presenting an Opportunity to Understand, Prevent, or Alleviate a Serious Problem Affecting Children	▪ Assent of child and permission of both parents/legally authorized representative ▪ IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children ▪ The DHHS Secretary or the FDA Commissioner approves, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following public comment

c. Assent of the Child. HHS regulations at 45 CFR 46.408(a) and FDA regulations at 21 CFR 50.55 require that the IRB take the following specific actions concerning the assent of child-subjects:

The IRB must determine that adequate provisions are made for soliciting the assent of the children when, in the judgment of the IRB, the children are capable of providing assent.

In determining when children are capable of providing assent, the IRB must take into account the ages, maturity, and psychological state of the children involved.

The assent of the children is not necessary if the IRB determines that the capability of the children is so limited that they cannot reasonably be consulted.

The assent of the children is not necessary if the IRB determines that the research holds out the prospect of direct benefit that is only available in the context of the research.

The IRB may waive assent if:

(i) The research involves no more than minimal risk to subjects; ***and***

(ii) The waiver will not adversely affect subjects' rights and welfare; ***and***

(iii) The research could not practicably be carried out without the waiver; ***and***

(iv) Where appropriate (for example, in social and behavioral research where mild deception is involved), subjects will be provided with pertinent information after participation.

The IRB must determine whether and how assent must be documented.

In accordance with these requirements, the IRB will determine and document that assent is a requirement of all, some, or none of the children in a study. When the IRB determines that assent is not a requirement of some children, the IRB will determine and document which children are not required to assent.

The IRB will require that the assent of the child-subject be obtained unless the IRB specifically determines that the (i) child-subject lacks the capacity for assent; (ii) the research offers an important direct benefit that cannot be obtained outside the research; or (iii) the assent requirement can be formally waived. Such determinations must be documented in a protocol-specific fashion in IRB meeting minutes and/or other IRB documents.

Where assent is to be obtained, the amount and complexity of the information provided to the child depends upon the child's level of cognitive and emotional maturation. If subjects include a wide age range, it may be necessary for the IRB to require that different information be given to different age groups.

As its discretion, the IRB may develop additional written guidance to assist investigators in proposing appropriate methods of obtaining and documenting assent for subjects of different ages or levels of maturation.

Ultimately, the responsibility for determining assent requirements rests with the IRB, not with the research investigator. As a general rule, the IRB will not require that assent be obtained if the minor is under 10 years of age.

d. Documentation of Assent. How assent is documented (e.g., written assent document, information sheet, note in medical or research record) will vary depending upon the child's level of cognitive and emotional maturity. If the IRB determines that the child's assent is required, the IRB will also determine the mode of documentation. For younger children (e.g., below age 10) a note in the medical or research record may suffice. A written information sheet or signed assent document will typically be required for older children.

In any case, the IRB will require that any information sheet or assent document be tailored to the developmental level of the child. For example, for pre-teens (e.g., ages 10-12), such documents should be relatively brief, with simple, age-appropriate language, presented in a manner understandable to the child; for teenagers (e.g., ages 13-17), the information may be more complete and the language more mature, and a signed assent document is usually required.

e. Parental/Legally Authorized Representative Permission. In accordance with DHHS and FDA requirements, the IRB will determine that adequate provisions have

been made for obtaining and documenting parental/legally authorized representative permission for the participation of children in research.

As indicated in Table 16.1, the permission of at least one parent/legally authorized representative will be required when the research presents no greater than minimal risk of harm to the child, or the research provides the prospect of direct benefit to the individual child. The permission of both parents/legally authorized representative will be required where the research presents greater than minimal risk of harm with no prospect of direct benefit to the child-subject, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

Any waiver or alteration of these permission requirements must be consistent with applicable Federal and State laws and regulations as described in Chapter 11, paragraph f. The waiver provision is not applicable to research governed by FDA regulations, and the IRB will not approve alterations or waivers for FDA-regulated research.

The IRB must determine whether and how assent must be documented.

(i) The research involves no more than minimal risk to subjects; ***and***

(ii) The waiver will not adversely affect subjects' rights and welfare; ***and***

(iii) The research could not practicably be carried out without the waiver; ***and***

(iv) Where appropriate (for example, in social and behavioral research where mild deception is involved), subjects will be provided with pertinent information after participation.

The IRB must determine whether and how assent must be documented.

f. Guardians and Legally Authorized Representatives. In the absence of the child's parents, permission for the involvement of the child in research may be obtained from the child's legal guardian(s) or others to the extent authorized under the laws of the State in which the research takes place.

