Medtronic **Clinical Investigation Plan**	
Clinical Investigation Plan/Study Title	Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF (PULSED AF)
Clinical Investigation Plan Identifier	MDT16027
Study Product Name	PulseSelect™ Pulsed Field Ablation (PFA) System *For the purpose of this document, the terms "PFA System" and "PulseSelect™ PFA System" are used interchangeably.*
Sponsor/Local Sponsor	**United States of America** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518 **Australia** Medtronic Australasia Pty Ltd. 2 Alma Road Macquarie Park, NSW 2113, Australia +61-2-9857-9000 **Canada** Medtronic Canada ULC 99 Hereford Street Brampton, Ontario, L6Y 0R3, Canada +1-905-460-3800 **Europe** Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht, The Netherlands +31-43-3566566 **Japan** Medtronic Japan Co. Ltd. 1-2-70 Konan, Minato-ku, Tokyo, Japan 108-0075 +81-3-6776-0105
Document Version	Version 6.0, 02-OCT-2020

Lead Principal/Coordinating Investigator	Atul Verma, MD Staff Cardiac Electrophysiologist/Cardiologist Southlake Regional Health Centre [redacted]

Confidentiality Statement

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Sponsor Contact Information

Medtronic contact information is provided in Table 1. This information is subject to change during the course of the clinical study. Periodic updates to study contact information will be sent to study sites as needed.

Table 1: Study Sponsor and Monitoring Contact Information

Study Contacts	*Worldwide Clinical Study Leader* Jen Diouf, Principal Clinical Research Specialist [redacted]

Study Contacts (continued)	*Australia* John Porreca, Associate Clinical Research Specialist [redacted] *Canada* Aarthi Kamath, Senior Clinical Research Specialist [redacted] *Europe* Enneke Prinsen, Clinical Research Specialist [redacted] *Japan* Yoshiko Ishiwatari, Clinical Research Manager [redacted] *US* Josh Treadway, Clinical Research Specialist [redacted]
Monitoring Contacts	*US, Canada* Patrick Lyons, Senior Clinical Research Monitor [redacted] *Europe, Australia* Anja Hesse, Monitoring Portfolio Specialist [redacted] *Japan* Kenji Shinkai, Senior Clinical Research Monitor [redacted]

Steering Committee

Changes to Table 2 will be provided under a separate cover.

Table 2: Steering Committee Contact Information

Committee Member	Contact Information
Atul Verma, MD FRCPC	Southlake Regional Health Centre [redacted]
Lucas Boersma, MD	St. Antonius Hospital Cardiology Department [redacted]
Hugh Calkins, MD	Johns Hopkins Hospital [redacted]
David Haines, MD	Beaumont Hospital [redacted]
Gerhard Hindricks, MD	Herzzentrum Leipzig GmbH [redacted]
Karl-Heinz Kuck, MD	Asklepios Klinik St. Georg [redacted]
Francis Marchlinski, MD	Hospital of the University of Pennsylvania Cardiovascular Division [redacted]
Andrea Natale, MD	Texas Cardiac Arrhythmia Institute St. David's Medical Center [redacted]
Douglas Packer, MD	Mayo Clinic St. Mary's Hospital [redacted]
Prashanthan Sanders, MBBS, PhD	Royal Adelaide Hospital Department of Cardiology [redacted]

Contract Research Organizations

Changes to Table 3 will be provided under a separate cover.

Table 3: Contract Research Organization Information

Contact Information	Duties Performed
NAMSA 400 Highway 169 South, Suite 500 Minneapolis, MN 55426 Phone: +1 866-666-9455 Fax: +1 419-662-4386	• Database development • Development of study electronic case report forms, edit checks, and study management reports.
Cognizant Technology Solutions 500 Frank W. Burr Blvd. Teaneck, NJ 07666, USA Phone: +1 201-801-0233 Fax: +1 201-801-0243	• Review of electronic case report forms and management of discrepancies
HeartCor Solutions 2403 Harnish Dr., Suite 201 Algonquin, IL 60102 Phone: +1 800-987-4117 Fax: +1 224-241-4117	• Distribution of equipment for rhythm monitoring • Adjudication of arrhythmias
Syntactx 150 Greenwich St, Floor 44 New York, NY 10007 Phone: +1 212-228-9000	[redacted] • Reviewing the baseline and 3-month cardiac CT or MRI scans to characterize of any potential occurrences of PV stenosis
HealthCarePoint.com Corporation 10713 N FM 620 Austin, TX 78726, USA Phone: +1 512-302-3113	• Providing access to BlueCloud® Networking Management Systems for NIHSS and MMSE translations, training, and certification tracking

1. Glossary

Term	Definition
AAD	Antiarrhythmic drug
ACT	Activated clotting time
ADE	Adverse device effect
AE	Adverse event
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-life
AFL	Atrial flutter
AHA	America Heart Association
AT	Atrial tachycardia
C	Celsius
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical investigation plan
CMAP	Compound motor action potential
CRF	Case report form
CTA	Clinical trial agreement
CTI	Cavotricuspid isthmus
CV	Curriculum vitae
DD	Device deficiency
EC	Ethics committee
ECG	Electrocardiogram
e.g.	For example,

Term	Definition
EMG	Electromyography
EP	Electrophysiology
EQ-5D	EuroQol 5 Dimensions Questionnaire
Ethics Committee	Term that will be used collectively in reference to an Institutional Review Board (IRB)/Medical Ethics Committee (MEC)/Human Research Ethics Committee (HREC)/Research Ethics Board (REB)/Head of Medical Institution (HOMI) unless otherwise stated
FAL	Foreseeable adverse event list
FD	Financial disclosure
FDA	Food and Drug Administration
GCP	Good clinical practice
HC	Health Canada
HOMI	Head of Medical Institution
HREC	Human research and ethics committee
IB	Investigator brochure
IC	Informed consent
ICE	Intracardiac echocardiography
ICMJE	International Committee of Medical Journal Editors
ID	Identification
IDE	Investigational device exemption
IFU	Instructions For Use
IRB	Institutional review board
IRE	Irreversible electroporation
ISO	International Organization for Standardization

Term	Definition
LAD	Left atrial diameter
LVEF	Left ventricular ejection fraction
MDD	Medical Device Directive
MEC	Medical ethics committee
MedDRA	Medical Dictionary for Regulatory Activities
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NIHSS	National Institute of Health Stroke Scale
NOAC	Novel oral anticoagulant
NYHA	New York Heart Association
OPC	Objective performance criterion
PAF	Paroxysmal atrial fibrillation
PFA	Pulsed Field Ablation
PMDA	Pharmaceutical and Medical Devices Agency
PV	Pulmonary vein
PVI	Pulmonary vein isolation
QoL	Quality of life
REB	Research ethics board
RF	Radiofrequency
RI	Right inferior
RS	Right superior
SAE	Serious adverse event
SADE	Serious adverse device effect

Term	Definition
SAP	Statistical analysis plan
SCE	Silent cerebral event
SCL	Silent cerebral lesion
TEE	Transesophageal echocardiogram
TGA	Therapeutic Goods Administration
TIA	Transient ischemic attack
TTE	Transthoracic echocardiogram
TTM	Transtelephonic monitoring
UADE	Unanticipated adverse device effect
US	United States
USADE	Unanticipated serious adverse device effect

2. Synopsis

Title	Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF (PULSED AF)
Clinical Study Type	Phased Study Design
Product Name	PulseSelect™ Pulsed Field Ablation (PFA) System
Sponsor	**United States of America** Medtronic, Inc. 8200 Coral Sea Street NE Mounds View, MN U.S.A. 55112 1-800-328-2518
Local Sponsors	**Canada** Medtronic Canada ULC 99 Hereford Street Brampton, Ontario, L6Y 0R3, Canada +1-905-460-3800 **Europe** Medtronic, Bakken Research Center B.V. Endepolsdomein 5 6229 GW Maastricht, The Netherlands +31(0)43-3566566 **Australia** Medtronic Australasia Pty Ltd. 2 Alma Road Macquarie Park, NSW 2113, Australia +61-2-9857-9000 **Japan** Medtronic Japan Co. Ltd. 1-2-70 Konan, Minato-ku, Tokyo, Japan 108-0075 +81-3-6776-0105
Indication under investigation	The planned indication for the PulseSelect™ PFA System evaluated in this Study is as follows: The PulseSelect™ PFA System, which includes a compatible Medtronic multi-electrode cardiac ablation catheter, is indicated for the treatment of atrial fibrillation. The Medtronic multi-electrode cardiac ablation catheter is also intended to be used for cardiac electrophysiological (EP) mapping and measuring of intracardiac electrograms, delivery of diagnostic pacing stimuli and verifying electrical isolation post-treatment.

<table>
<tr><td>Investigation Purpose</td><td>The purpose of the study is to provide data demonstrating the safety and effectiveness of the PulseSelect™ PFA System for the treatment of atrial fibrillation.</td></tr>
<tr><td>Product Status</td><td>
<table>
<tr><th>Product Name</th><th>Model Number</th><th>Geography Status at Study Start</th></tr>
<tr><td colspan="3">System Components</td></tr>
<tr><td>PFA Generator</td><td>M970163A001</td><td>Investigational in all geographies</td></tr>
<tr><td>Catheter Electrode Distribution System (CEDS)</td><td>M970165A001</td><td>Investigational in all geographies</td></tr>
<tr><td>Remote Control</td><td>M970127A001</td><td>Investigational in all geographies</td></tr>
<tr><td>Cable, Generator to Remote Control</td><td>M970169A001</td><td>Investigational in all geographies</td></tr>
<tr><td>Cable, Generator to CEDS</td><td>M970168A001</td><td>Investigational in all geographies</td></tr>
<tr><td colspan="3">System Accessories</td></tr>
<tr><td>Cable, CEDS to EP Recording System (EGM)</td><td>990027</td><td>CAN: Health Canada licensed
EU: CE Marked
AUS: TGA Approved
US/JPN: Investigational
Investigational when used with PulseSelect™ PFA System</td></tr>
<tr><td>Catheter Interface Cable</td><td>990004</td><td>CAN: Health Canada licensed
EU: CE Marked
AUS: TGA Approved
US/JPN: Investigational
Investigational when used with PulseSelect™ PFA System</td></tr>
<tr><td>[redacted] Catheter</td><td>990078</td><td>CAN: Health Canada licensed
EU: CE Marked
AUS: TGA Approved
US/JPN: Investigational
Investigational when used with PulseSelect™ PFA System</td></tr>
<tr><td>Cardiac Trigger Monitor (The monitor ships within the same finished good shipping package as the accessories, model 3254-55-15.)</td><td>7700</td><td>CAN: Health Canada licensed
EU: CE Marked
AUS: TGA Approved
US: FDA cleared
JPN: PMDA Approved
Investigational when used with PulseSelect™ PFA System</td></tr>
</table>
</td></tr>
</table>

	Cardiac Trigger Monitor Accessories (The accessories ship within the same finished good shipping package as the monitor, model 7700.)	3254-55-15	CAN: Health Canada licensed EU: CE Marked AUS: When supplied individually the accessories are considered investigational; however, since the accessories ship within the same finished good shipping package as the monitor, registration is not required. US: FDA cleared JPN: PMDA Approved *Investigational when used with PulseSelect™ PFA System*
	Power Cord	1038N - North America; Japan 1038K – Australia 1038E - EU	CAN: not regulated EU: self-certified AUS: not regulated US: FDA approved JPN: PMDA approved *Investigational when used with PulseSelect™ PFA System*
	Uninterruptible Power Supply (UPS)	SMART1200XL HG (120V) SMX1200XLHG (230V)	CAN: not regulated EU: not regulated (non-medical device) AUS: not regulated US: not regulated JPN: not regulated *Investigational when used with PulseSelect™ PFA System*
	Power Cord – C14M-C13F	P004-006-ABL	CAN: not regulated EU: not regulated (non-medical device) AUS: not regulated US: not regulated JPN: not regulated *Investigational when used with PulseSelect™ PFA System*
Study Design	The study is a prospective, multi-center, non-randomized, unblinded worldwide pre-market clinical study. The study is designed to have a continuously growing body of evidence across two phases, with data analyses planned at pre-specified timepoints. The data collected in this study will be used to support regulatory submissions around the world to obtain market approval for the PulseSelect™ PFA System, including, but not limited to, CE Mark, Health Canada, Therapeutic Goods Administration (TGA), Pharmaceutical and Medical Devices Agency (PMDA) and U.S. Food and Drug Administration (FDA) market applications.		

Description of Phased Study Design	**Pilot Phase** The Pilot Phase of the PULSED AF study will include an early assessment of safety and confirmation of acute procedural success of pulmonary vein isolation (PVI) ablation with the PulseSelect™ PFA System. Specifically, this phase will include treatment of up to 40 subjects (paroxysmal AF or persistent AF) across up to 8 clinical sites. [redacted] The Pilot Phase subjects will not be included in the Pivotal Phase primary or secondary endpoint analyses but will be treated and followed in accordance with all other protocol requirements. In addition, the Pilot Phase subjects will complete a cardiac CT or MRI scan at baseline and 3 months to allow characterization of any potential occurrences of pulmonary vein (PV) stenosis. If PV stenosis (≥70% diameter reduction) is identified in any of these Pilot Phase subjects, an additional report will be generated containing the 3-month PV stenosis analysis once all Pilot Phase subjects have completed their 3-month follow-up or exited. The report will be sent to regulatory authorities (as requested) while enrollment in the Pivotal Phase of the study continues. **Pivotal Phase** The purpose of the Pivotal Phase of the study is to provide data demonstrating the safety and effectiveness of the PulseSelect™ PFA System for the treatment of atrial fibrillation. Specifically, this phase will include treatment of 300 subjects (150 paroxysmal AF and 150 persistent AF) for analysis of primary objectives, across up to 48 total sites worldwide (including the Pilot Phase sites). For the Pivotal Phase of the study, subjects will be separated into paroxysmal AF and persistent AF arms and analyzed separately. It is expected that at least 50% of the treatments and supporting clinical data will come from the United States with no single site contributing more than 15% of the treatments to each arm of the Pivotal Phase. Each arm will have a primary safety objective and a primary effectiveness objective, in addition to secondary [redacted] objectives. To facilitate the investigators' familiarity with the System, a cohort of roll-in subjects will also be included in the Pivotal Phase. There will be up to 96 total roll-in subjects. Roll-in subjects will not be included in the Pivotal Phase primary or secondary endpoint analyses but will be treated and followed in accordance with all other protocol requirements.

<table>
<tr><td>Sample Size</td><td>Enrollment will consist of up to 40 Pilot Phase subjects, up to 96 Pivotal Phase roll-in cohort subjects and 300 Pivotal Phase primary analysis cohort subjects, all of whom will be treated with the PulseSelect™ PFA System. To account for subjects not treated prior to exit, up to 495 subjects may be enrolled.</td></tr>
<tr><td>Pilot Phase Objectives</td><td>Safety Objective: Assess the incidence of PulseSelect™ PFA System-related and PFA procedure-related serious adverse events (SAEs) within 30 days post-ablation:
<table>
<tr><th>Serious Adverse Event</th><th>Method of Analysis</th></tr>
<tr><td>Pulmonary vein stenosis (≥70% diameter reduction)</td><td rowspan="4">Review of symptoms post-procedure, at 7-day visit and at 30-day visit</td></tr>
<tr><td>Phrenic nerve injury/diaphragmatic paralysis (ongoing at 30 days post-ablation)</td></tr>
<tr><td>Atrioesophageal fistula</td></tr>
<tr><td>Cardiac tamponade/perforation</td></tr>
<tr><td>Cerebrovascular accident</td><td>Review of symptoms post-procedure, at 7-day visit and at 30-day visit;
Confirmed by formal neurology assessment if required due to NIHSS assessments</td></tr>
<tr><td>Major bleeding requiring transfusion</td><td rowspan="11">Review of symptoms post-procedure, at 7-day visit and at 30-day visit</td></tr>
<tr><td>Myocardial infarction</td></tr>
<tr><td>Pericarditis requiring intervention</td></tr>
<tr><td>Transient ischemic attack</td></tr>
<tr><td>Vagal nerve injury resulting in esophageal dysmotility or gastroparesis</td></tr>
<tr><td>Vascular access complications requiring intervention</td></tr>
<tr><td>Systemic/pulmonary embolism requiring intervention</td></tr>
<tr><td>Pulmonary edema</td></tr>
<tr><td>Death</td></tr>
<tr><td>Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours (excluding recurrent AF/AFL/AT)</td></tr>
</table></td></tr>
</table>

	Effectiveness Objective: Assess the acute procedural success of PVI ablation with the PulseSelect™ PFA System. Acute procedural failure is defined as the occurrence of any of the following: • Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure • Ablation using a non-study device to isolate any pulmonary vein Acute procedural success is the opposite of acute procedural failure.
Pivotal Phase Primary Objectives	Primary objectives, which will be reported separately by paroxysmal AF and persistent AF, are as follows: Safety Objective: Demonstrate an acceptable safety profile of PVI ablation with the PulseSelect™ PFA System. Effectiveness Objective: Demonstrate an acceptable chronic effectiveness of PVI ablation with the PulseSelect™ PFA System, based on freedom from treatment failure.
Pivotal Phase Secondary Objectives	The following secondary objective will be reported separately by paroxysmal AF and persistent AF: 1. Assess changes in quality of life from baseline through 12 months after the index ablation procedure.
[redacted]	[redacted]

	[redacted]
Primary Safety Endpoint	The primary safety endpoint definition, as follows, is identical for each arm (paroxysmal AF and persistent AF) of the Pivotal Phase. The following PulseSelect™ PFA System-related and PFA procedure-related serious adverse events (SAEs), as adjudicated by the Clinical Events Committee (CEC), will be considered a primary safety event: Within 6 months post-ablation: • Pulmonary vein stenosis (≥70% diameter reduction) • Phrenic nerve injury/diaphragmatic paralysis (ongoing at 6 months) • Atrioesophageal fistula Within 30 days of ablation procedure: • Cardiac tamponade/perforation • Cerebrovascular accident • Major bleeding requiring transfusion • Myocardial infarction • Pericarditis requiring intervention • Transient ischemic attack • Vagal nerve injury resulting in esophageal dysmotility or gastroparesis • Vascular access complications requiring intervention • Systemic/pulmonary embolism requiring intervention • Pulmonary edema • Death • Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours (excluding recurrent AF/AFL/AT)

Primary Effectiveness Endpoint	The primary effectiveness endpoint definition, as follows, is identical for each arm (paroxysmal AF and persistent AF) of the Pivotal Phase.
	
