TITLE: ~~Responsibilities of the Sponsor Conducting~~Investigator-Sponsored Research ~~Involving a Drug~~		
POLICY #: RCO-100	**Page:** 1 of 17	**Effective Date:** ~~1/31/19~~

1. POLICY STATEMENT:

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

2. BACKGROUND:

The 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.

An investigator who holds an Investigational New Drug Application (IND) or an Investigational Device Exemption (IDE) is considered the sponsor of all research under the IND/IDE by the Food and Drug Administration (FDA).

3. RESPONSIBLE PERSONNEL:

~~3.1. DF/HCC Investigator who holds the IND and is the Sponsor.~~
3.1. DF/HCC Investigators acting as Sponsors of Human Subject Research

4. DEFINITIONS:

4.1. **Investigator:** An individual who actually conducts the research. In the event the research is conducted by a team of individuals, the investigator is the responsible leader of the team. Within the DF/HCC, this term refers to the Overall Principal Investigator who is responsible for all sites within DF/HCC.

4.2. **Sponsor:** An individual, company, institution, or organization that takes responsibility for the initiation, management, and /or financing of a trial. When research is conducted under an IND/IDE, the IND/IDE holder is the Sponsor. This is sometimes referred to as the "Regulatory Sponsor".

4.3. **Sponsor-Investigator:** An individual who both initiates and conducts an investigation, and when applicable, under whose immediate direction the investigational drug is administered or dispensed is referred to as a Sponsor-Investigator. This individual is acting as both the Sponsor and Investigator on the same protocol.

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Commented [CC1]: Combined RCO-100 and RCO-101 (IND and IDE Sponsors) and broadened language to include non IND and IDE-Exempt research sponsored by an investigator.

Moved procedural language about obtaining and maintaining IND and IDE to 2 new operations (RCO-OP-X and RCO-OP-XX)

Referenced new DF/HCC document: Requirements for DF/HCC Collaborations with Third Parties and added language regarding collaborations and contract requirements.

Moved language regarding IND Safety Reports to RCO-204

4.4. **Investigator-Initiated Protocol:** A protocol where an investigator was pivotally involved with the initial design and development of the research.

4.5. **Investigator-Sponsored Protocol:** An Investigator-Initiated protocol where an investigator also serves as the regulatory Sponsor.

~~4.1.~~4.6. **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.

~~4.2. **Investigator:** An investigator (i.e., Site PI or 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".~~

~~4.3. **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.~~

~~4.4. **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.~~

~~4.5. **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.~~

~~4.6. **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.~~

~~4.7. **Sponsor (IND Holder):** An individual, company, institution, or organization that takes responsibility for the initiation, management, and /or financing of a clinical trial.~~

4.7. **Investigational Device Exemptions:** Sponsor and investigators of certain device studies are allowed to use an investigational device in a clinical study in order to collect safety and effectiveness data. The exemption only applies to investigations in which 510(k) products are being used in accordance with the labeling cleared by the FDA.

~~4.8. **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.~~

~~4.9.~~4.8. **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.

5. POLICY:

5.1. A DF/HCC investigator who is the sponsor of human subject research takes on additional responsibilities that include:

5.1.1. Study design and development of the protocol, including all protocol amendments, and the template informed consent document.

5.1.2. Selecting qualified investigators to participate in the research, performing feasibility assessments for potential sites, and establishing and enforcing accrual requirements Should the DF/HCC sponsor select non-DF/HCC investigators and sites to participate in the research, additional DF/HCC requirements apply (see MULTI-100).

~~4.10.~~ Ensuring ~~**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.~~

~~4.11. **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.~~

5.1.3. all necessary contracts, budgets, and agreements are executed and enforced. This may include payments to participating sites and vendors.

~~**5.1.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~~

~~5.1.3.~~5.1.4. Providing participating investigators with the information they need to conduct an investigation properly. This may include ongoing communication through email, phone, site visits, meetings, teleconferences, newsletters, etc.

5.1.5. Obtaining and maintaining an effective IND/IDE, when necessary, with respect to the investigations by complying with all applicable regulations.

~~5.1.3.1.~~Ensuring that the investigation(s) is conducted in accordance with the general investigational plan, protocol, IRB requirements, and ~~protocols contained in the~~ IND
/IDE requirements (as

~~5.1.3.2.Maintaining an effective IND with respect to the investigations by complying with all applicable regulations~~

~~5.1.3.3.Ensuring that FDA and all participating investigators are promptly informed of significant new adverse effects or risks with respect to the drug~~

~~5.1.4. The responsibilities of a ***Principal Investigator (PI)*** are:~~

~~5.1.4.1.Ensuring that an investigation is conducted according to the signed investigator statement, the investigational plan, and~~ applicable ~~regulations~~
) at

~~5.1.4.2.Protecting the rights, safety, and welfare of subjects under the investigator's care~~

~~5.1.4.3.The control of the investigational product(s)~~

~~5.1.5.~~5.1.6. ~~Ensuring that~~ all participating ~~investigators obtain the informed consent of each human subject to whom the drug is administered~~sites. This includes ensuring that any deviations or violations are reported appropriately.

~~5.2. **IND Application:**~~

Commented [CC2]: IND procedural language moved to RCO-OP-4

Note: IDE procedural language from RCO-101 moved to RCO-OP-5

~~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 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 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**~~

~~5.3.2.~~5.1.7. ~~The sponsor is required to promptly review all information relevant to the safety of the drug and~~Conducting a prompt review of all new information relevant to the safety of the research in order to determine the significance of the information in light of previous, similar reports or any other relevant information.