Chapter 17
IRB Review of Research Involving Adults as Vulnerable Subjects

In addition to children, DHHS regulations at 45 CFR 46.111(b), FDA regulation at 21 CFR 56.111(b), and the Common Rule require IRBs to give special consideration to protecting the welfare of other particularly vulnerable subjects, such as prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

The DFCI IRB makes every effort to obtain the expertise needed to consider specific kinds of research involving vulnerable populations in a satisfactory manner.

a. Considerations in Reviewing Research Involving Vulnerable Subjects. The DFCI IRB pays special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.

It is the responsibility of the IRB Chair, the OHRS Director and OHRS Associate Directors to ensure that there is adequate discussion at the IRB meetings of issues relating to vulnerable populations. For DHHS-funded research, the OHRS Director certifies to OHRP the duties of the IRB have been fulfilled.

Critical issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and voluntarism; coercion and undue influence; and confidentiality of data.

The IRB will carefully consider group characteristics, such as economic, social, physical, and environmental conditions, so that the research incorporates additional safeguards for vulnerable subjects.

Investigators will not generally be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available “captive” population.

As it determines necessary, the IRB will seek to obtain information regarding laws and science that bear on decision-making capacity of the potentially vulnerable populations to be involved in the research.

Just as in providing medical care, research studies that involve potentially vulnerable populations must have adequate procedures in place for assessing subjects’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB will look to see that such procedures are a part of the research plan.

In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly to gauge their understanding paragraph by paragraph.

The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each

signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

If the research is funded by the Department of Defense it is subject the DHHS Subparts B, C and D:

a. For purposes of applying Subpart B, the phrase "biomedical knowledge" shall be replaced with "generalizable knowledge."
b. The applicability of Subpart B is limited to research involving pregnant women as subjects in research that is more than minimal risk and included interventions or invasive procedures to the woman or the fetus or involving fetuses or neonates as subjects.
c. Fetal research must comply with the US Code Title 42, Chapter 6A, Subchapter III, Part H, 289g.
d. Research involving prisoners cannot be reviewed by the expedited procedure.
e. When the IRB reviews research involving prisoners, at least one prisoner representative must be present for quorum.
f. In addition to allowable categories of research on prisoners in Subpart C, epidemiological research is also allowable when:
    i. The research describes the prevalence or incidence of a disease by identifying all cases or studies potential risk factor association for a disease.
    ii. The research presents no more than minimal risk.
    iii. The research presents no more than an inconvenience to the subject.

If a subject becomes a prisoner, if the investigator asserts to the IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB chair may determine that the prisoner-subject may continue to participate until the convened IRB can review this request to approve a change in the research protocol and until the organizational official and DoD Component office review the IRB's approval to change the research protocol. Otherwise, the IRB chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol. The convened IRB, upon receipt of notification that a previously enrolled human subject has become a prisoner, shall promptly re-review the research protocol to ensure that the rights and wellbeing of the human subject, now a prisoner, are not in jeopardy. The IRB should consult with a subject matter expert having the expertise of a prisoner representative if the IRB reviewing the research protocol does not have a prisoner representative. If the prisoner-subject can continue to consent to participate and is capable of meeting the research protocol requirements, the terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research, and there are no other significant issues preventing the research involving human subjects from continuing as approved, the convened IRB may approve a change in the study to allow this prisoner-subject to continue to participate in the research. This approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

    a. Research involving a detainee as a human subjects is prohibited.
    b. This prohibition does not apply to research involving investigational drugs and devises when the same products would be offered to US military personnel in the same location for the same condition.

Research involving prisoners of war is prohibited.

The IRB is aware of the definition of "prisoner of war" for the DoD component granting the addendum.

For research supported or funded by the Department of Defense, if consent is to be obtained from the experimental subjects' legal representative, the research must intend to benefit the individual subject. The determination that the research is intended to be beneficial to the individual subject must be made by the IRB.

b. Pregnant Women, Human Fetuses and Neonates. DHHS regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, human fetuses, and neonates. Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk.

On the other hand, unilateral exclusion of non-pregnant women of reproductive potential from research, in order to avoid a risk, will not be permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

The regulations set out specific categories, each with their own requirements and IRB determinations, for research involving pregnant women, human fetuses and neonates. Table 17.1 summarizes these requirements.

