Q SUBMISSION: PRE-SUBMISSION MEETING REQUEST

Title of Proposed Trial

Name of Sponsor Investigator, PhD

X Professor, Department

DUKE UNIVERSITY

Date of Submission

# FDA Form 3514

*Link to FDA Form 3514:*

[*http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf*](http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM080872.pdf)

# Table of Contents

[1. FDA Form 3514 2](#_Toc99021081)

[2. Table of Contents 3](#_Toc99021082)

[3. Purpose 4](#_Toc99021083)

[4. Proposed Intended Use/Indications for Use 4](#_Toc99021084)

[5. Regulatory History 4](#_Toc99021085)

[6. Planned Follow-On Submission 4](#_Toc99021086)

[7. Background Information 4](#_Toc99021087)

[8. Device Description 4](#_Toc99021088)

[8.1 Proposed Predicate Devices 5](#_Toc99021089)

[9. Risk Analysis- Device Evaluation Strategy Table 7](#_Toc99021090)

[10. Overview of Product Development 14](#_Toc99021091)

[10.1 Completed Product Testing 14](#_Toc99021092)

[10.2 Proposed Nonclinical Testing 15](#_Toc99021093)

[10.3 Proposed Clinical Testing 16](#_Toc99021094)

[11. Specific Questions 16](#_Toc99021095)

# Purpose

*The overall purpose of the Pre-Sub, including goals for the outcome of the interaction with FDA.*

# Proposed Intended Use/Indications for Use

*Please provide sufficient information regarding the proposed intended use/indications for use, which may include:*

* *description of the disease or condition the device will prevent, mitigate, screen, monitor, treat, or diagnose;*
* *identification of the patient population for which the device is intended;*
* *part of the body or type of tissue to which the device will be applied or interacting;*
* *frequency of use;*
* *physiological use; and*
* *statement of whether the device is intended for prescription and/or over-the-counter use.*

# Regulatory History

*List any relevant previous communications with FDA about the subject device including but not limited to any marketing submissions, IDE, 513(g), and/or Q-Sub application numbers relevant to the Pre-Sub. Include submission numbers as appropriate. Include a brief summary of these previous FDA interactions and submissions, including feedback received and resolution of that feedback (or justification of alternative paths) as applicable.*

# Planned Follow-On Submission

*Clearly indicate what type of future submission (i.e. IDE, 510(k), etc.) is the focus of your Pre-Sub questions to help direct FDA’s feedback.*

*Requests for feedback regarding study design for non-significant risk (NSR) or IDE-exempt studies for which the results are not expected to support a future IDE or marketing application (i.e. 510(k), PMA) should use the Informational Meeting instead of a Pre-Sub and may omit this section.*

# Background Information

*Include information on the disease and problem that is being addressed. Please include sufficient background information to allow FDA to develop feedback for the Pre-Sub questions you pose. Keep your submission targeted and focused.*

# Device Description

*Please provide sufficient information regarding the device description, which may include:*

* *explanation of how the device functions*
* *pictures of the device (where applicable);*
* *engineering drawings (where applicable);*
* *physical, chemical and/or biological processes/principles used by the device to generate device output, if applicable*
* *significant physical, performance, and biological characteristics of the device , if applicable;*
* *samples to demonstrate the use of the device (where feasible and appropriate);*
* *explanation of the user interface and/or how the device interacts with other devices or with the user (medical professional and/or patient);*
* *explanation of the materials used in the device;*
* *brief description of the manufacturing process should be included if the manufacturing process may affect safety and/or effectiveness, and may therefore impact FDA’s recommendations regarding device testing; discussion of the mechanism of action and how the device and/or, if applicable, device output is used;*
* *basic scientific concepts that form the basis for the device; and*
* *the generic name of the device as well as any proprietary name or trade name, if applicable*

*Make sure your device description is clear and describes ALL elements of your proposed device, in addition to providing its dimensions and all of the dimensions of its components. Diagrams of both your device and an exploded view of your device with all of the components identified are very helpful.*

*Clearly identify how all components of your device fit together and are held together. Note that while the FDA does not ask for specific manufacturing information on how your device is assembled, it is still very useful for them to know if two components are glued together end to end, if one component can fit inside the other and is glued, etc.*

*Clearly describe the functional purpose of each element of your device. This helps FDA both understand the components of your device and your device as a whole.*

