DANA-FARBER / HARVARD CANCER CENTER
POLICIES FOR HUMAN SUBJECT RESEARCH

TITLE: Responsibilities of the Sponsor Conducting Research Involving a Drug		
POLICY #: RCO-100	**Page:** 1 of 13	**Effective Date:** ~~1/14/16~~

Commented [CC1]: Minor administrative updates – due for 3 year review

1. POLICY STATEMENT:

~~An Overall Principal~~A DF/HCC Investigator ~~(PI)~~ who holds an Investigational New Drug Application (IND) and who is the Sponsor of the research has additional responsibilities that must be adhered to in order to properly conduct the research within DF/HCC.

2. BACKGROUND:

The Food and Drug Administration (FDA) drug 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.

3. RESPONSIBLE PERSONNEL:

3.1. ~~Overall Principal~~DF/HCC Investigator ~~(PI),~~ who holds the IND and is the Sponsor.

4. DEFINITIONS:

4.1. **Adverse Event (AE) (FDA definition):** An untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

4.2. **IND Exemption:** After an IND application is submitted to the FDA, the FDA determines the status of the IND or issues an exemption. If the clinical investigation is IND Exempt, the trial does not need to follow the reporting requirements set by the FDA for the conduct of the clinical investigation under an IND. Therefore, the Institutional Review Board (IRB) becomes the regulatory body of record and all IRB reporting requirements continue to apply. Including, but not limited to, the requirement for initial and continuing IRB review, for informed consent, and for the reporting of any adverse experience associated with the use of the drug that is both serious and unexpected.

4.3. **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.

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4.4. **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 necessary for a drug or biological drug that has not been approved by the FDA for clinical use and which is used in a clinical investigation. FDA approval 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.

4.5. **Investigator:** An investigator (i.e., Site PI or ~~co~~sub-investigator) is any other member (i.e., other than the principal investigator) of the study team who will make clinical decisions during the study or make a direct and significant contribution to the data. The Good Clinical Practice (GCP) guideline defines sub-investigator as "any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions".

4.6. **Life-threatening Adverse Event:** An adverse event that places the subject, in the view of either the investigator or sponsor, at immediate risk of death. It does not include a reaction that had it occurred in a more severe form, might have caused death.

4.7. **Monitor**: An individual or contract research organization (CRO) delegated by the sponsor to ensure the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND.

4.8. **Principle Investigator (PI):** When a clinical trial is conducted by a team of individuals at a trial site, the principal investigator is the responsible leader for the conduct of the clinical trial at that site. At DF/HCC this would be the Overall Principal Investigator named on the single Form FDA 1572.

4.9. **Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction (FDA definition):** An adverse event occurring at any dose that, in the view of either the investigator or sponsor, results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.10. **Sponsor (IND-Holder):** An individual, company, institution, or organization that takes responsibility for the initiation, management, and /or financing of a clinical trial.

4.11. **Sponsor-Investigator:** An individual who both initiates and conducts a clinical investigation and under whose immediate direction the investigational drug is administered or dispensed is referred to as a Sponsor-Investigator by the FDA.

4.12. **Sponsor Regulatory File:** The compilation of specific Essential Documents for a clinical investigation. Essential Documents individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements.

4.13. **Suspected Adverse Reaction (FDA definition):** An adverse drug event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.

4.14. **Unexpected Adverse Event or Unexpected Suspected Adverse Reaction (FDA definition):** An adverse event that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected" as used in this definition, also refers to an adverse event or suspected adverse reaction that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the drug.

5. POLICY:

5.1. **Responsibilities:**

5.1.1. The responsibilities of a ***Sponsor-Investigator*** include both those of a sponsor and overall principal investigator.

5.1.2. The responsibilities of a ***Sponsor*** are:

5.1.2.1. Selecting qualified investigators

5.1.2.2. Providing participating investigators the information they need to conduct an investigation properly

5.1.2.3. Ensuring that the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND

5.1.2.4. Maintaining an effective IND with respect to the investigations by complying with all applicable regulations

5.1.2.5. Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug

5.1.3. The responsibilities of a ***Principal Investigator (PI)*** are:

5.1.3.1. Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and applicable regulations

5.1.3.2. Protecting the rights, safety, and welfare of subjects under the investigator's care

5.1.3.3. The control of the investigational product(s)

5.1.3.4. Ensuring that all participating investigators obtain the informed consent of each human subject to whom the drug is administered

5.2. **IND Application:**

5.2.1. An accepted IND format must be followed by the sponsor to ensure an efficient review of the application. A sponsor-investigator should consult his or her institutional clinical trials office for guidance in preparing the IND submission.

5.2.2. Once the IND is submitted to the FDA, the sponsor must wait thirty (30) calendar days before initiating any clinical trials. The FDAs 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. If the sponsor does not receive notification from the FDA within the thirty (30) day period, the IND is considered acknowledged and in effect by the FDA.

5.2.2.1. After thirty (30) calendar days, the sponsor-investigator ~~should~~must 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.

5.2.3. The FDA will provide the sponsor with an acknowledgment letter and an IND number. The acknowledgment from the FDA may occur in one of three ways:

5.2.3.1. 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.

5.2.3.2. 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.

5.2.3.2.1. After thirty (30) calendar days, the sponsor-investigator ~~should~~must confirm that the FDA does not have any issues or concerns with the application before proceeding with the clinical trial.