Table 17.1
Summary of Requirements for Research Involving Pregnant Women, Fetuses and Neonates

Regulatory Category	Requirements
Pregnant Women or Fetuses	▪ Where appropriate, preclinical data identify potential risks ▪ Direct benefit for pregnant woman or fetus, or risk to fetus not greater than minimal ▪ Any risk is least possible for achieving research objectives ▪ Persons consenting are fully informed ▪ Consent of pregnant woman if direct benefit to her, or risk to fetus not greater than minimal ▪ Consent of pregnant woman and father (if reasonably available) if research offers direct benefit solely to fetus ▪ For pregnant children, assent and permission per Subpart D ▪ No inducements to terminate a pregnancy ▪ Researchers have no part in decisions to terminate pregnancy ▪ Researchers have no part in determining viability
Neonates of Uncertain Viability	▪ Where appropriate, preclinical data identify potential risks ▪ Persons consenting are fully informed ▪ Researchers have no part in determining viability ▪ Enhance probability of survival and risk is least possible ***or*** no added risk to neonate and important medical knowledge will result ▪ Informed consent of one parent or legally authorized representative
Nonviable Neonates	▪ Where appropriate, preclinical data identify potential risks ▪ Persons consenting are fully informed ▪ Researchers have no part in determining viability ▪ Vital functions not artificially maintained ▪ No termination of heartbeat or respiration ▪ No added risk to neonate ▪ Important medical knowledge will result ▪ Informed consent of both parents, unless one unable ▪ No legally authorized representatives

Viable Neonates	▪ Refer to DHHS Subpart D for research involving children
Placenta, Dead Fetus, Fetal Material	▪ Refer to applicable Federal, State of Massachusetts, or local law
Not Otherwise Approvable	▪ IRB finds reasonable opportunity to advance health or welfare ▪ Approval of HHS Secretary after expert and public consultation

IRB determinations regarding the applicable category and protocol-specific findings relative to the specific requirements of the relevant category will be clearly documented in IRB meeting minutes and/or other IRB records. DHHS regulations at 45 CFR Part 46, Subpart B provide the following in pertinent part:

§ 46.204 Research involving pregnant women or fetuses.

Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;

(b) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or, if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

(c) Any risk is the least possible for achieving the objectives of the research;

(d) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions of subpart A of this part;

(e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.

(f) Each individual providing consent under paragraph (d) or (e) of this section is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;

(g) For children as defined in §46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of subpart D of this part;

(h) No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

(i) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(j) Individuals engaged in the research will have no part in determining the viability of a neonate.

§ 46.205 Research involving neonates.

(a) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates.

(2) Each individual providing consent under paragraph (b)(2) or (c)(5) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate.

(3) Individuals engaged in the research will have no part in determining the viability of a neonate.

(4) The requirements of paragraph (b) or (c) of this section have been met as applicable.

(b) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this subpart unless the following additional conditions have been met:

(1) The IRB determines that:

(i) The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective, or

(ii) The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(2) The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with subpart A of this part, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(c) Nonviable neonates. After delivery nonviable neonate may not be involved in research covered by this subpart unless all of the following additional conditions are met:

(1) Vital functions of the neonate will not be artificially maintained;

(2) The research will not terminate the heartbeat or respiration of the neonate;

(3) There will be no added risk to the neonate resulting from the research;

(4) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(5) The legally effective informed consent of both parents of the neonate is obtained in accord with subpart A of this part, except that the waiver and alteration provisions of §46.116(f) does not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph (c)(5), except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph (c)(5).

(d) Viable neonates. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of subparts A and D of this part.

§ 46.206 Research involving, after delivery, the placenta, the dead fetus or fetal material.

(a) Research involving, after delivery, the placenta; the dead fetus; macerated fetal material; or cells, tissue, or organs excised from a dead fetus, shall be conducted only in accord with any applicable federal, state, or local laws and regulations regarding such activities.

(b) If information associated with material described in paragraph (a) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of this part are applicable.

§ 46.207 Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of pregnant women, fetuses, or neonates.

The Secretary will conduct or fund research that the IRB does not believe meets the requirements of §46.204 or §46.205 only if:

(a) The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates; and

(b) The Secretary, after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, ethics, law) and following opportunity for public review and comment, including a public meeting announced in the FEDERAL REGISTER, has determined either:

(1) That the research in fact satisfies the conditions of §46.204, as applicable; or

(2) The following:

(i) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of pregnant women, fetuses or neonates;

(ii) The research will be conducted in accord with sound ethical principles; and

(iii) Informed consent will be obtained in accord with the informed consent provisions of subpart A and other applicable subparts of this part.

c. Prisoners. DHHS regulations at 45 CFR Part 46, Subpart C detail special protections for research involving prisoners, who, due to their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research. The DF/HCC does not target prisoners in research. In the event that a subject becomes incarcerated during the course of a research study, or a prisoner is identified for a research study, the research study must be re-reviewed by the convened IRB prior to the commencement of any research activities involving the prisoner.

