Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	ex**C**lusion of the **L**eft atr**I**al appendage with **P**end**IT**ure™ (CLIP-IT) Post-Market Study Clinical Investigation Plan
Clinical Investigation Plan/Study Identifier	MDT22049
Study Product Name	Penditure™ LAA Exclusion System
Sponsor/Local Sponsor	Medtronic, plc. Cardiac Surgery Clinical Research and Medical Science 8200 Coral Sea Street N.E. Mounds View, MN 55112, United States
Document Version Number and Date	Version 3.0, 19-Jun-2025
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Investigator Agreement and Signature Page

Study Product Name	Penditure™ LAA Exclusion System
Sponsor	Medtronic Inc., Cardiac Surgery Clinical Research and Medical Science
Clinical Investigation Plan Identifier	MDT22049
Version Number/Date	Version 3.0 / 19-Jun-2025
I have read the protocol, including all appendices, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated. I agree to comply with the Declaration of Helsinki, the Clinical Investigation Plan, and Good Clinical Practice, as well as local laws, regulations, and standards. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of Medtronic. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Medtronic. I will discuss this material with them to ensure that they are fully informed about the products and the study.	
Investigator's Signature:	
Investigator's Name:	
Institution:	
Date:	

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1. Glossary

Acronym	Term
ACC	American College of Cardiology
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AHA	American Heart Association
ANP	Atrial Natriuretic Peptide
ASADE	Anticipated Serious Adverse Device Effect
BARC	Bleeding Academic Research Consortium
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CHA_2DS_2-VASc	Clinical prediction rule for estimating the risk of stroke based on congestive heart failure, hypertension, age ≥75 years (doubled), diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism (doubled), vascular disease, age 65 to 74 years, sex category
CIP	Clinical Investigation Plan
CT	Computed Tomography
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency
DOA	Delegation of Authority Log
DoH	Declaration of Helsinki
ECG	Electrocardiogram

Acronym	Term
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FD	Financial Disclosure
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRS	Heart Rhythm Society
ICF	Informed Consent Form
ID	Identification
IFU	Instructions For Use
INR	International Normalized Ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
IV	Intravenous
LA	Left Atrium
LAA	Left Atrial Appendage
MDCT	Multi-detector Computed Tomography
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
NOAC	Non-vitamin K Oral Anticoagulant
NYHA	New York Heart Association
OAC	Oral Anticoagulation

Acronym	Term
PCI	Percutaneous Coronary Intervention
PHI	Protected Health Information
PI	Principal Investigator
PRBC	Perfused Red Blood Cells
RA	Regulatory Authority
RAA	Right Atrial Appendage
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAVR	Surgical Aortic Valve Replacement
SCD	Sudden Cardiac Death
SID	Subject ID
SOP	Standard Operating Procedure
STS-PROM	Society of Thoracic Surgeons Predicted Risk of Mortality
TEE	Transesophageal Echocardiogram
TIA	Transient Ischemic Attack
UAE	Unavoidable Adverse Event
V/Q	Ventilation–Perfusion Scan

2. Synopsis

Clinical Study Title	exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study Clinical Investigation Plan
Clinical Study Type	Multi-center, single-arm, nonrandomized, interventional, unblinded, post-market study
Product Name	Penditure™ Left Atrial Appendage (LAA) Exclusion System
Sponsor	Medtronic, Inc. Cardiac Surgery Clinical Research and Medical Science 8200 Coral Sea Street N.E. Mounds View, MN 55112, United States
Indication under investigation	The Penditure™ LAA Exclusion System is indicated for the exclusion of the LAA of the heart. The device is indicated for use, under direct visualization, in conjunction with other cardiac surgical procedures.
Investigation Purpose	The purpose of this study is to collect post-market clinical evidence on performance and clinical outcomes of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery.
Product Status	The Penditure™ LAA Exclusion System received FDA 510(k) clearance and is commercially available in the US.
Primary Endpoints	**Efficacy:** Rate of successful exclusion of the LAA from the heart defined as the absence of residual communication (≤ 3 mm residual contrast communication) between the left atrium (LA) and the LAA. For those successfully placed devices, exclusion will be confirmed at 3 months as demonstrated by multi-detector computed tomography (MDCT) scan. **Safety:** Composite rate of device-related serious adverse cardiac events at 30-days post procedure.
Secondary Endpoint(s)	**Efficacy:** The secondary efficacy endpoint is defined as the rate of successful placement of the Penditure™ LAA Exclusion System defined as < 10 mm of residual stump proximal to the clip at the time of the procedure (measured by intraoperative TEE with doppler) without tissue damage requiring intervention. **Safety:** Composite device-related serious adverse cardiac event rate at 12-months and annually through 36 months.
Study Design and Sample Size	Multi-center, single-arm, nonrandomized, interventional, post-market study. Up to 150 subjects will be enrolled and implanted with the Penditure™ LAA Exclusion Clip at up to 25 sites in the United States. Subjects will be followed at 30 days, 3 months, 12 months and annually for 36 months.
Inclusion/Exclusion Criteria	Inclusion Criteria:

Clinical Study Title	exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study Clinical Investigation Plan
	• Patient is indicated to be treated with the Penditure™ LAA Exclusion System • Greater than or equal to 18 years of age • The subject is willing and able to provide written informed consent and comply with study visit requirements Exclusion Criteria: • Prior LAA isolation attempt(s) • Need for emergent cardiac surgery • Subject is contraindicated for MDCT and/or TEE • Life expectancy of less than 12 months • History of cardiac surgery • Pericarditis • Presence of thrombus in the left atrium or LAA, prior to or during the procedure • Patients requiring a heart transplant, insertion of a ventricular assist device or total artificial heart, and/or ascending aortic aneurysm or dissection repair requiring circulatory arrest • STS-PROM score greater than 4 or subject deemed to be high or extreme risk per surgeon assessment • Ejection fraction less than 30% • Chronic Kidney Disease Stage IV or V (eGFR <30 ml/min) • NYHA Class IV heart failure symptoms • Patient has a documented history of substance (drug or alcohol) abuse • Known allergy to device components (Nickel and/or Titanium) • In the opinion of the investigator, the subject is not a suitable candidate for LAA isolation due to risks outweighing potential benefits including complexity of planned concomitant procedures, or other pre-existing medical conditions • Currently participating in an investigational drug or another device trial or study (excluding registries)

Study Procedures and Assessments	These procedures and assessments will be conducted at the following visits:
	Baseline:
	• Clinical Assessment
	  ○ New York Heart Association (NYHA) classification
	  ○ CHA_2DS_2-VASc score
	  ○ Current Cardiac Rhythm
	  ○ Anticoagulation medication status
	• Subject Demographics
	• Medical History

Clinical Study Title	exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study Clinical Investigation Plan
	Procedure: • Surgical approach • Concomitant procedure(s) performed • Recapture/redeployment information if required • LAA measurements and morphology • TEE results prior to clip placement to assess absence/presence of thrombus in LAA • TEE results immediately following clip placement to assess placement success and blood communication/exclusion success • Clip placement distance from circumflex artery, if possible • Appendage conduction isolation measurement post clip placement • Number of devices used, and clips placed • Device identifiers (model, size, serial, and disposition) • Serious adverse cardiac events, deaths, and device deficiency assessment **Discharge:** • Clinical Assessment • Serious adverse cardiac events, deaths, and device deficiency assessment **30 days follow-up:** • Clinical Assessment • Serious adverse cardiac events, deaths, and device deficiency assessment **3-Month Follow-up**: • Clinical Assessment • MDCT Scan to confirm LAA exclusion and clip placement status • Serious adverse cardiac events, deaths, and device deficiency assessment **12-36 Month Annual Follow-up:** • Clinical Assessment • Serious adverse cardiac events, deaths, and device deficiency assessment
Statistics	The primary analysis for the primary endpoints and secondary efficacy endpoints will occur when all implanted subjects have completed their 90-day post-procedure follow-up visit or exited the study. Secondary safety endpoint analysis will be based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the 36-month follow-up visit or have been

Clinical Study Title	exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study Clinical Investigation Plan
	exited. Additional interim analyses may be conducted to support regulatory requirements.
Professional Services	• Independent Imaging Core Lab • Independent Clinical Events Committee

3. Introduction

3.1 Background

The left atrial appendage (LAA) is a long, tubular or finger like, hooked structure which is often crenellated and has a narrow junction with the venous component of the atrium[1].

The function of the LAA, as well as the right atrial appendage (RAA), is to secrete the hormone, atrial natriuretic peptide (ANP). This peptide regulates blood pressure and volume by maintaining body diuretics, sodium, potassium, vasodilation, and adiposity. The physiological properties and anatomical relations of the LAA make it well suited to act as a decompression chamber during left ventricular systole as well as during other periods when left atrial pressure is high[1].

With an increase in age, chronic disease, comorbidities, and arrythmia, the risk for stroke rises. Stroke is the fifth leading cause of death, behind heart disease, cancer, chronic lower respiratory disease, and unintentional injuries/accidents[2]. The overwhelming majority (87%) of all strokes are ischemic in nature, the remaining being hemorrhagic[2].

The LAA is ideally suited for thrombus formation especially when coupled with atrial fibrillation (AF). Of all cardiogenic stroke causes, approximately 50% are attributed to LAA thrombus[3]. AF is often undetected and may be underestimated as a stroke risk, potentially effecting the relationship between LAA thrombus and AF to be higher[2]. It has been documented in published peer review journals that 90% of LAA thrombus are associated with stroke[4].

Patients with AF who have a CHA_2DS_2-VASc score of ≥2 are recommended to be prescribed oral anticoagulation (OAC) or non-vitamin K oral anticoagulation (NOAC)[5]. Studies conducted with patients in AF demonstrate 69% stroke risk reduction on an intention-to-treat basis and >80% stroke risk reduction in patients who remained on OAC[6]. However, frequent International Normalized Ratio (INR) monitoring, bleeding risks and renal injury in patients with long term use can cause poor subject compliance. In addition, INR is affected by numerous drug, physiological and dietary factors making it challenging to medically manage.

While OAC remains the gold standard in stroke prevention for at-risk subjects, recent updates to the ACC/AHA/HRS Guidelines include recommendations for non-pharmacological options, such as LAA exclusion, for subjects undergoing cardiac surgery with a history of AF as part of their composite heart team management of AF. A recent study found that LAA exclusion was associated with a lower rate of thromboembolism and all-cause mortality especially amongst subjects >65 years[5].

Evidence suggests that surgical exclusion may effectively manage thrombus formation in the LAA in subjects with AF, ultimately lowering risk of stroke[5]. Current surgical LAA management options include excision, suturing, stapling, banding or ligation. Although all LAA exclusion surgical techniques may reduce the flow of blood between the LAA and the LA, many times inflow/outflow is still present post procedure. Adverse events specifically associated with surgical LAA exclusion include tearing, bleeding, device migration, tissue damage and re-operation.

The current commercial device landscape for LAA closure include transcatheter occlusion devices such as the WATCHMAN™ (Boston Scientific, Inc.) and Amulet™ (Abbott Medical), devices that use a suture

loop (LARIAT™ by SentreHeart), and, finally, an epicardial LAA exclusion clip, the AtriClip (ArtiCure, Inc). The AtriClip™ was approved by the FDA in 2009 with a 98.4% successful left atrial appendage exclusion rate by computed tomography angiography or transesophageal echocardiography imaging at 3 months[7]. It was one of the only epicardial LAA exclusion devices with FDA approval until 510(k) clearance to commercialize the Penditure™ LAA Exclusion System was received.