	Treatment success is defined as freedom from treatment failure. The study requires 24-hour Holter monitoring at 6 and 12 months in addition to weekly and symptomatic patient activated ambulatory monitoring transmissions through 12 months, and 12-lead ECGs at all follow up visits. Treatment failure is defined as any of the following components:
	
	• Acute procedural failure (see definition below)
	• Documented AF/AT/AFL on Holter/patient activated ambulatory monitoring/12-lead ECG after the 90-day post-ablation blanking period
	  ○ Minimum of 30 seconds on Holter/patient activated ambulatory monitoring or 10 seconds on 12-lead ECG recording
	  ○ Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter is not considered a failure if confirmed by entrainment maneuvers during EP testing.
	• Any subsequent AF surgery or ablation in the left atrium, except for one repeat PVI ablation using PFA within the 90-day blanking period.
	• Direct current cardioversion for atrial tachyarrhythmia recurrences after the 90-day blanking period.
	• Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90-day blanking period.
	  ○ Note: remaining on the same pre-ablation dose or decreased dose of a previously failed or not tolerated Class I or III AAD after the 90-day blanking period is not considered a failure. Re-initiation, at any point during follow-up, of a Class I or III antiarrhythmic medication that was failed or was not tolerated prior to the ablation procedure at any dose will be considered a primary endpoint failure.
	
	Blanking period is defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period will not be counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias can be managed with antiarrhythmic drugs or cardioversions. Titration of Class I and III antiarrhythmic medications are allowed during the blanking period.
	
	Acute procedural failure is defined as the occurrence of any of the following:
	
	• Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure
	• Ablation using a non-study device to isolate any pulmonary vein

Inclusion/ Exclusion Criteria	Inclusion Criteria 1. Failure of at least one AAD (class I or III) for AF as evidenced by recurrent symptomatic AF, or intolerable side effects due to AAD. 2. A diagnosis of recurrent symptomatic paroxysmal or persistent AF: a. Symptomatic paroxysmal AF, which is defined as AF that terminates spontaneously or with intervention within 7 days of onset, documented by the following: 1) physician's note indicating at least 2 symptomatic paroxysmal AF episodes occurring within 6 months prior to enrollment; and 2) at least 1 ECG documented AF episode from any form of rhythm monitoring within 12 months prior to enrollment OR b. Symptomatic persistent AF, which is defined as continuous AF sustained beyond 7 days and less than 1 year, documented by the following: 1) physician's note indicating at least 1 symptomatic persistent AF episode occurring within 6 months prior to enrollment; and 2) any 24-hour continuous ECG recording documenting continuous AF within 6 months prior to enrollment; OR 2 ECGs from any form of rhythm monitoring taken at least 7 days apart, both showing continuous AF within 6 months prior to enrollment 3. Age 18 through 80 years old (or older than 18 if required by local law) Exclusion Criteria 1. Long-standing persistent AF (continuous AF that is sustained >12 months) 2. Left atrial diameter > 5.0 cm (anteroposterior) 3. Prior left atrial ablation or surgical procedure (including left atrial appendage closures) 4. Planned LAA closure procedure or implant of a permanent pacemaker, biventricular pacemaker, loop recorder/insertable cardiac monitor (ICM), or any type of implantable cardiac defibrillator (with or without biventricular pacing function) for any time during the follow-up period 5. Patient who is not on oral anticoagulation therapy for at least 3 weeks prior to the ablation procedure 6. Presence of a permanent pacemaker, biventricular pacemaker, loop recorder/insertable cardiac monitor (ICM), or any type of implantable cardiac defibrillator (with or without biventricular pacing function) 7. Presence of any pulmonary vein stents 8. Presence of any pre-existing pulmonary vein stenosis 9. Pre-existing hemidiaphragmatic paralysis 10. Presence of any cardiac valve prosthesis

	11. Moderate to severe mitral valve stenosis 12. More than moderate mitral regurgitation (i.e., 3+ or 4+ MR) 13. Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 3-month interval preceding the consent date 14. Unstable angina 15. NYHA Class III or IV congestive heart failure or documented left ventricular ejection fraction (LVEF) less than or equal to 35% measure by acceptable cardiac testing (e.g. TTE) 16. Primary pulmonary hypertension 17. Rheumatic heart disease 18. Thrombocytosis, thrombocytopenia 19. Any condition contraindicating chronic anticoagulation 20. Active systemic infection 21. Hypertrophic cardiomyopathy 22. Known reversible causes of AF, including but not limited to uncontrolled hyperthyroidism, severe untreated obstructive sleep apnea, and acute alcohol toxicity 23. Any cerebral ischemic event (strokes or TIAs) which occurred during the 6-month interval preceding the consent date 24. History of thromboembolic event within the past 6 months or evidence of intracardiac thrombus at the time of the procedure 25. Any woman known to be pregnant or breastfeeding, or any woman of childbearing potential who is not on a reliable form of birth regulation method or abstinence 26. Patient with life expectancy that makes it unlikely 12 months of follow-up will be completed 27. Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of the study not pre-approved by Medtronic 28. Known allergies or hypersensitivities to adhesives 29. Unwilling or unable to comply fully with study procedures and follow-up 30. Unable to provide own informed consent
Study Procedures and Assessments	Adult subjects with history of drug refractory recurrent symptomatic atrial fibrillation (AF) will undergo ablation of pulmonary veins and confirmation of entrance block and, where assessable, exit block with the PulseSelect™ PFA System. Following the index ablation procedure and hospital discharge, all study subjects from all participating geographies will be followed at 7 days, 30 days, 3 months, 6 months, and 12 months, and will be exited from the study at the conclusion of the 12-month follow-up visit and associated 24-hour Holter.

Safety Assessments	All adverse events will be collected starting at the time of signing the IC Form through the duration of the subject's participation in the study. Clinical Events Committee (CEC): An independent committee comprised of electrophysiologists and a neurologist not participating in the study will review and adjudicate, at a minimum, all procedure- and system-related adverse events, as well as adverse events resulting in death.
Additional Assessments	[redacted] A subset of subjects in the Pivotal Phase will be consented to participate in the pulmonary vein (PV) stenosis assessment, including a cardiac computed tomography (CT) or MRI at baseline and at the 3-month follow-up visit. The purpose of this assessment is to screen for potential PV stenosis in patients who receive an ablation with the PulseSelect™ PFA System. [redacted]
Planned Primary Analyses	The paroxysmal and persistent arms will be analyzed separately. [redacted] [redacted] [redacted] [redacted] all subjects will be followed for 12 months, and a final report will be prepared for each arm.

3. Introduction

3.1. Background

Atrial fibrillation (AF) is a common and disabling cardiac arrhythmia with a heterogeneous clinical presentation. The fundamental pathophysiology consists of atrial wavelets propagating in different directions, causing disorganized atrial depolarizations without effective atrial contraction, with concomitant rapid and irregular ventricular contractions. As published in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, there are several classifications for AF: paroxysmal AF (PAF) is defined as AF that terminates spontaneously or with intervention within 7 days of onset; persistent AF is defined as continuous AF that is sustained beyond 7 days; and long-standing persistent AF is defined as continuous AF of greater than 12-month duration.[1]

AF is the most common of the sustained arrhythmias affecting millions of people worldwide. The estimated global prevalence of AF is 33 million patients, and the number of AF patients in the US is expected to double by 2035.[2,3] Prolonged AF may lead to electrical, mechanical, and structural changes to the left atrium, which may then progress to tachycardia-induced cardiomyopathy, heart failure and persistent AF. Persistent AF represents approximately 25% of AF cases.[4] The prognosis is related to the underlying cause of the disease, with idiopathic causes having the best prognosis and ischemic cardiomyopathy having a poor prognosis. The mortality rate in patients with AF is twice that of patients without AF, and the risk of AF-related stroke is 5-fold compared to the risk in patients without AF.[5] In comparison to patients with paroxysmal AF, patients with persistent AF are at a significantly greater risk for cardiac mortality (hazard ratio [HR], 2.37; 95% confidence interval [CI], 1.19-4.73) and all-cause mortality (HR, 1.89; CI, 1.30-2.74).[6]

Catheter ablation is established as an acceptable line of treatment for patients with recurrent symptomatic atrial fibrillation (both paroxysmal and persistent) who have failed anti-arrhythmic drug therapy. In 2017, the HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation continued the Class I Level A recommendation (as previously published in the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter

[1] Calkins H, et al., 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, Heart Rhythm (2017), doi:10.10106/j.hrthm.2017.05.012.

[2] Chugh, S. S., et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation* **129**, 837-847, doi:10.1161/circulationaha.113.005119 (2014).

[3] Naccarelli, G. V., Varker, H., Lin, J. & Schulman, K. L. Increasing prevalence of atrial fibrillation and flutter in the United States. *The American journal of cardiology* **104**, 1534-1539, doi:10.1016/j.amjcard.2009.07.022 (2009).

[4] Zoni-Berisso M, et al. Epidemiology of atrial fibrillation: European perspective. Clinical Epidemiology. 2014;6:213-220. doi:10.2147/CLEP.S47385.

[5] Wolf P, et al. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke. 1991;22(8):983-988.

[6] Ghanbari H, et al. Mortality and cerebrovascular events after radiofrequency catheter ablation of atrial fibrillation. Heart Rhythm. 2014;11:1503-1511.

and Surgical Ablation of Atrial Fibrillation[7]) for catheter and surgical ablation of AF for symptomatic paroxysmal AF (refractory or intolerant to at least one Class I or III AAD). Although in the US there are no approved catheter ablation options for treating persistent AF, there is a growing body of evidence supporting catheter ablation as a reasonable option for this patient population. The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement continued the Class IIa Level B recommendation for catheter and surgical ablation of AF for symptomatic persistent AF (refractory or intolerant to at least one Class I or III AAD), stating "the benefits of an AF ablation procedure exceed the risks, and that it is reasonable to perform AF ablation".[1] In the previously published 2014 AHA/ACC/HRS Guideline for the Management of Patients with Atrial Fibrillation, the level of evidence supporting the recommendation moved to Class Iia, Level A.[8]

Catheter ablation treatment strategies for AF have evolved over time and currently include pulmonary vein isolation (PVI) as the cornerstone of ablation therapy in all types of AF (paroxysmal and persistent),[9, 10] with several recent studies reporting benefit using a minimal PVI-only type strategy.[11,12,13,14] AF arises primarily from the left side of the heart in the atrium, particularly where the pulmonary veins (PVs) join the atrium. The fundamental basis for the AF ablation procedure is the elimination of initiating triggers and the creation of myocardial lesions that block the propagation of AF wave fronts from the triggering source. The muscular sleeves both within and near the PVs have been established as a critical source of AF triggers.[15]

Currently approved catheter ablation options for the treatment of drug refractory recurrent symptomatic paroxysmal AF include radiofrequency (RF) ablation, cryoablation, and visually guided

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[7] Calkins H, et al. 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Patient Selection, Procedural Techniques, Patient Management and Follow-up, Definitions, Endpoints, and Research Trial Design. Heart Rhythm 2012;9:632-696.

[8] January C, Wann L, Alpert J, Calkins H, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* 2014.

[9] Raviele, et al. Venice Chart International consensus Document on Atrial Fibrillation: 2011 Update. J Cardiovasc Electrophysiol, 2012;23:890-923.

[10] Jais P, et al. Stepwise Catheter Ablation of Chronic Atrial Fibrillation: Importance of Discrete Anatomic Sites for Termination. *J Cardiovasc Electrophysiol*. 2006;17: S28-S36, Suppl. 3.

[11] Dong JZ, Sang CH, Yu RH, et al. Prospective randomized comparison between a fixed "2C3L" approach vs. stepwise approach for catheter ablation of persistent atrial fibrillation. *Europace*. doi:10.1093/europace/euv067.

[12] Wynn GJ, Panikker S, Morgan M, et al. Effect of linear ablation in substrate-based AF: Results of the substrate modification with ablation and antiarrhythmic drugs in non-permanent atrial fibrillation trial. *Heart Rhythm*. 2015;12:1715.

[13] Verma A, Jiang CY, Betts TR, et al, STAR AF II Investigators. Approaches to Catheter Ablation for Persistent Atrial Fibrillation. *N Engl J Med*. 2015;372:1812-1822.

[14] Scott P, Silberbauer J, Murgatroyd F. The impact of adjunctive complex fractionated atrial electrograms ablation and linear lesions on outcomes in persistent atrial fibrillation: a meta-analysis. *Europace* 2016; 18, 359-367.

[15] Calkins H, et al. HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for personnel, Policy, Procedures and Follow-Up. *Europace*. 2007;9(6):335-379.

laser balloon ablation. The goal of ablation technology is to create a safe and effective lesion without causing damage to adjacent structures or surrounding tissue thus resulting in no need for a maintenance treatment regimen (medications or cardioversions). The two dominant energy sources being utilized for catheter ablation today are radiofrequency and cryoablation. RF generators deliver energy to ablate cardiac tissue using a resistive heating mechanism applied through endocardial catheter electrodes.[16] RF catheters maintain temperature control to provide electrode cooling, minimize heat and prevent charring by employing irrigation or modifying the electrode surface area.[17] Cryoablation delivers pressurized refrigerant (liquefied nitrous oxide) to the distal end of endocardial catheters to treat AF using a freeze-thaw mechanism.[18,19] RF catheter ablation and cryoablation are established treatment options for paroxysmal and persistent atrial fibrillation but are subject to safety risks and AF recurrence for AF patients. The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement summarizes AF ablation complication occurrence rates, as listed in Table 4, and further indicates that "our efforts to eliminate complications associated with AF ablation are incomplete and there is more work to do."[1]

Table 4: Complication Occurrence Rates for Catheter Ablation[1]

Complication	Occurrence rate due to catheter ablation
Air embolism	<1%
Asymptomatic cerebral emboli	2-15%
Atrial-esophageal fistula	0.02 – 0.11%
Cardiac tamponade	0.2 – 5%
Coronary artery stenosis occlusion	<0.1%
Death	<0.1% to 0.4%
Gastric hypomotility	0-17%
Mitral valve entrapment	<0.1%
Pericarditis	0 to 50%
Permanent phrenic nerve paralysis	0-0.4%
Pulmonary vein stenosis	<1%
Radiation injury	<0.1%
Stiff left atrial syndrome	<1.5%
Stroke and TIA	0-2%
Vascular complications	0.2% to 1.5%

[16] Avitall, B. et al. The safety and efficacy of multiple consecutive cryo lesions in canine pulmonary veins-left atrial junction. Heart rhythm 1, 203-209, doi:10.1016/j.hrthm.2004.03.058 (2004).

[17] Dinerman, J. L., Berger, R. D. & Calkins, H. Temperature monitoring during radiofrequency ablation. Journal of cardiovascular electrophysiology 7, 163-173 (1996)

[18] Harrison, L. et al. Cryosurgical ablation of the A-V node-His bundle: a new method for producing A-V block. Circulation 55, 463-470 (1977).

[19] Georgiopoulos, G., Tsiachris, D. & Manolis, A. S. Cryoballoon ablation of atrial fibrillation: a practical and effective approach. Clinical cardiology 40, 333-342, doi:10.1002/clc.22653 (2017).

Reducing safety risks as compared to current catheter ablation technologies is warranted. The Medtronic Pulsed Field Ablation (PFA) System is a novel method of PVI ablation that has the potential to offer a safer and more effective treatment option for AF over existing, approved methods of AF ablation. Medtronic proposes there is a need to investigate PVI ablation with a novel technology (i.e., PulseSelect™ PFA System) that is capable of potentially reducing or eliminating collateral damage, improving lesion formation and durability, and reducing the AF ablation procedure time. The PulseSelect™ PFA System is expected to be a safe and effective alternative to the currently approved technologies used to achieve PVI ablation in a paroxysmal AF patient population. Indication in the US would fulfill an unmet clinical need for symptomatic persistent AF patients in which antiarrhythmic drugs fail or are not tolerated.

3.2. Purpose

The purpose of the study is to provide data demonstrating the safety and effectiveness of the PulseSelect™ PFA System for the treatment of atrial fibrillation. The study will also provide first in human insights into clinical safety and device function of the PulseSelect™ PFA System for pulmonary vein isolation as a treatment for AF. To this end, the clinical study has been designed into phases (Pilot and Pivotal), with each phase comprising a separate data set that will be analyzed and reported on per the below objectives.

The proposed indication for the PulseSelect™ PFA System evaluated in this Study is as follows:

The PulseSelect™ PFA System, which includes a compatible Medtronic multi-electrode cardiac ablation catheter, is indicated for the treatment of atrial fibrillation. The Medtronic multi-electrode cardiac ablation catheter is also intended to be used for cardiac electrophysiological (EP) mapping and measuring of intracardiac electrograms, delivery of diagnostic pacing stimuli and verifying electrical isolation post-treatment.

[redacted]

A subset of subjects in the Pivotal Phase will be consented to participate in the pulmonary vein (PV) stenosis assessment, including a cardiac computed tomography (CT) or MRI at baseline and at the 3-month follow-up visit. The purpose of this assessment is to screen for potential PV stenosis in patients who receive an ablation with the PulseSelect™ PFA System.

[redacted]

4. Objectives and Endpoints

Endpoint definitions for all study objectives are described in Section 12. [redacted]

4.1. Pilot Phase Objectives

4.1.1. Pilot Phase Safety Objective

Assess the incidence of PulseSelect™ PFA System-related and PFA procedure-related serious adverse events (SAEs) within 30 days post-ablation.

4.1.2. Pilot Phase Effectiveness Objective

Assess the acute procedural success of PVI ablation with the PulseSelect™ PFA System.

4.2. Pivotal Phase Objectives

4.2.1. Primary Objectives

Primary objectives, which will be reported separately by paroxysmal AF and persistent AF, are as follows:

4.2.1.1. Primary Safety Objective

Demonstrate an acceptable safety profile of PVI ablation with the PulseSelect™ PFA System.

4.2.1.2. Primary Effectiveness Objective

Demonstrate an acceptable chronic effectiveness of PVI ablation with the PulseSelect™ PFA System, based on freedom from treatment failure.

