Obtaining and Maintaining an Investigational New Drug Application (IND)

1. BACKGROUND:

The Food and Drug Administration (FDA) regulations establish specific responsibilities of sponsors for ensuring (1) the proper conduct of research for submission to the FDA and (2) the protection of the right and welfare of subjects involved in this research.

A DF/HCC Investigator who sponsors drug research may be required to hold and maintain an Investigational New Drug Application (IND). Additional information on IND Application requirements can be found on the FDA website.

Note: Information on single patient INDs and Emergency Use at DF/HCC can be found on the DF/HCC website.

2. ASSOCIATED DF/HCC POLICIES:

2.1. RCO-100
2.2. RCO-204

3. DEFINITIONS:

3.1. **Investigational New Drug (IND):** IND means an investigational new drug application. "IND" is synonymous with "Notice of Claimed Investigational Exemption for a New Drug." An IND is the means by which the FDA approves transportation or distribution of a drug or biological drug for use in a clinical investigation when said drug/biologic has not been approved by the FDA for clinical use. An IND may also be required for a biological product that is used in vitro for diagnostic purposes, especially if this test will be used with the new agent if it is approved.

3.2. **Clinical Hold:** An order issued by FDA to the sponsor of an IND application to delay a proposed clinical investigation or to suspend an ongoing investigation. All or some of the investigations conducted under an IND application may be placed on a clinical hold.

3.3. **IND Number:** A unique number assigned by the FDA for an investigational agent used in a clinical investigation. It references the drug(s) or product(s) used under a specific IND application. This number must be referenced on all correspondence to the FDA.

3.4. **IND Exempt:** After an IND application is submitted to the FDA, the FDA may determine that the clinical investigation is IND Exempt. The research does not need to follow the reporting requirements set by the FDA for the conduct of the clinical investigation under an IND.

3.5. **IND Anniversary Date:** The month and day the IND application went into effect. In the event the FDA sends a letter indicating that the research is clear to proceed, the Anniversary Date is the date indicated on that communication. If no communication is received, the IND goes into effect thirty (30) calendar

days after receipt by the FDA and day 30 is the Anniversary Date.

4. PROCEDURE:

4.1. IND Application:

4.1.1. The investigator sponsoring the research must use an accepted IND format to ensure an efficient review of the application. Within the DF/HCC, the sponsor should consult his or her institutional clinical trials office for guidance in preparing the initial IND submission.

4.1.2. Once the IND is submitted to the FDA, the sponsor must wait thirty (30) calendar days before initiating any clinical trials. The FDA's primary review objective during this time is to assess the IND for safety of research subjects and assure that they will not be subjected to unreasonable risk.

4.1.3. The acknowledgment from the FDA may occur in one of three ways:

4.1.3.1. The FDA may provide the sponsor with the assigned IND number along with the date of receipt. The sponsor may initiate research thirty (30) days after the date of receipt unless earlier written notification by FDA is received stating that the research may begin.

4.1.3.1.1. If the sponsor receives no communication from FDA after thirty (30) calendar days, the sponsor should confirm that the FDA received the application and that they do not have any issues or concerns with the application before proceeding with the clinical trial.

4.1.3.2. The FDA may request additional information and may place a clinical hold on the IND. The research cannot begin until all concerns raised by the FDA have been addressed to their satisfaction and the clinical hold has been lifted.

4.1.3.3. The FDA may conclude that the research is IND Exempt. The research may be conducted without obtaining an IND application or following the reporting requirements set by the FDA for the conduct of the clinical investigation under an IND. The Institutional Review Board (IRB) becomes the regulatory body of record and all IRB reporting requirements continue to apply. These requirements include, but are not limited to, the requirement for initial and continuing IRB review, for informed consent, and for the reporting of adverse events.

4.1.4. Regardless of how the acknowledgment occurs, IRB approval must always be obtained prior to conducting any research.