The Penditure™ LAA Exclusion System was designed to exclude the LAA by means of a clip placed at the base of the LAA delivered by an adjustable, disposable, delivery device. The device is intended to be recapturable to obtain optimal placement on the LAA. The Penditure™ LAA Exclusion System device is indicated for use, under direct visualization, in conjunction with other open cardiac surgical procedures to exclude the LAA.

Medtronic is conducting the exClusion of the Left atrIal appendage with PendITure™ Post-Market Study, hereby referenced as CLIP-IT, to collect post-market clinical evidence on performance and clinical outcomes of the Penditure™ LAA Exclusion System to successfully exclude the LAA in subjects undergoing concomitant cardiac surgery commercially.

3.2 Purpose and Objective

The purpose of the CLIP-IT, multi-center, single arm, non-randomized, interventional, unblinded, post-market study, is to collect post-market clinical evidence on performance and clinical outcomes of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery.

4. Objective and Endpoints

4.1 Objective

The study objective is to collect post-market clinical evidence on performance and clinical outcomes of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery.

4.2 Endpoints

4.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the rate of successful exclusion of the LAA from the heart defined as the absence of residual communication (≤3 mm residual contrast communication) between the left atrium (LA) and the LAA. For those successfully placed devices, exclusion will be confirmed at 3 months as demonstrated by multi-detector computed tomography (MDCT) scan.

4.2.2 Primary Safety Endpoint

The primary safety endpoint is defined as the composite rate of device-related serious adverse cardiac events at 30-days post procedure.

4.2.3 Secondary Efficacy Endpoint

The secondary efficacy endpoint is defined as the rate of successful placement of the Penditure™ LAA Exclusion System defined as <10 mm of residual stump proximal to the clip at the time of the procedure (measured by intraoperative TEE with doppler) without tissue damage requiring intervention.

4.2.4 Secondary Safety Endpoint

The secondary safety endpoint is defined as the composite device-related serious adverse cardiac event rate at 12 months and annually through 36 months.

5. Study Design

This is a multi-center, single arm, non-randomized, interventional, unblinded, post-market study. The study will involve up to 150 subjects implanted with the Penditure™ LAA Exclusion System at up to 25 sites across the United States. The first implant occurred April 2024 and study subjects will be followed for 36 months. No site will implant more than 20% of the total implanted subject population without prior authorization from Medtronic.

This study will capture all serious adverse cardiac events, deaths, and device deficiency rates, while intra-operative transesophageal echocardiography (TEE) and post-operative MDCT scan evaluations of the LAA will be performed to demonstrate the Penditure™ LAA Exclusion System's ability to effectively exclude the LAA from the heart.

Information on the data analyses methods is provided in section 13.

5.1 Duration

The expected study enrollment period is 12-18 months with a 30-day, 3-month, 12-month and annual follow-up through 36 months. The duration of individual subject participation will vary based on timing of study site activation and their enrollment; however, at a minimum, participation of an individual subject will be at least 36 months.

Study subjects will be followed until official study closure, defined as when requirements have been satisfied per the CIP (or a decision to close made by Medtronic/Institutional Review Board/FDA), or study exit, whichever occurs first.

5.2 Rationale

This study is intended to obtain high quality clinical evidence on post-market performance and clinical outcomes of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery and may further demonstrate therapeutic benefits to decrease thrombus formation in the LAA. There are limited commercially available options for LAA exclusion, and the CLIP-IT Post-Market study will support global regulatory submissions as well as applicable post-market activities initiated by Medtronic and directed by a government and/or a regulatory authority in support of the ongoing post-market surveillance and clinical evaluation process. The study endpoints are clinically relevant and consistent with the studies objective. The study design is based on clinical evaluation and aligned with risk assessment results.

6. Product Description

6.1 General

The study will be conducted using the Medtronic Penditure™ LAA Exclusion System described below and is a 510(k) cleared, commercially available device in the United States.

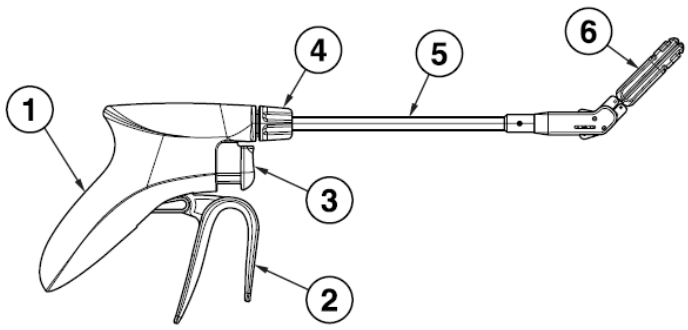
6.1.1 Medtronic Penditure™ LAA Exclusion System

The Medtronic Penditure™ LAA Exclusion System contains a curved clip for exclusion of the heart's left atrial appendage (LAA). The system is comprised of the Medtronic Penditure™ LAA Exclusion clip (implant) which is pre-loaded on a disposable delivery system and is recapturable. A separate Penditure™ LAA Exclusion System Selection Guide is used for determining the size of system needed (Table 1).

The system components for the Medtronic Penditure™ LAA Exclusion System are shown in Figure 1. Refer to the Medtronic Penditure™ LAA Exclusion System Instructions for Use for product information.

Table 1. Penditure™ LAA Exclusion System Size and Model

Penditure™ Model Number	Penditure™ Size	LAA Size Range
LAAC35	35 mm	29-35 mm
LAAC40	40 mm	34-40 mm
LAAC45	45 mm	39-45 mm
LAAC50	50 mm	44-50 mm



1 Handle
2 Actuation lever
3 Release trigger
4 Rotation knob
5 Shaft
6 Clip

Figure 1. Medtronic Penditure™ LAA Exclusion System

6.2 Manufacturer

The manufacturer and design site of the Penditure™ LAA Exclusion System is as follows:

Medtronic, Inc.
710 Medtronic Parkway,
Minneapolis, MN 55432
USA

6.3 Intended Population

The Penditure™ LAA Exclusion System is indicated for the exclusion of the left atrial appendage of the heart, performed under direct visualization and in conjunction with other cardiac surgical procedures. Direct visualization, in this context, requires that the surgeon can see the heart directly, with or without assistance from a camera, endoscope, etc., or any other appropriate viewing technologies.

6.4 Product Use

Penditure™ LAA Exclusion System will be used within the 510(k) cleared indication as is commercially approved in the United States. The only exception to the cleared indication includes any exclusion criteria per this protocol and obtained by the study sites according to standard hospital procedures for commercial products and per the product Instructions for Use.

6.5 Product Training Requirements

Prior to site activation, Medtronic will provide product training to the study staff. Additional support will be provided as needed.

6.6 Product Receipt and Tracking

Typical hospital procurement and replenishment procedures for commercial product at individual study sites will be followed. The lot numbers of devices used for study procedures, and final disposition of the devices used will be tracked within the study database.

6.7 Product Storage

The Penditure™ LAA Exclusion System is a 510(k) cleared, commercially available product. It is the responsibility of the investigator to correctly handle and store 510(k) cleared, commercially available product. These products will be used according to their labeling.

6.8 Product Return

All explanted devices should be returned to Medtronic for analysis when permissible by local laws and regulations. If the products are explanted but not returned, a justification will be reported on the appropriate case report forms. To receive a Returned Product Mailer Kit, please contact your Medtronic field personnel.

6.9 Product Accountability

The product used in this study is a 510(k) cleared, commercially available device in the United States. Device Traceability may be required per local laws and regulations. If there are additional local requirements related to the Penditure™ LAA Exclusion System beyond what is collected by Medtronic in

the database, it is the Investigator's responsibility to record this data, and the data should also be recorded in the subject's medical records according to local/national requirements. Additional requirements will not be collected by Medtronic (eg, national registration card number, identification code linked to names and contact information, log of all subjects enrolled in the study, lot, or batch number).

As this is a post-market study, Product Accountability Logs will not be utilized. Additional device traceability is not applicable, and a full device tracking/reconciliation as required by ISO 14155:2020 will not be performed.

7. Study Site Requirements

7.1 Investigator/Investigation Site Selection

7.1.1 Investigation Site Selection

The following criteria at a minimum, will be used to select sites for participation:

- The site will have the presence or capacity of establishing an investigative team consisting of the following roles:
  - A board certified, licensed cardiothoracic surgeon with experience and proficiency in management of LAA during cardiac procedures
  - A cardiologist or radiologist with expertise in Multi-Detector Computed Tomography (MDCT) of epicardial LAA interventional procedures
  - A designated study coordinator
- The site has the necessary cardiovascular facilities and services (eg, MDCT) for all pre, peri, and post-procedural aspects of the study (ie, 3D echocardiography, cardiac MDCT).
- The site expects to have adequate time and resources to conduct the study throughout the duration of the study.
- The site is willing to comply with all requirements of the relative regulatory agencies, IRBs, and the Clinical Investigational Plan (CIP).

Study site personnel training will be completed and documented prior to participation in this study.

7.1.2 Site Principal Investigator

Each site will have a PI who has overall responsibility for the conduct of the study at the site, including protecting the rights, safety, and welfare of the study subjects, maintaining integrity of the study data generated, and for ensuring the study is conducted in compliance with the CIP and IRB requirements.

The following criteria at a minimum, will be used to select PIs for participation:

- Investigator is qualified by training, education, and relevant experience appropriate to the use of the product and associated procedures
  - All PIs must be a board certified, licensed cardiothoracic surgeon with experience and proficiency in management of LAA exclusion during cardiac procedures
- Investigator expects to have adequate time and resources to conduct the study throughout the duration of the study
- Investigator has access to an adequate number of eligible subjects
- Investigator has the ability and willingness to comply with applicable IRB requirements, local and federal regulations, and the CIP
- Investigator is not debarred, disqualified, or working under sanctions in applicable regions

7.1.3 Implanting Investigators

All implanting physicians must be board certified, licensed, cardiothoracic surgeons experienced in the diagnosis and treatment of subjects undergoing LAA exclusion and trained in the handling of the Penditure™ LAA Exclusion System.

7.2 Study Site Activation

During the activation process (prior to subject enrollment), Medtronic will train study site personnel on the CIP, informed consent form (ICF) and process, data collection and reporting tools. If new members join the study site team, they will receive training on applicable study requirements relevant to their role prior to participating in the study.

Prior to performing study related activities, all regulatory requirements shall be fulfilled, including, but not limited to the following:

- IRB approval letter of current version of the CIP, patient ICF and any other applicable documents
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure (FD) for all participating investigators
- Investigator Agreement and Signature Page from the Principal Investigator
- Curriculum Vitae (CV) of investigators and key members of the investigation study site team
- Documentation of delegation of authority (DOA)
- Documentation of study training
- Additional requirements per local regulations or IRB as applicable

Medtronic will provide each study site with documentation of study site/investigator readiness; this notification must be received prior to performing study related activities.

7.3 Role of the Sponsor Representatives

Sponsor representatives may provide support at the study site as required for the study under supervision of the PI, including:

- Providing study training relevant and pertinent to the involvement of personnel conducting study activities and investigator responsibilities
- Standard of care technical support under the supervision of a study investigator, but no data entry, shall be performed by Medtronic personnel or their representatives at study sites
- Monitoring and auditing activities

8. Selection of Subjects

8.1 Study Population

The study population includes subjects who are undergoing a concomitant cardiac surgery procedure, who are indicated to receive the device, and who meet the inclusion and no exclusion criteria described in section 8.3 and 8.4.