4.2.2. Secondary Objective

The following secondary objective will be reported separately by paroxysmal AF and persistent AF:

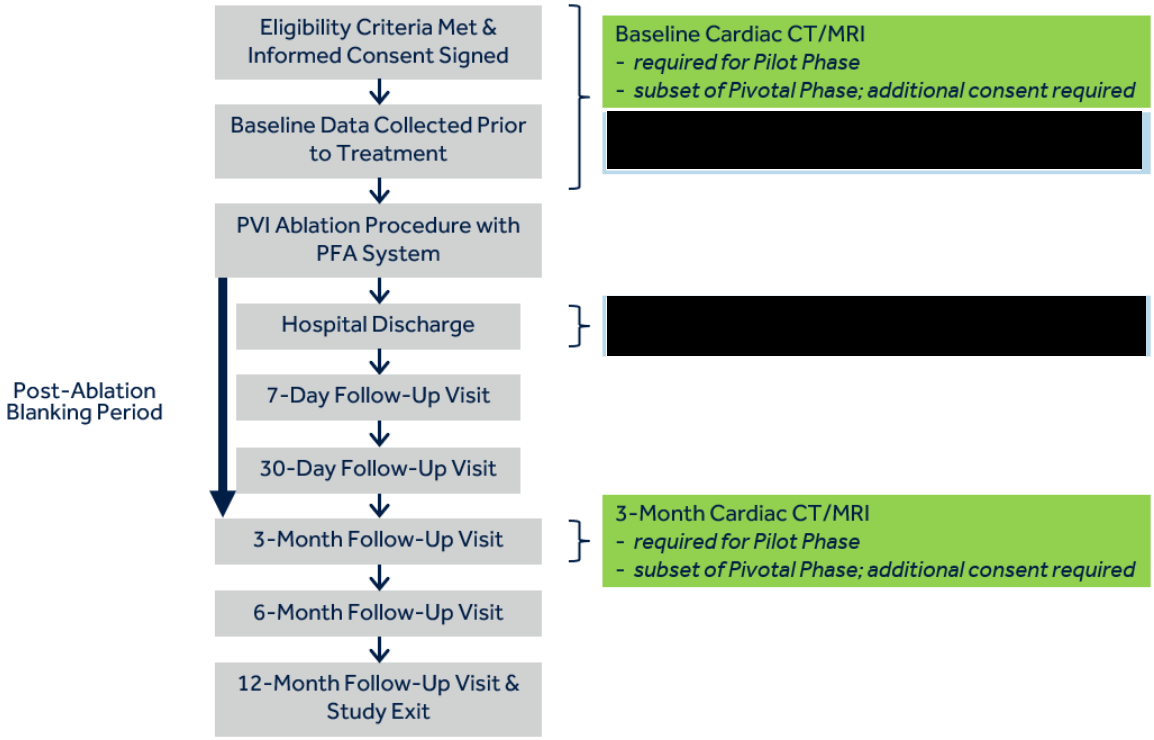
1. Assess changes in quality of life from baseline through 12 months after the index ablation procedure.

[redacted]

5. Study Design

The study is a prospective, multi-center, non-randomized, unblinded worldwide pre-market clinical study. Adult subjects with a history of drug refractory recurrent symptomatic atrial fibrillation (AF) will undergo ablation of pulmonary veins and confirmation of entrance block and, where assessable, exit block with the PulseSelect™ PFA System. Following the index ablation procedure and hospital discharge, all study subjects from all participating geographies will be followed at 7 days, 30 days, 3 months, 6 months, and 12 months, and will be exited from the study at the conclusion of the 12-month follow-up visit and associated 24-hour Holter. The subject-level study design diagram is shown in Figure 1.

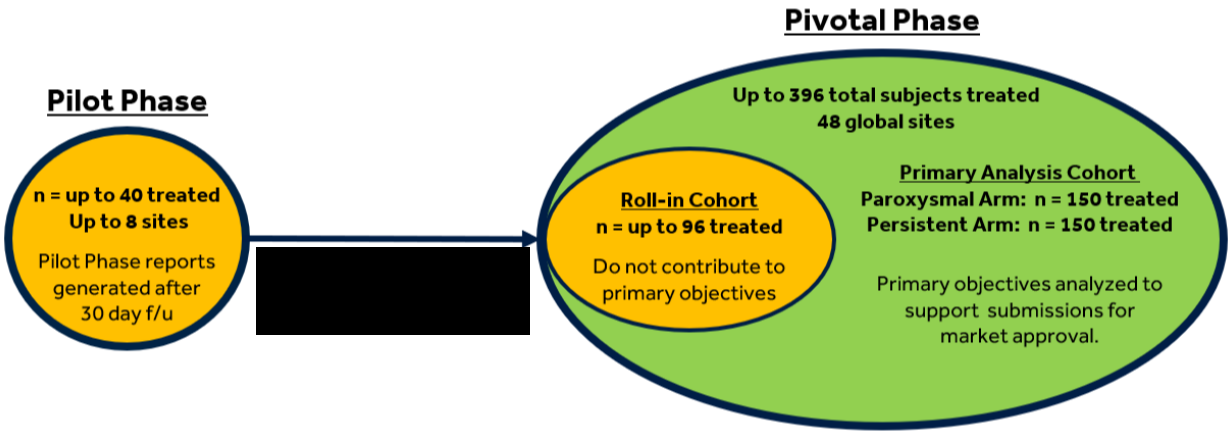
Figure 1: Subject-Level Study Design



As depicted in Figure 2 below, the study is designed to have a continuously growing body of evidence across two phases, with data analyses planned at pre-specified timepoints. The data collected in this study will be used to support regulatory submissions around the world to obtain market approval for the PulseSelect™ PFA System, including, but not limited to, CE Mark, Health Canada (HC), Therapeutic Goods Administration (TGA), Pharmaceutical and Medical Devices Agency (PMDA) and U.S. Food and Drug Administration (FDA) market applications.

The study consists of a Pilot Phase and a Pivotal Phase. Overall, up to 495 subjects will be enrolled to ensure there are up to 40 Pilot Phase subjects, up to 96 Pivotal Phase roll-in cohort subjects, and 300 Pivotal Phase primary analysis cohort subjects treated with the PulseSelect™ PFA System, and to account for subjects not treated prior to exit.

Figure 2: Phased Study Design



Pilot Phase

The Pilot Phase of the PULSED AF study will include an early assessment of safety and confirmation of acute procedural success of PVI ablation with the PulseSelect™ PFA System. Specifically, this phase will include treatment of up to 40 subjects (paroxysmal AF or persistent AF) across up to 8 clinical sites. [redacted]

The Pilot Phase subjects will not be included in the Pivotal Phase primary or secondary endpoint analyses but will be treated and followed in accordance with all other protocol requirements. In addition, the Pilot Phase subjects will complete a cardiac CT or MRI scan at baseline and 3 months to allow characterization of any potential occurrences of PV stenosis. If PV stenosis (≥70% diameter reduction) is identified in any of these Pilot Phase subjects, an additional report will be generated containing the 3-month PV stenosis analysis once all Pilot Phase subjects have completed their 3-month follow-up or exited. The report will be sent to regulatory authorities (as requested) while enrollment in the Pivotal Phase of the study continues.

Pivotal Phase

The purpose of the Pivotal Phase of the study is to provide data demonstrating the safety and effectiveness of the PulseSelect™ PFA System for the treatment of atrial fibrillation. Specifically, this phase will include treatment of 300 subjects (150 paroxysmal AF and 150 persistent AF) for analysis of primary objectives, across up to 48 sites worldwide (including the Pilot Phase sites). For the Pivotal Phase of the study, subjects will be separated into paroxysmal AF and persistent AF arms and analyzed separately. It is expected that at least 50% of the treatments and supporting clinical data will come from the United States with no single site contributing more than 15% of the treatments to each arm of the Pivotal Phase. Each arm will have a primary safety objective and a primary effectiveness objective, in addition to secondary [redacted] objectives. For each study arm to be considered a success, both the primary safety and effectiveness objectives must be met.

To facilitate the investigators' familiarity with the system, a cohort of roll-in subjects will also be included in the Pivotal Phase. It is estimated that there will be up to 96 total roll-in subjects. Roll-in subjects will not be included in the Pivotal Phase primary or secondary endpoint analyses but will be treated and followed in accordance with all other protocol requirements. Roll-in subjects are defined in Section 7.2.1.

5.1. Duration

Subjects will be followed for 12 months after the index ablation procedure and then be considered exited from the study upon completion of the 12-month visit. Accordingly, the expected total study duration is approximately 2 years and 8 months, representing 20 months of enrollment and 12 months of subject follow-up. Treated subjects will not be replaced with newly enrolled subjects upon early study exit.

5.2. Rationale

The study has primary objectives designed to evaluate the safety and effectiveness of the PulseSelect™ PFA System for treatment of AF. This evaluation will support the proposed indication of the PulseSelect™ PFA System. The study will be scientifically sound and successful if it meets both primary safety and effectiveness objectives for one or both arms (paroxysmal and/or persistent).

The potential benefits related to the use of the PulseSelect™ PFA System have been determined to outweigh any potential risks, providing justification to proceed with clinical investigation. Clinical data are needed to demonstrate that the safety profile and proper lesion creation established in preclinical testing is confirmed in a clinical setting. Also, as demonstrated in preclinical studies[20,21,

[20] Stewart, Mark T., et al. "Intracardiac pulsed field ablation: proof of feasibility in a chronic porcine model." *Heart rhythm*. 16.5 (2019): 754-764.

[21] Howard, Brian T., et al. "Pulsed Field Ablation Reduces Pulmonary Vein Stenosis Risk: An Advanced Model for Assessment of PV Stenosis." Circulation 138.Suppl_1 (2018): A16516-A16516.

[22], the PulseSelect™ PFA System offers potential advantages over existing approved or cleared alternatives such as reducing/eliminating collateral damage, improving lesion formation and durability, and reducing the AF ablation procedure time. A phased clinical study design with continuous enrollment and prospective data collection to demonstrate safety and effectiveness of the PulseSelect™ PFA System potentially reduces the time to patient access for this breakthrough device, as opposed to running separate pilot and pivotal studies. A multi-site, multi-national design helps to ensure a representative sample of the global population as well as maintain a reasonable enrollment duration.

5.3. Minimization of Bias

Selection of subjects, treatment of subjects, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- Subject demographics will be collected at baseline in order to later assess possible characteristics that may influence endpoints.
- All investigational site personnel and Medtronic personnel will be trained on their respective aspects of the study using standardized training materials.
- All investigational site personnel will be trained on and required to follow the CIP.
- An independent Clinical Events Committee (CEC) will be utilized to regularly review and adjudicate reported adverse events and deaths in the study.
- An independent core lab will be utilized to regularly review and adjudicate the arrhythmia component of the primary endpoints.
- A statistical analysis plan (SAP) will be developed prior to analyzing data. The plan will document all pre-specified analyses and analysis methods.
- Monitoring will be conducted to review adherence to the CIP and perform source data verification per the Monitoring Plan.
- No single site may contribute more than 15% of the treatments to each arm of the Pivotal Phase (22 paroxysmal AF subjects and 22 persistent AF subjects, excluding Pilot Phase and roll-in subjects) to ensure a reasonable distribution of subjects across sites.
- An independent core laboratory will be used [redacted] to evaluate baseline and 3-month cardiac CT or MRI scans to characterize of any potential occurrences of PV stenosis.

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

[22] Verma, A., et al. "Pulsed field ablation-feasibility, safety and comparison to radiofrequency." EUROPEAN HEART JOURNAL. Vol. 39. GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND: OXFORD UNIV PRESS, 2018.

6. Product Description

6.1. General

Device information is described below and provided in Table 5 and Table 6. Investigator's Brochure (IB) and Instructions For Use (IFU) of the PulseSelect™ PFA System will be provided to investigational sites for use in the clinical study.

Any changes made to these devices during the investigation will be subject to IDE Change or Modification Reporting Requirements per 21 CFR Part 812, as applicable (see Section 13.1).

Table 5: PulseSelect™ PFA System Components

Component	Model Number	Geography Status at Study Start	[redacted]
PFA Generator	M970163A001	Investigational in all geographies	
Catheter Electrode Distribution System (CEDS)	M970165A001	Investigational in all geographies	
Remote Control	M970127A001	Investigational in all geographies	
Cable, Generator to Remote Control	M970169A001	Investigational in all geographies	
Cable, Generator to CEDS	M970168A001	Investigational in all geographies	

Table 6: PulseSelect™ PFA System Accessories

Accessory	Model Number	Geography Status at Study Start*	[redacted]
Cable, CEDS to EP Recording System (EGM)	990027	Commercially available in Europe, Canada, and Australia. Investigational in other geographies.	
Catheter Interface Cable	990004	Commercially available in Europe, Canada, and Australia. Investigational in other geographies.	
[redacted]	990078	Commercially available in Europe, Canada, and Australia. Investigational in other geographies.	
Cardiac Trigger Monitor	7700	Commercially available in all geographies	
Cardiac Trigger Monitor Accessories	3254-55-15	Commercially available in Canada, Europe, Japan and US. In Australia, when supplied individually the accessories are considered investigational; however, since the accessories ship within the same finished good shipping package as the monitor, registration is not required	
Power Cord	1038N – North America; Japan 1038K – Australia 1038E – EU	Commercially available in all geographies	
Uninterruptable Power Supply (UPS)	SMART1200XLHG (120V) SMX1200XLHG (230V)	Commercially available in all geographies (non-medical device)	
Power Cord – C14M-C13F	P004-006-ABL	Commercially available in all geographies (non-medical device)	

*All PulseSelect™ PFA System accessories will be considered investigational when used with PulseSelect™ PFA System

It is anticipated that at least 436 [redacted] catheters and 436 Catheter Interface Cables will be used to ensure the study sample size is met. It is anticipated that at least one each of the remaining PulseSelect™ PFA System components and accessories will be used per site in the study.

6.1.1. System Description

The Medtronic PulseSelect™ Pulsed Field Ablation (PFA) System applies bipolar, biphasic pulsed electric fields through a circular multi-electrode array catheter to perform cardiac tissue ablation through irreversible electroporation. The system is intended to be used for the treatment of atrial fibrillation in humans by isolation of the major cardiac veins.

Each PFA therapeutic delivery consists of a series of electric pulses delivered as a pulse train containing individual brief biphasic pulses. During each pulse, current flows in a bipolar manner between individual electrodes on the multi-electrode catheter array which radiates an electric field that surrounds the array. Cardiac tissue within the electric field undergoes cellular hyper-permeabilization, which irreversibly disrupts the integrity of the cellular membrane leading to cell death in the targeted tissue site. This mechanism of cell death is known as irreversible electroporation (IRE). The ablated myocardium then undergoes replacement fibrosis over a period of days to weeks creating a fibrotic lesion.

[redacted] catheters are sterile, single-use only intravascular devices designed for short-term use (< 24 hours) within the human vasculature and heart. [redacted] makes contact with the central circulatory system (blood contact). [redacted] is also intended for cardiac EP mapping of pulmonary vein potentials, delivery of diagnostic pacing stimuli and verifying electrical isolation of the pulmonary veins post-treatment. The PulseSelect™ PFA System is utilizing this catheter as a platform to deliver pulsed electric fields to cardiac tissue.

The PulseSelect™ PFA System is for use by physicians in a clinical setting (e.g. a fully equipped electrophysiology laboratory) and has been developed for use under a clinical protocol and not for general commercial use.

[redacted]

6.2. PFA Generator

[redacted]

6.3. Catheter Electrode Distribution System (CEDS)

[redacted]

6.4. Remote Control

[redacted]

[redacted]

6.5. Cable, Generator to Remote Control

[redacted]

6.6. Cable, Generator to CEDS

[redacted]

6.7. Cable, CEDS to EP Recording System (EGM)

[redacted]

6.8. Catheter Interface Cable

[redacted]

[redacted]

[redacted]

6.10. Cardiac Trigger Monitor

[redacted]

6.11. Cardiac Trigger Monitor Accessories

[redacted]

6.12. Power Cord

[redacted]

6.13. Uninterruptible Power Supply (UPS)

[redacted]

6.14. Power Cord – C14M-C13F

[redacted]

6.15. Packaging

In all geographies, the following PulseSelect™ PFA System components will be provided to sites and will be labeled as investigational:

- PFA Generator
- CEDS
- Remote Control
- Cable, Generator to CEDS
- Cable, Generator to Remote Control

In the US, Australia, and Japan, the following PulseSelect™ PFA System accessories will be provided to sites and will be labeled as investigational:

- [redacted] catheter
- Catheter interface cable
- CEDS to EP recording cable (EGM cable)

In Canada and Europe, the following PulseSelect™ PFA System accessories are commercially available and will not be provided to sites but will be considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP:

- [redacted] catheter
- Catheter interface cable
- CEDS to EP recording cable (EGM cable)

In all geographies, the cardiac trigger monitor and accessories are commercially available (registration not required in Australia, as described in Table 6). This accessory will be provided to sites and will be considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP.

In all geographies, the power cords (models 1038N, 1038K, 1038E, P004-006-ABL) are commercially available, but will be provided to sites and will be considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP. Medtronic personnel trained on the study will affix a sticker denoting the accessory model number. The appropriate geography-specific model cord should be used by each study site.

In all geographies, the UPS is commercially available, but will be provided to sites and will be considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP.

Market released components used in this study will be labeled investigational according to local requirements. See Appendix A (Study-Specific Requirements by Country) for details of investigational labeling of market released components.

6.16. Product Training Requirements

Investigators responsible as operators for the PulseSelect™ PFA System ablation procedure will be required to undergo product training (to include hands on experience) prior to treating any subject with the PulseSelect™ PFA System. A separate training document will overview topics and include details on the format of delivery.

6.17. Product Receipt, Tracking and Return

The Medtronic PulseSelect™ Pulsed Field Ablation System components will be considered investigational in geographies in which the product is not available commercially and will be labeled for exclusive use in clinical investigations.

Investigational product will be distributed to a site only when Medtronic has received all required documentation, has notified the site of site activation and the site has been authorized to enroll in the study. Distribution of the investigational product to study sites during the clinical study will be managed by Medtronic. Investigational product can only be ordered by Medtronic personnel. Investigational products will be used only in the study according to the CIP and PulseSelect™ PFA System IFU. In Japan, the device control manager, assigned by the Head of Medical Institution controls the investigational device once the product arrives at the study site.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include:

- The date of receipt
- Identification of each investigational device (batch number/serial number or unique code)
- The expiration date (if applicable)
- The date(s) of use
- Subject identification
- The date of return of unused, expired or malfunctioning investigational devices (if applicable)

All potentially defective products should be returned to Medtronic for analysis whenever possible and when permissible by local laws and regulations. Local Medtronic field personnel or representative can be contacted to receive a Return Mailer Kit.

PulseSelect™ PFA System components and accessories are to be returned to Medtronic by each study site as described below:

If no device deficiency, devices can be destroyed/disposed of according to local laws and regulations. If unused, device should be returned as described in the note below:

- [redacted]
- Catheter interface cable

Note: For PulseSelect™ PFA System accessories shipped to sites as investigational, unopened or expired accessories are required to be returned to Medtronic. For PulseSelect™ PFA System accessories only considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP, there is no requirement to return unopened product to Medtronic.

Upon completion of the study, unless otherwise directed by the Medtronic study team:

- PFA Generator
- CEDS
- Remote Control
- Cable, Generator to CEDS
- Cable, Generator to Remote Control
- CEDS to EP recording cable (EGM cable)
- Cardiac Trigger Monitor and accessories
- Power cord (models 1038N, 1038K, 1038E, P004-006-ABL)
- Uninterruptible Power Supply (UPS)

Note: In all geographies, these PulseSelect™ PFA System components and accessories (including unopened or expired product) are required to be returned to Medtronic except in cases where the device is only considered investigational upon opening to be used with the PulseSelect™ PFA System per the CIP, in which case there is no requirement to return this product to Medtronic if unopened.

Any sheath or guidewire used in conjunction with the PulseSelect™ PFA System with a reportable device deficiency should be returned to Medtronic following the study ablation procedure.

Device disposition logs will be provided to all sites and used for tracking of all investigational product throughout the duration of the study. The logs must be maintained and updated when product is disposed of or returned to Medtronic. If the products are not returned to Medtronic, a justification is required to be reported on the appropriate case report form(s) or disposition log(s).

