



UFHCC Process for Investigator-Initiated Trial Development

This document outlines the UF Health Cancer Center’s policy for all investigator-initiated, cancer-relevant, clinical trials conducted at the University of Florida, UF Health, and the UF Proton Therapy Institute.

The University of Florida defines human subject “cancer relevant” research study as one that:

- Specifies enrolling patients with a known or suspected diagnosis of cancer as part of the eligibility criteria; or
- Includes research endpoints related to cancer, associated symptoms or established cancer risk factors (including smoking or tobacco-associated studies, surveys, hepatitis or HPV vaccines, etc.); or
- The local PI plans to exclusively enroll current, former or potential cancer patients into the study

Investigator-Initiated Trials (IITs) are institutional priorities and represent the combination of intellectual property and scientific output from our UFHCC translational science programs. These studies are proposed upon the initiative of clinical investigators and are without a company or industry partner assuming the role of the principal sponsor. They require rigorous scientific review, monitoring and resources to support their conduct. Those without funding suffer from limited resource allocation. Our intention is to support the successful completion of every IIT inclusive of peer-review for scientific rigor, a detailed budget with identification of appropriate funding sources and full compliance with the UFHCC oversight committees (i.e., SRMC and DISC). This will help the trial move efficiently through the activation pipeline and avoid failure due to inadequate study design or resources.

The aims of this comprehensive, 2-stage review are to 1) improve the feasibility, scientific merit and ultimate success in completing cancer-relevant IITs, 2) shorten the timeframe from concept approval to protocol activation and 3) maximize staff and investigator effort in protocol development. Importantly, UFHCC Protocol Development Office (PDO) resources will not be utilized to construct the full protocol or any study related regulatory submissions until the concept has received first stage review and approval. **Protocols not having undergone first stage review and approval often suffer significant setbacks during the development and implementation phases of the study.** This 2-stage review process enables institutional concepts, without a full protocol, to be reviewed for scientific merit and allows constructive feedback prior to significant investment of time and resources. Concepts approved in this first stage, which have secured adequate support, are then sent forward for full protocol development.

This document outlines the process and party responsibilities associated with these important studies. **Figure 1** outlines the workflow for UFHCC IIT development.

Initial Concept Phase (First Stage Review & Approval)

All cancer-relevant IITs conducted at UF and categorized as “**interventional treatment**” (see **Appendix 1**) or otherwise involving **investigational drugs, devices or medical procedures** must

receive approval by the UFHCC. This approval process involves documentation of provisional peer support through the respective Disease Specific Group (DSG) or Cancer Population Science (CPS) research program, valid statistical plan, scientific rigor, appropriate institutional budget development, and confirmation of appropriate staff resources for conduct. The UFHCC Associate Director for Clinical Investigation (ADCI) through the UFHCC PDO provides final approval for initial concept submission upon verification of the above pre-requisites. **Concepts must receive approval from all parties (DSG or CPS, PDO, statistician, budget reviewer, scientific pre-reviewer, and ADCI) to proceed with submission to external collaborators.** With rare exception, UF IIT concepts should be capable of conduct and completion within an 18-24 month period following study activation.

The UFHCC PDO serves as the clearing house for this initial phase of initial concept approval. It is recommended that the PI reach out to the PDO, via the 'CTO Protocol Development Services Request' web form (accessible through the UFHCC website) at the initiation of a concept or letter of intent. PDO resources are assigned by the Administrative Director of the CTO (AD-CTO).

During this phase, the PI will be responsible for the following actions:

- Assurance that the concept has been preliminarily reviewed by the appropriate representatives from external collaborators
- Development of the initial concept/letter of intent, inclusive of the scientific justification and rationale
- Presentation of the concept to the appropriate peer group (DSG or CPS) to obtain feedback and ensure alignment with clinical algorithms and non-competing protocols
- Work with appropriate clinicians and CTO staff to conduct a needs assessment (resources and personnel requirements) and confirm feasibility
- Determine study design and sample size in conjunction with a statistician (UFHCC statistical support will be provided for validation if not used for primary development)
- Determine co-investigators and key protocol personnel
- Work with PDO staff in developing initial concept draft budget and identification of all potential and/or actual funding sources for study completion