8.2 Inclusion Criteria

Prospective subjects must meet all the following inclusion criteria to be eligible for the study:

- Patient is indicated to be treated with the Penditure™ LAA Exclusion System
- Greater than or equal to 18 years of age
- The subject is willing and able to provide written informed consent and comply with study visit requirements

8.3 Exclusion Criteria

If any of the following exclusion criteria are present, the prospective subject is not eligible for the study:

- Prior LAA isolation attempt(s)
- Need for emergent cardiac surgery
- Subject is contraindicated for MDCT and/or TEE
- Life expectancy of less than 12 months
- History of cardiac surgery
- Pericarditis
- Presence of thrombus in the left atrium or LAA, prior to or during the procedure
- Patients requiring a heart transplant, insertion of a ventricular assist device or total artificial heart, and/or ascending aortic aneurysm or dissection repair requiring circulatory arrest
- STS-PROM score greater than 4 or subject deemed to be high or extreme risk per surgeon assessment
- Ejection fraction less than 30%
- Chronic Kidney Disease Stage IV or V (eGFR <30 ml/min)
- NYHA Class IV heart failure symptoms
- Patient has a documented history of substance (drug or alcohol) abuse
- Known allergy to device components (Nickel and/or Titanium)
- In the opinion of the investigator, the subject is not a suitable candidate for LAA isolation due to risks outweighing potential benefits including, complexity of planned concomitant procedures, or other pre-existing medical conditions
- Currently participating in an investigational drug or another device trial or study (excluding registries)

8.4 Subject Enrollment

The process of subject enrollment is as follows:

- Patients identified by or presented to the study site who are indicated for concomitant cardiac surgery will be screened by the investigator or designee for the selection criteria described in section 8.3, Inclusion Criteria, and section 8.4, Exclusion Criteria, using available medical records, including relevant imaging previously performed for diagnostic or standard of care purposes.
- If the patient is deemed a potential candidate for the study, all aspects of the study will be explained to the patient and the patient will then be invited to participate in the CLIP-IT Post-Market study.
- If the patient agrees to participate, electronic (only applicable per IRB) or written informed consent will be obtained. This will be considered the point of enrollment and the patient will be assigned a subject ID number.
- Baseline assessments required per the study will be performed and the subject's clinical information will be submitted in the study database for review and confirmation of eligibility.
- A subset of study investigators will review subject data to ensure appropriate and consistent patient selection across sites and will determine if the subject meets eligibility criteria and should proceed to study treatment or exited from the study.

Each investigation site shall maintain a log of the subjects enrolled in the study, assigning a unique identification code linked to their names, alternative subject identification or contact information. Site(s) will also maintain an Enrollment and Screening Log of patients consented/enrolled, screened and treated (or attempted treatment). When a subject and the PI or authorized designee, as required, have personally or electronically signed, and dated the ICF, the subject is considered a subject enrolled in the study. The date the subject signed the ICF must be documented in the subject's medical records. Subjects must give informed consent before undergoing any protocol required assessments. However, if any of the protocol required baseline evaluations (eg, recent clinical assessments) have been performed for clinical purposes prior to consent, the assessments may be used as the protocol required assessments, provided they were obtained within the protocol required timeframe and contain the necessary information.

8.5 Subject Consent

Prior to enrolling in the study, patients must be fully informed of the details of study participation as required by applicable regulations, the site's Institutional Review Board (IRB) and by Medtronic. Informed consent must be obtained from each patient prior to conducting any protocol-induced activities beyond standard of care, by using the site IRB and Medtronic approved informed consent form (ICF). All ICF documents, including Authorization/Data Protection or other consenting forms required per local requirements, must be approved by Medtronic and the site's IRB prior to use. The ICF must be signed and dated by the patient. Any additional persons required by the site's IRB to sign the ICF must also comply. In the event the subject cannot read and/or write, a witnessed (impartial third party) ICF will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the ICF.

If applicable, an independent witness must be present throughout the entire informed consent process, and the written informed consent form and any other information related to the trial must be read aloud and explained to the prospective subject. If applicable, the witness must also sign and personally date the consent form to attest that the information in the ICF was accurately explained and clearly understood by the subject, and that informed consent was freely given.

Prior to the patient signing the ICF, the investigator or authorized designee will fully explain the nature of the research, study procedures, anticipated benefits, and potential risks of participation in the study to the patient. The investigator or delegate will allow adequate time for the patient to read and review the consent form and to ask questions. Signing the ICF serves to document the written/electronic and verbal information the investigator or authorized delegate provides to the patient, the patient's understanding of the information, and their agreement to participate. The investigator must document in the subject's medical records that the subject was consented and the date on which the consent was obtained. If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's medical record that consent was obtained prior to participation in any study related procedures.

The original signed and dated consent form (physical or electronic) will be retained in the subject's study records and a copy of the ICF will be provided to the subject. The ICF must be available for monitoring and auditing. Patients unable to provide their own informed consent, legally incompetent, or otherwise vulnerable are not allowed in the trial. Vulnerable subjects include individuals whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

Medtronic will provide each site with the study specific informed consent separately from this CIP.

8.5.1 Revision in Subject Information and Informed Consent Form

Medtronic will inform the investigators whenever information becomes available that may be relevant to the subject's continued participation in the study. The revised information will be sent to the investigator for approval by the IRB (as applicable). After approval by the IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated, if required by the IRB. The investigator or authorized designee must inform the subject in a timely manner.

9. Study Procedures

9.1 Schedule of Events and Data Collection

The protocol required evaluations and data collection requirements for each study interval are listed as follows and summarized in Table 2. All information is to be collected and reported in the Electronic Data Capture (EDC) system. Protocol-required evaluations must be performed by a delegated site individual. Follow-up clinical assessments may be performed by telephone or video communication if the subject is unable to come to the study site.

Subjects that have an attempted implant, but the clip is not successfully placed, the subject will be followed through the resolution of any serious cardiac AEs or through 30 days, whichever comes first, and then exited from the study.

Routine care post procedure differs from site to site. Follow-up visits that are not routine care are not considered burdensome and/or invasive.

Subject Baseline Visit (within 45 days of procedure)

- Clinical Assessment (including NYHA classification, CHA_2DS_2-VASc score, current cardiac rhythm and anticoagulation medication status)
- Subject demographics
- Medical history
- Confirmation of subject eligibility

Penditure™ LAA Exclusion System Procedure:

The procedure is performed according to the standard procedures of the implanting physicians and according to the Penditure™ LAA Exclusion System Instructions for Use. If during the procedure, and prior to device exposure, the physician deems, in their professional opinion, that the subject is contraindicated for Penditure™ LAA Exclusion System clip placement or actively meets an exclusion criterion (ie, thrombus in the LAA/LA), the subject will be exited from the study and the Study Exit form must be completed. The variables collected during the procedure include, but are not limited to:

- Surgical approach
- Concomitant procedure(s) performed
- Recapture/redeployment information, if applicable
- LAA measurements and morphology
- TEE results prior to clip placement to assess absence/presence of thrombus in LAA
- TEE results immediately following clip placement to assess placement success and blood communication/exclusion success
- Clip placement distance from circumflex artery, if possible
- Appendage conduction isolation measurement post clip placement
- Number of devices used, and clips placed
- Device identifiers (model, size, lot, and disposition)
- Current cardiac rhythm status prior to leaving Operating Room
- Serious adverse cardiac events and device deficiency assessment

Discharge (7 days post procedure or discharge, whichever comes first):

- Clinical Assessment (including discharge information, current cardiac rhythm, and anticoagulation medication status)
- serious adverse cardiac events and device deficiency assessment

30-day Follow-up (between 30 and 60 days):

- Clinical Assessment (including NYHA classification, CHA_2DS_2-VASc score, current cardiac rhythm, and anticoagulation medication status)
- Serious adverse cardiac events and device deficiency assessment

3-Month Follow-up (between 90 and 150 days):

- Clinical Assessment (including NYHA classification, CHA_2DS_2-VASc score, current cardiac rhythm, and anticoagulation medication status)
- MDCT scan (or TEE if subject is contraindicated to receive an MDCT) to confirm LAA exclusion and clip placement status
- Serious adverse cardiac events and device deficiency assessment

12-36 Month Annual Follow-up (between 60 days before and 60 days after the subject's procedure visit anniversary date):

Evaluations will be conducted by the investigative site team at the investigative center or via telephone/video communication. The subject will be asked to report any serious adverse cardiac events experienced since their 3-month evaluation.

- Clinical Assessment (including NYHA classification, CHA_2DS_2-VASc score, current cardiac rhythm and anticoagulation medication status)
- Serious adverse cardiac events and device deficiency assessment

Table 2. Data collection, visit windows, and study procedure requirements at subject visits

Evaluation/Visit	Baseline	Procedure[1]	Discharge	30 Days[3]	3 Month[3]	12 - 36 Months[3]
Visit Window	**Prior to procedure (within 45 days of procedure)**	**Procedure date**	**Prior to hospital discharge or 7 days post procedure, whichever comes first**	**Between 30- and 60 days post procedure**	**Between 90- and 150 days post procedure**	**Between 60 days before and 60 days after the subject's procedure visit anniversary date**
Informed Consent	X					
Clinical Assessment[3]	X		X	X	X	X
NYHA Assessment	X			X	X	X
CHA2DS2-VASC Score	X			X	X	X
Current Cardiac Rhythm	X	X	X	X	X	X
Anticoagulation Medication Status	X		X	X	X	X
Subject Demographics	X					
Medical History	X					
Confirmation of Subject Eligibility	X					
Discharge Information			X			
Concomitant Procedures		X				
Placement Assessment via TEE		X				
Exclusion Assessment via MDCT[2]					X[2]	
Serious Adverse Cardiac Event /Device Deficiency		X	X	X	X	X
Protocol Deviations	Upon occurrence					

Evaluation/Visit	Baseline	Procedure[1]	Discharge	30 Days[3]	3 Month[3]	12 - 36 Months[3]
Visit Window	**Prior to procedure (within 45 days of procedure)**	**Procedure date**	**Prior to hospital discharge or 7 days post procedure, whichever comes first**	**Between 30- and 60 days post procedure**	**Between 90- and 150 days post procedure**	**Between 60 days before and 60 days after the subject's procedure visit anniversary date**
Death	Upon occurrence					

[1] Post-procedure care is carried out according to the standard post-procedure care of the cardiac surgeon
[2] A TEE is acceptable only if the subject is contraindicated to receive an MDCT
[3] Telehealth/video communication visits are allowed for all applicable follow-up assessments, with the exception of the MDCT at 3 months.

9.2 Unscheduled Visits

Additional visits not detailed in Table 2 are considered unplanned/unscheduled for the purposes of this protocol and do not need to take place at the investigational site. Only data that are relevant to cardiac care, that can be obtained by the investigational site, are required to be reported. If the subject presents with symptoms or conditions attributable to the study treatment at the investigative center or other institution/clinic between scheduled follow-up visits, an Adverse Event eCRF must be completed if applicable, and relevant unscheduled visit data and/or imaging studies must be provided to the sponsor as applicable.