*Clearly identify all of the different sizes and configurations your device comes in. It is often helpful if this is done in a tabular format.*

*Always make sure you use consistent terminology for each component of your device in your submission.*

*In addition to pictures and a written description, other information about the clinical use of the device, such as a surgical technique guide or video of how the device is used in the clinical setting, may be helpful.*

## Proposed Predicate Devices

*The 510(k) review process focuses on the comparison of a proposed device with a predicate device in terms of indications for use, technological characteristics, and, as appropriate, performance testing. As a result, you should provide a summary of the predicate device(s) you plan to use for your comparison of these characteristics, along with the indication(s) for use and technology of the device you would like to market (i.e., draft of your labeling).*

*For each predicate device you identify, we suggest you provide:*

* *the predicate device trade name, including model, if available;*
* *the 510(k) number under which the predicate device was cleared;*
* *the classification of the predicate device; and*
* *a comparison with the proposed device in terms of indications for use, technological characteristics, and performance testing.*
* *Proposed indication for use*
* *Technology of the device*

Table 1: Potential Predicate Device(s)

| **Predicate Trade Name** | **510(k) Number** | **Classification** | **Intended Use** | **Device Technology** |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
|  |  |  |  |  |

*Use the 510(k) summary sheet for your proposed predicate to guide the completion of comparison table below. The 510(k) summary of the device should include the intended use, an explanation of how the device functions, the scientific concepts that form the basis for the device, and the significant physical and performance characteristics of the device, such as device design, material used, and physical properties. You can search for 510(k) devices and their summaries here: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm*

Table 2: Comparison Table

| **Device** | **Name**  **(Predicate)** | **Name**  **(New Device)** |
| --- | --- | --- |
| Intended Use |  |  |
| Indications for Use |  |  |
|  |  |  |
| **Materials** |  |  |
|  |  |  |
|  |  |  |
| **Characteristics** |  |  |
|  |  |  |
|  |  |  |
| **Usage** |  |  |
|  |  |  |
|  |  |  |

**Discussion**

*Discuss the information in the comparison table above. Point out the similarities and differences between the new device and the predicate device and comment on whether new questions of safety and effectiveness are raised.*

# Risk Analysis- Device Evaluation Strategy Table

*A description and analysis of all increased risks to which subject will be exposed by the investigation; the manner in which these risk will be minimized; a justification that the risks are reasonable in relation to the expected benefits for the investigation; and a description of the patient population including the number, age, sex, and condition.*

*The risk analysis should include the anticipated benefits and potential clinical effects of failure identified in the device evaluation strategy, as well as risks independent of the device that may be related to the underlying disease comorbidities, or inherent to the procedure, and benefits unique to the device concept. For example, a risk analysis may include the risks associated with use of anesthetic and contrast agents and the benefits of a less invasive intervention.*

*The process of constructing the device evaluation strategy table can be divided into four parts:*

1. *Device Deconstruction – identify the attributes needed for the device to achieve the design goals (Column 1), the potential failure modes (Column 2), and the effects of failure (Columns 3 and 4).*
2. *Knowledge Base and Mitigation Strategies – describe what is known from the device design (Column 5), leveraged nonclinical and clinical information from internal or external sources (Columns 6 and 7), and the clinical study mitigation strategies (Column 9)(for early feasibility studies) applicable to the attributes and failure modes.*
3. *Evidence Gaps – identify gaps in the existing information indicating that additional testing may be needed to justify study initiation, considering the Knowledge Base and focusing on the following:*
   1. *attributes most important for the intended use;*
   2. *potential failure modes most likely to be associated with catastrophic failures; and*
   3. *basic safety requirements (e.g., biocompatibility).*
4. *Filling the Gaps – identify in Column 8 the bench, laboratory, analytical, and/or animal testing to complete the evaluation of the device attributes and the potential associated failure modes, considering the following:*
   1. *Evidence Gaps;*
   2. *clinical context for the early feasibility study;*
   3. *potential types, frequency, and severity of the clinical effects of failure that may be associated with the device or procedure; and*
   4. *Mitigation Strategies.*