The UFHCC PDO can perform the following services:

- Facilitation of initial concept review by all applicable parties, including the DSG, Biostatisticians, AD-CTO and the ADCI or their designee
- Soliciting and incorporating feedback from the study team and pre-review team into proposed concepts
- Development of study budgets
- Preparation of the concept and support documentation for submission to the potential collaborators
- Triaging and archiving of all communications with external collaborators

All concepts submitted in this manner will be vetted for completeness by CTO PDO staff, who will provide feedback on next steps needed. During the concept development phase, PIs should be aware that adequate financial support is necessary to cover minimal pre-defined expenses related to the conduct of the proposed study. They must develop a detailed budget with funding sources identified as part of the letter of intent or initial concept development. The CTO PDO office will

provide a draft budget template based on the initial concept design. Funding sources can include any combination of internal, external and industry support. PIs will identify all potential and/or actual funding sources when submitting new concepts to the PDO.

PIs should seek to manage trial costs by evaluating, for example:

- Have the use of standard of care testing and scheduling been optimized?
- Can fewer patients be accrued?
- Can fewer scans be scheduled?
- Can the spacing of testing be adjusted?
- Can correlatives be adjusted?
- Can PI costs be waived? (Requires departmental approval)
- Can the number of sites be minimized?
- Are there other costs that can be avoided, waived or re-negotiated?

PIs are responsible for addressing budget shortfalls and should actively seek support from one or more of the following sources:

- Industry (drug, funds, etc.);
- Federal or extramural (e.g., NIH/NCI R21, Florida Biomedical Research, FACCA);
- PI start-up or discretionary funds;
- College/Department/Division (e.g., academic enrichment);
- UFHCC Research Program(s), Pilot Program or other intramural RFA;
- Philanthropy/Development.

NOTE: Support requested from any of the intramural UFHCC Research Programs and most extramural sources require written applications and peer-review. Please allow time for this process.

All studies that will be supported in any form by UFHCC CTO staff must have a preliminary budget developed and approved by the AD-CTO prior to submission to any external entity regardless of whether the submission is a request for the study agent, monetary support or both. For all non-CTO managed studies, estimates for any requested services (PDO, coordination, etc.) will be provided by the AD-CTO as part of draft budget development. Please note, PDO services rendered during the first stage of initial concept development are available free of charge to all Cancer Center Members.

Protocol Development (Second Stage Review & Approval)

For qualifying concepts that have achieved first stage approval and will move forward, PDO resources are available on a fee for service basis or bundled into site level fees for studies that will be managed fully by the UFHCC CTO. The UFHCC CTO supports Cancer Center Members who serve as PIs of qualifying IITs with protocol development. However, only IITs that meet the NCI definition of **Interventional Treatment** (see **Appendix 1**) or otherwise involving **investigational drugs, devices or medical procedures** will be supported by the PDO resource.

The UFHCC PDO can perform the following services:

- Protocol authoring, including revisions and protocol clarification memos (allow 15 business days from the original request for the initial working protocol draft)

- Informed Consent Form authoring (allow 5 business days from the release of the initial protocol draft for initial consent form draft)
- Triaging and archiving of all communications with external collaborators
- Initial and ongoing submission of IND/IDE documents to the FDA
- Assistance with study submission to the IRB
- Assistance with CRF design
- Protocol entry into ClinicalTrials.gov and other central trial clearinghouses
- Facilitation of study sub-site identification and assessment of qualification
- Budget finalization based upon protocol specifications

During the second-stage review process, PIs must be personally engaged in the drafting of the protocol document. PIs will furnish the PDO with a full scientific background, basic eligibility parameters, description of the intervention, basic schedule of events and planned adjustments to the intervention if applicable. The PI must be responsive to all PDO requests for information with the expectation that all queries will be addressed within two business days. The PI's responsibilities during the full protocol development process also include:

- Meet with PDO as requested to review protocol details
- Evaluation of the draft protocol to confirm that it contains adequate descriptions of the research and content required by the UFHCC and applicable regulations
- Submission of the final draft protocol to the DSG for further evaluation of scientific merit, ensure alignment with group priorities and needs, and resource allocation
- Presentation of the study to SRMC to include key points addressing study rationale, design, selected endpoints, and potential scientific impact
- Attend calls or meeting with the FDA if requested
- Ensuring collaborating site selection is approved by the SRMC, DISC, and IRB prior to site initiation
- Be involved in the design, review and sign off for data collection forms
- Attend any IRB meetings where the study will be discussed

For all qualifying clinical trials at UF, the SRMC application must be accompanied by ADCI approval. This review is significantly expedited by the first stage review. Regardless, SRMC will not place an IIT protocol on the agenda for review without ADCI approval (please refer to the SRMC Policies and Procedures Manual). Additionally, budget reconciliation is required as part of protocol review by SRMC. For investigators using the UFHCC PDO, the budget will be finalized. Regardless, if there is a budget shortfall for which funding has not been identified, this will be explicitly noted by the SRMC as a potential serious impact on study feasibility. SRMC rejection or approval with stipulations regarding resolution of the budget deficit may be appropriate.

Final protocol refinement and ultimate consideration of approval, human subject protection and risk assignment for monitoring will be provided by the UFHCC SRMC and UF IRB. No clinical trial may proceed with activation at UF without both SRMC and IRB approvals.

Protocol Activation and Management

For IITs conducted at UF (with or without additional affiliate sites), the study team including the PI must prepare and conduct training for team members, clinic staff and associated personnel. For studies that will use CTO resources, the PDO will conduct a site initiation visit that will serve as training for the PI, other study staff, clinic staff, and associated personnel. In addition, the PDO can continue to assist with all of the activities outlined in the “Protocol Development” section, along with maintenance and reporting for ClinicalTrials.gov and general data review and export. The PDO does not perform routine data verification (i.e. comparison of data against source documentation) however, the UFHCC CTO does have clinical research monitoring resources available.

Following protocol activation, PI responsibilities include:

- Oversight of all aspects of study conduct, especially ensuring that study staff are appropriately trained to perform all responsibilities delegated to them
- Ensuring that the study is conducted according to all applicable regulations, that research follows the protocol, and that all rights and welfare of subjects are maintained
- Maintenance of data and CRFs in accordance with IRB guidelines and federal regulations
- Assurance that all investigational product records are maintained, including records of drug receipts, shipments, dispensing and destruction or return
- Timely reporting of serious adverse events to UF IRB, as well as the FDA and industry partners (if applicable), as specified by the protocol
- Review of the study to validate data and to maintain safety of enrolled subjects
- Adherence to the proscribed DISC monitoring plan

The investigator may delegate any of these responsibilities to appropriately trained study personnel. However, the investigator must retain knowledge of and overall authority for the conduct of all aspects of the study. The investigator will personally supervise study staff who are qualified by their education and training to accept these responsibilities for study-related activities.

Following protocol activation, the UFHCC PDO can perform the following services:

- Protocol amendments, including revisions and protocol clarification memos
- Informed consent form revisions
- Continued triaging and archiving of all communications with external collaborators
- Distribution of related external unexpected serious adverse reaction (SUSAR) reports
- Ongoing submission of IND/IDE documents to the FDA, including protocol amendments and annual reviews
- Maintain protocol records within ClinicalTrials.gov and other central trial clearinghouses
- Facilitation of study sub-site identification and assessment of qualification

Protocol Resulting and Completion

For IITs conducted at UF (with or without additional affiliate sites), the PI is responsible for approving the authorship of any presentations, publications or abstracts associated with the study. These presentations must adhere to the reporting requirements, if any, that were established with any collaborating industry or private/public partners including reporting timelines and submission for review and feedback prior to submission/presentation. The PI is responsible for assurance that all co-I or collaborating investigators have met requirements for authorship and that conflicts of interest have been accurately disclosed. In general, IITs should support authorship inclusion of all collaborating team members, particularly from intra or inter-programmatic UFHCC Programs. For all UF IITs, primary study outcomes must be reported within 12 months of study completion or as required per contractual obligations.