9.3 Missed Visit

Every effort must be made to ensure subjects return to or are in contact with the study site for all protocol required follow-up visits, tests, and assessments. If the subject is unable to attend their in-person or virtual protocol required clinic visit, the Investigator, or designee, must document in the subject record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in section 9.11, Deviation Handling.

If a subject will not be seen for a protocol required follow-up visit, the investigator must make every effort to contact the subject within the visit window to collect the subject's vital status as well as information related to potential AEs, safety data, and hospitalizations.

9.4 Transesophageal Echocardiogram (TEE)

During the surgical procedure, prior to device exposure and exclusion of the LAA, the LAA must be assessed to ensure thrombus in the LAA is not present via TEE. If thrombus is present, the subject must be exited from the study and treated per standard of care.

When it is confirmed the LAA is free of thrombus, the Penditure™ LAA Exclusion System will be opened and used for exclusion of the LAA. After Penditure™ LAA Exclusion Clip placement, an assessment for blood communication and device success will be conducted via TEE.

The results of these TEE evaluations, pre and post implant, will be recorded on the procedural eCRF.

9.5 Left Atrial Appendage Morphology

Before any surgical intervention, identify and assess the LAA morphology of the LAA as either a chicken wing, windsock, cauliflower, or cactus (per Figure 2 below)[8].

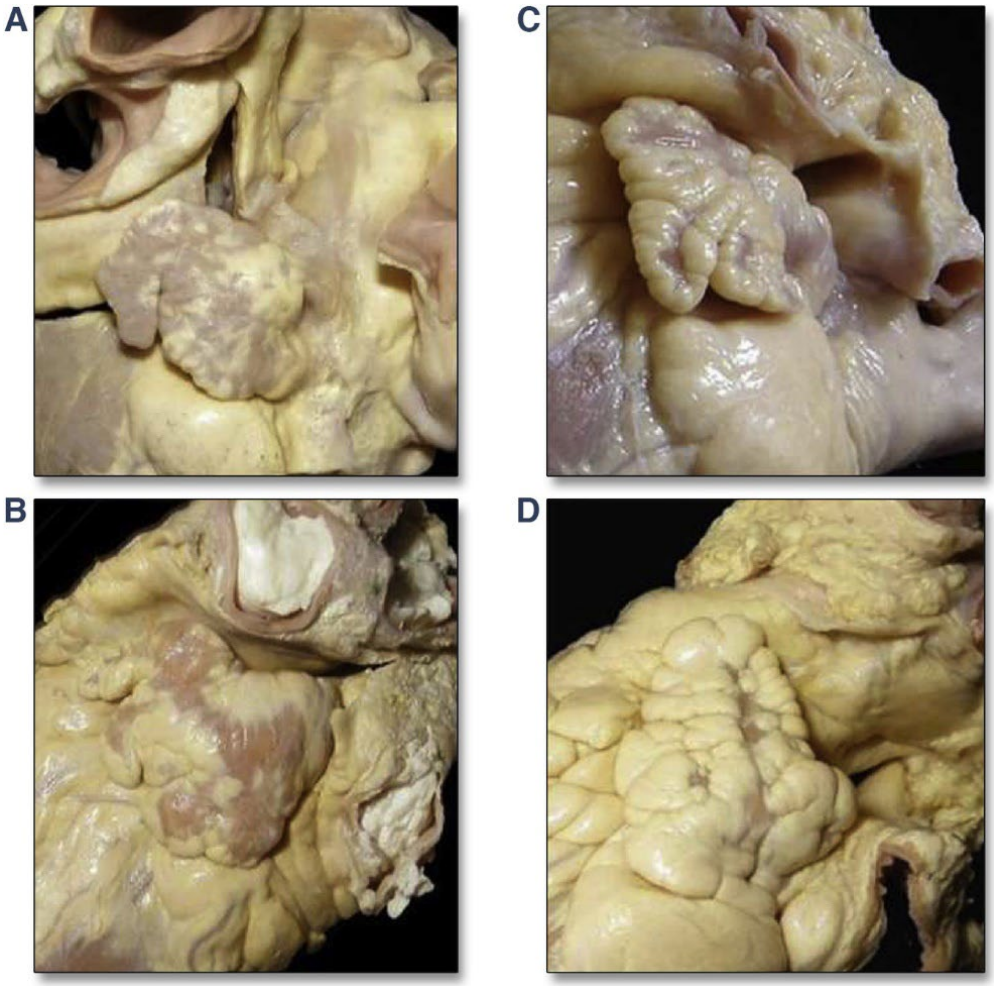


Figure 2. Anatomic variants of the left atrial appendage: Sample images taken from explanted hearts demonstrating different LAA morphologies (top). (A) Chicken wing. (B) Windsock. (C) Cauliflower. (D) Cactus.

9.6 Electrical Isolation of the LAA

Electrical isolation testing of the LAA may be performed around 20 minutes after the clip has been placed[9] using temporary pacing and sensing. It is recommended to pace the LAA at 10.0 V/0.5 ms for 30 seconds to confirm block to the left atrium.

9.7 Multi-detector Computed Tomography (MDCT)

At the 3-month visit a post-procedure cardiac MDCT is required to confirm successful exclusion and placement of the Penditure™ LAA Exclusion Clip. The MDCT exam must be performed at the study center, obtain visualization of all required variables accompanied by 3-dimensional reconstruction, and the subject's ID number should be present on all images. A dual-source CT scanner system, with a minimum of a 256-slice CT scanner with nonionic contrast medium should be used.

9.8 Oral Anticoagulants

Oral Anticoagulants (OAC) are at the discretion of the physician in accordance with standard of care at the operational site. For subjects on warfarin, International Normalized Ratio (INR) should be monitored to ensure an appropriate therapeutic level, as determined by the investigator, is maintained. The need for long-term anticoagulation should be at the subject's heart team's discretion.

9.9 Assessment of Safety

All serious adverse cardiac events (AEs), deaths, and device deficiencies (DD) will be collected from the time of LAA measurement for clip placement within the procedure for possible implant of the Penditure™ clip through study exit. See Section 11 for further information on the collection of AEs and safety information.

An external, independent CEC will review and adjudicate all deaths and device-related serious adverse cardiac events.

9.10 Recording Data

Study sites will assign a unique subject ID number to each enrolled subject. Individual subject medical information collected during this study will be considered confidential. The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation. This study will utilize an internet based Electronic Data Capture (EDC) system. Required data will be recorded on eCRFs by authorized site personnel as indicated on the Delegated of Authority Log (DOA). Study personnel delegated for eCRF completion and/or approval per the DOA will be trained on the use of the EDC system and thereafter provided with a username and password to access the system. The eCRFs must be completed and updated to reflect the latest observations on the subjects participating in the study accurately and timely. The Principal Investigator (or delegated sub-investigator) will electronically sign the appropriate pages of each eCRF.

The Device Identification eCRF must be completed as soon as possible after device use. As a best practice, study sites should strive to complete and approve all other eCRFs within 2 weeks of the applicable follow-up visit.

Data from the Core Lab will be entered into the EDC system and approved by Core Lab personnel per the executed contract and their procedures established for the study.

The EDC system maintains an audit trail of entries, changes, and corrections in eCRFs. If a person authorized to complete eCRFs makes changes to an already signed eCRF, the investigator will re-approve this eCRF.

All study-related documents must be retained for a period of at least 2 years after study closure (or longer if required by local law). Medtronic will inform the investigator/institution when these documents are no longer required to be retained.

No study document or image should be destroyed without prior written agreement between Medtronic and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

9.10.1 Source Documents

Data entered must be traceable to source documents. Source documentation is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical investigation necessary for the reconstruction and evaluation of the clinical investigation (eg, hospital records, clinical and office charts, procedure reports, laboratory notes, autopsy reports, etc.) and/or any other material that contains original information used for study data collection or adverse event reporting. Identified discrepancies between source documents and the eCRFs will be resolved through the on-line query resolution process per the Data Management plan.

The eCRFs may not serve as source documents except to capture the device use/disposition information for each treatment and the relatedness assessment for an (S)AEs and/or device deficiency in which the eCRF can be considered source per ISO 14155:2020 and as specified in the Monitoring plan. Source documentation for data elements not routinely captured in medical records (eg, echocardiography variables, MDCT variables, implant procedural variables, etc.) may vary from center to center: the site may use technical worksheets if identified as source documents.

Source documents must be retained by the investigational site for a period of at least two years after study conclusion (or longer as required by local law) and made available for monitoring or auditing by the sponsor's representative or representatives of the US FDA, IRB, and other applicable regulatory agencies. Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

The Investigator must ensure the availability of source documents from which the information on the eCRFs was derived. Where printouts of electronic medical records are provided as source documents, or where copies of source documents are retained as source documents, they must be signed and dated by a member of the investigation site team indicating they are a true reproduction of the original source document. The investigator will clearly mark clinical records to indicate that the subject is enrolled in this clinical investigation. Per ISO 14155:2020, the type and location of all source documents must be documented.

9.11 Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA. All study deviations must be reported on the eCRF regardless of whether medically justifiable, pre-approved by Medtronic, an inadvertent occurrence, or taken to protect the subject in an emergency.

Examples of study deviations include but are not limited to:

- Failure to obtain informed consent prior to participation
- Incorrect version of the ICF used
- Failure to obtain IRB approval before the start of the study
- Enrolled subject does not meet inclusion/exclusion criteria

- Required testing and/or measurements not done
- Follow-up visit or assessment performed outside window or not completed
- Adverse events not reported in the required time frame as required by regulation or as specified in the CIP
- Source data permanently lost
- Enrollment of patients during lapse of IRB approval

Prior approval by Medtronic is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Such approval shall be documented in writing and maintained in the Investigator Site File and Sponsor Trial Master File. Prior approval is not required when a deviation is necessary to protect the safety, rights, or well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control.

Protocol deviations must be reported to Medtronic via the protocol deviation eCRF. This also applies to protocol deviations that are applicable to a world pandemic (ie, COVID-19), regional epidemic, natural disaster, or similar uncontrolled situation. In addition, investigators are required to adhere to local IRB procedures for reporting deviations.

Investigators must report the following deviations to Medtronic and their reviewing IRB within 5 working days of the occurrence of the deviations:

- Failure to obtain written informed consent prior to participation
- Deviations to protect the life or physical well-being of a subject in an emergency

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any corrective and/or preventive actions that may be warranted. Repetitive or serious investigator compliance issues may represent a need to initiate a corrective action plan, which may include suspension of enrollment or the investigator or site's participation in the study.

9.12 Subject Exit, Withdrawal or Discontinuation

Subjects who discontinue participation prematurely will be included in the analysis of results (as appropriate) and will not be replaced in the enrollment of total study subjects. If a subject is discontinued from the study early, the reason for discontinuation must be documented in the subject file and a Study Exit eCRF must be completed. Details regarding the subject exit must be included in the eCRF.

The study site will make every effort to have all subjects complete the follow-up visit schedule. If the subject is unable to return for an in-person clinic visit or telephone/video communication study required visit, the Investigator, or designee, must document in the subject record the reason the subject was unable to complete the visit and, if applicable, follow the requirements for deviation reporting as outlined in Section 9.11. The investigator must also make every effort to contact the subject within the visit window to collect the subject's vital status as well as information related to potential serious adverse cardiac events.

