

Clinical Research Protocol

***iNSERT tITLE OF THE PROTOCOL***

*[Include* ***design*** *(e.g. randomized, double blind, placebo controlled, etc),**if the study* ***is multi-center****,* ***type*** *(e.g. pilot study, first-in-human study etc.), the* ***investigational device****, and* ***target disease(s****)]*

|  |  |
| --- | --- |
| **Regulatory Sponsor:** | *Insert the Name of the Sponsor-Investigator*  *Insert Department Name*  *Insert Address*  *Insert Phone Number* |
| **Funding Sponsor:** | *Insert the Name of Primary Funding Institution*  *Insert Address*  *Insert Phone Number* |
| **Study Product:** | *Insert Study Device Name – Generic, followed by marketed name if applicable* |
| **Protocol Number:** | *Insert Protocol Number Used by Sponsor* |
| **IDE Number:** | *Insert IDE Number if applicable* |

**Initial version:** [date]

**Amended:** [date]

**Amended:** [date]

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**List of Abbreviations**

# Study Summary

|  |  |
| --- | --- |
| **Title** | *Full title of protocol* |
| **Short Title** | *Shortened title, if one is typically used by you or your Center/Dept.* |
| **Protocol Number** | *The standard protocol number used to identify this study.* |
| **Methodology** | *Design attributes such as single blind, double blind or open label; Randomized, placebo or active placebo control; cross-over design, etc.* |
| **Study Duration** | *Estimated duration for the main protocol (e.g. from start of screening to last subject processed and finishing the study)* |
| **Study Center(s)** | *Single-center or multi-center. If multi-center, note number of projected centers to be involved.* |
| **Objectives** | *Brief statement of primary study objectives* |
| **Number of Subjects** | *Number of subjects projected for the entire study (e.g. not for simply one site, rather for entire study, all sites combined)* |
| **Diagnosis and Main Inclusion Criteria** | *Note the main clinical disease state under study and the key inclusion criteria (i.e. NOT the entire list that will appear later in the full protocol –rather only the few key inclusion criteria)* |
| **Study Product and Planned Use** | *Study device name (generic name and specific marketed name).*  *Also note device use/administration (for example, for a vascular stent: The [device] is inserted intravascularly as a scaffold to maintain vessel patentcy)* |
| **Reference therapy** | *Note if there is a standard reference therapy against which the study product is being compared, or if the reference is no device intervention or a placebo sham procedure* |
| **Statistical Methodology** | *A very brief description of the main elements of the statistical methodology to be used in the study. (As few lines as possible).* |

# Introduction

*The introduction should open with remarks that state that this document is a clinical research protocol and the described study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated Federal regulations, and all applicable University research requirements. The rest of the introduction is broken out into subsections. Example language for the first paragraph under “Introduction” and before the section “1.1 Background”:*

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

## Background

## Background

*This section should contain a background discussion of the target disease state to which the investigational product(s) hold promise, and any pathophysiology relevant to potential study treatment action.*

## Investigational Device

*This section should contain a description of the investigational device, including category of device, and an overview of its intended use/purpose in the research study. The following paragraphs describe the 2 main device categories for studies conducted under an IDE, as well as overviews the 3 FDA classes of devices:*

*Category A and B devices are FDA categorizations for devices used in research conducted under and Investigational Device Exemption (IDE) application:*

***Category A Device***

*A Category A device refers to an innovative device believed to be in Class III for which "absolute risk" of the device type has not been established (that is, initial questions of safety and effectiveness have not been resolved, and the FDA is unsure whether the device type can be safe and effective).*

***Note****: Category A devices ARE NOT eligible for Medicare coverage.*

***Category B Device***

*A Category B device refers to a device believed to be in Class I or Class II, or a device believed to be in Class III for which the incremental risk is the primary risk in question (that is, underlying questions of safety and effectiveness of the device type have been resolved), or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type.*

***Note****: Category B devices ARE eligible for Medicare coverage consideration.*

*The following overviews the 3 classes of devices as noted in the FDA regulations:*

***Class I Device*** *- a device with the following characteristics:*

* *Risk: low; e.g. Crutches, elastic bandages, examination gloves, and hand-held surgical instruments*
* *General FDA Controls: Registration and listing, prohibitions against adulteration and misbranding, notification, repair/replace/refund, recall, records and reports, and adherence to Good Manufacturing Practices*