*Contact the ORAQ team for assistance with the 510(k) risk analysis. Early incorporation of risk analysis is highly recommended.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| ***For early feasibility studies*** | | | | | | | | |
| **Column 1** | **Column 2** | **Column 3** | **Column 4** | **Column 5** | **Column 6** | **Column 7** | **Column 8** | **Column 9** |
| **Device Attribute** | **Potential Failure Modes** | **Potential Effects of Failure** | | **Device Design Information** | **Supportive Information** | | **Nonclinical Device Testing** | **Clinical Study Mitigation Strategies** |
| **Potential Device**  **Effects of Failure** | **Potential Clinical Effects of Failure** | **Leveraged Nonclinical Information** | **Supportive Clinical Information** |  |
| *List each procedure-related function needed for the device to be used successfully.*  *List each performance-related function or feature needed for acceptable device performance.*  *List each necessary basic safety-related feature.* | *For each attribute, list the failure modes that could result if the attribute is not attained.* | *For each failure mode, list the potential effects of the failure mode on the device.* | *For each failure mode, list the potential effects of the failure mode on the study subject.* | *List the design characteristics intended to:*  *a) provide the function or feature, identifying any anticipated benefits that may be associated with the characteristics; or b) address or mitigate the potential failure mode.*  *And, if applicable,*  *identify and reference the relevant information considered in the design of the device (i.e., design input) to support the assertions that:*  *a) the function or feature will be attained; and/or*  *b) the failure mode will not likely occur or will not be catastrophic if it does occur.* | *Identify and reference the nonclinical information leveraged from internal or external sources to support the assertions that:*  *a) the function or feature will be attained; and/or*  *b) the failure mode will not likely occur or will not be catastrophic if it does occur.*  *Explain and justify how the specific aspects of the testing or analysis are relevant to the evaluation of the attribute or failure mode under consideration.* | *Identify and reference any relevant clinical experience obtained from internal or external sources for a similar device or indication to support the assertion that:*  *a) the function or feature will be attained; and/or*  *b) based on an evaluation of the clinical effects of failure, the failure mode will not likely occur or will not be catastrophic if it does occur.*  *Explain and justify how the specific aspects of the clinical experience are relevant to the evaluation of the attribute or failure mode under consideration.* | *List and reference the testing and/or analyses on the study device (i.e., the device that will be used in the clinical study) to evaluate the attribute and the potential associated failure mode(s).*  *For tests or analyses intended to address multiple attributes, identify the specific aspects of the testing or analysis relevant to the evaluation of the attribute or failure mode under consideration.* | *Identify any applicable mitigation strategies that will be utilized during the clinical study to minimize the frequency or severity of the potential clinical effects resulting from a failure to attain the attribute.* |

*The device evaluation strategy table below shows a hypothetical example for an innovative, covered, metallic implant to treat a disease common in the elderly. The device is unique in that delivery of the treatment will be through a catheter, rather than by open surgery (the standard of care). There are aspects of the new device that are similar to a device approved for a different indication.*