A prisoner is defined as any individual involuntarily confined or detained in a penal institution. Research involving prisoners, minimal risk is defined as the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons. In order to consider research involving prisoners, the IRB must:

- Have a majority of its members not otherwise associated with the prison
- Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.

For research involving prisoners reviewed by the convened IRB:

a. The prisoner representative must be a voting member of the IRB.
The prisoner representative may be listed as an alternative member who becomes a voting member when needed.

b. The prisoner representative must review research involving prisoners, focusing on the requirements in Subpart C or equivalent protections.
The prisoner representative must receive all review materials pertaining to the research (same as primary reviewer)

c. The prisoner representative must be present at a convened meeting when the research involving prisoners is reviewed. If the prisoner representative is not present, research involving prisoners cannot be reviewed or approved.
The prisoner representative may attend the meeting by phone, video-conference, or webinar, as long as the representative is able to participate in the meeting as if they were present in person at the meeting.

d. The prisoner representative must present his/her review either orally or in writing at the convened meeting of the IRB when the research involving prisoners is reviewed.

e. Minor modifications to research that do not pertain to the incarcerated subject may be reviewed using the expedited procedure. For example, a new research site addition.

f. Modifications involving more than a minor change reviewed by the convened IRB – must use the same procedures for initial review including the responsibility of the prisoner representative to review the modification and participate in the meeting (as described above).

g. Continuing review – must use the same procedures for initial review including the responsibility of the prisoner representative to review the

continuing review materials and participate in the meeting (as described above).

If a subject becomes a prisoner while enrolled in a research study that was not reviewed according to Subpart C:

- When Subpart C applies:
  - Confirm that the subject meets the definition of a prisoner.
  - If the subject cannot be withdrawn for health or safety reasons
  - Keep the subject enrolled in the study and review the research under Subpart C.
  - If some of the requirements of Subpart C cannot be met, but it is in the best interests of the subject to remain in the study, keep the subject enrolled and inform OHRP of the decision along with the justification.
  - Remove the subject from the study and keep the subject on the study intervention under an alternate mechanism such as compassionate use, off label use, etc.
- When Subpart C does not apply, the same process as above should be followed. The research will be reviewed under the requirements of Subpart C (including the requirement for a prisoner representative), with the exception that communication with OHRP will not be required.

Note: If a subject is incarcerated temporarily while enrolled in a study:

- If the temporary incarceration has no effect on the study, keep the subject enrolled.
- If the temporary incarceration has an effect on the study, handle according to the above guidance.

The regulations set out specific categories and IRB determinations for research involving prisoners. Table 17.2 summarizes these requirements.

Table 17.2
Summary of Requirements for Research Involving Prisoners

Permissible Categories	Additional Required Findings, Regardless of Category
A. Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behavior **B. Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons** **C. Research on particular conditions affecting prisoners as a class (providing the Secretary of DHHS has consulted with appropriate experts and published the intent to support such research in the Federal Register)** **D. Research on practices, both innovative and accepted that has the intent and reasonable probability of improving the health or well-being of the subject. For DHHS-funded research which require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups which may not benefit from the research, the study may proceed only after OHRP has consulted with appropriate experts, including experts in penology, medicine, and ethics, and published notice, in the Federal Register, of its intent to approve such research.**	▪ Any possible advantages to the prisoner, when compared with general living conditions, medical care, quality of food, amenities, and opportunity for earnings are not of such a magnitude that ability to weigh risks of the research against the value of such advantages in the limited choice environment of the prison is impaired ▪ Risks involved in the research are commensurate with risks that would be accepted by nonprisoner volunteers ▪ Procedures for selecting subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners ▪ Unless the investigator provides to the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project ▪ Information is presented in language that is understandable to the subject population ▪ Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole ▪ Each prisoner is clearly informed in advance that participation in the research will have no effect on his or her parole ▪ Where the IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact. ▪ Epidemiologic studies that meet the following criteria: • The sole purposes are one of the following: 1. To describe the prevalence or incidence of a disease by identifying all cases. 2. To study potential risk factor associations for a disease. • The research presents no more than minimal risk and no more than inconvenience to the prisoner-subjects, and Prisoners are not a particular focus of the research.