***Class II Device*** *- a device with the following characteristics:*

* *Risk: higher than Class I; technology well understood, but bench test data required e.g. powered wheelchairs, infusion pumps, and surgical drapes*
* *Special FDA Controls: In addition to general controls, post-market surveillance studies and performance standards*

***Class III Device*** *- a device with the following characteristics:*

* *Risk: high; devices that present serious risk; most typically are implanted and life-supporting or life-sustaining, e.g. replacement heart valves, silicone gel-filled breast implants, cerebral stimulators*
* *Special FDA controls through Pre-market review*

*The pre-market review involves a comprehensive evaluation, including data from clinical studies, and is required to ensure safety and effectiveness prior to marketing of the devices. This involves bench and animal tests, clinical trials, the submission of a Premarket Approval Application (PMA)*

## Preclinical Data

*Summarize the available non-clinical data (published or available unpublished data) that could have clinical significance.*

## Clinical Data to Date

*Summarize the available clinical study data (published or available unpublished data) with relevance to the protocol under construction -- if none is available, include a statement that there is no available clinical research data to date on the investigational product.*

## Research Risks & Benefits

### Risk of Investigational Device

*Describe the key risks of the investigational device and as applicable how that risk will be minimized.*

### Other Risks of Study Participation

*Describe the key risks, beyond study drug exposure, to study subjects and how those risks will be minimized.*

### Potential benefits

*Describe potential benefit(s), if any, for subjects participating in the research. If there are no anticipated benefits, this should be stated. [Note: Payment to subjects is not considered to be a benefit of research].*

# Study Objectives

*Describe the overall objectives and purpose of the study. This should include both primary and any secondary objectives, e.g.:*

## Primary Objective

*Example: To assess the efficacy of [device name], in subjects with coronary disease, in maintaining coronary vascular patency at 6 months and 1 year.*

## Secondary Objective(s)

*Example: To assess the effect of [device name] on need for repeat percutaneous coronary intervention.*

*To assess the safety of [device name] as measured by procedure related and post-procedure blood loss, intravascular complications related to the device and/or device insertion, and need for coronary artery bypass grafting.*

# Study Design

## General Design

*Include:*

* The type/design of the study (e.g. Randomized, single-blind, parallel group, etc.)
* A schematic diagram of the trial design, procedures and stages is advisable
* Expected duration of subject participation
* A summary description of the sequence and duration of all trial periods including follow-up, if any

## Primary Study Endpoints

*Describe the primary endpoint to be analyzed in the study. Section 2.1 Objectives provides the overall primary aim of the study, and this section 3.2 provides the detail on the specific endpoint(s) that will support the primary objective of the study (how it/they are to be measured, etc.)*

## Secondary Study Endpoints

*Describe any secondary endpoints to be analyzed in the study. For example if one of the study objectives noted above in section 2.2 includes “blood loss” as a measure of safety, this section should describe the specific parameters that would constitute important blood loss and how that will be measured for the purposes of the protocol and study analysis. This might include statements like “estimated intra-operative blood loss of > 300cc”, or “blood loss requiring transfusion of > 2 units PRBCs”*

## Primary Safety Endpoints

*All studies should include the primary safety endpoints to be measured. If the primary or secondary objective of the study is safety, then the safety endpoints should be clarified, as applicable, in section 3.2 or 3.3 above and this subsection 3.4 can be deleted.*

# Subject Selection and Withdrawal

## Inclusion Criteria

*Create a numbered list of criteria subjects must meet to be eligible for study enrollment (e.g. age, gender, target disease, concomitant disease if required, etc.). Typically, this list should include items such as: “subjects capable of giving informed consent”, or if appropriate, “ subjects who have an acceptable surrogate capable of giving consent on behalf of the subject.”*

## Exclusion Criteria

*Create a numbered list of criteria that would exclude a subject from study enrollment. If appropriate, this list should mention that subjects cannot be homeless persons, or have active drug/alcohol dependence or abuse history. If exposure to certain medications or treatments at screening is prohibited, that must be noted in the exclusion criteria—if these are also prohibited concomitant medications during the study period that should be noted here as well.*

