***NOTE: Maintain all of the headings*** *in this document and if not applicable to your IDE, simply state this. Use of the headings ensures you fulfill all of the requirements and is easier for the reviewers to follow.*

INVESTIGATIONAL DEVICE EXEMPTION APPLICATION

IDE Title (if title being used)

Name of Sponsor Investigator, MD

X Professor, Department

Duke University

Date of Submission

# FDA Form 3514

*The use of this form is not required, but is strongly recommended. If you choose not to use the form, ensure that the relevant information is contained in the cover letter:*

* *Statement that this is an original IDE submission*
* *Device name and intended use*
* *Sponsor’s contact information*
  + *Name, address, telephone number, fax number, email address*
* *Manufacturer information* 
  + *Name, address, contact person, telephone number, fax*

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

# Table of Contents

[FDA Form 3514 2](#_Toc99020368)

[Table of Contents 3](#_Toc99020369)

[1 Name and Address of the Sponsor 4](#_Toc99020370)

[2 Report of Prior Investigations 5](#_Toc99020371)

[3 Investigational Plan 6](#_Toc99020372)

[3.1 Purpose 6](#_Toc99020373)

[3.2 Protocol 6](#_Toc99020374)

[3.3 Risk Analysis 7](#_Toc99020375)

[3.4 Description of Device 12](#_Toc99020376)

[3.5 Monitoring Procedures 13](#_Toc99020377)

[4 Manufacturing Information 14](#_Toc99020378)

[5 Example of the Investigators Agreement 15](#_Toc99020379)

[6 Investigator Certification 16](#_Toc99020380)

[7 IRB Information 17](#_Toc99020381)

[8 Name and Address of Other Investigational Institutions 18](#_Toc99020382)

[9 Sale of the Device 19](#_Toc99020383)

[10 Environmental Assessment 20](#_Toc99020384)

[11 Labeling 21](#_Toc99020385)

[12 Consent Materials 22](#_Toc99020386)

[13 Additional Information 23](#_Toc99020387)

# Name and Address of the Sponsor

*Name*

*Address*

*Phone number*

*Fax*

*Email address*

*Name and contact information of alternate contact (if applicable)*

# Report of Prior Investigations

*In this section, sponsor should provide a complete report of prior investigations of the device. The report of prior investigations shall include reports of all prior clinical, animal, and laboratory testing of the device and shall be comprehensive and adequate to justify the proposed investigation. Specific contents of the report must include:*

*a) A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device, copies of all published and unpublished adverse information, and, if requested by an IRB or FDA, copies of other significant publications.*

*b) A summary of all other unpublished information (whether adverse or supportive) in the possession of, or reasonably obtainable by, the sponsor that is relevant to an evaluation of safety or effectiveness of the device*.

*c) If information on nonclinical laboratory studies is provided, a statement that all such studies have been conducted in compliance with applicable requirements in the good laboratory practice (GLP) regulations in 21 CRF part 58. If the study was not conducted in compliance with such regulations, a brief statement of the reason for the non-compliance and describe in detail all deviations from the regulations. Please be aware that for certain early phase, nonclinical feasibility studies or nonclinical effectiveness studies, the requirement to conduct studies in compliance with GLP regulations may not apply.*

# Investigational Plan

*At the beginning of this section, the sponsor can give a brief overview of the investigational plan, including the rationale for the trial, whether it is a single or multi-site study, and a description of the endpoints.*

## Purpose

*The name and intended use of the device and the objectives and duration of the investigation.*

## Protocol

*A written protocol describing the methodology to be used and an analysis of the protocol demonstrating that the investigation is scientifically sound.*

*Rather than insert the protocol within this document, we recommend that you assemble the IDE after separately printing this IDE document and the protocol. To ensure that the TOC on Page 3 reflects the true number of pages in the IDE, format the page number in subsequent sections to reflect the additional pages in the protocol and other inserted documents (informed consent, labeling, etc.).*

*To format the page number, highlight the page number in the footer, right click and choose “Format Page Numbers”. Then click “Start numbering at” and put the new number accounting for the number of inserted pages.*

## Risk Analysis

*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; 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.*

*Methods to minimize risks may include the use of standard approaches, with additional mitigation strategies to protect individual study subjects and future study participants during the ongoing study. Examples of both standard and additional risk mitigation strategies include:*

* *use of study sites that have sufficient expertise and resources to manage adverse events and provide appropriate alternative therapies if needed;*
* *identification of qualified investigators with adequate training to conduct the early feasibility study;*
* *a plan to capture human factors information during the course of the study to modify the procedures or device as necessary based on the information obtained;*
* *specifying appropriate study inclusion and exclusion criteria;*
* *limiting the sample size to a reasonable number for an early feasibility study (e.g., 5-10 initial subjects);*
* *follow-up assessments at regular intervals to monitor subject safety and device effectiveness (i.e., potentially more frequent than for a traditional feasibility or pivotal study);*
* *timely reporting of serious adverse events (e.g., after each occurrence rather than only in a periodic progress report);*
* *timely reporting of device performance parameters, which help determine whether the device functions as intended (e.g., measurements of deliverability, stability, handling, visualization, patency, integrity);*
* *non-sequential enrollment, that is, initial device use in subjects with more favorable anatomical characteristics as compared to the population otherwise eligible for the early feasibility study (e.g., selecting subjects that meet study eligibility requirements but do not have anatomic features that may increase the difficulty of device use); and*
* *a pre-specified plan for periodic patient outcome assessments and reporting prior to enrollment of additional patients (e.g., as frequently as after each use of the device).*

