| Medtronic<br>**Statistical Analysis Plan** | |
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| **Clinical Investigation Plan Title** | exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study |
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| **Sponsor/Local Sponsor** | Medtronic, plc.<br>Cardiac Surgery Clinical Research and Medical Science<br>8200 Coral Sea Street N.E.<br>Mounds View, MN 55112, United States |

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# 1. Version History

| Version | Summary of Changes | Author(s)/Title |
|---|---|---|
| 1.0 | • Not Applicable, New Document | Yan Hu, Principal Statistician |
| **2.0** | • Section 7.1.2 remove covid related PD due to covid data is not required to collect<br>• Section 7.2 update last known clinical follow up date and last contact date to help analysis.<br>• Section 7.3, slightly revised the site pooling analysis method<br>• Section 7.4, removed the sensitivity analysis due to missing data<br>• Sections 7.9., 7.9.4 and 7.10; slightly updated primary and secondary safety endpoints to align with updated CIP<br>• Section 7.9.7: added the definition for malposition or migration. Added the clarification for the evaluation of cardiac rhythm, anticoagulation medication and removed the subject demographics and medical history related analysis.<br>• Section 7.10, slightly updated AE listing reporting by replacing AE starting and ending dates with days to AE, and AE term<br>• Section 8, remove the validation for the analysis dataset.<br>• Minor adjustments made throughout to ensure consistency with the CIP | Yan Hu, Sr Principal Statistician |

# 2. List of Abbreviations and Definitions of Terms

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AF | Atrial Fibrillation |
| CEC | Clinical Event Committee |
| CHA2DS2-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 Investigational Plan |
| CLIP-IT | exClusion of the Left atrIal appendage with PendITure™ |
| CTA | Clinical Trial Agreement |
| DD | Device Deficiency |

| Abbreviation | Definition |
|---|---|
| KM | Kaplan-Meier |
| LA | Left Atrium |
| LAA | Left Atrial Appendage |
| MDCT | Multi-detector Computed Tomography |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MI | Myocardial Infarction |
| NYHA | New York Heart Association |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| TEE | Transesophageal Echocardiogram |
| TIA | Transient Ischemic Attack |
| UADE | Unanticipated Adverse Device Effect |

# 3. Introduction

The purpose of this Statistical Analysis Plan (SAP) is to document, before data are analyzed, the rationale for the study design, evaluation of the safety and efficacy endpoints, and the planned analyses that will be included in study reports for the exClusion of the Left atrIal appendage with PendITure™ (CLIP-IT) Post-Market Study.

This SAP is developed under the Clinical Investigational Plan (CIP) Revision 3.0 (19-Jun-2025).

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 LAA is ideally suited for thrombus formation especially when coupled with atrial fibrillation (AF).

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; for the purpose of collecting post-market clinical evidence on 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 and reduce stroke risk.

As this is a descriptive study, and the required “up to 150 subjects implanted with the Penditure™ LAA Exclusion System” was not determined by typical statistical sample size method; the study endpoints will be summarized using descriptive statistics and no statistical hypothesis test will be performed.

# 4. Study Objectives 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

The study endpoints are summarized in section 7.9 of this SAP.

# 5. Investigation Plan

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. Study subjects will be followed for 36 months. 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.

The expected study enrollment period is 12-18 months with a 30-day, 3-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.

All follow-up periods are defined as the number of days after the date of the index procedure (first attempted procedure). The index procedure = Day 0.

- **Screening/Baseline** = Prior to procedure (within 45 days of procedure)
- **Index Procedure** = First attempted procedure date
- **Discharge** = 7-days post procedure or discharge, whichever comes first
- **30 Days** = 30 – 60 days post procedure
- **3 Months =** 90 – 150 days post procedure
- **Annual** = procedure anniversary (based on 365-day year) +/- 60 days
    - **1 Year** = 305 – 425 days post procedure
    - **2 Years =** 670 –790 days post procedure
    - **3 Years** = 1035 – 1155 days post procedure

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 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.

# 6. Determination of Sample Size

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 1)[2].