6.18. Product Storage

The PulseSelect™ PFA System is investigational and will be maintained in locked, secure storage with access limited only to approved study staff.

7. Selection of Subjects

7.1. Study Population

The population being studied has documented drug refractory recurrent symptomatic paroxysmal or persistent atrial fibrillation with generally otherwise good cardiovascular health. The AF classifications that will be used for this study are defined in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.[1]

Paroxysmal AF is defined as AF that terminates spontaneously or with intervention within 7 days of onset.

Persistent AF is defined as continuous AF that is sustained beyond 7 days.

Patients in long-standing persistent AF are excluded from the study. Long-standing persistent AF is defined as continuous AF of greater than 12 months' duration.

7.2. Subject Screening and Enrollment

Patients will be screened to ensure they meet all of the inclusion and none of the exclusion criteria prior to study enrollment. Information on screening failures will be captured on the screening log, including the reason(s) for screening failure. Eligible patients who refuse trial participation should also be documented on the screening log, including the reason(s) for refusal to participate. IRB/MEC and Medtronic approval of the Clinical Investigation Plan and the Patient Informed Consent Form must be obtained prior to enrolling subjects in the study. Enrollment of the subject must occur prior to performing any study procedures. Subjects are enrolled at the time the Patient Informed Consent Form is signed and dated. Pilot and Pivotal Phase subjects must meet the same inclusion and exclusion criteria and will follow the same consent process.

7.2.1. Roll-in Subjects

To facilitate the investigators' familiarity with the system, a cohort of roll-in subjects will be included in the Pivotal Phase enrollments. The roll-in subjects will not be included in the subjects included in the analysis for the Pivotal Phase primary and secondary objectives but will be consented, enrolled, treated, and followed in accordance with all other protocol requirements. With the exception of investigators that participate as PulseSelect™ PFA System operators in the Pilot Phase, each investigator's first treated subject will be considered a roll-in subject. Since paroxysmal AF and persistent AF subjects will be treated with the same ablation procedure approach (PVI-only), subjects with either AF type can contribute to the roll-in cohort. Subjects will be identified as roll-in subjects prior to the ablation procedure. There will be up to 96 total roll-in subjects.

[redacted]

7.2.3. Enrollment Strategy for the PV Stenosis Assessment

Subjects will be selected if they are in the study Pivotal Phase and upon their willingness to consent to participate in the PV stenosis assessment (i.e., undergo a baseline and a 3-month cardiac CT/MRI). Subjects will continue to be consented to the PV stenosis assessment until 50 full sets (baseline and 3-month cardiac CT/MRI scans) are obtained. There are no additional inclusion or exclusion criteria for participation in this PV stenosis assessment. The PULSED AF main study patient informed consent (IC) includes an option for subjects to consent to PV stenosis assessment. IRB/EC approval of the PULSED AF IC Form is required prior to enrolling subjects in study. The consent process described in Section 8.2 should be followed for the study IC Form.

7.3. Inclusion Criteria

1. Failure of at least one AAD (class I or III) for AF as evidenced by recurrent symptomatic AF, or intolerable side effects due to AAD.
2. A diagnosis of recurrent symptomatic paroxysmal or persistent AF:
    a. Symptomatic paroxysmal AF, which is defined as AF that terminates spontaneously or with intervention within 7 days of onset, documented by the following:
        1) Physician's note indicating at least 2 symptomatic paroxysmal AF episodes occurring within 6 months prior to enrollment; and
        2) at least 1 ECG documented AF episode from any form of rhythm monitoring within 12 months prior to enrollment

    OR

    b. Symptomatic persistent AF, which is defined as continuous AF sustained beyond 7 days and less than 1 year, documented by the following:
        1) physician's note indicating at least 1 symptomatic persistent AF episode occurring within 6 months prior to enrollment; and
        2) any 24-hour continuous ECG recording documenting continuous AF within 6 months prior to enrollment;
        OR
        2 ECGs from any form of rhythm monitoring taken at least 7 days apart, both showing continuous AF within 6 months prior to enrollment
3. Age 18 through 80 years old (or older than 18 if required by local law)

7.4. Exclusion Criteria

1. Long-standing persistent AF (continuous AF that is sustained >12 months)
2. Left atrial diameter > 5.0 cm (anteroposterior)
3. Prior left atrial ablation or surgical procedure (including left atrial appendage closures)
4. Planned LAA closure procedure or implant of a permanent pacemaker, biventricular pacemaker, loop recorder/insertable cardiac monitor (ICM), or any type of implantable cardiac defibrillator (with or without biventricular pacing function) for any time during the follow-up period
5. Patient who is not on oral anticoagulation therapy for at least 3 weeks prior to the ablation procedure
6. Presence of a permanent pacemaker, biventricular pacemaker, loop recorder/insertable cardiac monitor (ICM), or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
7. Presence of any pulmonary vein stents
8. Presence of any pre-existing pulmonary vein stenosis
9. Pre-existing hemidiaphragmatic paralysis
10. Presence of any cardiac valve prosthesis

11. Moderate to severe mitral valve stenosis
12. More than moderate mitral regurgitation (i.e., 3+ or 4+ MR)
13. Any cardiac surgery, myocardial infarction, PCI / PTCA or coronary artery stenting which occurred during the 3-month interval preceding the consent date
14. Unstable angina
15. NYHA Class III or IV congestive heart failure or documented left ventricular ejection fraction (LVEF) less than or equal to 35% measure by acceptable cardiac testing (e.g. TTE)
16. Primary pulmonary hypertension
17. Rheumatic heart disease
18. Thrombocytosis, thrombocytopenia
19. Any condition contraindicating chronic anticoagulation
20. Active systemic infection
21. Hypertrophic cardiomyopathy
22. Known reversible causes of AF, including but not limited to uncontrolled hyperthyroidism, severe untreated obstructive sleep apnea, and acute alcohol toxicity
23. Any cerebral ischemic event (strokes or TIAs) which occurred during the 6-month interval preceding the consent date
24. History of thromboembolic event within the past 6 months or evidence of intracardiac thrombus at the time of the procedure
25. Any woman known to be pregnant or breastfeeding, or any woman of childbearing potential who is not on a reliable form of birth regulation method or abstinence
26. Patient with life expectancy that makes it unlikely 12 months of follow-up will be completed
27. Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of the study not pre-approved by Medtronic
28. Known allergies or hypersensitivities to adhesives
29. Unwilling or unable to comply fully with study procedures and follow-up
30. Unable to provide own informed consent

8. Study Procedures

8.1. Schedule of Events

Data collection requirements are summarized in Table 7, below.

Table 7: Study Procedures and Data Collection per Subject Visit

	Baseline	Procedure	Discharge	7 Day [1]	30 Day	3 Month [1]	6 Month [1]	12 Month	Unscheduled	Repeat Ablation [9]
Informed Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
Physical Exam	X		X		X					
Pregnancy Screen [2]	X									
AAD & Anticoagulation Medication Review	X		X	X	X	X	X	X	X	X
Arrhythmia Symptom Review	X				X	X	X	X	X	X
12 Lead ECG	X		X		X	X	X	X	X	
NIHSS Assessment	X		X		X					X
Cardiac CT Scan or MRI [3]	X					X	X	X		
AFEQT & EQ-5D-5L	X						X	X		
Transthoracic Echocardiogram (TTE) [4]	X									
Transesophageal Echocardiogram (TEE) [5]	X									
Intracardiac Echocardiography (ICE) [5]	X									
INR Assessment [6]	X									
Ablation Procedure Data		X								X
[redacted]										
24h Continuous Monitoring with Holter							X	X		
Patient Activated Ambulatory ECG Monitor [8]			Weekly and symptomatic episodes							
Adverse Events	As they occur									
Device Deficiencies	As they occur									
Study Deviations	As they occur									

Notes:

[1] Multiple modes of data collections may be employed to support the collection of required visit data at the 7-day and 3- and 6-month visits such as: In office patient clinic visit, direct to patient contact (i.e. telephone, email, mail contact, etc.), and remote technology transmissions/uploads.

[2] Female subjects of childbearing potential only.

[3] Baseline and 3-month cardiac CT/MRI required for all subjects in the Pilot Phase, and for Pivotal Phase subjects consenting to the PV stenosis assessment. For the remaining Pivotal Phase subjects, cardiac CT/MRI is required only for subjects with suspected PV stenosis at 3-, 6- or 12-month visits and who did not undergo cardiac CT/MRI at a previous visit.

[4] Only required if data not available from within 6 months prior to consent date.

[5] Imaging to rule out left atrial thrombus must be performed in all subjects within one day (on the day of or within the day prior to) the planned ablation procedure. TEE is the preferred method, but ICE may be used in the event TEE is not preferred or possible for the subject or site.

[6] Subjects taking a vitamin K antagonist (VKA) are required to have a therapeutic INR (2-3.5) on the day of the planned ablation procedure. INR assessment is not required for subjects on other types of anticoagulants.

[redacted]

[8] Subjects shall submit ECG transmissions weekly and whenever symptoms occur from discharge through 12-month follow-up. Of note, the first 20 pilot phase subjects were required to start submitting ECG transmissions weekly and whenever symptoms occur after the post-ablation blanking period through 12-month follow-up, although some of these pilot phase subjects started submitting earlier (at the 30-day visit) following a pre-planned protocol deviation.

[9] The pre-ablation and discharge NIHSS assessments and the discharge physical examination are not required if the physician will not use the PFA System for any portion of the repeat ablation.

8.2. Subject Consent

Patient informed consent (IC) is defined as a legally effective documented confirmation of a subject's voluntary agreement to participate in a particular clinical study after information has been given to the subject on all aspects of the clinical study that are relevant to the subject's decision to participate. This process includes obtaining an IC Form and an Authorization to Use and Disclose Personal Health Information (US only) that has been approved by the study site's IRB/REB/MEC and signed and dated by the subject. A subject may only consent after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate.

Prior to enrolling subjects, the IC Form must have been approved by each site's IRB/REB/MEC. Each site must also use an Authorization to Use and Disclose Personal Health Information/Research Authorization (US only) or other privacy language as required by law. The IC Form must be controlled (i.e. versioned and dated) to ensure it is clear which version(s) were approved by the IRB/REB/MEC. Any adaptation of the sample IC Form must be reviewed and approved by Medtronic and the IRB/REB/MEC reviewing the application prior to enrolling subjects.

The Investigator must notify the subject of any significant new findings about the study that become available during the study which are pertinent to the safety and well-being of the subject. This could impact a subject's willingness to participate in the study. If relevant, approval may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, documented informed consent must be obtained from the subject. Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize sites to submit subject information to the study sponsor. The informed consent process must be conducted by the Principal Investigator or an authorized designee, and the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be

given to the subject in a language he/she is able to read and understand. The process of informed consent must be conducted without using coercion, undue or improper influence on, or inducement of the subject to participate by the Investigator or other site personnel. The informed consent process shall not waive or appear to waive the subject's legal rights. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the IC Form, to inquire about details of the study, and to decide whether to participate in the clinical study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the clinical study, the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be signed and personally dated by the subject and either the Investigator or the Investigator's authorized designee, as required by local law. If applicable, independent witness must be present throughout the entire informed consent process, and the written informed consent form and any other information related to the study must be read aloud and explained to the prospective subject. If applicable, witness shall also sign and personally date the consent form to attest that the information in the IC Form was accurately explained and clearly understood by the subject, and that informed consent was freely given.

A copy of the IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law (US only), signed and dated as required by law, must be provided to the subject.

If consent is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study related procedures. It is best practice for the informed consent process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, a witnessed (impartial third party) IC Form will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the IC Form.

The original of the signed IC Form and the Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language (US only) as required by law must be filed in the hospital/clinical chart and/or with the subject's study documents and should also be available for monitoring and auditing. Any Medtronic Field personnel who support the study procedure must be able to review the subject's signed and dated IC Form and verify its completeness prior to proceeding with the procedure. In the event the Medtronic Field personnel identify an IC Form as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

8.3. Enrollment, Baseline, and Pre-ablation

When a patient and the Principal Investigator or authorized designee, as required, have signed and dated the IC Form, the patient is considered a subject enrolled in the study. The date the subject signed the IC Form and Authorization to Use and Disclose Personal Health Information/Research Authorization/other privacy language as required by law must be documented in the subject's medical records.

The baseline visit can be a standalone visit or can be performed on the same day but prior to the PulseSelect™ PFA System ablation procedure. The following evaluations will be performed after consent, unless previously performed as part of routine clinical evaluations within the specified windows:

Within 6 months prior to consent date:

- Trans-thoracic echocardiogram (TTE) for the collection of left atrial size, left ventricular ejection fraction, and mitral valve impairment. A repeat TTE procedure for the purpose of the study after the consent date is not required if a TTE was performed within 6 months of the consent date and all data are available.
- Pilot Phase subjects (all) and Pivotal Phase subjects consenting to the PV stenosis assessment only: cardiac Magnetic Resonance Imaging (MRI) or Computerized Tomography Scanning (CT scan) of the four PVs or their anomalous equivalent.

Within 30 days prior to consent date:

- 12-lead ECG
- Physical examination
- CHA_2DS_2-VASc Score
- Demographics
- Medical history

After consent date but prior to procedure:

Note: The time between the consent date and the procedure should not exceed 30 days. If 30 days are exceeded, the subject must be re-evaluated against inclusion and exclusion criteria to ensure they still qualify for the study.

- Final assessment of all factors specified for evaluation under Inclusion Criteria and Exclusion Criteria (Section 7)
    - Note: After required study testing, if a subject no longer meets the inclusion criteria or now meets exclusion criteria, the subject will be exited from the study.
- Pregnancy screen (female subjects of childbearing potential only)

  - Note: For this study, a woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant
- Review of AF symptoms
- Review of medications to treat atrial arrhythmias and anticoagulation medications
- EQ-5D (5L version) and AFEQT Questionnaires
- INR assessment
  - Subjects taking a vitamin K antagonist (VKA) are required to have a therapeutic INR (2-3.5) on the day of the planned ablation procedure.
  - INR assessment is not required for subjects on other types of anticoagulants.
- Imaging to rule out left atrial thrombus must be performed in all subjects. This imaging should occur within one day (on the day of or within the day prior to) the planned ablation procedure. The subject will not proceed with the study ablation procedure and will be exited from the study if a left atrial thrombus is visualized.
  - Transesophageal Echocardiogram (TEE) is the preferred imaging method.
  - In the event TEE is not preferred or possible for the subject or site, intracardiac echocardiography (ICE) may be used to rule out left atrial thrombus.
- National Institute of Health Stroke Scale (NIHSS) Assessment
  - The NIHSS will be administered to all subjects within 3 days prior to, including day of, planned ablation procedure.
  - The NIHSS will be administered by study site personnel who have been certified to perform the NIHSS assessment and are delegated by their respective site to perform such assessment
- [redacted]

8.4. Procedure

Note: The time between the consent date and the procedure should not exceed 30 days. If 30 days are exceeded, the subject must be re-evaluated against inclusion and exclusion criteria to ensure they still qualify for the study.

Perform the pulmonary vein isolation procedure using the PulseSelect™ PFA System with the [redacted] cardiac ablation catheter. [redacted] The Investigator is to perform the procedure according to the procedural steps in this CIP and the PulseSelect™ PFA System Instructions For Use. Appropriate sedation and venous access should be attained at the Investigator's standard practice according to their institution's pre-established procedures/guidelines at the time of the procedure. Investigator may choose compatible guidewires, sheaths and mapping catheters at their discretion. ACT analyzer calibration records must be made available for sponsor review prior to each PFA ablation procedure.

The anticoagulation protocol for PULSED AF is as follows:

- Pre-procedure
  - Subjects who are not on oral anticoagulation therapy for at least 3 weeks prior to the ablation procedure are excluded from the study.
  - If VKA is used, 1 therapeutic INR reading (2-3.5) is required day of procedure.
  - Prior to ablation, imaging to rule out left atrial thrombus is required of all patients regardless of CHA_2DS_2-VASc score or anticoagulation.
- Procedure
  - Continuous, uninterrupted oral anticoagulation (e.g. no bridging with low molecular weight heparin) is required.
  - Administer heparin bolus prior to (or immediately after) the transseptal puncture and start continuous heparin infusion to maintain a target ACT ≥ 350 seconds.
  - The ACT level should be checked at approximately 15–30 minute intervals for the duration of the procedure.
  - In the event of persistent bleeding or cardiac tamponade, protamine may be administered to reverse heparin. If bleeding resolves, reversal of oral anticoagulant is not recommended.
- Post-procedure
  - Oral anticoagulation must be continued for at least 2 months post-procedure (e.g. no bridging post-procedure) for all subjects unless contraindicated.
  - Discontinuation of systemic anticoagulation therapy after 2 months post ablation is not recommended in male subjects with a CHA_2DS_2-VASc score >1 or female subjects with a CHA_2DS_2-VASc score >2.

8.4.1. Esophageal Visualization and Temperature Monitoring

a. An esophageal temperature monitor is not required to be used for PFA therapy profile applications. If an esophageal temperature monitor is used, it should have an insulated tip.

8.4.2. Diaphragm Movement

a. Prior to the first PFA application, the Investigator must confirm absence of pre-existing hemidiaphragmatic paralysis.

8.4.3. Peri-procedural Anticoagulation

a. Heparin should be administered prior to (or immediately following) transseptal puncture during AF ablation procedures and adjusted to achieve and maintain a target ACT of at least 350 seconds. ACT should be checked approximately every 15-30 minutes.

b. Performance of AF ablation in a subject systemically anticoagulated with VKA or novel oral anticoagulants (NOACs) does not alter the need for intravenous heparin to maintain a therapeutic ACT during the procedure.

c. Performance of the ablation procedure on continuous, uninterrupted oral anticoagulation (e.g. no bridging with low molecular weight heparin) is required.

d. In the event of persistent bleeding or cardiac tamponade, protamine may be administered to reverse heparin. If bleeding resolves, reversal of oral anticoagulant is not recommended.

8.4.4. Pulmonary Vein (PV) Ablation with the PulseSelect™ PFA System

a. Deploy diagnostic catheters and perform transseptal puncture. Introduction of the [redacted] catheter should be performed according to the PulseSelect™ PFA System IFU.

b. Every effort consistent with subject welfare should be made to treat all PVs or their anomalous equivalents.