## Subject Recruitment and Screening

*Describe how subjects will be recruited for the study, e.g. from investigator or sub-investigator clinical practices, referring physicians, advertisement, etc. Note in this section that information to be disseminated to subjects (handouts, brochures, etc.) and that any advertisements must be approved by the IRB/EC for the site; include a sample of such information in the attachment section of the protocol. Also in this section, list any screening requirements such as laboratory or diagnostic testing necessary to meet any noted inclusion or exclusion criteria (greater detail of timing, etc. can be included later in section 6 “Study Procedures” section of the protocol).*

***Note****: IRB = Institutional Review Board (a US term); EC = Ethics Committee (a non-US term synonymous with IRB)*

## Early Withdrawal of Subjects

### When and How to Withdraw Subjects

*Describe the scenarios under which a subject may be withdrawn from the study prior the expected completion of that subject (e.g. safety reasons, failure of subject to adhere to protocol requirements, subject consent withdrawal, disease progression, etc.) Also, if abrupt termination of study treatment could affect subject safety, describe procedure to remove the investigational device (if appropriate) and or alternate or adjunctive therapies.*

### Data Collection and Follow-up for Withdrawn Subjects

*Even though subjects may be withdrawn prematurely from the study, it is imperative to collect at least survival data on such subjects throughout the protocol defined follow-up period for that subject (though careful thought should be give to the full data set that should to be collected on such subjects to fully support the analysis). Such data is important to the integrity of the final study analysis since early withdrawal could be related to the safety profile of the study device. If a subject withdraws consent to participate in the study, attempts should be made to obtain permission to record at least survival data up to the protocol-described end of subject follow-up period. IT MUST BE A HIGH PRIORITY TO TRY TO OBTAIN AT LEAST SURVIVAL DATA ON ALL SUBJECTS LOST TO FOLLOW-UP AND TO NOTE WHAT METHODS SHOULD BE USED BEFORE ONE CAN STATE THE SUBJECT IS TRULY LOST TO FOLLOW-UP (e.g. number of phone calls to subject, phone calls to next-of-kin if possible, certified letters, etc.).*

# Study Device

## Description

*This section should be a very brief synopsis of section 1.2 “Investigational Device” describing the study device.*

## Treatment Regimen

Describe the planned study treatment regimen, including any comparator treatments.

## Method for Assigning Subjects to Treatment Groups

*Describe how a randomization number and associated treatment assignment will be made. This could be selection of a sequentially numbered device kit/box, or communication with a randomization center that assigns a number associated with a specific treatment kit/box, etc.*

## Implantation of Study Device

*Describe in detail all the steps necessary to properly prepare study treatment. Include description of how a specific device is selected for implantation (i.e. whether device needs to be sized, configured, etc). Fully describe how the study device and any associated treatment are to be administered. If the study device is stored and managed by the NYULMC OR supply management staff or stored and dispensed from the Investigator’s office or the NYULMC Investigational Pharmacy), that should be noted here, including the contact number to the responsible service office. The Operating Room administration and the IDS may also be able to provide standard language text for this section of the protocol.*

## Subject Compliance Monitoring

*Delete this section if not applicable. Describe how the study team will assess and track subject compliance with the study intervention, and what procedures must be followed for any subject who is significantly non-compliant with the study treatment regimen.*

## Prior and Concomitant Therapy

*In this section, describe:*

* What prior and/or concomitant medical therapy will be collected (if applicable).
* Which concomitant medicines/therapies (including rescue therapies) are permitted during the study
* Which concomitant medicines/therapies are not permitted during the study (if applicable)

## Packaging

* Describe how the study device and any comparator device will be packaged
* Describe if the device is to be shipped in bulk (e.g. “Study devices will be shipped as bulk orders of [X] devices individually boxed.”) or as separate subject-specific kits/boxes
* When subject device kits are constructed, describe all the contents of the kit/box and associated labeling

## Blinding of Study

*Delete if not applicable. Describe how the study intervention is to be blinded to the subject and others as applicable. For example, if a sham operative procedure is to be conducted in the control group to blind subjects to whether the device was used or implanted.*

## Receiving, Storage, Dispensing and Return

### Receipt of Study Device

*Describe how the study device will be obtained i.e. what entity will ship the device to the investigative site, and to what location at the site, (e.g. operating room/department, investigational pharmacy, etc.) Additional language that should be included:*

Upon receipt of the of the study device supplies, an inventory must be performed and a device receipt log filled out and signed by the person accepting the shipment. It is important that the designated study staff counts and verifies that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study devices in a given shipment will be documented in the study files. The investigator must notify the study sponsor of any damaged or unusable study devices that were supplied to the investigator’s site.