*One way to present the risk/benefit assessment is through a device evaluation strategy table. See the example below for a hypothetical covered, metallic implant.*

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **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.* |
|  |  |  |  |  |  |  |  |  |

| ***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 2 of the IDE 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 2 of the IDE 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 were conducted on the study device:  -Acute and 30-day animal study (see study protocol in Section 2  - Simulated use testing (see protocol in Section 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 2 of the IDE 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 2 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 were 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 |

*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) 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.*

## Description of Device

*A description of each important component, ingredient, property and principle of operation of the device and of each anticipated change in the device during the course of investigation. Include any drawings, photos, videos, or design information.*

*Make sure your device description is clear and describes ALL elements of your proposed device (e.g., physical description, figures, materials of construction, software documentation), 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.*

*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.*

## Monitoring Procedures

*The sponsor’s written procedures for monitoring the investigation and the name and address of each monitor. Written monitoring procedures must be provided for all studies involving more than one investigator.*

# Manufacturing Information

*If you are using a marketed device, then it is appropriate to refer to the FDA clearance/approval documentation and provide a copy or a URL to the clearance/approval documentation. If any modifications have been made, provide details on all changes.*

*If you have a Letter of Authorization (LoA) from another sponsor referencing their FDA submission (PMA, 510(k), IDE, master files, etc.), include the LoA in this section. The LoA allows the FDA reviewer to reference the other sponsor’s submission on file in support of your IDE application.*

*If you are manufacturing the device, include a description of the methods, facilities, and controls used for the manufacture, processing, packing, storage, and, where appropriate, installation of the device, in sufficient details so that a person generally familiar with good manufacturing practice can make a knowledgeable judgment about the quality control used in the manufacture of the device.*

# Example of the Investigators Agreement

*An example of the agreement to be entered into by all investigators who will participate in the investigation to comply with investigator obligations under this part, and a list of the names and addresses of all investigators who have signed the agreement. Information that must be included in the written agreement is listed below and can be found in §812.43.*

1. *the investigator's curriculum vitae;*
2. *where applicable, a statement of the investigator's relevant experience (including the dates, location, extent and type of experience);*
3. *if the investigator was involved in an investigation or other research that was terminated, an explanation of the circumstances that led to termination; and*
4. *a statement of the investigator's commitment to:*

* *conduct the investigation in accordance with the agreement, the investigational plan, Part 812 and other applicable FDA regulations, and conditions of approval imposed by the reviewing IRB and FDA;*
* *supervise all testing of the device involving human subjects;*
* *ensure that the requirements for obtaining informed consent are met; and*
* *provide sufficient and accurate financial disclosure information and update information if any relevant changes occur during the investigation and for one year following the completion of the study.*

*A template for the investigators agreement is available on the Office of Regulatory Affairs and Quality (ORAQ) website.*

# Investigator Certification

*A statement that all investigators who will participate in the investigation have signed the agreement, that the list of investigators includes all the investigators participating in the investigation, and that no investigator will be added to the investigation until they have signed the agreement.*

*The following statement can be used to satisfy this requirement: “*As required for an IDE study, we commit to obtain a signed investigator agreement from all current investigators who are participating in the investigation. Additionally, no future investigators will be added until they have signed the agreement.”

# IRB Information

*A list of the name, address, and chairperson of each IRB that has been or will be asked to review the investigation and a certification of the action concerning the investigation taken by such IRB.*

# Name and Address of Other Investigational Institutions

*The name and address of any institution at which a part of the investigation may be conducted that has not been identified in accordance with Section 7.*

# Sale of the Device

*If the device is to be sold, the amount to be charged and an explanation of why sale does not constitute commercialization of the device. If the device will not be sold, this should be stated here.*

# Environmental Assessment

*A claim for categorical exclusion under § 25.30 or § 25.34 or environmental assessment under § 25.40.*

*Please maintain this header and include the following statement*: Please note that an environmental assessment as required under 21 CFR 25.40 or a claim for categorical exclusion under 21 CFR 25.30 or 25.34 is no longer required [§25.34(g)].

# Labeling

*Include copies of all labeling for the device. (If you are using a marketed device, then it is appropriate to refer to the most current product labeling and provide a copy or a URL link to the most current labeling here.)*

*Labeling is defined as ‘all labels and other written, printed, or graphic matter upon any article or any of its containers or wrappers, or accompanying such article at any time while a device is held for sale after shipment or delivery for shipment in interstate commerce.”*

*An investigational device or its immediate package must bear a label with the following information:*

* *the name and place of business of the manufacturer, packer, or distributor;*
* *the quantity of contents, if appropriate; and*
* *the statement, "CAUTION ­­ Investigational device. Limited by Federal (or United States) law to investigational use."*

*The label must also describe all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions.*

*The labeling of an investigational device must not contain any false or misleading statements nor imply that the device is safe or effective for the purposes being investigated.*

# Consent Materials

*Copies of all forms and informational materials to be provided to subjects to obtain informed consent. Information that should be included in informed consent documents can be found in 21 CFR §50.25.*

# Additional Information

*Any other relevant information FDA requests for review of the application, including information previously submitted.*