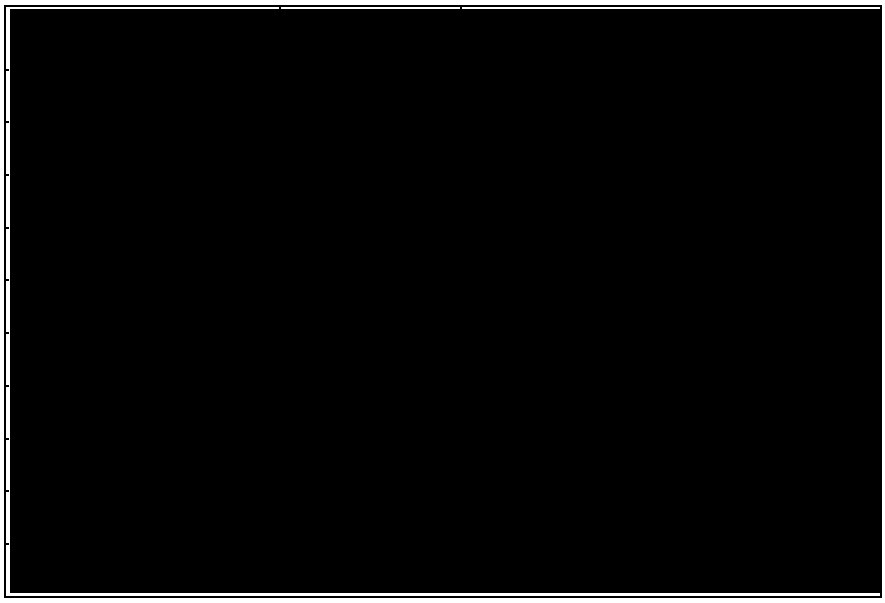
c. The [redacted] catheter will be advanced into the left atrium and tracked over the guidewire so that it is positioned at the entrance of the PV.

d. Assess the catheter's spiral array positioning at the PV by fluoroscopy or other imaging technique. Reposition as needed.

e. Map for pulmonary vein potentials.

f. Perform ablations. [redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]



g. Verify ostial isolation of each pulmonary vein a minimum of 20 minutes after the last PFA application of the initial PVI in that PV. Each pulmonary vein should be minimally assessed for entrance block and, where assessable, exit block to demonstrate electrical isolation.

h. Upon the Investigator's assessment of procedure completion, Isoproterenol and/or adenosine may be used to assess pulmonary vein isolation or non-PV triggers.

i. In the event of an inability to electrically isolate all accessible targeted pulmonary veins with the PulseSelect™ PFA System, any commercially released catheter deemed appropriate for the procedure may be used to complete the ablation procedure. Ablation using a non-study device to isolate any pulmonary vein will be considered a primary endpoint failure.

8.4.5. Other Ablations during Index Procedure

a. Additional left atrial ablations outside the pulmonary veins, except for complex fractionated atrial electrogram (CFAE) ablations, may be performed if clinically necessary after the 20-minute waiting period and verifying isolation of all pulmonary veins. Any commercially released catheter deemed appropriate for the procedure may be used.

b. Ablation of the cavotricuspid isthmus, with the goal of achieving bi-directional isthmus block, is recommended for subjects with a history of typical atrial flutter or inducible cavotricuspid isthmus dependent atrial flutter. It is recommended to attempt an induction of cavotricuspid isthmus dependent atrial flutter if the subject does not have a history of this arrhythmia. Any commercially released catheter deemed appropriate for the procedure may be used.

c. Additional right atrial ablations may be performed if clinically necessary. Any commercially released catheter deemed appropriate for the procedure may be used.

8.4.6. Procedure Documentation

During the procedure, the following data will be collected:

- Catheters used
- Vein location for each PFA application (e.g. right superior PV)
- Use of test pulse or other phrenic nerve monitoring technique for each PFA application
- PFA therapy profile and electrode configuration used for each PFA application
- Procedural sedation methods/type, including any modifications to procedural sedation as a result of subject reaction to PFA applications
- Stimulation of diaphragm or skeletal muscle as a result of PFA applications
- Demonstrated electrical block and the device used to demonstrate
- Adjunctive catheters, mapping or visualization devices, procedure information, ACT, cardioversion use and fluoroscopy time will be collected; esophageal temperature may be collected

8.4.7. Cardioversion

Direct Current (DCCV) or pharmacological cardioversion may be considered at any point during the procedure when restoration of SR will assist in assessing the effectiveness of PFA or deemed necessary for the benefit of the patient. Electrical or pharmacological cardioversion to sinus rhythm must be attempted at the conclusion of the procedure if sinus rhythm was not restored.

8.4.8. Role of Medtronic Personnel at Study Procedure

Medtronic personnel will provide technical support at the ablation procedures under the supervision of a study investigator, but no data entry into the electronic database shall be performed by Medtronic personnel at sites. Medtronic personnel may support completion of the study worksheets. Medtronic personnel will collect procedural data from the PFA generator post-procedure via data download. It is the responsibility of the study site to ensure the subject is identified via subject ID number to prevent the distribution of personally identifiable information.

8.5. Hospital Discharge

At or shortly before hospital discharge, the following will be performed and collected:

- Adverse event assessment
- Review medications
- 12-lead ECG
- Physical examination
    - The discharge physical examination will include, at a minimum, a cardiopulmonary examination.
- NIHSS Assessment
    - The NIHSS will be administered by study site personnel who have been certified to perform the NIHSS assessment and are delegated by their respective site to perform the assessment. The discharge NIHSS assessment will be conducted no earlier than the day following the procedure and no later than the subject's discharge. If the subject is discharged the same day as the ablation procedure, the NIHSS assessment will be conducted no earlier than 6 hours following the procedure. If the subject's discharge NIHSS total score is higher (worse) than the baseline NIHSS total score, a formal neurology consult will be initiated by the study site team to confirm the presence or absence of stroke or TIA. If the site's neurology team deems it necessary, imaging will be performed.
- Provide the subject with patient activated ambulatory monitoring equipment and provide instructions for weekly and symptomatic transmissions.
- Review study requirements with the subject to help ensure compliance with follow-up procedures.

[redacted]

8.5.1. Phrenic Nerve Injury Screening

Post-ablation testing to screen for phrenic nerve injury is required and must be performed prior to discharge. Investigators may choose method of screening at their discretion. Acceptable screening tests include, but are not limited to, use of a diagnostic catheter to pace the phrenic nerve and watch for diaphragmatic movement, fluoroscopy of diaphragm movement at the completion of the ablation procedure, a sniff test, or an inhalation-exhalation chest radiography of diaphragm prior to discharge.

8.6. Medications

Oral anticoagulation must be continued for at least two months post-ablation (e.g. no bridging post-ablation) for all subjects unless contraindicated. Decisions regarding the continuation of anticoagulation therapy more than two months following ablation should be based on the subject's risk factors for stroke as estimated by the CHA_2DS_2-VASc score and not on the presence or type of AF. Discontinuation of systemic anticoagulation therapy after two months post-ablation is not recommended in male subjects with a CHA_2DS_2-VASc score >1 or female subjects with a CHA_2DS_2-VASc score >2.

Information regarding medications prescribed for anticoagulation or to treat atrial arrhythmias will be collected from subject enrollment through study exit. The following information will be collected for medications to treat atrial arrhythmias: medication name, purpose for use, start and stop dates, dose, dosage changes (and reasons for changes), and route of administration. Data collection for anticoagulation medication will be limited to medication name and start and stop dates.

Requirements for use of antiarrhythmic medications for the Paroxysmal AF and Persistent AF cohorts are identical, as described below. For both patient populations, the 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF should be consulted for AAD prescriptions.[8] All other medications (those that are not specified below) are permitted in the study, with the exception of investigational drugs that may confound the study results. Beta-blockers may be prescribed per standard of care.

8.6.1. Antiarrhythmic Medication Requirements

Up-titration of the Class I or III antiarrhythmic medication dose is allowed only in the 90-day post-procedure blanking period.

Re-initiation, at any point during follow-up, of a Class I or III antiarrhythmic medication that was failed or was not tolerated prior to the ablation procedure at any dose will be considered a primary endpoint failure.

Class I and III antiarrhythmic medication use after the 90-day blanking period:

- Subjects are allowed to remain on Class I or III antiarrhythmic medications at or lower than the historic maximum ineffective dose (prior to the ablation procedure) after the 90-day post-procedure blanking period.
- Initiation of a new Class I or III antiarrhythmic medication after the 90-day post-procedure blanking period will be considered a primary endpoint failure.
- Remaining on a dose higher than the historic maximum ineffective dose (prior to the ablation procedure) after the 90-day post-procedure blanking period will be considered a primary endpoint failure.

8.7. Repeat Ablations with PFA

One repeat PVI ablation using PFA, performed according to the procedural steps in Section 8.4 including other ablations as described in Section 8.4.5, is permissible within the 90-day blanking period. More than one repeat PVI ablation using PFA during the blanking period will be considered a primary endpoint failure. Any repeat PVI using the PulseSelect™ PFA System throughout the study follow-up period should be performed according to the procedural steps in Section 8.4. Note, a repeat ablation after the 90-day blanking period will be considered a primary endpoint failure.

Subsequent ablations in the right atrium are allowed (e.g., typical atrial flutter ablation) at any time throughout the study follow-up period. Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter must be confirmed by entrainment maneuvers during electrophysiology (EP) mapping.

If a repeat left atrial ablation is deemed necessary and performed by the Investigator, the following should be performed:

- [redacted]
- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- NIHSS Assessment
    - An NIHSS assessment will be administered to all subjects within 3 days prior to, including day of, repeat ablation procedure.
    - The NIHSS will be administered by study site personnel who have been certified to perform the NIHSS assessment and are delegated by their respective site to perform such assessment.
    - Note, the pre-ablation NIHSS assessment is not required if the physician will not use the PulseSelect™ PFA System for any portion of the repeat ablation.
- Discharge procedures will be completed in accordance with Section 0, with the following exceptions:
    - [redacted]
    - The discharge physical examination and NIHSS assessment are not required if the physician does not use the PulseSelect™ PFA System for any portion of the repeat ablation.
    - Subjects do not need to be provided with patient activated ambulatory monitoring equipment after a repeat ablation procedure as they will have already received it after the index ablation procedure.

Repeat ablation procedures where the PulseSelect™ PFA System is used, even if only for a portion of the ablation, will be documented on an electronic case report form (eCRF) and as described in accordance with Section 8.4.6.

The subject's procedures and follow-up windows will continue based on the index PFA ablation procedure date.

8.8. Post-Procedural Cardioversions

Electrically and pharmacologically cardioverting the subject to sinus rhythm is allowed in the 90-day post-procedure blanking period at the discretion of the Investigator. Electrically or pharmacologically cardioverting the subject to sinus rhythm after the 90-day blanking period will be considered a primary endpoint failure.

8.9. Scheduled Follow-up Visits

After receiving notice of a completed index ablation procedure, Medtronic will provide the target dates and windows for each visit to the site. Should a subject miss a visit or the visit fall outside the pre-specified window, a study deviation must be reported and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation. Follow-up visit windows are listed in Table 9 and are based on days after the index ablation procedure.

Table 9: Follow-up Schedule

Occurrence/ Visit	Window (Calculated days after the ablation procedure)	
	Window Start	Window End
Enrollment/Baseline[1]	-30 days	Day 0
Index PulseSelect™ PFA System Ablation Procedure	Day 0	Day 0
7 day (phone call or office)	7 days	14 days
30 day	30 days	44 days
3 month	91 days	111 days
6 month	183 days	213 days
12 month	365 days	395 days
[1]Note: if the time between the consent date and the procedure exceeds 30 days, the subject must be re-evaluated against inclusion and exclusion criteria to ensure they still qualify for the study.		

Multiple modes of data collections may be employed to support the collection of required visit data at the 7-day and 3- and 6-month visits such as: In office patient clinic visit, direct to patient contact (i.e. telephone, email, mail contact, etc.), and remote technology transmissions/uploads.

The following information is required to be collected at the follow-up visits.

Alternative methods of data collection may be necessary in the case of extenuating circumstances, such as a global pandemic, when subjects are prohibited from coming into the office for required assessments. Alternative methods in such circumstances are listed below as "alternative processes used only during extenuating circumstances". For all assessments completed via alternative methods in these circumstances, sites are not required to enter a protocol deviation for missing/alternative/late data collection. Data unable to be collected remotely or via an alternative method (physical exam and CT/MRI) should be collected at the next possible in-person visit.

8.9.1. Seven Day Phone or Office Visit

- Review medications
- Adverse event assessment

8.9.2. Thirty Day Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
- Physical examination
  - The 30-day physical examination will include, at a minimum, a cardiopulmonary examination.
- NIHSS Assessment
  - The 30-day visit NIHSS will be administered by study site personnel who have been certified to perform the NIHSS assessment and are delegated by their respective site to perform the assessment. If the subject's 30-day visit NIHSS total score is higher (worse) than the baseline or discharge NIHSS total score, a formal neurology consult will be initiated by the study site team to confirm the presence or absence of stroke or TIA. If the site's neurology team deems it necessary, imaging will be performed.

[redacted]

- Alternative processes used only during extenuating circumstances:
  - 12-lead ECG: In place of a 12-lead ECG, subject rhythm will be collected via patient-activated ambulatory monitor.
  - NIHSS assessment[redacted]: Alternatively, a telemedicine visit will be conducted to complete an assessment for stroke symptoms using a worksheet provided by Medtronic. The completed worksheet should be saved in the subjects' EMR and subject binder. If the subject has any stroke symptoms, they will be referred to the physician for further evaluation.

8.9.3. Three Month Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
- Remind subject of instructions on patient activated ambulatory monitoring equipment for weekly and symptomatic transmissions
- Cardiac MRI or CT scan:
    - Pilot Phase subjects are required to complete a cardiac MRI or CT scan (whichever technology was used at Baseline) of all PVs or their anomalous equivalents.
    - Pivotal Phase subjects consenting to the PV stenosis assessment are required to complete a cardiac MRI or CT scan (whichever technology was used at Baseline) of all PVs or their anomalous equivalents.
    - Pivotal Phase subjects **not** consenting to the PV stenosis assessment: only in the case of suspected PV stenosis, is cardiac MRI or CT scan required. It is not required at this visit if it was already completed at an earlier visit where PV stenosis was confirmed.
- [redacted]

- Alternative processes used only during extenuating circumstances:
    - 12-lead ECG: In place of a 12-lead ECG, subject rhythm will be collected via patient-activated ambulatory monitor.

8.9.4. Six Month Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
- Remind subject of instructions on patient activated ambulatory monitoring equipment for weekly and symptomatic transmissions
- Pivotal Phase subjects **not** consenting to the PV stenosis assessment: only in the case of suspected PV stenosis, is cardiac MRI or CT scan required. It is not required at this visit if it was already completed at an earlier visit where PV stenosis was confirmed.
- 24h continuous monitoring with Holter
- EQ-5D and AFEQT Questionnaires

- Alternative processes used only during extenuating circumstances:
    - 12-lead ECG: In place of a 12-lead ECG, subject rhythm will be collected via patient-activated ambulatory monitor.

8.9.5. Twelve Month Visit

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG
- Pivotal Phase subjects **not** consenting to the PV stenosis assessment: only in the case of suspected PV stenosis, is cardiac MRI or CT scan required. It is not required at this visit if it was already completed at an earlier visit where PV stenosis was confirmed.
- 24h continuous monitoring with Holter
- EQ-5D and AFEQT Questionnaires
- Collect or ensure return of ambulatory monitoring equipment

- Alternative processes used only during extenuating circumstances:
    - 12-lead ECG: In place of a 12-lead ECG, subject rhythm will be collected via patient-activated ambulatory monitor.

8.10. Unscheduled Office Visits

An unscheduled visit is defined as any unplanned cardiovascular-related office visit (or telehealth visit completed in place of the unplanned cardiovascular-related office visit) or early study exit at the study site that occurs between CIP required visits. If the subject exits the study early, the site should attempt to complete an unscheduled office visit. The following information is required to be collected at unscheduled follow-up visits:

- Review medications
- Adverse event assessment
- Review symptoms suggestive of recurrent AF/AT/AFL
- 12-lead ECG

If a telehealth visit is completed in place of an unplanned cardiovascular-related office visit, the 12-lead ECG is not required.

8.11. Holter and Patient Activated Ambulatory ECG Monitor Management

Market-released Holters will be distributed by a core lab to sites or subjects (where allowed by state/local law) after activation has occurred. All subjects will wear a Holter in conjunction with their 6- and 12-month office visits. Holters will be sent back to the core lab after they have been worn by the subject. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objective of the study. The core lab will manage maintenance, calibration and tracking of the Holters.

Market-released Patient Activated Ambulatory ECG Monitors will be distributed by a core lab to sites or subjects (where allowed by state/local law) after activation has occurred. All subjects will transmit weekly and symptomatic ECGs following their index ablation procedure. The monitors will be returned to the core lab at the end of the study. The core lab will be responsible for adjudication of atrial arrhythmias for the primary effectiveness objectives of the study. The core lab will manage maintenance, calibration and tracking of the monitors.

8.12. 12-lead Electrocardiograms

12-lead ECGs collected at baseline and the 3-month, 6-month, and 12-month visits will be sent to the core lab. The core lab will be responsible for adjudication of atrial arrhythmias for the primary objectives of the study. Copies of additional source documents may be requested.

8.13. Assessment of Safety

The Pilot Phase safety objective is based on the data collected as discussed in Sections 4.1 and 12.1.

The Pivotal Phase primary safety objective is based on the Adverse Event data collected. Further information on the collection of Adverse Events is discussed in Section 10.

8.14. Assessment of Effectiveness

The Pilot Phase effectiveness objective is based on the data collected as discussed in Sections 4.1 and 12.1.

The Pivotal Phase primary effectiveness objectives are based on the data collected as discussed in Sections 4.2 and 12.2.

[redacted]

[redacted]

8.17. Recording Data

The study will collect data using an electronic data management system for clinical studies. Sites will enter data onto case report forms (CRFs) within the electronic database.

Data reported on the CRFs shall be derived from source documents, which may include, but is not limited to, worksheets, quality of life questionnaires, patient medical records and ECG data. These source documents must be maintained by the site personnel. Further detail on data management is provided in Section 14.2.

8.18. Deviation Handling

A study deviation is defined as an event within a study that did not occur according to the CIP or the Clinical Trial Agreement. Prior approval by Medtronic is expected in situations where the Investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval for study deviations will be reported to local authorities and ethics boards per local requirements. 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 (e.g. subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, inability to perform required procedures due to subject illness). If the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study, prior approval from IRB/REB/MEC may also be required, depending on local requirement. Subjects' failure to submit ambulatory monitoring transmissions per the CIP does not require a deviation to be reported. Ambulatory monitoring transmission compliance will be tracked by Medtronic personnel and the Core Lab.

For medically justifiable conditions which preempt a subject's ability to complete a study-required procedure, it may be permitted to report only one deviation which will apply to all visits going forward. This may also apply for other unforeseen situations (e.g. the subject permanently refuses to complete a study required procedure and the data will not contribute to the primary endpoint analysis). However, prior approval from Medtronic is required for such situations.

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. The deviation description must be recorded with an explanation for the deviation.

In the event the deviation involves a failure to obtain a subject's consent or is made to protect the life or physical well-being of a subject in an emergency, the deviation must be reported to the IRB/REB/MEC as well as Medtronic within five (5) working days, or earlier according to local requirements. In Japan, the deviation must be immediately reported to Head of Medical Institute (HOMI), to the Ethics Board via the HOMI, and to Medtronic. Reporting of all other study deviations should comply with IRB/REB/MEC policies, local laws and/or regulatory agency requirements and must be reported to Medtronic as soon as possible upon the site becoming aware of the deviation. Refer to Investigator Reports, Section 14.6.2, for specific deviation reporting requirements and timeframes for reporting to Medtronic and/or regulatory bodies.