Ensuring prompt and appropriate reporting of significant new adverse effects or risks with respect to the research to other investigators, IRBs, and regulatory authorities per the applicable regulations and RCO-204.

~~5.3.2.1.~~Protecting~~**IND Safety Reports**~~

5.1.7.1.~~The sponsor is required to notify~~ the ~~FDA~~rights, safety, and welfare of subjects

5.1.7.2.Ensuring proper control and labeling of any investigational product(s) or investigational device(s). Assuring return or other authorized disposition of unused investigational product(s) and device(s) from each investigator whose participation in the clinical study is discontinued or terminated.

5.1.7.3.Ensuring that all participating sites obtain and maintain active IRB approval, and all investigators ~~in an IND safety report of potentially serious risks within 15 calendar days after~~obtain the informed consent of each human subject.

5.1.7.4.Maintaining up-to-date sponsor ~~receives~~regulatory files as per RCO-203.

5.1.7.5. Ensuring proper registration (and randomization, when applicable) of research subjects.

5.1.7.6.Ensuring appropriate monitoring of the investigation in accordance to the study monitoring plan.

5.1.7.7.Maintaining the Clinicaltrials.gov registration, including results reporting (when applicable), as per REGIST-200.

5.1.7.8.Managing all databases related to the research, including those that capture research data (including CRFs), safety information~~. "Participating,~~ and/or biospecimen collection.

5.1.8. Typically, a DF/HCC investigator serving as the Sponsor also serves as the DF/HCC Overall PI and is, therefore, a Sponsor-Investigator. The responsibilities of a Sponsor-Investigator include those of both a sponsor and investigator. Investigator responsibilities are defined in RCO-102.

5.2. DF/HCC investigators~~" include all investigators to whom the~~ may collaborate with academic institutions, industry, and cooperative groups in the design and

conduct of human subject research. When this occurs, the transfer of certain sponsor ~~is providing drug~~ responsibilities may occur. However, the DF/HCC is unable to allow the transfer of certain responsibilities due to the risk, infrastructure strain, and resource consumption that may result.

~~5.3.3.~~5.2.1. Any transfer of sponsor responsibilities between a DF/HCC Investigator and an external party must occur through a written agreement of obligations and responsibilities (i.e. Transfer of Obligations) that clearly identifies the sponsor of the research, the responsibilities transferred, and the party accepting the transferred responsibilities. For each trial, the Transfer of Obligations document must be approved by the institutional clinical trials office, sent to the FDA under ~~any of its INDs or~~ a Form 1571 (when under ~~any investigator's IND.~~and IND), and attached to the contract as an appendix.

~~5.3.3.1.1. 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:~~

~~5.3.3.1.1.1.Suspected adverse reaction that is both serious and unexpected.~~

~~5.3.3.1.1.2.Findings from clinical studies or findings from animal or in-vitro testing that suggest a significant risk in humans exposed to the drug.~~

5.2.2. ~~An increased occurrence of serious suspected adverse reactions over that listed in the~~ When agreeing to a Transfer of Obligations, DF/HCC Investigators must follow the current Requirements for DF/HCC Collaborations with Third Parties available on the DF/HCC website.

5.2.3. Any responsibility not specifically transferred in writing remains with the sponsor. Changes to the Transfer of Obligations requires a renegotiation of the contract and budget.

~~5.3.3.1.1.3.~~The protocol ~~or investigator brochure.~~

~~5.3.3.1.2. Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information,~~ informed consent document, and other study documents must ~~be~~

~~reported no later than seven (7) calendar days after the sponsor's initial receipt of the information.~~

~~5.3.3.1.3. A follow up report may be submitted as relevant information becomes available.~~

~~5.3.3.1.4. It is~~clearly and correctly indicate the ~~responsibility~~ identity 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.~~

~~5.3.3.2.~~**~~Annual Report~~**

~~The~~, even if some 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.~~

~~5.3.3.2.1. Submission of the IND annual report does not preclude the sponsor responsibility to submit continuing review reports to the IRB.~~

~~5.3.3.3.~~**~~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.~~

~~5.3.3.4.~~**~~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.~~

~~5.3.3.5.~~**~~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.~~

~~5.3.3.6.~~**~~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.~~

~~5.3.3.6.1. 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.~~

~~5.3.3.6.2. 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.~~5.2.4. ~~The Sponsor Regulatory File is established at the beginning of the research and its contents are updated as necessary~~have been transferred to another party.

~~5.5.2.~~5.2.5.

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 809 – In-Vitro Diagnostic Products
21 CFR 312 - Investigational New Drugs – Drugs for Human Use
21 CFR 812 – Investigational New Device Exemptions
FDA Industry Guidelines and Information Sheets
FDA Compliance Policy Guidance Programs: 7348.809, 7348.810, and 7348.811

7. RELATED REFERENCES:

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International Conference on Harmonisation – E6

8. RELATED RESOURCES:

RCO-OP-4: Obtaining and Maintaining an IND
RCO-OP-5: Obtaining and Maintaining an IDE
Requirements for DF/HCC Collaborations with External Parties
DF/HCC Transfer of Obligations Template

~~8.~~9.RELATED ~~FORMS & TOOLS~~RESOURCES:

RCO-OP-X: Obtaining and Maintaining an IND
RCO-OP-X: Obtaining and Maintaining an IDE
DF/HCC List of Institutional IND Contacts
Requirements for DF/HCC Collaborations with Third Parties
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)

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