**Table 1. 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.*[3] | 291 | 100 % | 100 % | 0 | 0 |
| van Laar *et al.*[4] | 222 | 95.0 % | 96.8 % | 0 | NA |
| Kurfirst *et al.* [5] | 155 | 98.0 % | 98.1 % | 0.9 %* | 5.4 %* |
| Ailawadi *et al.*[6] | 71 | 98.4 % | NA | 0 | 0 |
| Ellis *et al.*[7] | 65 | 93.9 % | 96.9 % | 0 | NA |
| Osmancik *et al.*[8] | 40 | 97.5 % | 55.0 % | 0 | 0 |
| Emmert *et al.*[9] | 40 | 100 % | 100 % | 0 | 0 |

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

# 7. Statistical Methods

## 7.1 Study Subjects

### 7.1.1 Disposition of Subjects

Subject disposition will be summarized, including the number of subjects enrolled, attempted implant, implanted, died, withdrawn, lost to follow-up, exited the study due to other reasons, and completed each visit per follow-up schedule during the study.

### 7.1.2 Clinical Investigation Plan (CIP) Deviations

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

All study deviations will be summarized by deviation category and visit. For each category, both event and subject counts will be reported. The percentage of subjects with deviations will be calculated based on the number of subjects eligible for the specified visit (screening/baseline, procedure, discharge, etc.).

### 7.1.3 Analysis Sets

The relevant analysis sets for the study include enrolled set, attempted implant set and implanted set, and they are defined as below.

- **Enrolled set**: All subjects who provide an informed consent form will be considered enrolled and all available data will be entered into the EDC system. Time zero begins on the date of the enrollment. 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, Transesophageal Echocardiogram (TEE) placed, or any monitoring line placed. Time zero begins on the date of 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. Time zero begins on the date of the first implant procedure with an actual implant (first successful implant). 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. The analyses of the endpoints are conducted on the implanted set.

## 7.2 General Methodology

Descriptive statistics will be used to summarize the preoperative, operative, discharge, and follow up clinical variables for the attempted implant and/or implanted sets when applicable. Continuous

variables will be summarized with 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 (KM) method will be applied on time-to-event endpoints. For the implanted set, day zero begins on the first successful implant procedure date, if a patient has an explant, day zero will not be reset and day zero still begins on the index procedure date. For the attempted implant set, time zero begins on the first attempted implant procedure date. Subjects without events will be censored at their last known event-free date (last known clinical follow-up date): defined as the latest date of all follow-up visits, assessments, adverse events, death or study exit (excluding the study exit date if the exit reason is "lost to follow up").

For subjects whose exit reason is "lost to follow-up", the lost to follow up date will be included as part of the last contact date definition. The last contact date is defined as the latest date of the follow-up visits, assessments, adverse events, death or study exit. The last contact date (instead of the last known clinical follow-up date) will be used in the follow-up visit compliance assessment.

The KM estimate, the number of subjects with events, the number of events, 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 date.

As descriptive analyses are planned for the primary endpoints, no formal hypothesis testing will be performed.

## 7.3 Center Pooling

The analyses will pool the data across all study sites. Primary and secondary endpoints will be based on assessments made by the independent Clinical Events Committee (CEC) and/or echocardiographic core lab. Therefore, data are expected to be poolable across sites and analysis will be based on data combined across sites.

Sites should contribute at least 5 implanted subjects for the pooling analysis. If this is not the case, the site is considered a "small site"; small sites will be ordered by the date of procedure in the implanted set. Starting with the first "small site", a pseudo-site will be created by adding subjects from successive "small sites" (all subjects from a "small site" will be in the same pseudo-site). Once the number of subjects reaches or exceeds the size of the median enrollment of the "large sites (defined as sites with implanted subject number n>=5)", then a second pseudo-site will be created, beginning with the next site not already included in the first pseudo-site. Additional pseudo-sites, if needed, would be created in a similar manner. A pseudo-site will not have less than the minimum subjects.

Center-to-center heterogeneity across the study sites will be assessed for the primary endpoints by performing a chi-square test (for the primary efficacy endpoint) or log rank test (for the primary safety endpoint), whenever applicable. If the test shows statistically significant ($p <= 0.05$) then a further evaluation will be conducted by using a logistic regression model (for primary efficacy endpoint) or a proportional hazards model (for the primary safety endpoint) and including site as a fixed effect whenever appropriate. Evidence of between-site heterogeneity will not preclude pooling data; rather, it may result in further investigation into the sources of the apparent differences in event rates between sites. In addition, the primary endpoints' results along with 95% confidence intervals for each center will be displayed.

## 7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, drop-outs will be censored at the time of discontinuation. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data.

In the case of partial dates, the general rule is as follows:

- If only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15$^{th}$ of that month.
- If only the year is known, the event or assessment will be analyzed as if it occurred on June 30$^{th}$ of that year.