When subjects are lost to follow-up the investigator will make efforts to confirm the vital status/health status of the subject, as described in the informed consent. A subject will not be considered lost to follow-up unless all efforts to obtain compliance are unsuccessful. At a minimum, the effort to obtain follow-up information must include 3 attempts to make contact via the subject's last known telephone number, or e-mail and if contact via these methods is not successful, a traceable letter from the

investigator must be sent to the subject's last known address. Should telephone, e-mail, and mail efforts to contact the subject be unsuccessful, the subject's primary physician (or other contact as appropriate) must be contacted. Subjects will then be deemed lost to follow up. All contact efforts to obtain follow-up must be documented in the subject's medical records.

If a subject discontinues the study at any time, is withdrawn from the study early, or completes all protocol required follow-up, they should continue to be followed by the site according to their routine clinical care. Study data will not be collected after a subject has ended their participation in the study.

10. Risks and Benefits of the Use of the Device and Procedures of the Clinical Investigation

10.1 Potential Risks

Standard risks associated with any cardiac surgery being performed in conjunction with LAA exclusion must be discussed with the subject in detail by the Investigator. There are possible risks and side effects connected to the Penditure™ LAA Exclusion System implant, but the risks are the same as those undergoing a commercial implant outside of participation in this study. Standard risks associated with the Penditure™ LAA Exclusion System are provided in the Instructions for Use.

Risks and events will be continuously monitored, assessed, and documented by the investigator. Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product.

The device will be used within the local commercially approved indication in the United States.

Possible additional risks for participating in this study, which will be outlined in the ICF provided under separate cover, may include but are not limited to:

- Potential risks associated with MDCT scans:
  - Risks associated with heavy sedation, if used
  - Allergic reaction to contrast
  - Risk of cancer from radiation

10.2 Risk Minimization

Any potential risks associated with this study are further minimized and mitigated by:

- Selecting qualified and trained investigators and training study personnel on the CIP
- Designing the clinical investigation to be conducted in accordance with relevant international standards and good clinical practice
- Adverse event oversight involving an independent Clinical Event Committee

In addition, investigators will be actively involved in the implantation and follow-up of the subjects implanted with the Penditure™ LAA Exclusion System. Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the Penditure™ LAA Exclusion System through rigorous follow-up.

10.3 Potential Clinical Benefits

Participation in this clinical study may offer no benefit to the subject. Study subjects implanted with the Penditure™ LAA Exclusion System receive the same medical treatment as if they were not participating in this post-market study. Participation contributes to the characterization of the safety and efficacy of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery.

10.4 Risk-Benefit Rationale

The Penditure™ LAA Exclusion System received 510(k) clearance as being equivalent to predicate devices already commercially available with established safety and effectiveness. As part of the 510(k) process, appropriate risk management activities were performed resulting in a positive risk-to-benefit

rationale. Other than the potential MDCT risks, the risks and potential benefits are identical for subjects implanted as part of this study when compared to the commercial setting.

11. Adverse Events and Device Deficiencies

Given this is a post-market study, Investigators are required to evaluate and document in the subject's medical records all deaths, all serious adverse cardiac events, and all device deficiencies (DD) (per the definitions in Table 3) observed in study subjects from the time of LAA measurement for clip placement within the procedure for possible implant of the Penditure™ clip through study exit. In addition, all non-subject AEs are collected throughout the trial duration on a non-subject AE eCRF.

11.1 Serious Adverse Cardiac Events

Reporting of all serious adverse cardiac events to Medtronic will occur on an AE eCRF. Each event must be reported separately. Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Investigators must follow their IRB requirements and local regulations (if applicable) for reporting AEs.

Unavoidable adverse events (UAEs), listed in Table 4, need not be reported unless the adverse event worsens or is present outside the stated timeframe, and otherwise considered to be a serious adverse cardiac event according to the treating investigator, or is suspected or confirmed to be a reportable AE.

For AEs that require immediate reporting (see Table 6), initial reporting may be done by phone, email, or on the eCRF completing as much information as possible. The completed AE eCRF must be submitted to Medtronic as soon as possible.

Any medication/treatment associated with the treatment of a CIP required AE must be reported.

All serious adverse cardiac events will be followed prospectively for all subjects with an attempted Penditure™ LAA Exclusion clip implant, beginning at the time of LAA measurement for clip placement through study exit.

11.2 Device Deficiency

The DD definition is provided in Table 3. DD information will be collected throughout the study and reported to Medtronic. Note that DDs that result in an AE to the subject will be captured as an AE only.

DD that did not lead to an AE but could have led to a SADE (ie, if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting (see Table 6).

11.3 Definitions/Classifications

The definitions to be applied for the purpose of reporting adverse events are provided in Table 3. Where the definition indicates "device", it refers to any Penditure™ LAA Exclusion System used in the study. Serious adverse events are only to be reported if they are related to the cardiovascular system (heart, arteries, veins, and bleeds, including stroke) or led to death.

Table 3. Adverse event and device deficiency definitions for reporting requirements

Event Type	Definition
General	
Adverse Event (AE) (ISO 14155:2020 3.2)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device, and whether anticipated or unanticipated.

	NOTE 1: This definition includes events related to the investigational medical device or the comparator. *NOTE 2: This definition includes events related to the procedures involved.* *NOTE 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.*
Adverse Device Effect (ADE) (ISO 14155:2020 3.1)	Adverse event related to the use of an investigational medical device. *NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device* *NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.* *NOTE 3: This includes 'comparator' if the comparator is a medical device.*
Device Deficiency (ISO 14155:2020 3.19)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety, or performance. NOTE 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labeling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator
Seriousness	
Serious Adverse Event (SAE) (ISO 14155:2020 3.45)	Adverse event that led to any of the following a) Death, b) Serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function including chronic diseases, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury, or permanent impairment to a body structure or a body function, c) Foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment. *NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.*
Serious Adverse Device Effect (SADE) (ISO 14155:2020 3.44)	Adverse device effect that has resulted in any of the consequences characteristic of a Serious Adverse Event.
Serious Health Threat (ISO 14155:2020 3.46)	A signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. *NOTE: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.*
Relatedness	
Device Related	An AE that results from the presence or performance (intended or otherwise) of the device.

Notes:

- The interpretation of Seriousness will exclude certain interventions considered standard of care during hospitalization (eg, IV hydration, certain medications delivered intravenously due to available intravenous access or NPO (nothing by mouth) status, and the delivery of electrolytes to maintain electrolyte balance or to address mild electrolyte depletion).

Any nonoral medication or fluid delivery used to treat an acute physical decompensation/deterioration episode or to otherwise resuscitate a subject will be considered serious by definition, in that it prevents a permanent impairment of a body structure or deterioration of the health of a subject.

- Hospitalization requires admission for at least 24 hours or as measured by a change in calendar date.

11.3.1 Unavoidable Adverse Events

The events included in Table 4 below are unavoidable adverse events, which are conditions expected and appropriate to occur with any open-heart surgery and therefore do not fulfill the definition of a serious adverse cardiac event, and do not need to be reported as AEs, unless they occur outside of the stated timeframe, or are otherwise considered to be a reportable event according to the treating investigator.

Table 4. Non-Reportable Medical Occurrences Associated with Open-Heart Surgery

Body category	Occurrence	Timeframe from Index Procedure (hours)
Hematologic	Blood transfusion and anemia occurring during the index procedure within expected ranges (part of the regular hospital protocol)	0
Hematologic	Any bleeding during the index procedure	0
Hematologic	Any bleeding after index procedure with <2 units PRBC or whole blood	24
Cardiac	Short transient episode of arrhythmia (including ventricular fibrillation) during index procedure	0
Central nervous system	Confusion, anxiety and/or disorientation (other than TIA/stroke) starting within 48 hours with or without medical intervention	120 (5 days)
Central nervous system	Temporary change in mental status (other than TIA/stroke) not requiring additional medical interventions or new medical assessments (eg, CT)	72
Central nervous system	Dizziness and/or lightheadedness with or without treatment	24
Central nervous system	Headache with or without treatment	72
Central nervous system	Sleep problems or insomnia with or without treatment	120 (5 days)
Respiratory/pulmonary	Mild dyspnea or cough with or without treatment	72
Respiratory	Oxygen supply after extubation/“forced breathing therapy”	48
Gastrointestinal	Diarrhea with or without treatment	48
Gastrointestinal	Obstipation / Constipation with or without treatment	72

Body category	Occurrence	Timeframe from Index Procedure (hours)
Gastrointestinal	Anesthesia-related nausea and/or vomiting with or without treatment	24
Body Temperature	Low-grade fever (<101.3°F or <38.5°C) without confirmed infection	48
Body Temperature	Low body temperature	6
Pain	Pain (eg, back, shoulder) related to laying on the procedure table with or without treatment	72
Pain	Incisional pain (pain at access site) with or without standard treatment and patient not returning to clinic to have additional treatment	No time limit
Pain	Pain in throat and/or trachea due to intubation	72
Skin and Subcutaneous System	Mild to moderate bruising or ecchymosis	168 (7 days)
Respiratory	Atelectasis/Pleural Effusion not requiring punctuation	168 (7 days)
General	Edema resulting in weight increase up to 4 kg/9 lbs. from baseline	168 (7 days)

11.4 Classification of Serious Adverse Cardiac Event and Device Deficiencies

All reported serious adverse cardiac events and DDs will be reviewed by a Medtronic representative. AEs will be classified according to the definitions provided.

Upon receipt of AE/DD at Medtronic, a Medtronic representative will review the AE/DD for completeness and accuracy and when necessary, will request clarification and/or additional information from the Investigator. Medtronic will utilize medical coding systems (eg, MedDRA) for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the investigator.

Refer to the Instructions for Use for a list of AEs related to the system that may be experienced by subjects.

Serious adverse cardiac events, deaths, and DDs will be classified according to the standard definitions as outlined below.

Table 5. Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Device (both clip and delivery system)
	Sponsor	Device (both clip and delivery system)
Seriousness	Investigator	SAE, DD with SADE potential
	Sponsor	SAE, DD with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator

11.4.1 Serious Adverse Cardiac Event and Device Deficiency Reporting Requirements

Serious adverse cardiac events, deaths, and device deficiencies that occur from the time of LAA measurement for clip placement within the study procedure are required to be reported to Medtronic via the AE or device deficiency eCRF. Events should be reported as soon as possible after the event occurs and the site's first knowledge of the event. Events are recommended to be reported within the timeframes listed in Table 6 or local requirements, whichever is more stringent.

Table 6. Recommended Reporting Timeframes for Investigators

Event Type	Timeframe for Reporting
Serious Adverse (SAE) cardiac events, deaths, device deficiencies, serious adverse device effect (SADE), and serious health threat	Immediately, but no later than 72 hours of the investigator's/site's first knowledge of the event

In addition, Investigators are obligated to report adverse events in accordance with the requirements stipulated by local law, local regulations, regulatory authorities and of their reviewing IRB.

The Sponsor is obligated to report adverse events and device deficiencies that occur during this study to the Regulatory Authorities and IRB as per local requirements outlined in Section 15.8.2.

11.4.2 Emergency Contact for Reporting Serious Adverse Cardiac Events, Deaths, and Device Deficiencies

Investigators should contact the Medtronic study manager or site manager if they have any questions regarding reportable AE/DDs. Medtronic will maintain a listing of current study contact details and provide to each site.