### Storage

*Describe any specific storage requirements and any special handling requirements during storage for the study device.*

### Dispensing of Study Device

*Describe how the study device will be assigned to each subject and dispensed. This section should include regular device reconciliation checks (i.e. which device was implanted in a given subject; which device containers were opened to select the specific device to be implanted in the subject; whether the subject actually received the assigned device; which devices were inadvertently damaged in handling/dispensing; etc. --- e.g. “Regular study device reconciliation will be performed to document device assigned and implanted, devices consumed in selecting the subject-specific device, and number of devices remaining. This reconciliation will be logged on the device reconciliation form, and signed and dated by the study team.”)*

### Return or Destruction of Study Device

*This section should note the procedures for final reconciliation of the site’s study device supply at the end of the study, and whether study devices are to be shipped back to a source or destroyed on site. If a device is to be shipped back to a source, note the address and contact information here.*

At the completion of the study, there will be a final reconciliation of study devices shipped, devices consumed, and devices remaining. This reconciliation will be logged on the device reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study devices. Devices destroyed on site will be documented in the study files.

# Study Procedures

*In this section, describe all the procedures and treatments required at each visit, broken out by visit.* ***Create a study schedule of events*** *(sometimes called a procedures flowchart/table) that describes the activities and procedures to be followed at each visit****.***

***Include the schedule of events here or in the Attachment section and refer to that attachment in this section****. See an example of such a schedule of events at the end of this document.*

## Visit 1

## Visit 2

## etc.

# Statistical Plan

## Sample Size Determination

*Describe the statistical methods for determining the sample size for the study. State the total number of subjects expected to participate. In the case of multicenter protocols, include the overall total.*

## Statistical Methods

*Summarize the overall statistical approach to the analysis of the study. The section should contain the key elements of the analysis plan, but does not need to be a full reiteration of a detailed study analysis plan created by the study biostatistician. The full Statistical Analysis Plan can then be a “stand-alone” document that can undergo edits and versioning outside of the protocol and therefore not trigger an IRB re-review with every version or edit –AS LONG AS THE KEY ELEMENTS OF THE ANALYSIS PLAN DO NOT CHANGE – OTHERWISE IRB REVIEW IS REQUIRED.*

*Be clear on primary as well as any applicable secondary analyses*

## Subject Population(s) for Analysis

*This section should be very specific in defining the subject populations whose data will be subjected to the study analysis – both for the primary analysis and any applicable secondary analyses. Examples of such populations include:*

* *All-randomized population: Any subject randomized into the study, regardless of whether they received the study device*
* *All-treated population: Any subject randomized into the study that received the study device.*
* *Protocol-compliant population: Any subject who was randomized and received the study device and complied with all protocol required processing*

# Safety and Adverse Events

## Definitions

**Unanticipated Problems Involving Risk to Subjects or Others**

Any incident, experience, or outcome that meets all of the following criteria:

* Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, the investigators brochure, etc)
* Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
* Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

**Unanticipated Adverse Device Effect**

An Unanticipated Device Effect is any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Serious injury**

Any injury or illness that is any one of the following:

* life-threatening
* results in permanent impairment of a body function or permanent damage to body structure
* necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

**Adverse Event**

An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

* results in study withdrawal
* is associated with a serious adverse device effect
* is associated with clinical signs or symptoms
* leads to additional treatment or to further diagnostic tests
* is considered by the investigator to be of clinical significance

## Recording of Adverse Device Effects

At each contact with the subject, the investigator must seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects should be recorded immediately in the source document, and also in the appropriate adverse effect module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse device effects occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse device effects that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse device effects that occur after the study period should be recorded and reported promptly (see section 8.3 below).