Medtronic is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, and terminate the investigation). Repetitive or serious Investigator compliance issues may result in initiation of a corrective action plan with the Investigator and site, and in some cases, necessitate suspending enrollment until the problem is resolved or ultimately terminating the Investigator's participation in the study. Medtronic will provide site-specific reports to Investigators summarizing information on deviations that occurred at the investigational site on a periodic basis.

8.19. Subject Withdrawal or Discontinuation (Subject Exit)

A subject can exit from the study at any time and is not obliged to provide a reason. If the subject wishes to exit early from the study, the site is required to document the reason, if available, for exit on an eCRF and in the subject's medical record. Completion of an early study exit eCRF is not required in the case of a subject death. In addition, sites shall follow the regulations set forth by their IRB/REB/MEC. It is recommended that Investigators follow the subject until all device and/or procedure-related adverse events are recovered / resolved. For countries following ISO 14155:2011, permission may be requested to follow-up with the subject outside of the study based on problems related to the study device safety or performance. Following completion of the 12-month visit or early study exit, subjects will continue to receive standard medical care. All data available through the time of the subject's exit will be available for analysis.

Potential reasons for early study exit include:

- Subject lost to follow-up
- Subject did not meet inclusion/exclusion criteria after consent and did not undergo an ablation procedure
- The PulseSelect™ PFA System was not used during the subject's ablation procedure
- Subject did not provide proper consent or data use protection authorization
- Subject chooses to withdraw (e.g., consent withdrawal, relocation to another geographic location)
- Investigator deems withdrawal necessary (e.g., medically justified, failure of subject to maintain adequate study compliance)
- The sponsor decides the study will be closed or a particular site will be closed

In the case that the subject is determined to be lost to follow-up, details of a minimum of two attempts and the method of attempt (e.g., one letter and one phone record or two letters) to contact the subject must be recorded.

An unscheduled office visit should be attempted if the subject exits the study outside of a scheduled follow-up visit. Subjects treated with the PulseSelect™ PFA System who exit from the study should continue to be followed by an electrophysiologist for follow-up of any potential adverse events at the recommended interval of 12 months from the index PulseSelect™ PFA System ablation procedure.

9. Risks and Benefits

9.1. Potential Risks

Medtronic follows rigorous Quality Assurance and Control procedures throughout the life of a product, from the business analysis phase through development, market release, and post-market surveillance. The risk management process for the PulseSelect™ PFA System is being performed in accordance with ISO 14971 (Medical Device Risk Management) and will ensure that the level of risk has been reduced as low as possible prior to starting the clinical study. A summary of the risk analysis and risk assessment is provided in the Investigator Brochure.

Risk analysis for the PulseSelect™ PFA System includes both Preliminary Hazard Analysis (PHA) and Failure Mode and Effect Analysis (FMEA) techniques. Risk controls are implemented at both the design inputs stage and through evaluation via design verification and validation activities to demonstrate effectiveness of risk controls.

If changes are made to components of the PulseSelect™ PFA System throughout the course of the study, Medtronic will ensure these changes do not impact the scientific soundness and safety of the study.

Risk control strategies for the PULSED AF study risks were developed by a cross-functional team and in accordance with the Risk Management process. Potential risks associated with this study are further minimized by providing hands-on training to qualified investigators and training site personnel on the Clinical Investigation Plan.

9.2. Risk Minimization

The potential risks associated with the PulseSelect™ PFA System and other potential risks of study participation were identified and risk control measures were defined.

Table 10: Potential Risks and Mitigation Strategies

Risks	Mitigation Strategies
Thromboembolic complications resulting in: stroke / transient neurological ischemia, or asymptomatic cerebral embolism due to embolic particulates or gas bubble ingress into blood.	Maintaining procedural ACT ≥350 and requiring 3-week anticoagulation prior to the ablation will reduce the likelihood of thromboembolic events associated with the procedure. Section 8.4 describes the full PULSED AF anticoagulation strategy. Rigorous sheath management during catheter introduction and exchanges has demonstrated a reduced likelihood of air egress during the ablation procedure. Sheath management will be covered in hands-on training of PulseSelect™ PFA System operators.

Risks	Mitigation Strategies
	Patients who are predisposed to thromboembolic complications, for example patients with a large left atrial diameter >5.0 cm, or patients with a history of prior stroke/ TIA (within 6 months of consent to the procedure), or present with an intracardiac thrombus are excluded from this study.
Arrhythmia induction (e.g. atrial flutter, bradycardia, heart block, tachycardia)	The pre-programmed PFA therapy profiles were refined over the course of pre-clinical research to identify the range of PFA deliveries that do not impart charge of significance to the target tissue and reduce the risk of induced arrhythmias. PFA therapy profiles are not modifiable by the investigator. The patient's ventricular R-wave is detected by a Cardiac Trigger Monitor, which allows synchronization of PFA therapy with the QRS complex. [redacted]
Neuromuscular stimulation upon delivery.	Extensive pre-clinical testing has been performed to refine the PFA delivery waveform to minimize neuromuscular stimulation. Medtronic data on file.
Collateral damage to cardiac structures (e.g. pulmonary vein stenosis).	Extensive pre-clinical testing has been performed to refine the PFA delivery parameters to ablate myocardial tissue without incurring significant pulmonary vein stenosis. Medtronic data on file. [redacted] has been designed with safety features such as rounded edges and an 'over the wire' type design to minimize collateral damage during maneuvering when in the heart.
Collateral damage to non-cardiac tissues	Extensive pre-clinical testing has been performed to refine the PFA delivery parameters to ablate myocardial tissue without damage to extracardiac tissue. Medtronic data on file.
Arcing or shorting of the catheter inside of the body.	Failure modes that could affect patient safety were considered in the design of the PulseSelect™ PFA System. The PulseSelect™ PFA System has incorporated safety features to confirm system integrity [redacted]
Catheter delivery outside of the body	Instructions regarding the connection between the catheter and CEDS after the catheter has been placed

Risks	Mitigation Strategies
	inside the body have been incorporated into the PulseSelect™ PFA System IFU.
Bleeding, or severe blood loss from introduction of a catheter into the left atrium through femoral access.	Instructions regarding catheter introduction into the body for the ablation procedure have been incorporated into the PulseSelect™ PFA System IFU.
Damage to Heart Tissue / Vasculature through excessive catheter manipulation, catheter entrapment, placement of [redacted] in non-pulmonary vein areas, or lack of careful management of the guide wire.	Procedural technique instructions intended to optimize safety are provided in the PulseSelect™ PFA System IFU. The protocol requires that the ablation procedure is to be performed by an investigator who has received hands-on training on all aspects of the procedure. Medtronic intends to use a proctorship strategy during the PULSED AF trial to ensure the knowledge and skills are transferred to new users. The PulseSelect™ PFA System is utilizing the [redacted] as a platform to deliver pulsed electric fields to cardiac tissue. [redacted] is designed to be used within the left atrium for mapping, pacing, and pulmonary vein isolation. The use of [redacted] with the PFA energy source will be within its intended use (mapping, pacing, and ablation of left atrial tissue).
Unintended/excessive ablation, leading to thermal damage including: debris/ clot or coagulum formation	The PulseSelect™ PFA System has specific therapy profiles pre-programmed and cannot be altered by the clinician. Extensive pre-clinical testing has been performed to refine the PFA therapy profiles to ablate myocardial tissue without evidence of complications due to debris/ clot or coagulum formation. Medtronic data on file. Procedural technique instructions to adjust catheter positioning during the procedure are provided in the PulseSelect™ PFA System IFU.
Device/System Fails to Function / Delay to Swap Out Capital Equipment	System design verification has been performed to confirm catheter reliability performance [redacted]
Device/System Fails to function During Procedure	System design verification has been performed to confirm catheter reliability performance [redacted]

Risks	Mitigation Strategies
This hazard is related to the functioning of the PFA equipment following a groin poke, in which case a backup unit would be required. Hazards can be attributed to incompatible equipment or equipment failures. The patient may or may not be under general anesthesia.	[redacted]
Electrical shock to patient or clinician	The PulseSelect™ PFA System is designed such that the patient and clinician is fully isolated to alleviate potential harmful electrical shock. [redacted]
Insufficient therapy resulting in an incomplete lesion and potential for re-entrant arrhythmogenic pathways to be formed	Section 8.4 and PulseSelect™ PFA System IFU instruct ablation to be performed until acute electrical isolation has been achieved. [i]
Physical Trauma to Clinician or Patient	The PulseSelect™ PFA System IFU describes placement of the PFA System on a stable table during clinical use.
X-ray Exposure	The PulseSelect™ PFA System is intended for use in a cardiac electrophysiology lab. Use of fluoroscopy is expected. Standard medical practices regarding limiting unnecessary radiation exposure is expected during electrophysiology procedures.
Use of non-biocompatible materials on patient contacting products.	[redacted] is constructed to contact blood and has undergone complete biocompatibility testing.
Product sterilization is compromised.	[redacted] is a sterile product designed for patient contact during an ablation procedure. The catheter has undergone complete sterility testing. The catheter is supplied sterile. Catheter sterilization will be performed by a subcontract manufacturer using electron beam irradiation at a contract sterilization facility. The Catheter Interface Cable will be supplied sterile and provides a connection between the sterilized catheter and non-sterilized PFA equipment. The PulseSelect™ PFA System IFU requires sterile packaging inspection prior to use during the procedure.

Risks	Mitigation Strategies
Procedural risks associated with endocardial catheter ablation, including: • Access site complications (e.g. bruising, ecchymosis, AV fistula, hematoma, pseudoaneurysm) • Allergic reaction to x-ray contrast media • Anesthesia reactions • Anemia • Back pain • Body temperature elevation • Cardiac tamponade • Chest discomfort • Cough • Cerebrovascular accident (CVA) • Collateral damage to the conduction system or coronary vasculature • Death • Hemoptysis • Hypotension • Hypertension • Infections • Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system • Perforation of the heart or other organs during transseptal puncture or other procedures • Pericarditis or endocarditis • Pericardial effusion • Pleural effusion • Pneumonia • Pneumothorax • Pulmonary edema • Respiratory depression • Sore throat • Vasovagal reaction	Procedural technique instructions intended to optimize safety are provided in the PulseSelect™ PFA System IFU. The protocol requires that the ablation procedure is to be performed by an investigator who has received hands-on training on all aspects of the procedure. Medtronic intends to use a proctorship strategy during the PULSED AF trial to ensure the knowledge and skills are transferred to new users.

[i] Per PULSED AF clinical study protocol in the interest of prioritizing patient care, in the event of an inability to electrically isolate all accessible targeted pulmonary veins with the PulseSelect™ PFA System, any commercially released catheter deemed appropriate for the procedure may be used to complete the ablation procedure.

9.3. Potential Adverse Events from Risk Assessment

The current PulseSelect™ PFA System IFU should be referenced as the list below may be updated during the course of the study. Possible additional risks for participating in the study include the following (although others are possible) and are further defined in Appendix C:

- Access site complications (e.g. bruising, ecchymosis, AV fistula, hematoma, pseudoaneurysm)
- Allergic reaction to x-ray contrast media
- Anesthesia reactions
- Anemia
- Arrhythmias, proarrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)
- Back pain
- Bleeding, possibly requiring transfusion
- Body temperature elevation
- Cardiac perforation of the heart or other organs during transseptal puncture or other procedures
- Cardiac tamponade
- Chest discomfort
- Cough
- Embolism
- Catheter entrapment in cardiac structures requiring intervention
- Cerebrovascular accident (CVA)
- Transient ischemic attack (TIA)
- Collateral damage to the conduction system or coronary vasculature
- Death
- Esophageal damage (including atrial esophageal fistula)
- Hemoptysis
- Hypotension
- Hypertension
- Infections
- Myocardial infarction or ischemia
- Nerve injury or nerve damage (e.g. phrenic nerve injury)
- Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system
- Pericarditis or endocarditis
- Pleural effusion
- Pericardial effusion

- Pneumonia
- Pneumothorax
- Pulmonary edema
- Pulmonary vein stenosis
- Radiation injury or damage and late malignancy
- Respiratory depression
- Sore throat
- Unintended complete or incomplete atrioventricular node (AV-Node) or sinus node block or damage
- Valvular insufficiency or damage
- Vasovagal reaction

There are additional potential risks to the patient that are outside of the ablation procedure. These are due to PULSED AF clinical study requirements and are not related to the PFA procedure or the PulseSelect™ PFA System. Potential additional risks identified for participation in this study include:

- Claustrophobia (sense of anxiety in small areas) related to an MRI scan
- Skin discomfort or irritation related to the Holter recorder
- Exposure to radiation or allergic reaction to the contrast dye related to a CT scan

9.4. Potential Benefits

The PulseSelect™ PFA System utilizes a novel energy source that may increase efficacy through field-based ablation without the dependency on tissue contact, which is expected to lead to higher clinical success by effectively treating patients with AF. PFA has the potential to create contiguous lesions in highly trabeculated anatomical locations with varying tissue thickness or blood flow conditions that limit the effectiveness of thermal ablation technologies. PFA requires the catheter to be in close proximity to the target locations, but not in contact with tissue.

PFA potentially increases the safety of catheter ablation for AF through applying a refined waveform with parameters (e.g. pulse width, number of pulses, voltage amplitude) that result in selective ablation of myocardial tissue. This could reduce collateral damage to extracardiac tissues such as the phrenic nerve, vagus nerve, and smooth muscle.

The safety profile of the Medtronic PFA delivery may also be improved over other commercially available ablation energy sources due to the bipolar energy delivery method through the multi-electrode array catheter that minimizes exposure of extracardiac tissue to the electric field compared to unipolar energy.

PFA also potentially improves safety due to its non-thermal field-based ablation approach. Operators using currently available technology must be careful to balance optimal contact force

required for transmural lesion formation with potential adverse events associated with thermal mechanisms of catheter ablation. Overall, the potential improvement in the safety profile of PFA is due to the refined waveform, bipolar delivery, and non-thermal field-based approach which may reduce collateral damage.

PFA delivery is performed within milliseconds and is predicted to achieve pulmonary vein isolation in approximately 1 minute. PFA may reduce both time to isolation and overall procedure time compared to standard of care ablation procedures that take up to 10 minutes and in some cases more than 10 minutes, to isolate each pulmonary vein[23]. The efficiency of PFA energy delivery is potentially increased in comparison to existing ablation technologies.

Ablation with the PulseSelect™ PFA System may reduce or eliminate atrial fibrillation in subjects; however, some subjects may not receive this benefit. Clinical benefit has not been demonstrated as this study is the first in human use of the PulseSelect™ PFA System. The information gained from the study could result in improved management of atrial fibrillation.

9.5. Risk-Benefit Rationale

PFA therapy offers the opportunity to reduce the episodes of atrial fibrillation and therefore reduce the subject's risk of stroke and symptoms. Results of the PULSED AF study are expected to be used to guide subsequent product development activities for the PulseSelect™ PFA System.

The PulseSelect™ PFA System has been examined and tested via modeling, bench, and preclinical animal testing and the residual risks associated with the PulseSelect™ PFA System have been found to be acceptable. These residual risks have been mitigated to the fullest extent possible through design, manufacturing, labeling and training. The potential benefits related to the use of the PulseSelect™ PFA System have been determined to outweigh any potential risks and justify this investigation.

[23] Attanasio, P. et al. Pain Reactions during Pulmonary Vein Isolation under Deep Sedation: Cryothermal versus Radiofrequency Ablation. Pacing and clinical electrophysiology: PACE 39, 452-457, doi:10.1111/pace.12840 (2016).

10. Adverse Events and Device Deficiencies

Timely, accurate, and complete reporting and analysis of safety information for clinical studies are crucial for the protection of subjects. Reporting and analysis of safety data are mandated by regulatory authorities worldwide. Medtronic has established procedures in conformity with worldwide regulatory requirements to ensure appropriate reporting of safety information. The study is conducted in accordance with these procedures and regulations.

Since the safety reporting requirements and classification systems vary for each regulatory agency, requirements from all geographies are taken into account for the collection and reporting of safety information.

10.1. Adverse Event Assessment

For the purposes of the study, all Adverse Events will be collected starting at the time of signing the IC Form through the duration of the subject's participation in the study.

10.2. Device Deficiencies Assessment

Device deficiency (DD) information will be collected throughout the study and reported to Medtronic, as per Table 13. A Medtronic representative will review the device deficiency for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Note that device deficiencies that result in an adverse device effect (ADE) to the subject should be captured as an Adverse Event only.

Device deficiencies that did not lead to an AE but could have led to a Serious Adverse Device Effect (SADE) (i.e., if suitable action had not been taken, if intervention had not been made, or if the circumstances had been less fortunate) require immediate reporting. For device deficiencies that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information.

10.3. Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be any component of the system under investigation, or any market-released component or accessory of the system. Adverse events (AE) will be classified according to the definitions below.

Table 11: Adverse Event and Device Deficiency Definitions

General	
Adverse Event (AE)	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 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 investigational medical devices. (ISO 14155:2011, 3.2)
Adverse Device Effect (ADE)	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 an error use or from intentional misuse of the investigational medical device. (ISO 14155:2011, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors and inadequate labeling (ISO 14155:2011, 3.15)
Relatedness	
Procedure related	An Adverse Event directly related to any portion of the procedure. NOTE: Only those Adverse Events that are directly related to the PFA portion of the procedure will be considered as PFA procedure related.
Sub-study [redacted] related	[redacted]

System related	An Adverse Event that results from the presence or performance (intended or otherwise) of the PulseSelect™ PFA System (including the PFA Generator, Catheter Electrode Distribution System (CEDS), Remote Control, Cable-Generator to Remote Control, Cable-Generator to CEDS, Cable-CEDS to EP Recording System, Catheter Interface Cable, [redacted] catheter, Cardiac Trigger Monitor and Accessories, Uninterruptible Power Supply, Power Cord) or any other device used during the procedure. NOTE: Only those Adverse Events that result from the presence or performance (intended or otherwise) of the PulseSelect™ PFA System will be considered as PulseSelect™ PFA System related.
Not related	Relationship to the device or procedures can be excluded when: • The event is not a known side effect of the product category the device belongs to or of similar devices and procedures; • The event has no temporal relationship with the use of the device or the procedures; • The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; • The discontinuation of medical 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 the serious event; • The event involves a body-site or an organ not expected to be affected by the device or procedure; • The serious event can be attributed to another cause (e.g., 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); • Harms to the subject are not clearly due to use error; • 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.

Unlikely	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possible	The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.
Causal Relationship	The event is associated with the device or study procedures 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 or the device or procedures have an effect on; • The serious event follows a known response pattern to the medical device (if the response pattern is previously known); • The discontinuation of medical 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 serious event (when clinically feasible); • Other possible causes (e.g., 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 serious event.