If the research is DHHS-supported, the Director, on behalf of the IRB, forwards any necessary regulatory certification to OHRP for concurrence on behalf of the Secretary of HHS. Certification to OHRP is not required for research not supported by DHHS. However, the IRB will apply the standards of Subpart C to all prisoner research, regardless of its source of funding or support. Should non-DHHS research fall outside the category stipulations under 45 CFR 46.306, the IRB will consult with appropriate experts before approving the research.

d. Research Involving Decisionally Impaired Subjects. Decisionally-impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive

or emotional functions. Other individuals who may be considered decisionally impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

In cases where research involving cognitively-impaired individuals is approved, the IRB will consider additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect subjects.

When investigators are likely to approach adults who lack the ability to consent, the IRB evaluates whether:

- The proposed plan for the assessment of the capacity to consent is adequate.
- Assent of the subjects is a requirement, and, if so, whether the plan for assent is adequate.

e. Research Involving Potentially Addictive Substances. Research involving potentially addictive, "abuse-liable" substances presents particular risks for subjects. These pharmacological substances, which may include legal as well as illegal drugs, have the potential for creating abusive dependency.

It is essential that the IRB conduct an extremely thorough and thoughtful analysis of the risks and benefits associated with any such research proposed at this Institution. The following are among the issues that the IRB will consider when reviewing research involving potentially addictive substances:

The IRB will not approve the participation of children as subjects in research involving potentially addictive substances unless the use of the relevant addictive substance(s) is dictated solely by the clinical needs of the individual child-subject and the usual standard of care for treatment of the child's disorder or condition.

The IRB will not approve the participation of adults as subjects in research involving potentially addictive substances unless appropriate protections are provided to ensure that subjects will be competent, uncoerced, and able to exercise continuous informed consent throughout the course of the research.

The IRB will consider carefully the requirements for equitable recruitment and selection of subjects; protections for maintaining privacy and confidentiality; and the need for data and safety monitoring.

The IRB will be sensitive to the ethical context of the research (e.g., the use of placebo controls; the special vulnerabilities of current or former addicts)

In addition to review by the IRB, research that involves potentially addictive substances will require the approval of the Institutional Official, who will consult with Legal Counsel and as appropriate other Institutional officials before rendering approval.

f. Research Involving Other Potentially Vulnerable Adult Subjects. The context of the research is an important consideration for the IRB when reviewing research that involves potentially vulnerable subjects. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence some types of subjects.

The IRB will generally consider the following groups of subject to be potentially vulnerable and will carefully consider the context of the research in determining appropriate protections for them:

- Individuals participating in research which is combined with treatment
- Members of potentially vulnerable minority groups
- Educationally disadvantaged persons
- Economically disadvantaged persons
- Homeless persons
- Institution's employees, students, and trainees

g. Human Fetal Tissue Transplantation Research. Human fetal transplantation research supported by DHHS is governed by NIH Public Law 103-43.

h. Research Involving Deceased Persons. Research involving deceased persons is not covered by FDA or DHHS human subject regulations, or the Common Rule.

Chapter 18
Conflict of Interest Requirements

This Institution's policies and procedures for the disclosure and management of investigator Conflict of Interest (COI) are fully delineated in separate Institutional policies and procedures. They are summarized here for convenience. However, the Institutional policies and procedures should be consulted directly for definitive information about these requirements.

Conflicts of Interest may be interpreted to include any situation in which financial, professional, or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research.

Federal regulations at Title 21 Part 50 and Title 42 Part 50 of the Code of Federal Regulations require the disclosure and management of financial Conflicts of Interest in research. Federal human subject protection regulations at 21 CFR 56.107(e) and 45 CFR 46.107(d) require IRB members to be free of any conflict.

a. Disclosure Requirements. Faculty and research staff (collectively "investigators") participating in human subject research ,at DFCI, whether or not employed by DFCI, must disclose to the Conflicts of Interest Official their relevant Financial Interests, ,as well as those held by their spouse and dependent **children**, as further defined below. In this context, "participating in human subject research" includes being responsible for the design, conduct, or reporting of research (e.g., study planning and design, conduct of the study, data analysis, subject recruitment, subject consent, authorship).

A current, up-to-date Financial Interest disclosure must be on file with the Conflict of Interest Official (i) before a proposal or application for external support can be submitted to the funding agency, organization, or sponsor; and (ii) must be included with submission materials before any application for initial or continuing IRB review can be processed.