APPENDIX AS RELATED TO FIGURE 1: Specific Personnel Responsibilities

The following sections outline the responsibilities of each party involved in the IIT protocol development process (see **Figure 1**).

Principal Investigator (PI)

- Fully responsible for general trial conduct, including timely and accurate communications with all collaborating partners, regulatory agencies and study-associated staff. While the UFHCC will support PIs with the workload as outlined during the protocol lifecycle in the specific sections above, the PI is ultimately responsible for trial oversight and management, which cannot be delegated.
- Responsible for all subjects and data enrolled on trial (i.e., ultimate study oversight). To that end, PI must have demonstrated full compliance with responsibilities in PI role for non-IITs at UF prior to serving as an IIT PI at UF. In the absence of such demonstrated experience, co-PI responsibilities with a more experienced mentor may be required (as determined by the UFHCC ADCI).
All UFHCC IITs incorporating any FDA regulated intervention must be reviewed to determine the need for an IND or IDE application, even if planning for exemption, as part of protocol development (see **Appendix 2**).
- The PI must complete all UFHCC PI training, including IIT-specific requirements established by the UFHCC
- Comply with all other requirements as outlined in this document and those related to the SRMC and DISC.
- Personally represent study when reviewed or discussed at SRMC, DISC and IRB. Delegation to a sub-I due to schedule conflicts should be minimized. Delegation to study staff is prohibited.

When PDO resources are in use, the PI must ensure:

- The PDO must be copied on, or initiate, all communications pertaining to study
- The PDO will retain version control of all essential study documents

- PIs must make available any pertinent documents which may aid in the development process; e.g., investigator's brochure, sponsor consent form templates, etc.
- PIs may not modify and/or distribute study documents without PDO review and approval
- PIs must respond to routine PDO queries in a timely fashion (within two business days)
- PIs must meet with the PDO quarterly to review study progress for trials that will be managed by the PDO throughout their life cycle

Disease Specific Group (DSG) or Research Program Review

The DSG Research Leader or Research Program Leader will ensure that IITs at a minimum:

- Are scientifically sound;
- Align with the clinical program and have adequate patient population to support the successful completion of the trial in the specified time;
- Has no competing studies within the DSG or UFHCC research portfolio without reasonable justification;
- Support UFHCC objectives, including prioritization of trial type, programmatic development, meeting needs of our community and national reputation building;
- Have a detailed budget with all funding sources identified to support feasibility.