These resolutions of partial dates are subject to the restrictions that post-procedure events and assessments must occur no earlier than the procedure date or later than the study exit date.

If a subject's data is missing for any reason, that subject will not be included in that portion of the analysis. The reasons for missing data will be described and evaluated for assessment of possible bias.

## 7.5 Adjustments for Multiple Comparisons

No multiple comparisons are planned for this study.

## 7.6 Demographic and Other Baseline Characteristics

Baseline demographic and clinical variables will be summarized for the implanted set. Continuous variables will be summarized as means, medians, standard deviations, first and third quartiles , minimum and maximum. Categorical variables will be summarized as frequencies and percentages.

## 7.7 Treatment Characteristics

Procedure data will be summarized for the Implanted set. Continuous variables will be summarized as means, medians, standard deviations, first and third quartiles, minimum and maximum. Categorical variables will be summarized as frequencies and percentages.

## 7.8 Interim Analyses

No formal interim analyses are planned for the purpose of potential termination or modification of the study. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected. Additional interim analyses may be conducted to support regulatory requirements.

## 7.9 Evaluation of Objectives

### 7.9.1 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 jet velocity) 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.

#### 7.9.1.1 Hypothesis Testing

There is no hypothesis testing for the primary efficacy endpoint.

### 7.9.1.2 Analysis Method

The analysis will be performed on the implanted set using descriptive statistics. The successful exclusion will be summarized as a binary proportion with its 95% confidence interval using Clopper-Pearson Exact Method. The numerator of the rate is the number of subjects who had successful exclusion; and the denominator is the number of subjects whose exclusion status (residual communication between LA and LAA) can be determined at their 3-month visit through MDCT scan.

## 7.9.2 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.

### 7.9.2.1 Hypothesis Testing

There is no hypothesis testing for the primary safety endpoint.

### 7.9.2.2 Analysis Method

This endpoint will be performed on the implanted set using the Kaplan-Meier method. The general method of KM analysis will follow the specifications described in section 7.2. The composite rate and its 95% confidence interval will be summarized at 30-days post procedure.

Data for this endpoint will be adjudicated through the Clinical Event Committee (CEC).

## 7.9.3 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.

The analysis will be performed on the implanted set using descriptive statistics. The successful placement rate will be summarized as a binary proportion with its 95% confidence interval using Clopper-Pearson Exact Method. The numerator of the rate is the number of subjects who had successful placement; and the denominator is the number of subjects whose LAA placement status (measurement of residual stump proximal to the clip) can be determined by TEE at the time of the procedure.

No statistical hypothesis tests will be performed for the endpoint.

## 7.9.4 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 (365 X 2 = 730 days), and 36-months (365 X 3 = 1095 days) post procedure.

The analysis will be performed on the Implanted analysis set. Day 0 begins on the first successful implant date. A Kaplan-Meier survival analysis will be performed. The general method of KM analysis will follow specifications as described in section 7.2. The composite event rate will be summarized at 365-days, 730-days, and 1095-days post procedure.

This endpoint is descriptive, and no statistical hypothesis tests will be performed.

### 7.9.5 Subgroup Analyses

Subgroup analyses will be performed for the primary endpoints to determine whether significant differences exist in the endpoint results between specified subgroups, wherever appropriate. The list of subgroup covariates includes the following:

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

Each subgroup covariate will be included as a single independent variable in a logistic regression model (for the primary efficacy endpoint) or in a Cox proportional hazard model (for the primary safety endpoint) with the primary endpoint outcome as the dependent variable, and descriptive statistics related to the primary endpoint results in corresponding subgroups will be provided.

### 7.9.6 Multivariable Analyses

For each primary endpoint, univariate analyses of the following covariates will be performed, whenever appropriate, and any found to be significantly associated with the outcome will be included as covariates in a multivariable regression model (logistic regression model for the primary efficacy endpoint and Cox proportional hazards regression model for the primary safety endpoint) whenever appropriate. Backward selection will be used to determine the final multivariable model.

The list of covariates includes, but is not necessarily limited to:

- Subject demographics (eg, age, gender)
- Subject baseline characteristics (eg, NYHA classification, CHA2DS2-VASc score, current cardiac rhythm, anticoagulation medication status)
- Procedural characteristics (eg, Surgical Method, LAA morphology, concomitant procedure)

### 7.9.7 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 (CT/TEE) or direct visualization.

The binary rate and the 95% confidence interval will be provided for the rate of migration or malposition at 3 months.