| ***For early feasibility studies*** | | | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Column 1** | **Column 2** | **Column 3** | **Column 4** | **Column 5** | **Column 6** | **Column 7** | **Column 8** | **Column 9** |
| **Device Attribute** | **Potential Failure Modes** | **Potential Effects of Failure** | | **Device Design Information** | **Supportive Information** | | **Nonclinical Device Testing** | **Clinical Study Mitigation Strategies** |
| **Potential Device**  **Effects of Failure** | **Potential Clinical Effects of Failure** | **Leveraged Nonclinical Information** | **Supportive Clinical Information** |  |
| Ability to access the implantation site | Inability to safely advance the system to target site | - Delivery system damage  - Implant damage | -Embolism  -Procedural failure  -Tissue damage at access site | Design characteristics:  -Unique tip to minimize trauma  -Enhanced flexibility to accommodate tortuous anatomy  - Safety features to prevent completion of deployment steps out of sequence  Relevant information considered in the design of the device:  -Use of same delivery mechanism as our similar device with a known clinical performance (without catastrophic failures), approved to treat a difference disease process in the same anatomic location | Section 10.1 of the Pre-Sub describes non-clinical testing conducted on our similar device  Reference to this information is appropriate because the study device has the same delivery mechanism as the approved, similar device. | Section 7 of the Pre-Sub describes the clinical use of our similar device.  Reference to this information is appropriate because the new intended use does not involve targeting a new anatomical implantation site and therefore would not likely negatively affect the ability of the study device to access the implantation site. | The following tests will be conducted on the study device:  -Acute and 30-day animal study (see study protocol in Section 10.2)  - Simulated use testing (see protocol in Section 10.2)  - Tensile bond strength  - Torsional bond strength | For all events  - Timely detection, treatment and reporting of adverse events  For ‘Embolism’  -Clinical evaluation and imaging post-procedure for early detection of distal organ damage to allow for early treatment and to identify the need to change the procedure or device  -Embolic protection device use  For ‘Procedure failure’  -Pre-operative imaging to confirm appropriate anatomy  -Plan to treat subjects with the current standard of care if the delivery system cannot be advanced  For ‘Tissue damage at access site’  -Pre-operative imaging to confirm appropriate anatomy |
| Implant integrity | Corrosion | -Component separation  -Fracture  -Movement from intended implant location | -Foreign body embolization  -Loss of biocompatibility    -Effectiveness failure (specify) due to component separation  -Effective failure (specify) due to implant movement  -Trauma to adjacent structures | Design characteristics:  -Electropolished metallic components to improve corrosion resistance  Relevant information considered in the design of the device:  -Use of the same metallic components and surface finishing as our similar, approved device with acceptable corrosion resistance | Section 10.1 of the Pre-Sub describes nonclinical testing conducted on our similar device with known corrosion resistance  Reference to this information is appropriate because risk of corrosion is similar to the previously approved device. The study device will be exposed to an in vivo environment that has the same relevant characteristics (e.g. body fluid contact, externally applied forces), has a similar design and is constructed with the same metal, using the same manufacturing methods. | Section 7 describes the clinical use of our approved device  Reference to this information is appropriate because the new device will be exposed to the same in vivo environment. | No device-specific testing needed prior to initiation of the early feasibility study. | For all events  -Timely detection, treatment, and reporting of adverse events  For ‘Foreign body embolization, trauma to adjacent structures and all other clinical effects of failure’  - No additional mitigation strategies beyond timely detection, treatment, and reporting of adverse events  For ‘Loss of biocompatibility’  - Assess inflammatory biomarkers post-procedure  -Monitoring of subjects for signs and symptoms of allergic reactions to allow for early treatment  For ‘Effectiveness failure (specify) due to implant movement or component separation’  -Imaging studies at regular intervals to evaluate device position  -Plan to implant additional devices if the original device moves from the targeted site |
| Biocompatibility | Non-biocompatibility | No device effects | Adverse biological response | Relevant information considered in the design of the device:  - Use of materials with histories of clinical use | No leveraged nonclinical information  Although the metallic component is identical to one of our approved devices, there are additional materials used in the construction of the device, and therefore, biocompatibility testing on the study device is needed. | No leveraged clinical information | The following tests will be conducted to support the initiation of the early feasibility study:  -Testing in accordance with Part 1 of ISO 10993 (see Section 10.2)  - Acute and 30-day animal study (see study protocol in Section 10.2)  The specific aspects of biocompatibility that will be assessed in the animal study are acute systemic and subchronic toxicity, in vivo thrombogencity, hemolysis and local irritation. These will be assessed through complete necropsy and target tissue gross and histologic evaluation. | For all events  - Timely detection, treatment, and reporting of adverse events  For ‘Adverse biological response or loss of biocompatibility’  -Assess inflammatory biomarkers past-procedure  - Monitoring of subjects for signs and symptoms of allergic reactions to allow for early treatment |