The minimum initial information to be captured in the subject’s source document concerning the adverse device effect includes:

|  |  |
| --- | --- |
| * Study identifier * Study Center * Subject number * Device model and serial number * A description of the event * Date of onset | * Investigator assessment of the association between the event and study treatment * Current status * Whether study treatment was discontinued * Whether the event is serious and reason for classification as serious |

## Reporting of Adverse Device Effects and Unanticipated Problems

### Investigator reporting: *Notifying the study sponsor*

*This section describes an investigator’s responsibility for reporting to the IDE Sponsor adverse device effects and unanticipated problems posing risks to subjects or others.*

*21 CFR 812.150 requires that participating investigators report* ***ALL*** *unanticipated adverse device events to the IDE Sponsor* ***regardless of seriousness or severity****. Example language for this section describing the reporting requirements is noted below.*

The following provides some example text for this section of the protocol. The example text incorporates FDA device regulation reporting requirements. Review the text carefully and modify or delete elements as appropriate to your specific study (i.e. taking into consideration issues such as single-site vs multi-site, NYULMC investigators and NYULMC IRB vs non-NYULMC investigators and non-NYULMC IRBs, etc.)

The following describes events that must be reported to the study sponsor in an expedited fashion.

**Initial Report: within 24 hours:**

The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

* Unanticipated adverse device effect, regardless of seriousness or severity
* Unanticipated problems related to study participation

Additionally, an FDA Form 3500A (MEDWATCH Form; see Attachment XXXX)) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the study site.

[Name of Sponsor contact phone, fax]

**Follow-up report: within 48 hours:**

Within the following 48 hours, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

**Other Reportable events:**

* **Deviations from the study protocol**

Deviations from the protocol must receive both Sponsor and the investigator’s IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator’s IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator’s IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

* ***Withdrawal of IRB approval***

An investigator shall report to the sponsor a withdrawal of approval by the investigator’s reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

### Investigator reporting: *Notifying the IRB*

*This section specifies the NYULMC IRB requirements for investigator reporting of unanticipated problems posing risk to subjects or other, including adverse events. The IRB requirements reflect the current guidance documents released by the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) and are respectively entitled “Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events” and “Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting – Improving Human Subject Protection.”*

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

**Report Promptly, but no later than 5 working days:**

Researchers are required to submit reports of the following problems promptly butno later than10 working days from the time the investigator becomes aware of the event:

* ***Unanticipated problems including adverse events* that are unexpected and related**
  + *Unexpected****:*** *An event is “unexpected” when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  + *Related to the research procedures****:*** *An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  + *Harmful: either caused harm to subjects or others, or placed them at increased risk*
* ***Unanticipated adverse device effect***: Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

**Other Reportable events:**

The following events also require prompt reporting to the IRB, though no later than10 working days:

* ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
* ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  + *one or more participants were placed at increased risk of harm*
  + *the event has the potential to occur again*
  + *the deviation was necessary to protect a subject from immediate harm*
* ***Breach of confidentiality***
* ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
* ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

**Reporting Process**

The reportable events noted above will be reported to the IRB using the form: “Reportable Event Form” or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator’s study file.

### Sponsor reporting: *Notifying the FDA*

*If this protocol is being conducted under a NYULMC Faculty held IDE, it is the responsibility of the NYULMC Faculty IDE holder to report certain adverse device effects to the FDA, the device manufacturer, and the participating investigators and participating IRBs. Delete this section if the study is not being conducted under a NYULMC faculty-held IDE.*

The study Sponsor is required to report certain adverse device effects in an expedited fashion to the FDA and in certain cases to the device manufacturer, and participating IRBs and investigators. These written notifications of adverse events are referred to as Medical Device Reports (MDR). The types of device effects and their reporting requirements are noted below.

**Adverse Device Effects**

The sponsor must submit to the FDA and the device manufacturer a report of any adverse event that is related to the device and includes any of the following:

* results in death
* is life-threatening
* results in permanent impairment of a body function or permanent damage to body structure
* necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

**-or-**

* A previous adverse event that was not initially deemed reportable but is later found to fit the criteria for reporting noted above (reporting such events within 10 working days from when event was deemed reportable).

Such reports must be submitted within ***10 working days***

**Unanticipated Adverse Device Effects**

* ***Evaluation***

The Sponsor shall immediately evaluate each Unanticipated Adverse Device Effect. Such evaluations shall be reported to the FDA, all participating IRBs, and participating investigators, and the manufacturer ***within 10 working days*** after the sponsor first receives notice of the effect.