Associate Director for Clinical Investigation

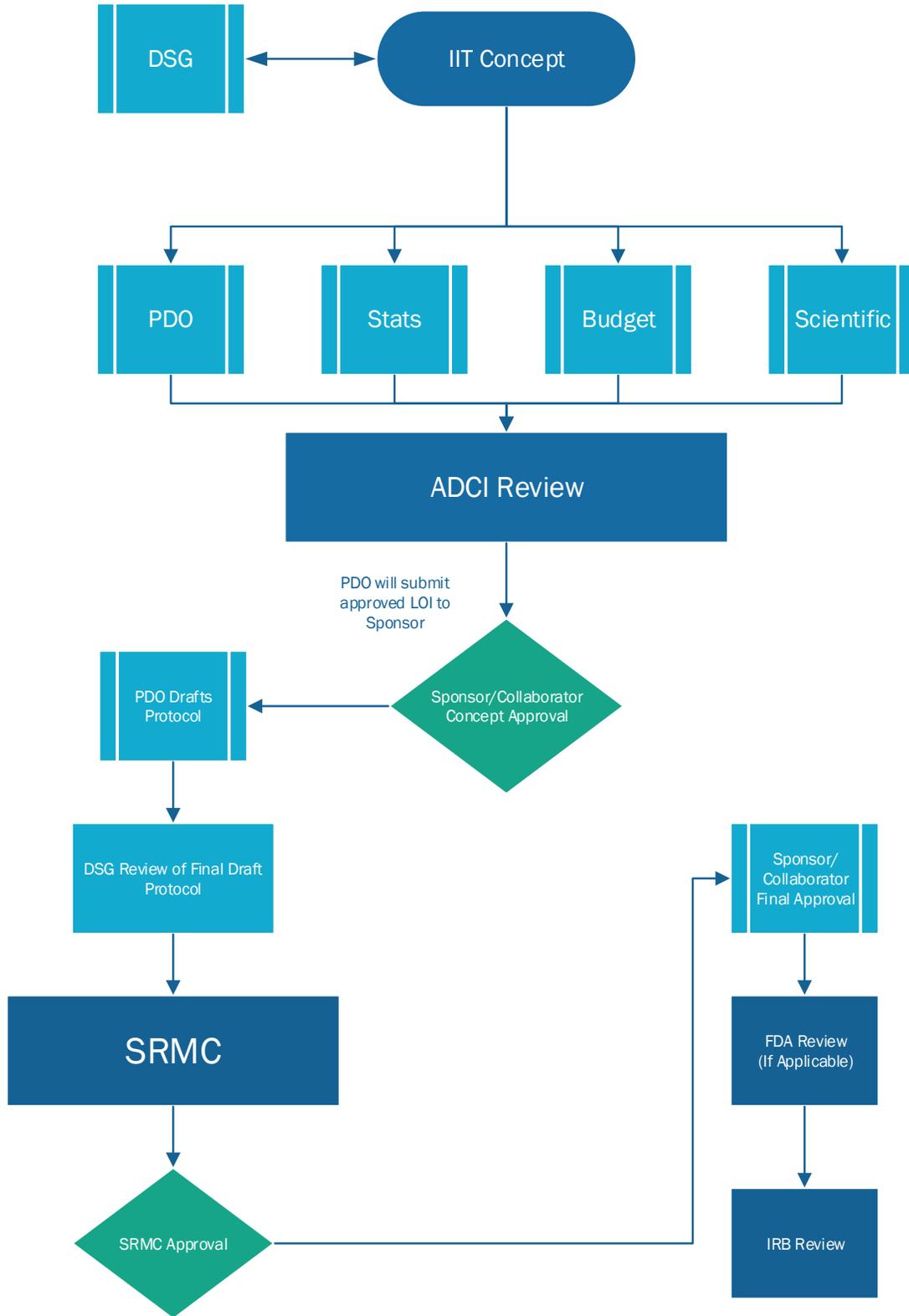
The ADCI must be involved in review of the study concept as early as is feasible. Regardless, before the IIT can be scheduled on the SRMC agenda, the ADCI will review the study, resource request and associated budget for completeness, and approve the submission to the SRMC. The ADCI may involve other experienced investigators in the review process to ensure study design is optimal and successful. If there are any concerns, the ADCI will communicate with the PI, copying the appropriate DSG Leaders, the UFHCC Deputy Director, the UFHCC Associate Director for Administration, and the AD-CTO. Appropriate steps will be taken to resolve any issues that arise.

NOTE: Funding sources do not need to be in hand prior to the SRMC review, particularly as part of initial concept development and feedback, but **must be received or contracts pertaining to funding must be fully executed prior to protocol activation.**

To successfully move IITs forward at UF, it is the responsibility of the DSG Research or Research Program Leader and the ADCI to evaluate the trial based on the following:

- Scientific merit.
- Feasibility: Accrual potential (target goal reflective of target population).
- Does the trial fill a need/niche within the DSG's portfolio?
- Does the trial bring synergy with other ongoing clinical/translational research?
- What is the likelihood of generating subsequent extramural funding?
- Does it align with UFHCC's priorities/research strategic plan?
- What importance does it bring to the PIs career?
- Does it involve a compound or translate a laboratory finding developed at UF?
- What impact will it have on the UFHCC national reputation and media presence?

Figure 1. Workflow of UFHCC Investigator Initiated Trial Development



Appendix 1: Clinical Research Definitions

Clinical Research Categories

Interventional: Individuals are assigned prospectively by an investigator based on a protocol to receive specific interventions. The participants may receive diagnostic, treatment, behavioral, or other types of interventions. The assignment of the intervention may or may not be random. The participants are followed and biomedical and/or health outcomes are assessed.