4.2. Ongoing IND Reporting Requirements

4.2.1. Once an IND is in effect, the sponsor must adhere to the following IND submission requirements:

Type	Description	Requirements
IND Amendment*	*New Protocol – when a sponsor-investigator intends to conduct a study that is not covered by a protocol already contained in the IND, a new protocol must be submitted under the IND. The submission must include the new protocol along with a brief description of the most clinically significant differences between it and the previous protocol(s).	The new protocol may be implemented after FDA submission and IRB approval.
	Change to a Protocol - Changes to a protocol that significantly affect the safety of subjects, scope of the investigation, or the scientific quality of the study must be submitted to the FDA. Submission should include a brief description of the change and reference (i.e., date and number) to the submission that is contained the protocol.	The changes may be implemented after FDA submission and IRB approval.
	Change to a Protocol (Minor/Administrative) - Minor changes or "administrative amendments" (e.g., correction of spelling mistakes, page renumbering, changing the name of study staff) to an existing protocol that may not have any impact on risk, scope or scientific quality of the study should also be submitted to the FDA.	The timeframe for "Administrative amendment" submission to the FDA can be at the discretion of the sponsor-investigator, but must be submitted, at a minimum, with the IND Annual Report. Administrative Changes must be submitted to the IRB prior to implementation.
	New Investigator – A protocol amendment must be submitted when a new Principal Investigator is added to a previously submitted protocol. The submission should include the Principal Investigator's name and address, qualifications to conduct the investigation (i.e., Curriculum Vitae), the name and address of the research facility used by the Principal Investigator, the name of each sub-investigator working under the supervision of the Principal Investigator; the name and address of the Principal Investigator's IRB of Record; this can be done via the Form FDA 1572.	FDA should be notified of the new Principal Investigator within thirty (30) days of being added to the study. Any sub-investigator changes should be included in the IND Annual Report. New Investigator changes must be approved by the IRB prior to implementation.
Information Amendment	Any essential information (e.g., toxicology, pharmacology, chemistry) on the IND that is not within the scope of a protocol amendment, IND safety report or annual report. Submission to the FDA should include purpose of the informational amendment; data in a format appropriate for scientific review, and a request for FDA's comment if desired by the sponsor.	Submit to the FDA as necessary but, to the extent feasible, not more than every thirty (30) days.

Safety Reports** Note: Additional IRB reporting requirements also apply.	Any suspected adverse reaction and observation associated with the use of the drug that is both serious and unexpected and suggests significant risk to subjects.	Initial reporting to the FDA must occur as soon as possible or no later than fifteen (15) calendar days following the sponsor's initial receipt of the information. Follow-up reporting should be submitted as soon as the information is available but no later than 15 calendar days after the sponsor receives the relevant additional information.
	Any unexpected fatal or life-threatening suspected adverse reactions.	Initial reporting to the FDA must occur as soon as possible or no later than seven (7) calendar days following the sponsor's initial receipt of the information. Follow-up reporting should be submitted as soon as the information is available but no later than 15 calendar days after the sponsor receives the relevant additional information.
Annual Reports	The annual report details the progress of each investigation under the IND. This report includes summary information obtained from the studies, update(s) to the general investigational plan, update(s) to the Investigator's Brochure, significant protocol updates, update on foreign marketing development and a log of outstanding business with the FDA with respect to the IND application (if applicable).	Must be submitted annually to the FDA within sixty (60) days after the IND Anniversary Date. Note: Submission of the IND annual report does not preclude the sponsor responsibility to submit continuing review reports to the IRB.
Other Required Reporting	Final Report – must be submitted for all IND applications.	Submitted as soon as the clinical studies have concluded or within six months of study completion.
	Financial Disclosure Report	A sponsor will promptly update the financial disclosure information if any relevant changes occur during the course of the investigation and for one (1) year following completion of the study.
	Withdrawal of IND for safety reasons	Must promptly inform the FDA, all participating investigators, and all reviewing IRBs, along with the reason(s) for the withdrawal.
	Discontinuation of a clinical investigation under the IND due to unreasonable or significant risk to humans	Must be submitted reported to FDA as soon as possible and no later than five (5) working days after making the determination.

*In some situations, it may be unclear whether a change to an existing protocol or a new protocol should be communicated as an amendment to an existing IND, or under a new IND, or if a new 30 day review period at the FDA is warranted. In such situations, the sponsor-investigator should seek case-by-case guidance from the relevant CDER or CBER review division to minimize the chance of an unexpected clinical hold.

**For DF/HCC requirements on IND Safety Reporting, please see policy RCO-204. For research reviewed under the DFCI IRB, please also see DFCI IRB Adverse Event Reporting Policy.

4.3. Clinical Hold or other Premature Termination or Suspension of Trial

4.3.1. If a proposed study is placed on clinical hold, subjects may not be administered the investigational drug/biologic. If an ongoing study is placed on clinical hold, no new subjects may be recruited to the study and administered the investigational drug/biologic and enrolled subjects must discontinue the investigational drug/biologic unless continuation is specifically permitted by the FDA in the interest of subject safety.

4.3.2. If a trial is prematurely terminated or suspended for any reason, such as a clinical hold placed on an IND by the FDA, the sponsor is required to inform the appropriate DF/HCC clinical trials office and the IRB within one business day of IND status change. The sponsor must also inform all participating investigators who have research under that IND.