11.4.3 Processing Updates and Resolution

For any changes in status of a previously reported AE or DD (ie, change in actions taken, change in outcome, change in relatedness), information needs to be updated on, or added to the original AE or DD eCRF. All serious adverse cardiac events must be followed until the AE has been resolved, is unresolved

with no further actions planned, the subject dies or exits the study, or until study closure, whichever occurs first.

At the time of study exit, all collected serious adverse cardiac events that are unresolved must be reviewed and an update to the original AE must be reported, at minimum, with an outcome to be updated to not recovered/not resolved.

11.5 Subject Death

All subject deaths must be reported by the investigator to Medtronic on an AE form (AE with outcome of fatal) as soon as possible after the investigator first learns of the death. In case of death, there must be only one AE with the outcome of fatal.

In the event of a subject's death, it is recommended that the implanted system be explanted and returned to Medtronic for analysis whenever possible per local process. Local laws and procedures must be followed where applicable. If any system component is returned to Medtronic, internal return product reporting systems may be used to gather additional information about the returned device.

A copy of the death certificate, if available and allowed by state/local law, should be sent to the Medtronic clinical study team. When a death occurs in a hospital, a copy of the death summary report and all relevant hospital records, if available should be sent to the Medtronic clinical study team. If an autopsy is conducted, a copy of the autopsy report should also be sent to the Medtronic clinical study team if available and allowed by state/local law. When the death occurs at a remote study site, it is the investigative study site's responsibility to attempt retrieval of information about the death. Additionally, device disposition information must be updated.

The CEC will review deaths and provide a final adjudication of the primary classification (Appendix I). Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements. In summary, the following information will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to device
- Device disposition information
- Death summary/hospital records (if available and allowed by state/local law)
- Autopsy report (if available and allowed by state/local law)
- Death certificate (if available and allowed by state/local law)

11.6 Product Complaint Reporting

It is the responsibility of the investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless of whether they are related to intended use, misuse, or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products. The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. Medtronic will notify the Regulatory Authorities (eg, FDA) as applicable for the following incidents immediately upon learning of them and is not limited to AEs and DDs only:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or IFU which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- Any serious deterioration in the state of health, including:
    - Life-threatening illness or injury
    - Permanent impairment of a body function or permanent damage to a body structure
    - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure

12. External Committees

12.1 Study Oversight

The study will have an Executive Committee that consists of the study Coordinating Investigators. The Executive Committee will provide clinical expertise to develop the clinical study design and oversight of study execution.

12.2 Clinical Events Committee Review

At regular intervals, an independent CEC will conduct a medical review of all device-related serious adverse cardiac events and deaths, for subjects participating in the study. Redacted source documentation to support adjudication may be requested from study sites.

The CEC membership, processes, and adjudication requirements will be outlined under separate cover, within a CEC Charter.

If the CEC disagrees with the investigator's classification of the event, the CEC assessment will be provided to the investigator. If the investigator agrees with the CEC's adjudication, the Case Report Form (CRF) documenting the AE will be updated accordingly. If the investigator does not agree with the CEC's adjudication classification, both determinations will be provided within the final report; however, the CEC's adjudication will be used for data analysis. The disagreement will also be included in reporting to IRBs and regulatory authorities, if required.

12.3 Clinical Research Organizations (CROs) and Core Lab

This study will utilize an imaging Core Lab, CEC, and imaging repository. Information and contact details for each of these parties will be maintained in a separate document and be provided to the study sites as needed. A definitive list of all participating parties will be provided under separate cover and within clinical study reports.

13. Statistical Design and Methods

13.1 General Aspects of Analysis

The statistical analysis will be performed by Medtronic or designee. As this is a descriptive study, there are no prospectively developed study hypotheses or powered clinical endpoints.

Descriptive statistics will be used to report patient baseline demographic and clinical variables for the attempted implant and/or implanted sets when appropriate. Continuous variables will be summarized with count, means, standard deviations (SD), medians, first and third quartiles, minimums, and maximums. Categorical variables will be summarized with frequencies and percentages. Survival analysis using the Kaplan-Meier method will be applied on time-to-event outcomes. The Kaplan-Meier estimate and the loglog transformed two-sided 95% confidence interval will report at 1-month (30 days), 12-month (365 days), 24-month (730 days), and 36-month (1095 days) post procedure. Subject disposition will be illustrated in a diagram. Subject visits will be tabulated and compliance to visit schedule and visit windows will be summarized.

For each of the objectives the available data will be summarized, and missing data will be discussed. The main analysis of the study objectives will be based on available data and missing data will not be imputed.

As descriptive analyses are planned for the primary endpoints, no formal hypothesis testing will be performed. Accordingly, the risk of drawing false conclusions based on the clinical data obtained, as well as the risk associated with inconclusive or difficult-to-interpret data is considered low.

Nonetheless, the potential for misleading interpretations from descriptive results is acknowledged. In cases where the data are inconclusive or difficult to interpret—such as those involving wide variability, missing data, or inconsistent patterns—sensitivity analyses may be considered to assess the robustness of the results.

13.1.1 Analysis Sets

Within the enrolled population the following analysis sets are distinguished:

Enrolled set: All subjects who provide informed consent will be considered enrolled and all available data will be entered into the EDC system. Data from subjects who were consented, but screen failed and exited prior to the implant procedure will not be analyzed and published.

Attempted Implant set: The attempted implant set consists of all enrolled subjects with an attempted implant procedure with the Medtronic Penditure™ LAA Exclusion System, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia or conscious sedation administered, vascular line placed, TEE placed, or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure introducing the Medtronic Penditure™ LAA Exclusion System (called the Index Procedure). Enrolled subjects that do not receive an attempted implant with the Medtronic Penditure™ LAA Exclusion System are to be exited from the study.

Implanted set: The implanted set consists of all attempted implant subjects who are successfully implanted with the Medtronic Penditure™ LAA Exclusion clip. Subjects that have an attempted implant, but the clip is not placed successfully, will be followed through the resolution of any serious cardiac AEs or through 30 days, whichever comes first, and then exited from the study.

13.2 Analysis Execution

The first primary analysis for the primary endpoints and secondary efficacy endpoints will occur when all implanted subjects have completed their 90-day post-procedure follow-up visit or exited the study. Secondary safety endpoint analyses will be based on available data. A final report will be prepared once all data collection has ended and all subjects have completed the 36-month follow-up visit or have been exited. The inferential analysis for the primary objectives will not be updated for the final report. Additional interim analyses may be conducted to support regulatory requirements.

13.2.1 Subgroup Analyses

Subgroup analyses will be performed to evaluate consistency of the primary endpoints across key factors. Subgroup analysis of the primary endpoints will be performed for the following groups:

- Sex (male versus female)
- Surgical Method (sternotomy versus mini thoracotomy versus thoracotomy versus thoracoscopy)

13.3 Study Objective and Endpoints

The study objective is to collect post-market clinical evidence on performance and clinical outcomes of the Penditure™ LAA Exclusion System in subjects undergoing concomitant cardiac surgery. All endpoints listed below will be performed on the implanted set.

13.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is defined as the rate of successful exclusion of the LAA from the heart defined as the absence of residual communication (≤ 3 mm residual contrast communication) between the left atrium (LA) and the LAA. For those successfully placed devices, exclusion will be confirmed at 3 months as demonstrated by multi-detector computed tomography (MDCT) scan.

This primary efficacy endpoint is descriptive, and no statistical hypothesis test will be performed.

13.3.2 Primary Safety Endpoint

The primary safety endpoint is defined as the composite rate of device-related serious adverse cardiac events at 30-days post procedure.

This primary safety endpoint is the rate of the defined composite event at 30 days post procedure. A Kaplan-Meier survival analysis will be performed with results summarized at 30 days. This endpoint is descriptive, and no statistical hypothesis test will be performed.

13.3.3 Secondary Efficacy Endpoint

The secondary efficacy endpoint is defined as the rate of successful placement of the Penditure™ LAA Exclusion System defined as <10 mm of residual stump proximal to the clip at the time of the procedure (measured by intraoperative TEE with doppler) without tissue damage requiring intervention.

This secondary efficacy endpoint is descriptive, and no statistical hypothesis test will be performed.

13.3.4 Secondary Safety Endpoint

The secondary safety endpoint is defined as the composite device-related serious adverse cardiac event rate at 12 months and annually through 36 months.

This secondary safety endpoint is the rate of the defined composite event at 12-months (365 days), 24-months (730 days), and 36-months (1095 days) post procedure. A Kaplan-Meier survival analysis will be performed with results summarized at 365, 730, and 1095 days. This endpoint is descriptive, and no statistical hypothesis test will be performed.

13.4 Other Analyses

Exploratory analyses are planned for all implanted subjects to assess the rate of clip migration or malposition of the Penditure™ LAA Exclusion System from initial procedural placement at 3 months as demonstrated by imaging (ie, CT or TEE) or direct visualization.

In addition to the analysis described above and others, the following exploratory analyses may be performed:

- Analyses to assess the rate of successful recapture and redeployment of the Penditure™ LAA Exclusion System during the procedure as well as electrical isolation of the LAA after the clip is placed
- Evaluation of changes and/or outcomes from baseline in variables related to NYHA classification, CHA2DS2-VASc score, current cardiac rhythm, anticoagulation medication status, subject demographics, and medical history
- Characterization of appendage morphology and its association with clinical outcomes
- Characterization of baseline CHA2DS2-VASc score and its association with clinical outcomes

13.5 Sample Size Determination

As this is a descriptive study, the sample size of up to 150 subjects implanted with the Penditure™ LAA Exclusion System was not determined by statistical sample size methods. The assumed rate for successful exclusion of the LAA at 3 months is 97%. With a sample size of 150 subjects, the 95% Confidence Interval (CI) would be 94.8% - 99.9% with the 95% CI lower bound of 94.8% providing adequate reassurance of a high rate of successful placement. A sample size of up to 150 subjects is similarly adequate to characterize the device-related adverse event rates based on combined historical literature examples (table 7)[10].

Table 7. Historical Clip Study Outcome Rates

Source	N	Successful Exclusion at 3 months	Successful Placement	Device-Related Events at 30-days	Device-Related Events at 12 months
Caliskan *et al*.[11]	291	100 %	100 %	0	0
van Laar *et al*.[12]	222	95.0 %	96.8 %	0	NA
Kurfirst *et al*. [13]	155	98.0 %	98.1 %	0.9 %*	5.4 %*
Ailawadi *et al*.[7]	71	98.4 %	NA	0	0
Ellis *et al*.[14]	65	93.9 %	96.9 %	0	NA

Osmancik *et al.*[15]	40	97.5 %	55.0 %	0	0
Emmert *et al.*[16]	40	100 %	100 %	0	0

*Only post-operative TIA/CVA events reported, and specific follow-up timeframe was not specified

13.6 Minimization of Bias

The study methods include the following measures to minimize potential sources of bias:

- All sponsors and external study personnel will be trained on the Clinical Investigation Plan (CIP) and related study materials.
- An external, independent Clinical Events Committee (CEC) will review and adjudicate, at minimum, all deaths and device-related serious adverse cardiac events. Safety endpoint results will be based on CEC adjudications.
- An independent imaging Core Lab will review study images, when appropriate, for implanted subjects. All sites will follow a standardized protocol for acquisition of TEE and MDCT endpoint data.
- A subset of study investigators will confirm subject eligibility prior to implant.
- No site will implant more than 20% of the total implanted subject population without prior authorization from Medtronic.
- Study sites will follow their institutional procedures for maintenance/management of equipment used for assessing the study variables.