* ***Unreasonable risk to subjects***

After evaluating an Unanticipated Adverse Device Effect, if the Sponsor determines the effect presents an unreasonable risk to subjects, the Sponsor shall terminate the study or parts of the study presenting that risk as soon as possible. Study termination shall occur ***no later than 5 working days after the Sponsor makes this determination*** and not later than 15 working days after the sponsor first received notice of the effect. Such determinations and actions shall also be reported to the FDA and the device manufacturer as soon as possible, though no later than 5 working days.

***Withdrawal of IRB approval***

The Sponsor shall notify the FDA, all participating IRBs and participating investigators of any withdrawal of approval of the study by a reviewing IRB ***within 5 working days*** after receipt of the withdrawal of approval.

**FDA Reporting Process**

Medical Device Reports, whether for anticipated or unanticipated device-related effects, are to be submitted on FDA Form 3500A (MEDWATCH Form; see Attachment XXXX). The contact information for submitting MDR reports is noted below:

Food and Drug Administration

Center for Devices and Radiological Health

Medical Device Reporting

PO Box 3002

Rockville, MD 20847-3003

## Unblinding Procedures

*This section only applies if treatment blinding of subjects or other personnel is used in the study (example: sham placebo procedures used in the study). Concerning unblinding, while the safety of the subject always comes first, it is still important to seriously consider if unblinding the study intervention is necessary to ensure a subject’s safety. This section should clearly describe the procedures for unblinding study intervention rendered to a subject, including documentation of this in the subject’s source document. For investigators, other than the sponsor-investigator, state that the investigator must inform the sponsor of all subjects whose treatment was unblinded – and describe the timelines for such reporting. In most cases, the unblinding will be part of managing an serious adverse event, and will be reported with the adverse event, however, in cases where unblinding was not associated with an adverse event, such actions should be reported in a timely manner. While there is no regulation governing this timeline, it is suggested to use the same timeline requirements for investigator reporting of adverse device effects, (i.e. notification of sponsor within 24 hours by phone or fax, followed by a written narrative of the event and details of the unblinding within 48 hours.)*

## Stopping Rules

*In studies with a primary safety endpoint or studies with high risk to study subjects, rules should be developed that clarify the circumstances and procedures for interrupting or stopping the study. If a central Data and Safety Monitoring Board (DSMB) or Committee (DSMC) is set up for the study, the stopping rules should be incorporated into their safety analysis plan as well.*

## Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of adverse device events.

### Data Monitoring Committee

**Reference**: The following section of guidance language draws from: the FDA Guidance Document: “Guidance for Clinical Trial Sponsors On the Establishment of Clinical Trial Data Monitoring Committees”

http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm

A Data Monitoring Committee (DMC), also sometimes called a Data and Safety Monitoring Board (DSMB), is a group of individuals with pertinent expertise that, on a regular basis, reviews accumulating data from an ongoing clinical trial. The DMC advises the IND sponsor regarding the continuing safety of current participants and those yet to be recruited, as well as the continuing validity and scientific merit of the trial.

**Do I need a DMC?**

All clinical trials require safety monitoring (21 CFR 312.32(c)), but not all trials require monitoring by a formal committee external to the trial organizers and investigators. DMCs have generally been established for large, randomized multi-site studies that evaluate interventions intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. Because monitoring of accumulating results is almost always essential in such trials, DMCs should be established for controlled trials with mortality or major morbidity as a primary or secondary endpoint. They may also be helpful in settings where trial participants may be at elevated risk of such outcomes even if the study intervention addresses lesser outcomes such as relief of symptoms. Although DMCs may prove valuable in other settings as well, a DMC is not needed or advised for every clinical study. Several factors are relevant to determining whether or not to establish a DMC for a particular trial. These relate primarily to safety, practicality, and scientific validity. For more information on determining the need for a DMC, see the reference cited above in this section.