Thereafter, investigators must update their **disclosures at least annually, and as new Financial interests are obtained or when there are material changes in previously disclosed financial interests.**

b. Financial Interests Defined. A Financial Interest is anything of monetary value or potential monetary value. DF/HCC investigators must disclose **all Financial Interests** related to their institutional responsibilities. This includes the following:

- Compensation for services, either in cash or in kind (e.g., consulting fees or honoraria);
- equity interests (e.g., stocks, stock options or other ownership interests);
- intellectual property rights (e.g., patents, copyrights and royalties from such rights.)
- Financial interests include interests held by a spouse and/or dependent children.

c. Review of Financial Interest Disclosures: By agreement, the Conflict of Interest Official, or his or her designee, is responsible for reviewing all Financial Interest Disclosures for investigators participating in human subject research requiring review by the DFCI IRB, and for identifying those Financial Interests that affect, or could affect, the design, conduct, or reporting of the research, and that may therefore constitute a conflict of interest ("COI").

d. Requirement for Management Plan. All actual or potential COIs related to human subject research must be reviewed by the DFCI Faculty Committee on Conflicts of Interest ("the DFCI Committee"). In each circumstance where the Financial Interest could reasonably appear to affect the integrity of the research, or the safety of human subjects, the DFCI Committee will review the circumstances of the financial interest and the research and will establish an appropriate plan to manage any resulting conflict of interest.

Examples of management plans include, but are not limited to, the following:

- Disclosure of the financial interest in the informed consent;
- Monitoring of the research by independent reviewers;
- Modification of the research plan;
- Complete divestiture of interests in the sponsor, product, or entity under study, or severance of the relationship creating the COI;
- Selection of another investigator or research staff person to perform the research or research-related function;
- Disclosure of the financial interest in publications and public presentations based upon the research in question.

If other DF/HCC institutions are involved (e.g. in the event that the conflicted investigator's primary faculty appointment is at a non-DFCI institution), the plan will be presented for review by the conflict of interest official at that institution, which can either approve the plan as presented, or choose to implement stricter management, but it may not choose a plan that is less stringent that than established by DFCI.

e. Implementation and Monitoring of the Management Plan. The investigator will be asked to acknowledge the proposed management plan and agree to the terms of the plan for managing the conflicting interest. If the affected individual accepts the management plan, the COI Official will notify the COI Committee and the relevant IRB of this outcome.

If the investigator does not accept the management plan, he or she may request a further review of the situation by the DFCI Committee. The DFCI Committee will review the disclosure, the proposed management plan, and any other information presented by the affected individual and COI Official. The COI Committee will then determine if the proposed management plan previously approved should be revised and shall inform the affected individual and the relevant IRB of such decision.

A plan to manage identified Conflicts of Interest must be approved by the IRB. The IRB has the final authority to determine whether the conflict of interest and its management allow the research to be approved. The plan must be in place before any research activities involving human subjects are initiated. In the event that the

plan is not approved by the IRB, the research may not be initiated.

Investigators and research staff must provide updates to the COI Official at DFCI or their home institution, and the DFCI IRB at least annually (at the time of Continuing IRB review) or as possible conflicting interests are identified or acquired during the course of the research and for one year after its completion.

f. Managing Conflicts of Interest in IRB Review. The Office for Human Research Protections (OHRP) interprets the HHS regulations to prohibit IRB members from participating in the deliberative discussion or vote relative to any research in which they participate in any way, including but not limited to study planning and design, conduct of the study, data analysis, subject recruitment, subject consent, and authorship. IRB members are likewise prohibited from participating in the deliberative discussion or vote relative to any research in which they have, or may appear to have, a financial, personal, or professional conflict as described in paragraphs b and c above. This applies to the review of unanticipated problems involving risks to participants or others and the review of non-compliance with the regulations or the requirements of the IRB.

1. Procedures for IRB Members. The following procedures govern the management of Conflicts of Interest in the review of research by the IRB.

If the IRB member believes that a conflicting interest might impact, or appear to impact, IRB deliberations or the protection of human subjects, the member must declare the presence of the conflict to the IRB and absent himself or herself from any deliberative IRB discussion or vote on the research. There are no exceptions from this requirement.