Seriousness	
Serious Adverse Event (SAE)	Adverse event that a) led to death, b) led to serious deterioration in the health of the subject, that either resulted in: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or 3) in-patient or prolonged hospitalization (>24 hours), 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) led to fetal distress, fetal death or a congenital abnormality or birth defect NOTE 1: 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. (ISO 14155:2011, 3.37)
Serious Adverse Event (SAE) – Germany Definition	A serious adverse event is an event that occurs in a clinical investigation subject to approval or occurring in a performance evaluation which led, might have led or could lead directly or indirectly to death or serious deterioration of health of the subject, the user or a third party, without consideration if the event has been caused by the medical device itself; this applies accordingly to serious adverse events occurring in a clinical investigation or performance evaluation for which an exemption of the approval authorization as per MPG § 20 paragraph 1 sentence 2 has been granted. (MPSV § 2 Definitions Abs 5)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2011, 3.36)

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, an (investigational) device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP or applicable (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. (ISO 14155:2011 3.42)
Significant Safety Issue (SSI)	A safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)
Urgent Safety Measure (USM)	A measure required to be taken in order to eliminate an immediate hazard to a participant's health or safety. NOTE: This type of significant safety issue can be instigated by either the investigator or sponsor and can be implemented before seeking approval from HRECs or institutions. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016)
Other	
Unavoidable Adverse Event	An Adverse Event inherent to a surgical procedure that is expected to occur in all subjects for a projected duration according to the Investigator's opinion, including, but not limited to those provided below. These are not reportable AEs unless they occur after or last longer than the timeframe specified. If any other events below are classified as serious they must be reported as an adverse event.

	Event Description / **Timeframe (hours) from the Surgical Procedure** Anesthesia related nausea / vomiting: 24 Low-grade fever (<100°F or 37.8°C): 48 Mild to moderate bruising / ecchymosis in groin area / groin pain: 168 Sleep problems (insomnia): 72 Back pain related to laying on table: 72
Hospitalization	A therapeutic inpatient hospitalization (excludes observation unit, emergency room and outpatient visits) lasting greater than or equal to 24 hours.

10.4. Reporting of Adverse Events, including Death

Reporting of Adverse Events to Medtronic will occur on an Adverse Event (AE) eCRF, including a description of AE, date of onset of AE, date of awareness of study site, treatment, resolution, assessment of both the seriousness and the relatedness to the investigational system and/or procedure. Each AE must be recorded on a separate AE eCRF. Exceptions include:

- Documented pre-existing conditions are not considered AEs unless the nature or severity of the condition has worsened. Additionally, arrhythmia episodes that are not new or worsening conditions and for which no action is taken are not reportable as AEs.
- Unavoidable Adverse Events listed in Table 11 need not be reported unless the adverse event worsens or is present outside the stated timeframe after the ablation procedure.
- Cardioversions (DC or Drug) for recurrent symptomatic atrial fibrillation and other atrial arrhythmias are not considered serious adverse events

For any changes in status of a previously reported adverse event (i.e. change in actions taken, change in outcome, change in relatedness), an update to the original AE must be provided. All adverse events must be followed until the adverse event has been recovered / resolved, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all procedure or system related adverse events that are not resolved, as classified by the Investigator, are recovered / resolved.

At the time of study exit, all adverse events with an outcome of "not recovered / not resolved", "recovering / resolving" or "unknown" must be reviewed and updates provided as applicable.

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

Upon receipt of adverse events at Medtronic, a Medtronic representative will review the adverse event for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. Medtronic will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each adverse event based on the information provided by the Investigator.

Regulatory reporting of AEs that could have led to a SADE will be completed according to local regulatory requirements. Refer to Section 10.4.2 for a list of required Investigator and Medtronic reporting requirements and timeframes. It is the responsibility of the Investigator to abide by any additional AE reporting requirements stipulated by the IRB/MEC responsible for oversight of the study.

For a list of Foreseeable Adverse Event List (FAL), refer to Appendix C. This is a list of adverse events related to the PulseSelect™ PFA System or procedure that may be experienced by subjects. This list may help to assess if an adverse event is unexpected in nature.

For emergency contact regarding a UADE/USADE, SAE, and/or SADE, contact a clinical study representative immediately (refer to the study sponsor per the sponsor contact information).

Adverse Events and Deaths will be classified according to the standard definitions in Table 11 and the responsibilities in Table 12 below:

Table 12: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Procedure related, System related, sub-study [redacted] related
	Sponsor	Procedure related, System related, sub-study [redacted] related
Seriousness	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, UADE/USADE, Device Deficiency 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
Death Classification	Investigator	Sudden Cardiac, Non-sudden Cardiac, Non-Cardiac, Unknown

10.4.1. Subject Death

All subject deaths must be reported by the Investigator to Medtronic on an adverse event eCRF (AE with outcome of fatal) as soon as possible after the Investigator first learns of the death. There should be one SAE with the outcome of fatal.

A de-identified 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 should be sent to Medtronic, if available. If an autopsy is conducted, the autopsy report should also be sent to Medtronic if available and allowed by state/local law. When the death occurs at a remote site, it is the investigative site's responsibility to attempt retrieval of information about the death. In summary, the following data will be collected:

- Date of death
- Detailed description of death
- Cause of death
- Relatedness to system and/or procedure
- 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/or allowed by state/local law)

Sufficient information will be required in order to properly classify the subject's death. The Investigator shall classify each subject death per the following definitions:

- Cardiac Death: A death directly related to the electrical or mechanical dysfunction of the heart.
    - 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.
- Non-cardiac Death: A death not classified as a cardiac death.
- Unknown Classification: Unknown death classification is intended for use only when there is insufficient or inadequate information to classify the death.

The CEC will review all deaths and provide an adjudication of the primary cause of death and death classification. Regulatory reporting of Subject Deaths will be completed according to local regulatory requirements.

10.4.2. Adverse Event Reporting Requirements

Regulatory reporting of AEs will be completed according to local regulatory requirements. Refer to Table 13 for a list of required investigator reporting requirements and timeframes, and of required Medtronic reporting requirements and timeframes.

The investigator is required to report all SAEs to Medtronic immediately, and to the Ethics Committee per local requirements. It is the responsibility of the investigator to abide by any additional AE reporting requirements stipulated by the Ethics Committee responsible for oversight of the study. Additionally, Medtronic is required to report these events to the local regulatory authority based on their requirements. In the case that the AE is related to a market-released device used during the study, post market surveillance is also applicable, and the Investigator is responsible for immediate reporting of the product complaint via the regular channels for market-released products.

For AEs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Table 13: Adverse Event and Device Deficiency Reporting Requirements

Serious Adverse Events (SAEs)	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (The National Health and Medical Research Council (NHMRC) Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Europe:** To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event (ISO 14155:2011 and local law) **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**All geographies:** Submit per local reporting requirements
Head of Medical Institution (HOMI)	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigators	**Japan:** Annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP*) **Japan:** Annually (Enforcement Regulation of the PMDL Article 274- 2) **All geographies**: Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Annually (Japan GCP Article 28)
Serious Adverse Device Effects (SADEs)	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** SADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigators	**Japan:** Annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** Report within 10 days after the sponsor becomes aware. **Japan:** [Life threatening or death] Individual reporting within 15 calendar days after awareness, and [All SADEs] Annually (Enforcement Regulation of the PMDL Article 274- 2) **All geographies:** Submit per local reporting requirements

Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Annually (Japan GCP Article 28)
Unanticipated Adverse Device Effects (UADEs) and Unanticipated Serious Adverse Device Effects (USADEs)	
Investigator submit to:	
Medtronic	**Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **US:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a)) **Europe:** Immediately after the investigator learns of the event or of new information in relation to an already reported event. (ISO 14155:2011 and local law) **Japan:** Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Regulatory Authority	**Canada:** USADEs on the patient, the user or any other person must be reported to the regulator and to the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
Ethics Committee	**Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g) **US:** An investigator shall submit to the sponsor and to the reviewing IRB a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect. (21 CFR 812.150(a)) **All geographies:** Submit per local reporting requirements
Institution	**Australia:** Report USADE to their institution without undue delay and no later than 72 hours of the Principal Investigator becoming aware of the event. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigator	**US:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)) **Japan:** Immediately (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Australia:** Fatal or life-threatening Australian USADE – No later than 7 calendar days after being made aware of the case with any follow up information within a further 8 calendar days. Other Australian USADEs- No later than 15 calendar days after being made aware of the case. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.f) **Canada:** Report within 10 days after the sponsor becomes aware. **Japan:** [Life-threatening or death) Individual reporting within 7 calendar days after awareness, [Non-life threatening or death) Individual reporting within 15 calendar days after awareness, and [All USADE] Annually. (Enforcement Regulation of PMDL Article 274-2) **US:** Notification as soon as possible to FDA, but not later than 10 working days after the sponsor first receives notice of the effect. (21 CFR 812.150(b)) **All geographies:** Submit per local reporting requirements
Ethics Committee	**US:** Notification as soon as possible, but not later than 10 working days after the sponsor first learns of the effect. (21 CFR 812.150(b)) **All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 28)

Significant Safety Issue (SSI): Sponsor reporting in Australia	
Events to Report	**Reporting Requirement and Timeframe**
Significant Safety Issue	• Urgent Safety Measure (USMs): within 24 hours (where possible) to TGA and without undue delay to investigators & HREC and in any case, no later than 72 hours of the measure being taken. - Reasons for the urgent safety measure, Measures taken, Further actions planned - Reasons for the termination, Measures taken, Further actions planned (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.1.k)
Significant Safety Issue (continued)	Submit to TGA • Notification of an amendment: Without undue delay and no later than 15 calendar days Note: TGA should receive notification that a SSI has occurred but the amendment revising trial documentation should be submitted to the HREC only • Action taken with respect to safety that has been taken by another country's regulatory agency (relevant to an ongoing clinical trial in Australia): Without undue delay and no later than 72 hours of the trial sponsor becoming aware of the action (Australian clinical trial handbook version 2.2)
Significant Safety Issue (continued)	Submit to TGA, any Australian investigator and HREC • Other significant safety measures: Without undue delay and no later than 15 calendar days of the sponsor being aware of the issue. Details of significant safety issue, Further actions planned • Temporary halt of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to halt the trial. Reasons for the halt, the scope of the halt, Measures taken, Further actions planned • Early termination of a trial for safety reasons: Without undue delay and no later than 15 calendar days of the sponsor's decision to termination the trial.
Significant Safety Issue (SSI): Investigator Reporting in Australia	
Events to Report	**Reporting Requirements and Timeframe to submit to Sponsor, HREC and institution**
Significant Safety Issues	• Urgent Safety Measure (USMs): Within 24 hours (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.c) • All other significant safety issues: without undue delay and no later than 72 hours of the principal investigator becoming aware of the event (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.g)
Device Deficiencies with SADE potential	
Investigator submit to:	
Medtronic	**Australia:** Without unjustified delay. (NHMRC Safety monitoring and reporting in clinical trials involving therapeutic goods November 2016 section C.2.b) **Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **Europe**: To the sponsor in acceptable timely conditions, but not later than within 3 calendar days after investigational site study personnel's awareness of the event, including new information in relation to an already reported event (ISO 14155:2011 and local law)

	Japan: Immediately (no later than 72 hours) (Japan GCP Article 68) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** DDs that have resulted in any of the consequences characteristic of an SAE on the patient, the user or any other person or could do so were it to reoccur must be reported to the regulator and the Sponsor within 72 hours after it comes to the attention of the qualified investigator. **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately (Japan GCP Article 68)
Sponsor submit to:	
Investigator	**Japan:** Immediately per the direction of PMDA and/or annually (Japan GCP Article 28) **All geographies:** Submit per local reporting requirements
Regulatory authorities	**Canada:** Submit to regulatory authorities within 30 calendar days of awareness by Sponsor. **Japan:** Within 30 calendar days after awareness and annually (Enforcement Regulation of PMDL Article 274-2) **Europe:** No later than 7 calendar days after awareness; Report immediately, but no later than 2 calendar days after awareness by sponsor for SAE and/or DD that may have led to a SADE which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it (occurred in the study under same CIP*) **All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
HOMI	**Japan:** Immediately per the direction of PMDA and/or annually (Japan GCP Article 28)
All other Adverse Events, Device Deficiencies, and new information that may adversely affect safety of the subjects or the conduct of the study	
Investigator submit to:	
Medtronic	**Europe:** Submit in a timely manner after the investigator first learns of the event **All geographies:** Submit per local reporting requirements
Regulatory Authorities	**All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements
Sponsor submit to:	
Investigator	**All geographies:** Submit per local reporting requirements
Regulatory authorities	**All geographies:** Submit per local reporting requirements
Ethics Committee	**All geographies:** Submit per local reporting requirements

10.5. Reporting of Product Complaints

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event and Device Deficiency reporting requirements. Refer to local regulations for reporting requirements.

Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the Investigator to report all product complaint(s) associated with a medical device distributed by Medtronic, regardless 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.

Medtronic will notify the regulatory authorities (e.g. FDA) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use 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.
- A serious deterioration in the state of heath includes:
    - 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

11. Data Review Committees

11.1. Data Monitoring Committee (DMC)

Study Oversight

Ongoing oversight for this study will be provided by an independent Data Monitoring Committee.

Who will be Involved

The DMC will have one statistician with experience in the evaluation of clinical trials and at least two physicians that are not participating Investigators for the study. A chairperson from among those members will be identified.

Responsibility of the DMC

The DMC will be responsible for assessing the accumulating data on safety of the therapy during the study. The DMC will be responsible for safeguarding the interests of study subjects, assessing the safety of the PulseSelect™ PFA System during the study, and for monitoring the overall conduct of the clinical study. To enhance the integrity of the study, the DMC may also formulate recommendations related to the selection, recruitment, and retention of subjects, their management, improvement of adherence to protocol-specified regimens and procedures for data management and quality control. [redacted]

Recommendations

The DMC will be advisory to the sponsor. The DMC may provide recommendations for early termination of the study. Review and consensus by the entire committee is required to recommend that the study should be stopped. The DMC may also make recommendations related to the selection, management and retention of subjects, improvement of adherence to protocol-specified regimens, and procedures for data management and quality control.

DMC Meetings

All DMC meetings may be conducted either in person or by teleconference. There will be an initial meeting prior to the start of the Pivotal Phase of the study. Additionally, the DMC will meet approximately every 6 months to review study data. The first meeting must be within 6 months of the first enrollment in the Pivotal Phase of the study. Reports will consist of data on study conduct and aggregate adverse events review. Once the study follow-up is completed, the DMC will be disbanded, with no need to review final results of the study.

11.2. Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will review and adjudicate, at a minimum, all procedure- and system-related adverse events, as well as all adverse events resulting in death.

The CEC will consist of a minimum of three (3) non-Medtronic employed physicians that are not participating Investigators for the study, including a CEC chairperson.

Medtronic personnel may facilitate and participate in a CEC meeting but will be non-voting members.

For adverse events and deaths reviewed by the CEC, Medtronic will provide the CEC with the Investigator's description and classification. The CEC is responsible for reviewing the Investigator's assessment and supportive documentation (when available), reviewing applicable definitions, and determining final classifications for all adjudication parameters. Additionally, the CEC will provide an adjudication of the death classification for all reported deaths including primary cause of death and death classification.

If the CEC disagrees with the Investigator's classification of the event, the difference will be provided to the Investigator. If the Investigator agrees with the CEC's adjudication, the eCRF documenting the event 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 IRB/REB/MECs and regulatory authorities, if required.

12. Statistical Design and Methods

This section includes a description of the statistical methods and analyses to be included in reports that include analysis of endpoints. Any change to the data analysis methods described in the CIP will require an amendment to the CIP only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

Standard baseline and relevant medical history will be collected on the CRFs for all enrolled subjects. Baseline variables to be summarized include, but are not limited to: age, sex, race (if allowed by local law), and physical exam findings. The number of screening failures, and the reasons for failure will also be reported.

Additional exploratory analyses of the data may be conducted as deemed appropriate.

Each arm (paroxysmal AF and persistent AF) of the Pivotal Phase of this study contains the following cohorts, with each enrolled subject belonging to one-and-only-one of the cohorts:

- Non-treated Cohort – Subjects enrolled in the study who exit prior to having the PulseSelect™ PFA System multielectrode catheter inserted into vasculature.
- Roll-in Cohort – roll-in subjects are defined in Section 7.2.1.
- Primary Analysis Cohort – Treated (those who have the PulseSelect™ PFA System multielectrode catheter inserted into vasculature) subjects who are not part of the Roll-in Cohort.

There is no intention to pool data from the Pilot Phase and the 3 Pivotal Phase cohorts. All will be analyzed separately.

12.1. Pilot Phase

12.1.1. Pilot Phase Safety Objective

Assess the incidence of PulseSelect™ PFA System-related and PFA procedure-related serious adverse events (SAEs) within 30 days post-ablation.

Endpoint Definition

Table 14 displays the PulseSelect™ PFA System-related and PFA procedure-related serious adverse events (SAEs) that will be considered a Pilot Phase safety event against the Pilot Phase safety endpoint.

Table 14: Analysis of Serious Adverse Events for Pilot Phase Subjects

Serious Adverse Event	Method of Analysis
Pulmonary vein stenosis (≥70% diameter reduction)	Review of symptoms post-procedure, at 7-day visit and at 30-day visit
Phrenic nerve injury/diaphragmatic paralysis (ongoing at 30 days post-ablation)	
Atrioesophageal fistula	
Cardiac tamponade/perforation	
Cerebrovascular accident	Review of symptoms post-procedure, at 7-day visit and at 30-day visit; Confirmed by formal neurology assessment if required due to NIHSS assessments
Major bleeding requiring transfusion	Review of symptoms post-procedure, at 7-day visit and at 30-day visit
Myocardial infarction	
Pericarditis requiring intervention	
Transient ischemic attack	
Vagal nerve injury resulting in esophageal dysmotility or gastroparesis	
Vascular access complications requiring intervention	
Systemic/pulmonary embolism requiring intervention	
Pulmonary edema	
Death	

Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours (excluding recurrent AF/AFL/AT)	

Analysis Methods

The percentage of procedures with a PulseSelect™ PFA System-related or PFA procedure-related SAE will be calculated as the number of procedures with at least one SAE meeting the endpoint definition divided by the number of PulseSelect™ PFA System ablation procedures. Each procedure will count, so subjects with repeat PulseSelect™ PFA System ablations will contribute more than once to the denominator. Exact methods will be used to construct a 95% confidence interval for the percentage of procedures with an SAE meeting the endpoint definition.

Determination of Subjects/Data for Analysis

All procedures in Pilot Phase subjects where the PulseSelect™ PFA System multielectrode catheter is inserted into vasculature will be included.

12.1.2. Pilot Phase Effectiveness Objective

Assess the acute procedural success of PVI ablation with the PulseSelect™ PFA System.

Endpoint Definition

Acute procedural failure is defined as the occurrence of any of the following:

a. Inability to isolate all accessible targeted pulmonary veins (assessed for entrance block and, where assessable, exit block) during the index ablation procedure.
b. Ablation using a non-study device to isolate any pulmonary vein.