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| ***For 510(k) Pre-submission*** | | | | | | | |
| **Column 1** | **Column 2** | **Column 3** | **Column 4** | **Column 5** | **Column 6** | **Column 7** | **Column 8** |
| **Device Attribute** | **Potential Failure Modes** | **Potential Effects of Failure** | | **Device Design Information** | **Supportive Information** | | **Proposed Nonclinical Device Testing** |
| **Potential Device**  **Effects of Failure** | **Potential Clinical Effects of Failure** | **Leveraged Nonclinical Information** | **Supportive Clinical Information** |
| *List each procedure-related function needed for the device to be used successfully.*  *List each performance-related function or feature needed for acceptable device performance.*  *List each necessary basic safety-related feature.* | *For each attribute, list the failure modes that could result if the attribute is not attained.* | *For each failure mode, list the potential effects of the failure mode on the device.* | *For each failure mode, list the potential effects of the failure mode on the patient.* | *List the design characteristics intended to:*  *a) provide the function or feature, identifying any anticipated benefits that may be associated with the characteristics; or b) address or mitigate the potential failure mode.*  *And, if applicable,*  *identify and reference the relevant information considered in the design of the device (i.e., design input) to support the assertions that:*  *a) the function or feature will be attained; and/or*  *b) the failure mode will not likely occur or will not be catastrophic if it does occur.* | *Identify and reference the nonclinical information leveraged from internal or external sources to support the assertions that:*  *a) the function or feature will be attained; and/or*  *b) the failure mode will not likely occur or will not be catastrophic if it does occur.*  *Explain and justify how the specific aspects of the testing or analysis are relevant to the evaluation of the attribute or failure mode under consideration.* | *Identify and reference any relevant clinical experience obtained from internal or external sources for a similar device or indication to support the assertion that:*  *a) the function or feature will be attained; and/or*  *b) based on an evaluation of the clinical effects of failure, the failure mode will not likely occur or will not be catastrophic if it does occur.*  *Explain and justify how the specific aspects of the clinical experience are relevant to the evaluation of the attribute or failure mode under consideration.* | *List and reference the testing and/or analyses on the study device (i.e., the final, manufactured device that will be the subject of the marketing application) to evaluate the attribute and the potential associated failure mode(s).*  *For tests or analyses intended to address multiple attributes, identify the specific aspects of the testing or analysis relevant to the evaluation of the attribute or failure mode under consideration.* |
|  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |

# Overview of Product Development

*Please provide an overview of the product development, including an outline of nonclinical and clinical testing either planned or already completed. However, please note that the review of a Pre-Sub will not address bench or clinical data that you have already collected.*

*If you intend to include complete copies of literature articles as part of this section, please try to include only those that are relevant to the questions you are asking. Additional articles can be provided in any subsequent marketing application or IDE.*

## Completed Product Testing

*Testing may include early proof-of-concept testing on prototypes (early in development) or performance testing intended to support clearance/approval (later in development).*

*Performance Testing*

*A summary of performance testing may include the following:*

* *bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or software, and comparison to the predicate device);*
* *animal studies (in vivo and histopathology); and*
* *clinical studies.*

*Please clearly distinguish any testing that has already been conducted from testing you plan to conduct in the future (Sections 10.2 and 10.3).*

*Information you may consider for inclusion with respect to performance may include a concise summary of the test report that includes:*

* *identification of the objective or purpose of the test;*
* *explanation of the sample size and statistical methods, as applicable;*
* *summary of the test methodology (if you are following a recognized standard, include the name of the standard and year of publication)*
* *explanation of study endpoints; and*
* *explanation of study acceptance criteria.*
* *results summary*
* *discussion of conclusions*

*A summary test report is appropriate for a Pre-Sub (not the full test report). For information on the content and level of detail that should be included in a summary test report, please see the guidance document “Recommended Content and Format of Test Reports for Complete Non-Clinical Bench Performance Testing in Premarket Submissions” (*[*https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM606051.pdf*](https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM606051.pdf)*).*

*If applicable, please make sure you address all of the testing required by an applicable standard, guidance, or special controls document.*

*Be sure you provide a clear rationale for why you chose specific acceptance criteria, samples, and sample size and why they are appropriate for the described testing.*

*For simulated use testing, make sure you provide a figure and a description of your simulated use model. Also, make sure you explain why you believe your model appropriately challenges your device (i.e. both why it models an appropriately challenging clinical anatomy and imposes the appropriate forces and/or torques on the device).*

*Provide a discussion of any deviations from your test protocol or any strange results that are produced during testing. Also, make sure you explain why these results are not concerning or how you have addressed them (either through design modification and additional testing to show the change helped, retraining of manufacturers, etc.).*

*Always make sure you use consistent terminology for each component of your device and for each of your tests in your submission.*

*As a reminder, test results and data do not need to be submitted in the Pre-Sub, as FDA will not make a final determination regarding substantial equivalence on the basis of the Pre-Sub. FDA will only make this comprehensive evaluation during its review of the 510(k) submission.*