The migration or malposition is the defined response of the residual stump size (Residual LAA pouch/stump from LAA ostium to proximal edge of clip) being greater than 10 mm at 3 months through core lab imaging data.

In addition, 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 from baseline in variables related to NYHA classification, CHA2DS2-VASc score.
- Evaluation of rhythm status, anticoagulation medication status by visits.

- Characterization of appendage morphology and its association with clinical outcomes
- Characterization of baseline CHA2DS2-VASc score and its association with clinical outcomes.

### 7.10 Safety Evaluation

All serious adverse cardiac events will be reported. The frequencies of the AEs and binary proportion of subjects who experienced the AE will be summarized in the attempted implant set by MedDRA coding (System Organ Class and preferred Term). Serious adverse events (SAEs), device related AEs, unanticipated adverse device effects (UADEs) will be reported similarly as binary proportion fashion in the attempted implant.

A listing of AEs will be provided with contents of relevant information (eg, days to AE, AE term, severity, outcomes, and causal relationship with the devices) in the attempted implant set.

A listing of device deficiencies (DD) will be compiled for that could have led to a serious adverse device effect (SADE) for the attempted implant subjects.

A listing of deaths and reasons will be provided.

### 7.11 Health Outcomes Analyses

No health outcomes analyses are planned.

### 7.12 Changes to Planned Analysis

Any changes to the planned analyses made prior to performing the analyses will be documented in the clinical study report or in an updated SAP prior to performing the analyses. Any change to the planned analyses made after performing the analyses will be documented in the clinical study report along with a reason for the change.

## 8. Validation Requirements

Statistical programming for primary endpoints and secondary endpoints will require Level 1 (independent) validation. Other objectives/endpoints and sub-group analyses will require Level 1 (independent) or Level 2 (peer review) validation.

## 9. References

[1] Al-Saady, N M et al. “Left atrial appendage: structure, function, and role in thromboembolism.” Heart (British Cardiac Society) vol. 82,5 (1999): 547-54. doi:10.1136/hrt.82.5.547

[2]Toale, Conor et al. “Outcomes of left atrial appendage occlusion using the AtriClip device: a systematic review.” Interactive cardiovascular and thoracic surgery vol. 29,5 (2019): 655-662. doi:10.1093/icvts/ivz156

[3] Caliskan, Etem et al. “Epicardial left atrial appendage AtriClip occlusion reduces the incidence of stroke in patients with atrial fibrillation undergoing cardiac surgery.” Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology vol. 20,7 (2018): e105-e114. doi:10.1093/europace/eux211

[4] van Laar, Charlotte et al. “Thoracoscopic Left Atrial Appendage Clipping: A Multicenter Cohort Analysis.” JACC. Clinical electrophysiology vol. 4,7 (2018): 893-901. doi:10.1016/j.jacep.2018.03.009

[5] Kurfirst, Vojtech et al. “Epicardial clip occlusion of the left atrial appendage during cardiac surgery provides optimal surgical results and long-term stability.” Interactive cardiovascular and thoracic surgery vol. 25,1 (2017): 37-40. doi:10.1093/icvts/ivx065

[6] Ailawadi, Gorav et al. “Exclusion of the left atrial appendage with a novel device: early results of a multicenter trial.” The Journal of thoracic and cardiovascular surgery vol. 142,5 (2011): 1002-9, 1009.e1. doi:10.1016/j.jtcvs.2011.07.052

[7] Ellis, Christopher R et al. “Angiographic Efficacy of the Atriclip Left Atrial Appendage Exclusion Device Placed by Minimally Invasive Thoracoscopic Approach.” JACC. Clinical electrophysiology vol. 3,12 (2017): 1356-1365. doi:10.1016/j.jacep.2017.03.008

[8] Osmancik, Pavel et al. “Residual echocardiographic and computed tomography findings after thoracoscopic occlusion of the left atrial appendage using the AtriClip PRO device.” Interactive cardiovascular and thoracic surgery vol. 26,6 (2018): 919-925. doi:10.1093/icvts/ivx427

[9] Emmert et al, Safe Effective and Durable Epicardial Left Atrial Appendage Clip Occlusion in Patients with AF Undergoing Cardiac Surgery: First Long-term Results from a Prospective Device Trial. European Journal of Cardio-Thoracic Surgery, 2014 Jan;45(1): 126-31