Observational: Studies that focus on cancer patients and healthy populations and involve no prospective intervention or alteration in the status of the participants. Biomedical and/or health outcome(s) are assessed in pre-defined groups of participants. The participants in the study may receive diagnostic, therapeutic, or other interventions, but the investigator of the observational study is not responsible for assigning specific interventions to the participants of the study.

Ancillary or Correlative:

- **Ancillary:** Studies that are stimulated by, but are not a required part of, a main clinical trial/study, and that utilize patient or other resources of the main trial/study to generate information relevant to it. Ancillary studies must be linked to an active clinical research study and should include only patients accrued to that clinical research study. Only studies that can be linked to individual patient or participant data should be reported.
- **Correlative:** Laboratory-based studies using specimens to assess cancer risk, clinical outcomes, response to therapies, etc. Only studies that can be linked to individual patient or participant data should be reported.

Primary Purpose

Basic Science (BAS): Protocol designed to examine the basic mechanisms of action (e.g., physiology, biomechanics) of an intervention.

Diagnostic (DIA): Protocol designed to evaluate one or more interventions aimed at identifying a disease or health condition.

Health Services Research (HSR): Protocol designed to evaluate the delivery, processes, management, organization, or financing of health care.

Prevention (PRE): Protocol designed to assess one or more interventions aimed at preventing the development of a specific disease or health condition.

Screening (SCR): Protocol designed to assess or examine methods of identifying a condition (or risk factor for a condition) in people who are not yet known to have the condition (or risk factor).

Supportive Care (SUP): Protocol designed to evaluate one or more interventions where the primary intent is to maximize comfort, minimize side effects, or mitigate against a decline in the participant's health or function. In general, supportive care interventions are not intended to cure a disease.

Treatment (TRE): Protocol designed to evaluate one or more interventions for treating a disease, syndrome, or condition. Note: This equates to therapeutic trials in previous versions of the guidelines.

Other (OTH): Not in other categories

Appendix 2: IND/IDE Basic Determination

IND Basic Determination		
1. Is the drug/biologic product lawfully marketed in the US?	YES	NO
2. Is there any intent to report the findings of your investigation to the FDA as a well-controlled study in support of a new indication or any other significant change in the labeling of the drug?	YES	NO
3. Is the study intended to support a significant change in the advertising of the drug?	YES	NO
4. Will the investigation involve a change in any of the following factors:		
a. Dosage level (either raising or lowering dose, frequency or duration compared to approved label)	YES	NO
b. Patient population	YES	NO
c. Any other factor that significantly increases (or decreases the acceptability of the risk) risk associated with the use of the drug product (21 CFR 312.2(b) (1)(iii)).	YES	NO
5. Is the Investigation intended to promote or commercialize the drug product (21 CFR part 312.7)?	YES	NO
If you selected any bolded responses, an IND application will be required		

IDE Basic Determination		
1. Will the study investigate a device that is the subject of a cleared 510(k) (ref §812(c)(1))?	YES	NO
2. Will the device be used in the study in accordance with the FDA-cleared indications for the device (ref. §812(c)(1))?	YES	NO
3. Is the test device invasive (ref. §812.2(c)(3)(i))?	YES	NO
4. Does the test device require an invasive sampling procedure that presents a significant risk (ref. §812.2(c)(3)(ii))?	YES	NO
5. Does the test device, by design or intention, introduce energy into a subject (ref. §812.(c)(3)(iii)):	YES	NO
6. Will the study only investigate consumer preferences with respect to the device?	YES	NO
7. Will the study test a modification of an approved or cleared device?	YES	NO
8. Is the device an implant (a device placed into a surgically or naturally formed cavity of the human body, and intended to remain there for a period of 30 days or more) (ref. §812.3(d)) that presents a potential for serious risk to the health, safety, or welfare of the subject (ref. §812(m)(1))?	YES	NO
9. Is the device purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject (ref. §812.3(m)(2))?	YES	NO
10. Is the device for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject (ref. §812.3(m)(3))?	YES	NO
11. Does your device present a potential for serious risk to the health, safety, or welfare of a subject in a way other than those described in Questions 8-10 (ref 21 CFR 812.3(m)(4))?	YES	NO
If you selected any bolded responses, an IND application will be required		