## Proposed Nonclinical Testing

*Types of nonclinical testing for which you may want to seek feedback include:*

* *the rationale for your test strategy based on your risk analysis*
* *bench testing (such as biocompatibility, mechanical, electrical safety, electromagnetic compatibility (EMC), wireless compatibility, magnetic resonance (MR) compatibility, or software)*
* *animal studies.*

*If your questions pertain to your nonclinical testing, it is recommend that you provide a concise summary of the test plan that includes:*

* *an identification of the objective or purpose of the test*
* *the sample size and statistical methods*
* *a summary of the test methodology (if you are following a recognized standard, include the name of the standard and year of publication)*
* *the acceptance criteria and a rationale for the selection of these criteria*

## Proposed Clinical Testing

*The most common reason for submitting a Pre-Sub for an IDE is to seek advice on major elements of a clinical trial design, including:*

* *target patient population*
* *sample size*
* *type of control*
* *statistical analysis plan*
* *study endpoints*
* *length and type of follow-up.*

*If your questions pertain to aspects of your clinical trial design, you should submit at least an outline of the trial design; however, if you are seeking very specific advice, more detailed information may be needed (e.g., details of the statistical analysis plan).*

*If the Pre-Sub is for a nonsignificant risk device, IDE exempt device, or a study you plan to conduct outside the US (OUS), you may submit the entire protocol*

# Specific Questions

*The Pre-Sub should include specific questions regarding review issues relevant to a planned IDE, or marketing application (e.g., questions regarding pre-clinical and clinical testing protocols or data requirements) to allow FDA and the submitter to focus their efforts on issues most relevant to the project moving forward. You may wish to describe your perspective on the questions you provide FDA to inform FDA’s review.*

*The number of questions and extent of feedback requested in a single Pre-Sub should be carefully considered to ensure that FDA has sufficient time to provide an in-depth response to each question. In general, FDA has found it difficult to address more than 3-4 substantial questions in a single Pre-Sub.*

*In FDA’s experience, questions that lead to productive Pre-Sub interactions share the following characteristics:*

* *Questions request specific feedback on a provided proposal (e.g., an animal model is proposed, including rationale, and FDA feedback is requested on the acceptability of the animal model)*
* *Questions have considered and include reference to applicable guidance documents, standards and previous discussions with FDA (e.g., chemical characterization testing is proposed with citations to relevant biocompatibility guidance document and standards as well as feedback FDA provided in previous Pre-Sub interactions)*
* *Questions clearly articulate a desired outcome including indications for use or labeled uses (e.g., FDA feedback is requested on clinical study endpoints, inclusion criteria, and follow up duration given that the study is intended to expand the currently approved indications for use from prescription use only to over the counter use)*
* *Questions are timed to inform future device development and submission preparation (e.g., prior to conducting fatigue testing, a submitter requests feedback regarding proposed pre-conditioning procedures)*
* *Questions do not request decisions regarding approval or clearance of a future IDE, CW, IND, or marketing submission; that is, a question should not ask “Will an IDE that includes results from the proposed testing be approved?”*
* *Questions do not provide data unless necessary as supportive context for a specific proposal; that is, a question might provide limited bench, animal or clinical study data, but only to provide FDA with the needed background information to develop feedback in response to a specific proposal (e.g., one page of preliminary feasibility clinical study results are provided when FDA feedback is requested for proposed pivotal study endpoints)*
* *Questions do not ask FDA to design a study or indicate how a submitter should proceed; that is, a question should not ask “What should my clinical study design be?”*
* *Questions do not request formal regulatory determination; that is, a question should not ask “Is my device a Class II medical device to be regulated under CFR 892.2050?”*

*The following are examples of questions, provided by review topic category, expected to lead to productive Pre-Sub interactions:*

*Regulatory Strategy Questions*

* *Are there concerns with the predicate device proposed?*
* *Can we obtain FDA's feedback and guidance on pursuing a De Novo request for classification pathway given that there is not a currently marketed device that we believe could serve as predicate under the 510(k) pathway?*
* *Based on the regulatory strategy provided, does FDA agree, based on the discussion provided, that additional clinical data is not needed to support a future 510(k)?*

*Indications for Use/Intended Use Questions*

* *Does FDA have any concerns with our proposal to label the described device as over the counter?*
* *Does FDA agree with the proposed definition of drug-resistant hypertension provided in the draft indications for use statement?*
* *Does the Agency agree with the proposed size range offered for the new device, based on the intended use?*