In most cases, it is not necessary for the IRB member to disclose to the COI Committee or to the IRB the details of any Conflict of Interest for which the member voluntarily absents herself or himself from the IRB's deliberative discussion and vote, and limits herself or himself to answering questions posed by the IRB. However, there may be circumstances in which it is in the best interests of the individual, the institution, and/or the human subjects involved for the member to make a complete, written disclosure to the COI Committee. IRB members are expected to use their best judgment to ensure that all IRB deliberations take place without any appearance or possibility of Conflict of Interest. In the case of expedited reviews, an IRB member, who has a conflict of interest with a protocol submission submitted for his/her review, must advise the OHRS staff that he/she has a conflict of interest so that the submission can be forwarded to another IRB member for an expedited review.

IRB members who declare a possible Conflict of Interest will leave the meeting during the IRB's deliberative discussion or vote on the relevant action.

At the beginning of every meeting, each member will complete an electronic Conflicts of the Interest form and submit it to the IRB staff.

Members found to have any (financial or non-financial) interest in the research under consideration will be recused from participation in or voting on the initial or continuing review of research. The member may be present to answer questions posed by the IRB, but any other IRB activity – including the final discussion in which a determination is made as to how the IRB will vote on the protocol – must be conducted without the presence or participation of the conflicted IRB member.

All recusals/absences of IRB members for Conflict of Interest must be noted as such in the official IRB minutes. Recused members may not be counted toward the quorum for IRB action on the affected research.

If the absence of the conflicted member results in a majority of the IRB members no longer being present at the meeting, no IRB actions or determination can take place until a majority of IRB members have again joined the meeting.

If the (now absent) conflicted member was the only non-scientist member present at the meeting, no IRB actions or determinations can take place until an additional non-scientist member has joined the meeting.

2. **Institutional Officials.** To eliminate possible conflicts of interest among Institutional officials, Institutional officials including, the Compliance Officer, and Institutional Official, will not serve as voting members of this Institution's designated IRBs

3. **Institutional Conflicts of Interest.** When the IRB is aware of a real or apparent Institutional Conflict of Interest, the IRB will request a management in accordance with the respective DF/HCC institution's process for evaluating and managing institutional conflicts of interest. The management plan will be reviewed and approved by the IRB before the research can be implemented or amended.

List of References

I. Ethics References

A. Nuremberg Code
B. Declaration of Helsinki (2000)
C. The Belmont Report

II. Additional Regulations and Standards

A. FDA Electronic Records and Signatures (21 CFR Part 11)
B. FDA Informed Consent (21 CFR Part 50)
C. FDA Child Safeguards (21 CFR 50 Subpart D)
D. FDA Financial Disclosure (21 CFR Part 54)
E. FDA Institutional Review Boards (21 CFR Part 56)
F. FDA/DHHS Expedited Review Categories
G. FDA Investigational New Drug Regulations (21 CFR Part 312 & 314)
H. FDA Biological Licensing (21 CFR Part 600)
I. FDA Investigational Device Regulations (21 CFR Part 812 & 814)
J. FDA Information Sheets on Medical Devices (FDA Guidance)
K. DHHS Human Subject Regulations (45 CFR Part 46)
L. DHHS/FDA Expedited Review List
M. DHHS Emergency Research Consent Waiver
N. DHHS Misconduct in Science Regulations (42 CFR Part 50 Subpart A)
O. DHHS Objectivity in Research Regulations (42 CFR Part 50 Subpart F)
P. Financial Relationships and Interests (HHS Guidance)
Q. Fetal Tissue Transplantation Research (Public Law 103-43)
R. Engagement of Institutions in Research (OHRP Guidance)
S. Non-English Short Form Consent (OHRP Guidance)
T. Data & Tissue Repositories (OHRP Guidance)
U. Inclusion of Children & Women and Minorities in Research (NIH Guidance)
V. Good Clinical Practice: FDA Guidance – ICH-GCP-E6

III. DF/HCC Policies and Procedures

A. DF/PCC Network Affiliate Contracts
B. DF/HCC Institutional and Cooperative Agreements
C. Office for Human Research Studies (OHRS) Website: http://www.dfhcc.harvard.edu/ohrs
D. Clinical Research Operations (CRO) Website: http://www.dfhcc.harvard.edu/clinical-research-support/clinical-research-operations-cro/
E. DF/HCC SOPs for Human Subject Research
F. Quality Assurance for Clinical Trials (ODQ) Website: http://www.dfhcc.harvard.edu/clinical-research-support/quality-assurance-office-for-clinical-trials-ODQ/
G. Quality Assurance for Clinical Trials (ODQ) Policies and Procedures
H. DF/HCC Data and Safety Monitoring Plan (DSMP)
I. DF/HCC Clinical Trials Audit Manual
J. Clinical Trials Education Office (CTEO) Website: http://www.dfhcc.harvard.edu/clinical-research-support/clinical-trials-education-office-cteo/
K. DF/HCC Guide to Human Research Activities (GHRA)
L. Clinical Policy and Oversight Committee (CLC) Policies and Procedures
M. DFCI Code of Ethics and Standard of Business Conduct
N. DFCI Patient Care and Administrative Policy
O. DFCI Research Administration's Policy and Procedure Manual