***Independence of a DMC***

Creating a committee whose members are considered to be independent of those sponsoring, organizing, and conducting the trial and have no financial or other important connections to the study sponsor or other trial organizers offers several advantages:

* The principal responsibilities of the DMC are first, to ensure protection of study participants and second, to protect the scientific validity of the trial. Independence from the sponsor and the conduct of the study helps ensure that the DMC is not unduly influenced by sponsor or investigator interests, thereby promoting objectivity in study participant safety assessments, and enhancing the credibility of the trails conclusions
* Independence of the DMC and complete blinding of the sponsor to interim outcome data preserve the ability of the sponsor to make certain modifications to a trial in response to new external information without introducing bias.
* Independence of the DMC, by maintaining the sponsor in a fully blinded situation, protects the sponsor (and thus the trial) from pressures toward premature disclosure of results due to SEC requirements, fiduciary responsibility, or other business considerations.

***Committee Composition:***

The selection of DMC members is extremely important as the DMC is assigned critical responsibilities in protecting the safety and well being of trial participants. The trial sponsor and/or trial Steering Committee generally appoints a DMC. Factors to consider in the selection of individuals to serve on a DMC should include relevant expertise, experience in clinical trials and in serving on other DMCs, and a lack of serious conflicts of interest. The objectives and design of the trial and the scope of the responsibilities given to the DMC determine the types of expertise needed for a particular DMC.

Most DMCs are composed of clinicians with expertise in relevant clinical specialties and at least one biostatistician knowledgeable about statistical methods for clinical trials and sequential analysis of trial data. Some DMCs may include a medical ethicist knowledgeable about the design, conduct, and interpretation of clinical trials. Prior DMC experience is helpful, but not essential, although it is desirable that at least some members have prior DMC service. Appropriate representation of gender and ethnic groups may be of particular importance for some trials. All appointees should be prepared to maintain confidentiality of the interim results they have reviewed.

A DMC may have as few as 3 members, but may need to be larger when representation of multiple scientific and other disciplines, or a wider range of perspectives generally, is desirable. For logistical reasons it is sensible to keep the DMC as small as possible, while still having representation of all needed skills and experience. Some redundancy may be desirable, however, in scientifically and/or ethically complex trials, trials of long duration in which DMC attrition might be anticipated, or in trials in which the DMC must meet fairly frequently so that not all members would likely be able to attend all meetings.

The study sponsor usually appoints the DMC chair. Prior DMC experience is more important for the chair than for other DMC members, as members will look to the chair for leadership on administrative as well as scientific issues. (If the DMC includes only one statistician, however, it is desirable for the statistician to have had prior DMC experience as well.). The chair should be capable of facilitating discussion, integrating differing points of view and moving toward consensus on recommendations to be provided to the trial sponsors. It is particularly important for the chair to make a firm commitment to participate for the duration of the trial.

***DMC Standard Operating Procedures***

All DMCs should have well-defined standard operating procedures (SOPs). These are often drafted in the form of a DMC Charter. For a sample template for creating a DMC Charter, see the following NIH example: [www.nhlbi.nih.gov/crg/word-templates/dsmb-charter-template-final.doc](http://www.nhlbi.nih.gov/crg/word-templates/dsmb-charter-template-final.doc)

The sponsor may create an initial draft of these SOPs or Charter and present them to the DMC for agreement, or the DMC may draft the SOPs/Charter with subsequent concurrence by the sponsor. Topics to be addressed would normally include:

* schedule and format for meetings
* interim analysis plans & format for presentation of data
* specification of who will have access to interim data and who may attend all or part of DMC meetings
* procedures for assessing conflict of interest of potential DMC members
* the method and timing of providing interim reports to the DMC.

**NOTE:** The sponsor should submit a description of the SOPs to FDA well in advance of the performance of any interim analyses, optimally before the initiation of the trial.

***For more information*** on determining the need for a DMC and other information about the constitution and management of a DMC, see the FDA Guidance Document: “Guidance for Clinical Trial Sponsors On the Establishment of Clinical Trial Data Monitoring Committees”

[www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM127073.pdf)

*DELETE this section If there is no Independent Data Monitoring Committee.*

# Data Handling and Record Keeping

## Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

* What protected health information (PHI) will be collected from subjects in this study
* Who will have access to that information and why
* Who will use or disclose that information
* The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

## Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects’ diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

## Case Report Forms

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write “N/D”. If the item is not applicable to the individual case, write “N/A”. All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

## Records Retention

*For non-FDA regulated studies, summarize the record retention plan applicable to the study (taking into account any applicable NYULMC Department, Division or Research Center requirements, or applicable funding sponsor requirements.)*

*For FDA-regulated studies the following sample language is appropriate:*

It is the investigator’s responsibility to retain study essential documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by an agreement with the sponsor. In such an instance, it is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

# Study Monitoring, Auditing, and Inspecting

## Study Monitoring Plan

This study will be monitored according to the monitoring plan in Attachment XXX. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study related facilities (e.g. pharmacy, diagnostic laboratory, etc.), and has adequate space to conduct the monitoring visit.

## Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC/IRB, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

# Ethical Considerations

*Please note that this section uses the term ‘Ethics Committee.’ This is the generally accepted international term for what in the US is known as the Institutional Review Board. If your study does not include sites outside the US, then references to an independent Ethics Committee as noted throughout this template can be removed.*

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. The investigator should provide a list of EC/IRB members and their affiliate to the sponsor.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment XXX for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

In addition, describe who will obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the subject/subject’s legally authorized representative. If children and/ or cognitively impaired adults will be subjects, include a specific plan to assess comprehension during assent or the subject’s agreement Individuals who are authorized to obtain consent must be listed on the protocol (or FDA form 1572) and consent form document. If necessary to use ‘Auditor/Witness’ and/or translator, these roles would be described in this section. Include a plan for assessing subject capacity in cognitively impaired subjects. Describe the anticipated degree of impairment relative to their ability to consent and the anticipated direct benefits to the subjects.

# Study Finances

## Funding Source

*This section should describe how the study will be financed, but should not contain specific dollar amounts (e.g. “This study is financed through a grant from the US National Institute of Health”, or “… a grant from the American Heart Association”, etc.). If referral treatments or counseling will be provided, note how the cost of the counseling or referral services will be paid.*

## Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study. All NYU investigators will follow the applicable University conflict of interest policy(ies).

## Subject Stipends or Payments

*Describe any subject stipend or payment here. If there is no subject stipend/payment, delete this section.*

# Publication Plan

*This section should include the requirements any publication policies of the University, Department, Division or Research Center. If, in addition to the sponsor-investigator, other investigators are involved with the study, identify who holds the primary responsibility for publication of the results of the study. Also define the need to first obtain approval from the primary responsible party before any information can be used or passed on to a third party.*

*Delete or modify the following sample language:*

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor. Any investigator involved with this study is obligated to provide the sponsor with complete test results and all data derived from the study.

# References

*This is the bibliography section for any information cited in the protocol. It should be organized as any standard bibliography.*

1. Author, Title of work, periodical and associated information.
2. Author, Title of work, periodical and associated information.

# Attachments

*This section should contain all pertinent documents associated with the management of the study. The following list examples of potential attachments:*

* Investigator Agreement (for any investigator, other than sponsor-investigator, who participates in the study)
* Sample Consent Form
* Study Procedures Flowchart/Table
* Core Lab Instructions To Investigators
* Specimen Preparation And Handling (e.g. for any specialized procedures that study team must follow to process a study specimen, and/or prepare it for shipment)
* etc.

**Attachment: [NUMBER]**

***Schedule of Events***

[Guidance and example use noted in blue]

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Activity** | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | **Visit Name**  [Day or Mo #,  Window] | Visit Name  [Day or Mo #,  Window] |
| **Study team procedures** |  |  |  |  |  |  |
| Consent | X |  |  |  |  |  |
| Medical History | X |  |  |  |  |  |
| Physical Exam | X |  | X |  | X |  |
| Height | X |  |  |  |  |  |
| Weight | X |  | X |  | X |  |
| Vitals signs | X |  | X |  | X |  |
| Randomization |  | X |  |  |  |  |
| Device implantation |  | X |  |  |  |  |
| Device check |  |  | X | X | X | X |
| Subject Survey |  |  | X |  |  | X |
| ***Cardiology assessments*** |  |  |  |  |  |  |
| Electrocardiogram | X |  | X |  | X |  |
| Doppler flow echo cardiogram | X |  |  |  |  |  |
| ***Laboratory Assessments*** |  |  |  |  |  |  |
| Chemistry panel | X |  | X |  | X |  |
| CBC with differential | X |  | X |  | X |  |
| AST and ALT | X |  | X |  | X |  |
| ***Imaging Assessments*** |  |  |  |  |  |  |
| Chest X-ray | X |  |  |  |  |  |