*Clinical Study Questions*

* *Does FDA have any comments on the provided OUS study protocol regarding its ability to support a future HDE?*
* *Does FDA agree with the revised clinical study designs, statistical analysis and acceptance criteria included in this Pre-Sub supplement?*
* *Are the primary and secondary analyses appropriate for the Indications for Use for the monitoring indication proposed?*

*Labeling Questions*

* *Does FDA agree with the proposed test plan in support of MR Conditional labeling for 1.5T scanners with an exclusion zone between the neck and groin?*
* *We intend to label our device for re-use if the attached cleaning instructions are followed. The test plan to support this label is provided in Attachment B. Does FDA agree with this plan?*

*Reprocessing, Sterilization & Shelf Life Questions*

* *Does FDA have any comments about the methods described in the Microbiology protocol "Microbiology Study Protocol" included in Appendix 3?*
* *Does FDA concur that accelerated testing outlined in Appendix 2 conducted to represent 1 year shelf life is sufficient for an IDE with real time testing provided in the PMA?*
* *To address FDA's deficiency regarding our sterilization validation, we propose using Small Lot Release in accordance with Annex E of ISO 11135-2014. Does FDA have objections?*
* *Does FDA agree with our recommendation to low level disinfect the cannula device between uses?*

*Benchtop Performance Testing Questions*

* *Does FDA agree with the provided justification for the proposed worst case comparison testing?*
* *In the event that the prospective collection does not meet the protocol’s intended number of specimens of a given type, we propose to use retrospective, characterized (banked) specimens to ensure these numbers are achieved. Is this approach acceptable to FDA?*
* *We have provided a justification of the worst-case testing volume that will be used, and provided an analysis of the sensitivity of the test, as requested. Does FDA find this justification and analysis adequate to support using the methodology described in our testing protocol? If not please provide further guidance.*
* *Does the Agency agree with our approach to use the average of valid measurements of the five replicate measurements?*
* *We have provided a response to FDA's question about sample sizes used in the in vitro test, along with a justification based on a power analysis. Is this plan acceptable? If not please provide further guidance.*

*Animal Study Questions*

* *Does FDA concur that the revised GLP Study design is sufficient to address potential device risks and support initiation of a pivotal clinical trial?*
* *Is our alternative approach to an animal study appropriate?*
* *Please advise if FDA believes that additional animal studies outside of those already conducted (and described in this submission) are recommended to support a future marketing application.*
* *Does the agency agree that the proposed animal study is designed to provide a sufficient assessment of the local tissue and systemic response?*
* *Is the animal model proposed appropriate based on the proposed intended use?*
* *Are the proposed animal study endpoints and follow up schedule appropriate?*

*Biocompatibility Questions*

* *We propose to conduct the biocompatibility testing identified in Tables 7-9 on only the largest model dialyzer. Does FDA concur with the testing protocol?*
* *We propose to conduct chemical characterization (described in Appendix 1) in lieu of chronic implantation testing. Please provide any comments on the acceptability of this approach.*
* *Is our justification for not conducting carcinogenicity studies adequate?*
* *Is our alternative test method to the material-mediated sensitization testing, which does not use a traditional rabbit model but an in vitro alternative, acceptable?*

*Software/Firmware Questions*

* *Does FDA agree that our software/instrument is a moderate level of concern and that the level of documentation that will be included in an upcoming marketing submission is consistent with FDA’s recommendations provided in FDA’s guidance entitled “Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?”43 as part of the upcoming device submission?*
* *Does FDA expect any further data validating functional operation of alerts and alarms in real or simulated circumstances beyond that recommended in FDA’s guidance entitled "Guidance for the Content of Premarket Submission for Software Contained in Medical Devices?"44 If so, can FDA give us additional guidance on what they might like to see?*
* *Does FDA agree that the software documentation defined in Section 4.2 of this Pre-Sub does not need to be included in the PMA supplement for the device as it was previously reviewed and approved in other PMA supplements (i.e., the PMA supplement will reference previously submitted information)?*

*Human Factors Questions*

* *Does the agency have comments on our proposed human factors engineering process?*
* *Is the attached use-related risk analysis plan adequate? Does the agency agree that we have identified all the critical tasks?*

*Does the agency agree with our proposed test participant recruitment plan for the human factors validation testing?*