In summary, potential sources of bias that may be encountered in this study have been considered and minimized by careful study design.

13.7 Missing Data

Every effort will be undertaken to minimize missing data. However, some missing data are inevitable. The reasons for missing data will be described and evaluated for assessment of possible bias.

14. Ethics

14.1 Statement(s) of Compliance

This study will be conducted in accordance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent IRB before initiating a study, continuing review of an ongoing study by an IRB, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The CLIP-IT Post-Market Study was designed in compliance with GCP principles, ISO 14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the clinical investigation and the definition of responsibilities of the sponsor and investigators. In accordance with ISO 14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any investigator(s), or other parties participating in, or contributing to, the clinical investigation. Because this is a post-market study, an exception of ISO 14155:2020 will be that only deaths, serious adverse cardiac events, and device deficiencies will be collected from the time of LAA measurement for clip placement within the procedure for possible implant of the Penditure™ clip through study exit. All investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other investigator(s), or other parties participating in or contributing to the clinical investigation.

The principles of the Declaration of Helsinki (DoH) have been implemented through the ICF process, IRB approval, study training, clinical study registration, pre-clinical testing, risk-benefit assessment, and publication policy.

Ultimately, all study sites will follow and comply with:

- Principles of DoH
- ISO 14155:2020
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 50 (Protection of Human Subjects)
- 21 CFR Part 56 (Institutional Review Boards)
- The CTA
- The procedures described within this CIP
- Local IRB Requirements

The study will be publicly registered in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered, and results may be posted in local regulatory databases where required by local law.

15. Study Administration

15.1 Monitoring

Participating sites will be monitored to ensure that the study is conducted in accordance with the CIP, the CTA, and the applicable regulatory and local requirements. Monitoring visits will be conducted primarily to ensure the safety and well-being of the subjects is preserved as well as to ensure accuracy of the study data. Medtronic, or delegates, must therefore be allowed direct access to the subjects' clinic and hospital records, and other source data/documentation upon request as per the ICF and CTA.

Frequency of monitoring visits may be based upon subject enrollment, study compliance, number of serious adverse cardiac events, number of deviations, observations from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents will be reviewed at each study site. Monitoring for the study, including site initiation visits, interim monitoring visits, and closeout visits, will be done in accordance with the study-specific monitoring plan.

The progress of the study will be monitored by:

- On-site or remote review, as deemed appropriate by Medtronic
- Telephone communications between the site personnel (eg, investigator, study coordinator) and study monitors
- Review of eCRFs and the associated clinical records
- Review of regulatory documents

Monitoring and monitoring oversight will be provided by Medtronic. Representatives of Medtronic (ie, contractors and designees) may also act as study monitors.

15.2 Data Management

Medtronic will be responsible for the processing and quality control of the data. Data review, database cleaning, and issuing and resolving data queries will be done according to Medtronic internal standard operating procedures (SOPs) and the Data Management Plan for this study. Procedures for verification, validation, and securing the EDC system will be done according to Medtronic internal processes. The study database will employ validation programs (eg, range and logic checks) on certain entered data to identify possible data entry errors and to facilitate data validation. Required images for Medtronic or Core Lab evaluation will be de-identified and electronically transferred using a secure file transfer or other secure methods as appropriate.

15.3 Direct Access to Source Data/Documents

Medtronic may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. Regulatory authorities, such as the FDA, may also perform inspections at participating study sites. The investigator and/or institution shall permit Medtronic, IRBs and Regulatory Authorities direct access to source data and documents during monitoring, audits, and regulatory inspections.

15.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique Subject ID (SID)

to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the clinical investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with the HIPAA of 1996. To maintain confidentiality, the subject's name or any other PHI must not be recorded on any study document other than the ICF. In the event a subject's name/PHI is included for any reason, it will be masked as applicable. In the event of inability to mask the identification, it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

Study information and data may be shared with the following for reasons including, but not limited to, monitoring or auditing purposes:

- With the study sponsor, Medtronic, Inc. and its agents and contractors (together "Medtronic")
- With other researchers in the study to support study conduct or processes (eg, patient eligibility confirmation)
- With government organizations and review boards required to watch over the safety and effectiveness of medical products and therapies and the conduct of research
- With other persons who are required to watch over the safety and effectiveness of medical products and therapies and the conduct of research

15.5 Liability/Warranty/Insurance Information

Subject compensation, indemnification, and liability insurance coverage are included In the Clinical Trial Agreement for each participating site.

Medtronic maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and customs concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the IRB.

Warranty information is provided in the product packaging for the commercially released Medtronic Penditure™ LAA Exclusion System and additional copies are available upon request.

15.6 CIP Amendments

Any revisions or amendments to the CIP or ICF document, will be submitted to governing IRBs, according to applicable regulations. Approval by the IRBs (where applicable) must be obtained prior to implementing a CIP revision at the study site. Furthermore, investigators shall sign any approved amendment for agreement.

15.7 Record Retention

All study-related documents must be retained for a period of at least 2 years after study closure (or longer if required by local law). Medtronic will inform the investigator/study site when these documents are no longer required to be retained.

No study document or image will be destroyed without prior written agreement between Medtronic and the investigator. The investigator must take measures to prevent accidental or premature destruction of documents. Should the investigator wish to assign the study records to another party or move them to another location, advance written notice must be given to Medtronic.

Medtronic will retain the study records according to Medtronic corporate policy and record retention schedule.

15.8 Reporting Requirements

15.8.1 Investigator Records and Reports

The investigator is responsible for the preparation, review, signature (as applicable), and retention of the below cited records. All records, with the exception of case history records and eCRFs, must be kept in the Investigator Site File or Subject Study Binder, including but not limited to:

- All essential correspondence that pertains to the investigation
- Records of each subject's case history and exposure to the device. Including, for example:
  - Signed and dated informed consent forms
  - Medical records, including, for example, medical history, progress notes of the physicians, the subject's hospital chart(s), nurses' notes, copies of signed and dated eCRFs
  - AE/DD information
  - A record of the exposure of each subject to the device (eg, date of procedure and follow-up assessment dates)
- Documentation of any deviation from the CIP, including the date and the rationale for such deviation
- Signed Investigator Agreement, current CV of the principal investigator (PI), sub-investigator(s) and key members, signed DOA
- Disclosure of conflict of interest and financial disclosure of the PI and sub-investigator(s)
- Subject Enrollment and Screening Log
- The approved CIP, Patient Information/ICF, and any amendments
- Signed and dated CTA
- Insurance certificate, where applicable
- IRB Approval documentation and IRB composition/voting list where required per local law, including written information that the investigator or other study staff, when member of the IRB, did not participate in the approval process
- Regulatory authority notification and approval documentation, where applicable
- Training records for study site staff, including documentation of training on the use of the Penditure™ LAA Exclusion System for implanters
- Maintenance/calibration documentation of imaging equipment used for assessing the study variables
- Final study report
- List of sponsor and monitoring contacts
- Any other records that local IRB and/or regulatory agencies require to be maintained

The investigator is responsible for the preparation (review and signature) and submission to the sponsor of all eCRFs, serious adverse cardiac events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the clinical investigation plan. If any action is taken by an IRB with respect to this study, copies of all pertinent documentation must be forwarded to Medtronic in a timely manner. Reports are subject to inspection and to the retention requirements as described above for investigator records.

Safety data investigator reporting requirements are listed in Section 11. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section. The investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in Table 8.

Table 8: Investigator reports applicable for all geographies per Medtronic requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB approval	Sponsor and Relevant Authorities	The investigator must report a withdrawal of approval by the reviewing IRB of the investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB	Any deviation from the clinical investigational plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs and Relevant Authorities	This report must be submitted within 3 months of study completion or termination.

15.8.2 Sponsor Records and Reports

Medtronic shall maintain the following accurate, complete, and current records, including but not limited to:

- All essential correspondence related to the clinical study
- Signed Investigator Agreement and Financial Disclosure information
- AE and DD information
- All eCRFs, prepared and signed by the investigators, received source documentation and core lab reports
- CIP, (and subsequent amendments)
- All approved ICF templates, and other information provided to the subjects and advertisements, including translations
- Copies of all IRB approval letters and relevant IRB/REB/EC correspondence and IRB voting list/roster/letter of assurance

- Site monitoring reports
- Contact lists of all participating investigators/investigative sites, study monitors and Sponsor staff members; Sponsor will maintain these lists and provide updates to the necessary parties
- Regulatory authority notification and approval documentation, where applicable
- Statistical analyses and underlying supporting data
- Clinical study report(s)
- Study training records for study site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

Medtronic records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in stored in secured file cabinets at Medtronic during the course of this study.

After closure of the study Medtronic will archive records and reports indefinitely.

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the table below. In addition to the reports listed below, Medtronic shall, upon request of the reviewing EC, RA, or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Medtronic reporting requirements are listed in Section 11. The Sponsor is responsible for the preparation of, the accuracy of the data contained in, the review of, and the submission of the reports listed in Table 9: Sponsor records and reporting responsibilities applicable to the United States.

Table 9: Sponsor records and reporting responsibilities applicable to the United States

Report	Submit To	Description/Constraints
Study Deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate clinical investigator(s), are reported on the eCRFs and the final report of the clinical investigation. Study site specific study deviations will be submitted to investigators periodically.
Premature termination or suspension of clinical study	IRB/REB/EC, Investigators, and regulatory authorities, where applicable	Medtronic will provide prompt notification of termination or suspension and reason(s) to investigator and where required to IRB/REB/EC and RAs.

15.9 Publication and Use of Information

Medtronic is committed to the widespread dissemination of all primary and additional endpoint results. A Publication Plan will be followed. At the conclusion of the study, a multisite abstract reporting the primary results will be prepared by the PIs (in collaboration with others) for subsequent presentation at an annual scientific meeting. A multisite publication will similarly be prepared for publication in a

reputable scientific journal. The publication of the principal results from any single site experience within the study is not allowed until both the preparation and publication of the multisite results, and then only with written permission from Medtronic. Following analysis and presentation of the endpoint results, active participation of all participating investigators, CEC members, and core laboratory personnel will be solicited for data analysis and abstract and manuscript preparation. Submission of all abstracts and publications from the study requires approval by the steering committee and publication committee.

A separate Publication Plan will provide detailed information about the publication committee, authorship, publication proposals, and requests for data.

15.10 Suspension or Early Termination

15.10.1 Suspension or Early Termination of the Study

Medtronic may decide to suspend or prematurely terminate the study. If the study is terminated prematurely or suspended, Medtronic shall promptly inform the clinical investigators and regulatory authorities (as applicable) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB. Medtronic will, as soon as possible, provide a written statement to the investigators to enable prompt notification of the IRB. If study enrollment is terminated early, follow-up visits will continue for all enrolled subjects.

15.10.2 Suspension or Early Termination of a Study Site

Medtronic may decide to suspend or prematurely terminate a study site (eg, in case of expiring approval of the reviewing IRB, non-compliance to the CIP, or lack of enrollment). If a study site is suspended or prematurely terminated, Medtronic shall promptly inform the investigator(s) of the termination or suspension and the reason(s) for this. The investigator shall then promptly inform the reviewing IRB.