P. DF/PCC Network Affiliate Policies and Procedures
Q. Harvard Faculty and Medicine Policy on Integrity in Science
R. Harvard Policy on Conflict of Interest and Commitment
S. IRB Policy Committee Charter

IV. Reviewer Quick Reference Reviewer Guidance

A. IND Exemptions Involving Marketed Drugs or Biological Products for Treatment of Cancer
B. Quick Reference for Research Involving Children

V. OHRS Information Sheets

OHRS Information Sheets: Policy

1. IS - Policy - Adverse Event Reporting
2. IS - Policy - Blood Draws from Healthy Volunteers
3. IS - Policy - Collecting - Sharing Data and Tissue Specimens
4. IS - Policy - Continued Participation
5. IS - Policy - Determining if Project Is Human Subjects
6. IS - Policy - Deviation-Violation-Exception and Other Event Reporting
7. IS - Policy - DFCI IRB Requirements Relating to the Honest Broker in Biobanking
8. IS - Policy - Drug Shortages
9. IS - Policy - Implementing Dose Escalation Changes in Phase I Research
10. IS - Policy - IND and IDE Safety Reports
11. IS - Policy - Legally Authorized Representatives
12. IS - Policy - Linked and Anonymous Specimens
13. IS - Policy - Non English Speaking Subjects
14. IS - Policy - Overall PI or Site PI Leave of Absence
15. IS - Policy - Pregnant Partner Consent and Data Collection
16. IS - Policy - Prisoners in Research
17. IS - Policy - Sharing Protocols
18. IS - Policy - Short Form Translation Procedure
19. IS - Policy - Single Patient IND and Emergency Use of a Test Article
20. IS - Policy - Sponsor Requests for PHI related to Adverse or Severe Adverse Events
21. IS - Policy - Two Year CR
22. IS - Policy - Use of Alert Pages

OHRS Information Sheets: Resource

1. IS - Resource - Additional Protections for Children
2. IS - Resource - Adverse Event Ranking Scale
3. IS - Resource - Common Language for Drug Risks
4. IS - Resource - Common Language for Risks and Events
5. IS - Resource - Criteria for IRB approval of Research
6. IS - Resource - Expedited and Exempt Categories
7. IS - Resource - FDA Drug Review Process
8. IS - Resource - FDA Guidance Recruitment
9. IS - Resource - FDA Medical Devices
10. IS - Resource - How to contact the FDA
11. IS - Resource - Massachusetts Law on Insurance Coverage
12. IS - Resource - MSWord Tips
13. IS - Resource - Partners Recruitment of Subjects
14. IS - Resource - Requirements for Informed Consent
15. IS - Resource - Successful Research Participation Communication

OHRS Information Sheets: Operations

1. IS - Operations - Common Issues in Protocol Reviews
2. IS - Operations - Completing Endorsement Forms
3. IS - Operations - Completing Nursing & Pharmacy Screening Form
4. IS - Operations - Completing the Protocol Front Sheet
5. IS - Operations - Frequently Asked Questions
6. IS - Operations - Guidance Priority List
7. IS - Operations - New Protocol Submission Requirement Chart
8. IS - Operations - Non-Clinical FAQ
9. IS - Operations - OHRS Submit Guide
10. IS - Operations - OncPro Guide

11. IS - Operations - Overview DFCI IRBs
12. IS - Operations - PDF Files and Electronic Signatures
13. IS - Operations - Quick Reference for New Protocol Submissions
14. IS - Operations - Request to Add Site Checklist
15. IS - Operations - Review Process for New Adult Clinical Trials
16. IS - Operations - Use of Informed Consent Documents Posted to OncPro

OHRS Information Sheets: Guidance

1. IS - Guidance - Procedures for Monitoring the Consent Process
2. IS - Guidance - Research Funded or Supported by the Department of Defense
3. IS - Guidance - Statistical Guidelines for Non-Clinical Research
4. IS - Guidance - Withdrawal of Consent to Continue in Research Form