5.2.3.3. The FDA may conclude that the research is exempt. An exemption means that the research may be conducted without filing an IND application or subsequent information to the FDA. An IND exemption does not release a sponsor-investigator from the submission and/or reporting requirements of the IRB.

5.2.3.3.1. IRB approval must be obtained prior to conducting any research.

5.3. **IND Post Acknowledgment:**

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

5.3.1.1. **Protocol Amendments** –The FDA identifies protocol amendments (defined as changes to an existing IND) in one of four ways:

5.3.1.1.1. **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 should 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 IRB approval.

5.3.1.1.1.1. 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 Center for Drug Evaluation and Research (CDER) or Center for Biologics Evaluation and Research (CBER) review division to minimize the chance of an unexpected clinical hold.

5.3.1.1.2. **Change in Protocol** – Any changes to a protocol that significantly affects 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 contained the protocol. The changes may be implemented after FDA submission and IRB approval.

5.3.1.1.2.1. 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.

5.3.1.1.3. **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 submitted to the IRB prior to implementation.

5.3.1.1.4. **Informational 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 may be submitted at time of occurrence.

5.3.1.2.**Multi Center Trials**

It is the responsibility of the sponsor to ensure that all protocol amendments (change to an existing protocol) are distributed to all participating sites. It is also the responsibility of the sponsor to confirm that the amendments have been sent and reviewed by the IRBs of Record for each participating site and that the current version of the study protocol and consent form and being used to conduct research at those sites.

5.3.1.3.**Review of Safety Information**

The sponsor is required to promptly review all information relevant to the safety of the drug and determine the significance of the information in light of previous, similar reports or any other relevant information.

5.3.1.4.**IND Safety Reports**

The sponsor is required to notify the FDA and all participating investigators in an IND safety report of potentially serious risks within 15 calendar days after the sponsor receives the safety information. "Participating investigators" include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND.

5.3.1.4.1. The sponsor must submit an IND safety report (on either FDA Form 3500A or in a narrative format) when any of the following criteria are met:

5.3.1.4.1.1. Suspected adverse reaction that is both serious and unexpected.

5.3.1.4.1.2. Findings from clinical studies or findings from animal or in-vitro testing that suggest a significant risk in humans exposed to the drug.

5.3.1.4.1.3. An increased occurrence of serious suspected adverse reactions over that listed in the protocol or investigator brochure.

5.3.1.4.2. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported no later than seven (7) calendar days after the sponsor's initial receipt of the information.

5.3.1.4.3. A follow up report may be submitted as relevant information becomes available.

5.3.1.4.4. It is the responsibility of the sponsor to ensure that all investigators participating in a multi-center trial are promptly informed of significant new adverse effects or risks with respect to the drug used in a study protocol.

5.3.1.5.**Annual Report**

The sponsor will submit a brief report of the progress of the investigation to the FDA within sixty (60) days of the anniversary date that the IND went into effect.

5.3.1.5.1. Submission of the IND annual report does not preclude the sponsor responsibility to submit continuing review reports to the IRB.

5.3.1.6.**Final Report**

A final report must be submitted for all IND applications. The final report is submitted as soon as the clinical studies have concluded or within six months of study completion.

5.3.1.7.**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.

5.3.1.8.**Withdrawal of IND**

A sponsor may withdraw an effective IND at any time. If an IND is withdrawn due to safety, the sponsor must promptly inform the FDA, all participating investigators, and all reviewing IRBs, along with the reason(s) for the withdrawal.

5.3.1.9.**Discontinuation of Investigation**

A sponsor is required to review and evaluate the evidence relating to the safety and effectiveness of the investigational agent. Discontinuation of any clinical investigation that presents unreasonable or significant risk to humans must be reported to the FDA as soon as possible and not later than (5) working days after making the determination. The IRB must also be notified.

5.3.1.9.1. 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 lead site clinical trials office and the IRB within twenty-four (24) hours of IND status change. The sponsor

must also inform all participating investigators who have research under that IND.

5.3.1.9.2. The lead site clinical trials office must contact the Office of Data Quality (ODQ) about the IND status change.

5.4. **Multi-Center Trials:**

5.4.1. The sponsor-investigator must ensure that:

5.4.1.1. All Principal Investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor-investigator and, if required, by the regulatory authority (ies), and given approval/favorable opinion by the IRBs of Record.

5.4.1.2. The case report forms (CRFs) are designed to capture the required data at all multi-center trial sites.

5.4.1.3. The responsibilities of the principal-investigator(s) and the other sub-investigators are documented prior to the start of the trial.

5.4.1.4. All sub-investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.4.1.5. A plan for routine communication between the sponsor-investigator and Principal Investigators is documented.

5.5. **Sponsor Regulatory File:**

5.5.1. The Sponsor Regulatory File is established at the beginning of the research and its contents are updated as necessary.

6. APPLICABLE REGULATIONS & GUIDELINES:

21 CFR 50 – Protection of Human Research Subjects
21 CFR 54 – Financial Disclosure by Clinical Investigators
21 CFR 56 – Institutional Review Boards
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811

7. RELATED REFERENCES:

International Conference on Harmonisation – E6

8. RELATED RESOURCES:

DF/HCC List of Institutional IND Contacts
Form FDA 1571 (Investigational New Drug Application)
Form FDA 1572 (Statement of Investigator)
Form FDA 3500A (Mandatory MedWatch Form)
Form FDA 3674 (Certification of Compliance)