16. Appendices

Appendix I: Endpoint Device-Related Serious Adverse Cardiac Event Definitions

17. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of affected study documents	Author(s)/Title
1.0	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Not Applicable, New Document	Jenell Lorenz, Senior Clinical Research Specialist Morgan Judkins, Principal Clinical Research Specialist Shuzhen Li, Senior Principal Statistician
2.0	• Clarified primary effectiveness endpoint contrast measurement verbiage	• To further clarify direct measurement by MDCT	No impact, primary effectiveness endpoint verbiage clarified but endpoint analysis remains unchanged	Updates to be reflected in applicable study documents	Morgan Judkins, Principal Clinical Research Specialist
	• Added additional exclusion criteria	• To reduce risk of subject missing the primary endpoint analysis follow-up at 3 months due to comorbidities identified			
	• Clarified treatment maximum allowance	• To clarify that more subjects can be implanted with prior authorization from Medtronic			
	• Adjustment of event reporting timeframe from required to recommended	• The reporting timeframe is recommended and not required			
	• Referred to CEC charter for further detail regarding roles and responsibilities	• Limit duplication across study documents			
	• Removal of compliance to regulations 21 CFR Part 54 and 21 CFR Part 803	• The regulations are not required for this study			
	• Section movement throughout due to protocol template update	• Template updated			
	• Administrative and clerical adjustments throughout	• To further clarify			
3.0	• Safety endpoints updated to "device-related serious adverse cardiac events" • Transferred to new CIP template • Administrative and clerical adjustments throughout	To clarify adverse event collection and analysis	• No impact, primary efficacy endpoint. • Safety endpoint analysis changed to include device-related serious cardiac events	Updates to be reflected in applicable study documents	Lisa Slusser, Senior Clinical Research Specialist

Appendix I: Mortality and Device-Related Adverse Cardiac Event Endpoint Definitions

Mortality and Device-Related Adverse Cardiac Event Definitions

Event Term	Device Related Adverse Event Endpoint Definition
All-Cause Mortality[17]	**Cardiovascular mortality:** Death meeting one of the following criteria: 1) Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (eg, mediastinitis, endocarditis), or other clear cardiovascular cause 2) Intraprocedural death 3) Sudden death • Sudden Cardiac Death (SCD): Natural death due to cardiac causes, indicated by abrupt loss of consciousness within one hour of the onset of acute symptoms; preexisting heart disease may have been known to be present, but the time and mode of death are unexpected. If time of onset cannot be determined, SCD will alternatively be defined as any unexpected cardiac death occurring out of the hospital or in the emergency room as dead on arrival. • Non-sudden Cardiac Death: All cardiac deaths that are not classified as sudden deaths, including all cardiac deaths of hospitalized subjects on inotropic support. 4) Death of unknown cause • Unknown Cardiac Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death. **Non-cardiovascular**: Death clearly related to a non-cardiovascular cause: such as respiratory failure not related to heart failure (eg, pneumonia), renal failure, liver failure, infection (eg, urosepsis), cancer, trauma, and suicide
Stroke and TIA[18]	**Diagnostic Criteria:** Acute episode of a focal or global neurological deficit with at least 1 of the following: • change in the level of consciousness • hemiplegia, hemiparesis • numbness or sensory loss affecting 1 side of the body • dysphasia or aphasia • hemianopia • amaurosis fugax 1. Other neurological signs or symptoms consistent with stroke **Stroke:** duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death **TIA:** duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct

	2) No other readily identifiable non-stroke cause for the clinical presentation (eg, brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist 3) Confirmation of the diagnosis by at least 1 of the following: • Neurologist or neurosurgical specialist, **OR** • Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone **Stroke Classifications** **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage **Undetermined**: insufficient information to allow categorization as ischemic or hemorrhagic
Systemic Embolism[19]	Pulmonary Embolism: An obstruction of the pulmonary arteries in the lungs, usually due to a blood clot or foreign matter. Patients commonly present with symptoms such as shortness of breath, cough, hemoptysis, pleuritic pain, or palpitations. Pulmonary embolism must be diagnosed by study such as V/Q scan or angiogram. Peripheral Arterial Embolism: An operative, autopsy, or clinically documented embolus that produces symptoms from complete or partial obstruction of a peripheral (noncerebral) artery.
Major Bleeding (BARC 3b and above) [20]	**Type 0:** no bleeding **Type 1:** bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional **Type 2:** any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation **Type 3** **Type 3a** • Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) • Any transfusion with overt bleeding **Type 3b**

- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4: CABG-related bleeding

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

Type 5: fatal bleeding
Type 5a
Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b
Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

Overt bleeding is defined by any of the following criteria being met:

- Reoperation after closure of sternotomy for the purpose of controlling bleeding (BARC Type 4)
- Chest tube output:
  - 2 L within a 24-hour period (BARC Type 4) OR
  - 350 cc within 1st hr. post op OR
  - ≥ 250 cc. 2nd hr. post op OR
  - 150 cc 3rd hr. post op
- Bleeding from the access site or the vascular system outside of the surgical site

CABG indicates coronary artery bypass graft. Platelet transfusions should be recorded and reported but are not included in these definitions until further information is obtained about the relationship to outcomes. If a CABG-related bleed is not adjudicated as at least a type 3 severity event, it will be classified as not a bleeding event. If a bleeding event occurs with a clear temporal relationship to CABG (ie, within a 48-h time frame) but does not meet type 4 severity criteria, it will be classified as not a bleeding event.
*Corrected for transfusion (1 U packed red blood cells or 1 U whole blood=1 g/dL hemoglobin).
†Cell saver products are not counted.

Tissue Damage to the LAA or Left Atrium	Inadvertent damage to the structure of the left atrium or LAA that requires surgical repair of any kind.
Heart Failure[21]	Heart failure (HF) event with or without hospitalization defined by each of the following: 1. The patient exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following: dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea); decreased exercise tolerance; fatigue; or other symptoms of worsened end-organ perfusion or volume overload. 2. The patient has objective evidence of new or worsening HF, consisting of at least two physical examination findings or one physical examination finding and one laboratory or invasively measured criterion, including: a) Physical examination findings considered to be due to HF include new or worsened: peripheral oedema; increasing abdominal distention or ascites (in the absence of primary hepatic disease); pulmonary rales/crackles/crepitations; increased jugular venous pressure and/or hepatojugular reflux; S3 gallop; clinically significant or rapid weight gain thought to be related to fluid retention. b) Laboratory evidence of new or worsening HF, if obtained within 24 h of presentation, include: increased BNP/NT-proBNP concentrations consistent with decompensation of HF (in patients with chronically elevated natriuretic peptides, a significant increase should be noted above baseline); radiological, ultrasonographic, or implantable monitor evidence of pulmonary congestion; non-invasive or implantable diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output. c) Invasive evidence of new or worsening HF including right heart catheterization showing elevated PCW pressure, elevated CVP, depressed cardiac index, or left heart catheterization showing elevated LVEDP consistent with decompensation of HF. 3. The patient receives at least one of the following treatments specifically for HF: a) Significant augmentation in oral diuretic therapy (including at least a doubling of loop diuretic dose, initiation of loop diuretic therapy, initiation of combination diuretic therapy). b) Initiation of intravenous diuretic (even a single dose). c) Initiation of an intravenous vasoactive agent (catecholamine, phosphodieaterase-3 inhibitor, other vasopressor, vasodilator. d) Mechanical fluid removal (ultrafiltration, hemofiltration, initiation of dialysis for what is felt to be a primary cardiac rather than renal cause).

	4. The patient has improvement in symptoms and objective signs of HF in response to therapy.
Pericardial effusion requiring intervention[22]	A pericardial effusion refers to the accumulation of excess fluid (> 50 mL) in the pericardial sac surrounding the heart. Interventions may include percutaneous treatment/drainage or intervention/repair.
Circumflex Artery Occlusion	A complete or partial blockage of the left circumflex artery resulting in cardiac ischemia or myocardial infarction as defined below.
Myocardial infarction[16]	**Type 1 (Spontaneous MI) (>48 h after the index procedure)** 1. Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following: • Symptoms of acute ischemia • New ischemic ECG changes (new ST-segment or T-wave changes or new LBBB) • New pathologic Q-waves in ≥2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischemic etiology • Identification of a coronary thrombus by angiography or autopsy 2. Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large, circumscribed area of necrosis with or without intramyocardial hemorrhage, meets the type 1 MI criteria regardless of cTn values **Type 2 (Imbalance between myocardial oxygen supply and demand)** Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following: • Symptoms of ischemia • ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) • New pathologic Q-waves in ≥2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality **Type 3 (MI associated with sudden cardiac death)** Patients who suffer cardiac death, with symptoms suggestive of myocardial ischemia accompanied by presumed new ischemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination. **Type 4A (Criteria for PCI-related MI ≤ 48 h after the index procedure)** 1. In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK-MB ≥5x ULN with one or more of the following:

- New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure

2. In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35X ULN with one or more of the following:
   - New pathologic Q-waves in ≥2 contiguous leads
   - New persistent LBBB
   - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
   - Substantial new loss of viable myocardium on imaging related to the procedure
3. In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

Type 4B (Stent thrombosis)

Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.

- Acute: 0 to 24 h
- Subacute: >24 h to 30 days
- Late: >30 days to 1 year
- Very late: >1 year after stent implantation

Type 4C (Coronary stent restenosis)

Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI

Type 5 Periprocedural (post-SAVR, TAVR or CABG) MI (≤48 h after the index procedure)

1. In patients with normal baseline CK-MB: The peak CK-MB measured within 48 h of the procedure ≥10x the local laboratory ULN or CK-MB ≥ 5x ULN with one or more of the following:
   - New pathologic Q-waves in ≥2 contiguous leads
   - New persistent LBBB
   - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
   - Substantial new loss of viable myocardium on imaging related to the procedure

   In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70x the local laboratory ULN or ≥35x ULN with one or more of the following:

	• New pathologic Q-waves in ≥2 contiguous leads • New persistent LBBB • Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch • Substantial new loss of viable myocardium on imaging related to the procedure 2. In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.
Clip displacement requiring reintervention	Any surgical procedure following exit from the procedure room to repair, alter, adjust, or replace a previously implanted clip due to displacement.

Classification of Causality Relatedness

The following definitions are intended as guidelines for classifying causality relatedness between the event and the Penditure™ LAA Exclusion System.

Not related to the Penditure™ LAA exclusion clip or delivery system	Relationship can be excluded when: • the event has no temporal relationship with the use of the device or procedure • the event does not follow a known response pattern to the device (if the response pattern is previously known) and is biologically implausible. • the discontinuation of device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event; • the event involves a body-site or an organ not expected to be affected by the device or procedure; • the event can be attributed to another cause (eg, an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); • the event does not depend on a false result given by the device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.
Possible relationship to the Penditure™ LAA exclusion clip or delivery system	The relationship is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable relationship to the Penditure™ LAA exclusion clip or delivery system	The relationship seems relevant and/or the event cannot reasonably explained by another cause.

Causal relationship to the Penditure™ LAA exclusion clip or delivery system	The event is associated beyond reasonable doubt when:
	• the event is a known side effect of the product category the device belongs to or of similar devices and procedures;
	• the event has a temporal relationship with device use/application or procedures;
	• the event involves a body-site or organ that
	  ○ the device or procedures are applied to;
	  ○ the device or procedures have an effect on;
	• the event follows a known response pattern to the device (if the response pattern is previously known);

	• the discontinuation of device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible); • other possible causes (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; • harm to the subject is due to error in use; • the event depends on a false result given by the device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

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