Acute procedural success is the opposite of acute procedural failure.

Analysis Methods

The percentage of procedures with acute procedural success will be calculated as the number of procedures meeting the endpoint definition of acute procedural success divided by the number of PulseSelect™ PFA System ablation procedures. Each procedure will count, so subjects with repeat PulseSelect™ PFA System ablations will contribute more than once to the denominator. Exact methods will be used to construct a 95% confidence interval for the percentage of procedures with acute procedural success.

Additionally, acute success at the pulmonary vein level will be calculated. Each accessible targeted pulmonary vein will be classified as acute success or not. The percentage of total pulmonary veins attempted with the PulseSelect™ PFA System will be calculated. Exact methods will be used to construct a 95% confidence interval.

Determination of Subjects/Data for Analysis

All procedures in Pilot Phase subjects where the PulseSelect™ PFA System multielectrode catheter is inserted into vasculature will be included.

12.2. Pivotal Phase

12.2.1. Planned Analyses

The paroxysmal and persistent arms will be analyzed separately. [redacted]

[redacted]

[redacted]

[redacted]

[redacted] all subjects will be followed for 12 months, and a final report will be prepared for each arm.

The objectives are identical for the paroxysmal and persistent arms of the study.

Primary objective results by age, sex, race, and site will be provided in the final report.

12.2.2. Primary Safety Objective

Demonstrate an acceptable safety profile of PVI ablation with the PulseSelect™ PFA System.

Hypothesis
The following hypothesis will be tested in a one-sided test:

Ho: PS ≥ 13%

Ha: PS < 13%

Where PS is the probability of a safety event through 6 months.

Endpoint Definition
The primary safety endpoint definition, as follows, is identical for each arm (paroxysmal AF and persistent AF) of the Pivotal Phase.

The following PulseSelect™ PFA System-related and ablation PFA procedure-related serious adverse events (SAEs), as adjudicated by the Clinical Events Committee (CEC), will be considered a primary safety event:

Within 6 months post-ablation:

- Pulmonary vein stenosis (≥70% diameter reduction)
- Phrenic nerve injury/diaphragmatic paralysis (ongoing at 6 months)
- Atrioesophageal fistula

Within 30 days of ablation procedure:

- Cardiac tamponade/perforation
- Cerebrovascular accident
- Major bleeding requiring transfusion
- Myocardial infarction
- Pericarditis requiring intervention
- Transient ischemic attack
- Vagal nerve injury resulting in esophageal dysmotility or gastroparesis
- Vascular access complications requiring intervention
- Systemic/pulmonary embolism requiring intervention
- Pulmonary edema
- Death
- Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours (excluding recurrent AF/AFL/AT)

Analysis Methods

The probability of a safety event at 6 months (183 days) will be estimated using survival analysis, the Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed.

For every treated subject, day 0 is defined as the day of the index ablation procedure. For subjects with a safety event, the survival date will be set to the onset date of the safety event. For subjects without a safety event, those subjects will be censored at the last study contact date recorded on CRF which may include the last study visit, the exit date, or death date. If a subject without a safety event is lost to follow-up, the censoring date will be set to the last known study visit date. If a subject undergoes a repeat ablation, the subject will be censored on the date of the repeat ablation.

Safety events related to a repeat ablation procedure with the PulseSelect™ PFA System will not be counted as safety events against the primary safety objective. However, all repeat PVI ablations using the PulseSelect™ PFA System and the safety events associated with them will be reported separately.

Additionally, the mean change in diameter and any cases of moderate (50-70% reduction in diameter) and mild (<50% reduction in diameter) PV stenosis from the subset of subjects in the PV Stenosis Assessment subgroup (cardiac CT/MRI scans at the baseline and 3-month follow-up visits) will be reported. Paroxysmal and persistent subjects will be pooled for this analysis, but also reported separately.

Performance Requirements

If the upper bound of the two-sided 95% confidence interval at 6 months is less than the performance goal of 13%, the objective will be considered met.

Rationale for Performance Criteria

Figure 4 and Table 15 display safety rates in recent studies in paroxysmal AF and persistent AF patients.[24,25,26,27,28,29,30,31,32] Included are published literature where the search criteria include large multi-centered studies where the therapy was the use of catheter ablation (RF ablation, cryoablation, or visually guided laser balloon [VGLB] ablation) for a PVI-only approach for paroxysmal AF or persistent AF. The summary includes study results published as manuscripts in peer reviewed medical journals. Note, these studies are the same studies utilized in rationales below for effectiveness performance criteria.

Varying complication rates are observed, and varying definitions of complication were used in each study, but to test a novel catheter ablation technology, an objective performance criterion (OPC) of 13% provides a reasonable margin to compare the PulseSelect™ PFA System against ablation technologies currently used to treat AF.

[24] P100010/R017 "STOP AF PAS Final Post-Approval Study Report".

[25] Kuck, K. H., Brugada, J., Fürnkranz, A., et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *New England Journal of Medicine* **374**, 2235-2245 (2016).

[26] Squara, F., Zhao, A., Marijon, E., et al. Comparison between radiofrequency with contact force-sensing and second-generation cryoballoon for paroxysmal atrial fibrillation catheter ablation: a multicentre European evaluation. *Europace* **17**, 718-724 (2015).

[27] Schmidt, M., Dorwarth, U., Straube, F., et al. Cryoballoon in AF ablation: impact of PV ovality on AF recurrence. *Int J Cardiol* **167**, 114-120 (2013).

[28] Providencia, R., Defaye, P., Lambiase, P., et al. Results from a multicentre comparison of cryoballoon vs. radiofrequency ablation for paroxysmal atrial fibrillation: is cryoablation more reproducible? *Europace* **19**, 48-57 (2017).

[29] Dukkipati, S., Cuoco, F., Kutinsky, I., et al. Pulmonary Vein Isolation Using the Visually Guided Laser Balloon: A Prospective, Multicenter, and Randomized Comparison to Standard Radiofrequency Ablation. *Journal of the American College of Cardiology* **66**, 1350-1360 (2015).

[30] Boveda, S., Metzner, A., Nguyen, D., et al. Single-Procedure Outcomes and Quality-of-Life Improvement 12 Months Post-Cryoballoon Ablation in Persistent Atrial Fibrillation: Results From the Multicenter CRYO4PERSISTENT AF Trial. *Journal of the American College of Cardiology*, doi:10.1016/j.jacep.2018.07.007 (2018).

[31] Tondo, C., Iacopino, S., Pieragnoli, P., et al. Pulmonary Vein Isolation Cryoablation for Persistent and Long-Standing Persistent Atrial Fibrillation Patients. Clinical Outcomes from Real Word Multicentric Observational Project. *Heart Rhythm* **15**, 363-368, doi:10.1016/j.hrthm.2017.10.038 (2017).

[32] Aryana, A., Baker, J., Espinosa Ginic M., et al. Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: A multicenter experience. *Heart Rhythm* **15**, 1121-1129 (2018).

Figure 4: Current Safety Rates in Catheter Ablation Technologies for Paroxysmal AF and Persistent AF

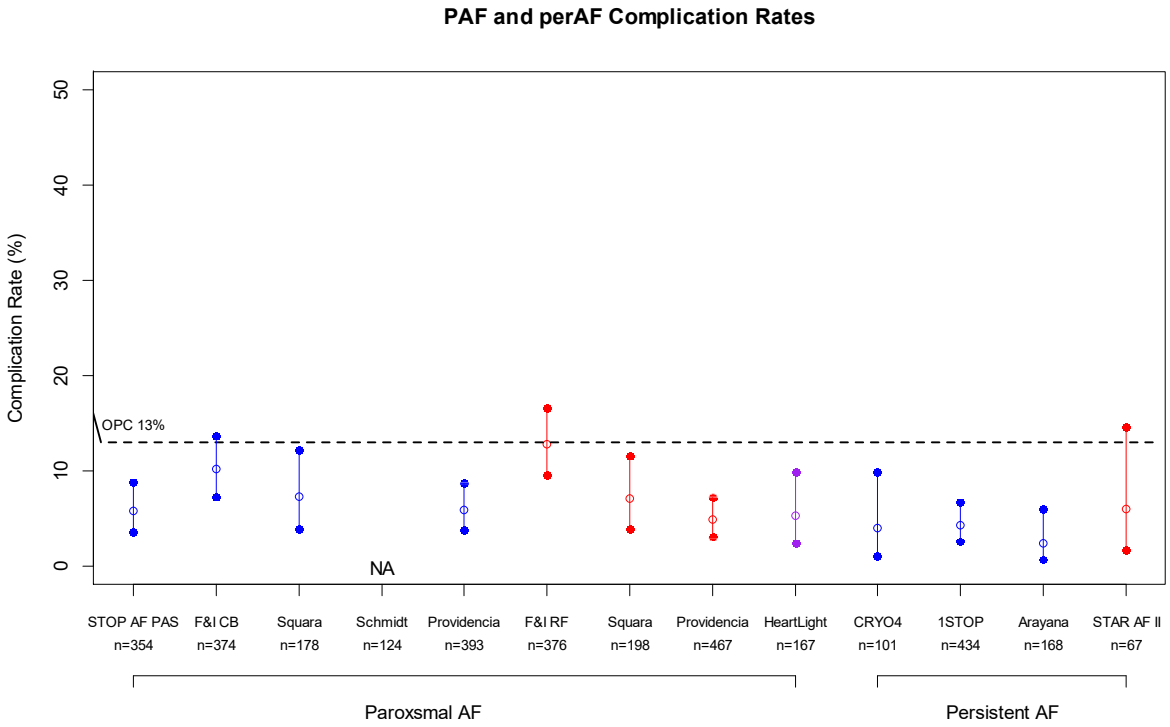


Table 15: Summary of Published Literature on Safety Rates of Catheter Ablation for AF

Reference	AF Type	Ablation Catheter Type	Subjects	Reported Safety Rate (95% CI) [i]
STOP AF PAS P100010/R017 "STOP AF PAS Final Report".[24]	Paroxysmal	Cryo	354	5.8% (3.6 – 8.8)
FIRE AND ICE Kuck KH, et al. N Engl J Med. 2016; 374:2235-45.[25]	Paroxysmal	Cryo	374	10.2% (7.3 – 13.7)
Squara F, et al. Europace. 2015;17:718-24.[26]	Paroxysmal	Cryo	178	7.3% (3.9 – 12.2)
Schmidt M, et al. Int J Cardiol. 2013;167:114-120.[27]	Paroxysmal	Cryo	124	Not reported
Providencia R, et al. Europace. 2017;19:48-57.[28]	Paroxysmal	Cryo	393	5.9% (3.8 – 8.7)
FIRE AND ICE Kuck KH, et al. N Engl J Med. 2016; 374:2235-45.[25]	Paroxysmal	RF	376	12.8% (9.6 – 16.6)
Squara F, et al. Europace. 2015;17:718-24.[26]	Paroxysmal	RF	198	7.1% (3.9 – 11.6)
Providencia R, et al. Europace. 2017;19:48-57.[28]	Paroxysmal	RF	467	4.9% (3.1 – 7.3)
HeartLight Dukkipati S, et al. J Am Coll Cardiol. 2015;66:1350-60.[29]	Paroxysmal	VGLB	167	5.3% (2.4 – 9.9)
CRYO4PERSISTENT AF Boveda S, et al. J Am Coll Cardiol. [Epub ahead of print].[30]	Persistent	Cryo	101	4.0% (1.1 – 9.9)
1STOP Tondo C, et al. Heart Rhythm. 2017;15:363-368.[31]	Persistent	Cryo	434	4.3% (2.6 – 6.7)
Aryana et al. Heart Rhythm 2018;15:1121–1129.[32]	Persistent	Cryo	168 (PVI only)	2.4% (0.6 – 6.0)
STAR AF II Verma A, et al. N Engl J Med. 2015;372:1812-22.[13]	Persistent	RF	67 (PVI only)	6.0% (1.7 – 14.6)

[i] 95% confidence interval calculated using binomial exact methods

Rationale for Timing of the Final Safety Analysis

The PulseSelect™ PFA System is a novel catheter ablation technology, but analogous in procedural use to currently approved catheter ablation systems for the treatment of AF. The major complications related to traditional catheter ablation systems will describe the safety profile of the PulseSelect™ PFA System. The 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation acknowledges that "AF ablation is an invasive procedure that entails risks, most of which are present during the acute procedural period. However, complications can also occur in the weeks or months following ablation." Symptoms and complications associated with AF ablation are stratified by those that occur within 1 month post-ablation and those that occur more than 1 month post-ablation.[3] To evaluate the safety profile of the PulseSelect™ PFA System, the primary safety events in this study align with the recognized AF ablation complications. Recognizing that most AF ablation complications present acutely, Medtronic proposes that the safety profile of the PulseSelect™ PFA System will be established with 6-month follow-up data. The study will continue to collect, analyze and report all adverse events for all subjects through 12 months follow-up.

Sample Size Calculation for the Primary Safety Objective

A sample size of 138 treated subjects followed for 6 months affords 90% power based on the following assumptions:

- 6-month safety rate = 5% (desired rate for new catheter ablation technology)
- OPC = 13% at 6 months
- Overall alpha = 0.025, one-sided
- One final analysis
- Binomial exact methods

The primary analysis will utilize Kaplan-Meier survival methods. Binomial exact methods were utilized for sample size and power calculations, as with very low expected attrition, Kaplan-Meier and binomial methods yield very similar results.

Sample Size for the PV Stenosis Assessment

The sample size will include approximately 50 subjects who will undergo baseline and 3-month CT/MRI scans to evaluate PV stenosis. With 50 subjects, if the severe PV stenosis rate (≥70% diameter reduction) is 2%, there would be a 64% chance of observing at least one PV stenosis. Additionally, with pre and post diameter measures, the mean change in diameter and any cases of moderate (50-70% reduction in diameter) and mild (<50% reduction in diameter) PV stenosis can be reported.

Determination of Subjects/Data for Analysis

All Primary Analysis Cohort subjects (only their index PFA procedure) will be included.

12.2.3. Primary Effectiveness Objective

Objective

Demonstrate an acceptable chronic effectiveness of PVI ablation with the PulseSelect™ PFA System, based on freedom from treatment failure.

Hypotheses

For the paroxysmal AF arm:

Ho: PS ≤ 50%
Ha: PS > 50%

For the persistent AF arm:

Ho: PS ≤ 40%
Ha: PS > 40%

Where PS is the probability of treatment success at 12 months.

Endpoint Definition

The primary effectiveness endpoint definition, as follows, is identical for each arm (paroxysmal AF and persistent AF) of the Pivotal Phase.

Treatment success is defined as freedom from treatment failure. The study requires 24-hour Holter monitoring at 6 and 12 months in addition to weekly and symptomatic patient activated ambulatory monitoring transmissions through 12 months, and 12-lead ECGs at all follow up visits. Treatment failure is defined as any of the following components:

- Acute procedural failure (see definition below)
- Documented AF/AT/AFL on Holter/patient activated ambulatory/12-lead ECG after the 90-day post-ablation blanking period
    - Minimum of 30 seconds on Holter/patient activated ambulatory or 10 seconds on 12-lead ECG recording
    - Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter is not considered a failure if confirmed by entrainment maneuvers during EP testing.
- Any subsequent AF surgery or ablation in the left atrium, except for one repeat PVI ablation using PFA within the 90-day blanking period.
- Direct current cardioversion for atrial tachyarrhythmia recurrences after the 90-day blanking period.
- Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90-day blanking period.
    - Note: remaining on the same pre-ablation dose or decreased dose of a previously failed or not tolerated Class I or III AAD after the 90-day blanking period is not

considered a failure. Re-initiation, at any point during follow-up, of a Class I or III antiarrhythmic medication that was failed or was not tolerated prior to the ablation procedure at any dose will be considered a primary endpoint failure.

Blanking period is defined as the first 90 days after the index ablation procedure. Recurrences of atrial arrhythmias during the blanking period will not be counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias can be managed with antiarrhythmic drugs or cardioversions. Titration of Class I and III antiarrhythmic medications are allowed during the blanking period.

Acute procedural failure is defined as the occurrence of any of the following:

- Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure
- Ablation using a non-study device to isolate any pulmonary vein

Analysis Methods
The probability of a subject achieving effectiveness success at 12 months (365 days) will be estimated using survival analysis, the Kaplan-Meier method. The standard error will be approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability will be constructed.

For every treated subject, day 0 is defined as the day of the index ablation procedure. For subjects with treatment failure, the survival date will be set to the date of the treatment failure. For subjects without treatment failure through 12 months, those subjects will be censored at the last study contact date recorded on a CRF which may include the last study visit, the last weekly patient activated ambulatory, the exit date, or death date. If a subject without a treatment failure is lost to follow-up, the censoring date will be set to the last known study visit date.

For the component of the endpoint, documented AF/AT/AFL, if this documentation resulted from rhythm monitoring occurring at the 12-month visit within the 12-month visit window, the date of recurrence will be set to 365 days from the study ablation procedure so that these events will be counted as treatment failures in the 12-month Kaplan-Meier analysis. Documentation of AF/AT/AFL via patient activated ambulatory monitoring after 365 days post-ablation will not count for purposes of this objective.

Sensitivity Analyses
A sensitivity analysis will be conducted to estimate the potential impact of subjects with less than 12 months of follow-up at the final analysis. The mortality rate in this patient population is anticipated to be low. The total assumed attrition rate through one year is 5%. Because the primary endpoint will be tested using survival methods, all treated subjects are included in the primary analysis, and therefore no subjects will have complete missing data. For subjects that exit early, a tipping point analysis will be conducted to estimate the potential impact of subjects with less than 12 months of follow-up. These subjects will be defined as subjects with partial data. The

tipping point analysis methods will be as follows. For each subject with less than 12 months of follow-up, each subject will be set to treatment failure (failure date set to date of study exit). The 12-month Kaplan-Meier estimate will be re-calculated with the earliest (closest to index ablation) sequentially added to the Kaplan-Meier analysis, and the results presented in table format. The tipping point will be defined as the number of additional failures in which the performance goal (50% for paroxysmal and 40% for persistent) is crossed by the lower 95% confidence bound.

Performance Requirements
If the lower bound of the confidence interval (coverage level determined by the alpha spending function) is greater than the performance goal (50% for paroxysmal and 40% for persistent), the objective will be considered met.

Rationale for Performance Criteria (Paroxysmal)
The choice of acceptable effectiveness performance criteria for paroxysmal AF with 12-month follow-up data is selected based on the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, which provides recommendations for success rates in clinical trials. The recommendation for evaluating the effectiveness of a treatment for paroxysmal AF is as follows: "*If minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for paroxysmal AF at 12-month follow-up is 50%.*"[3] Therefore, using a one-sided test, the null hypothesis for the paroxysmal arm is that the probability of success is less than or equal to 50%.

Table 16 displays effectiveness rates observed in recent clinical trials studying approved catheter ablation technologies in paroxysmal AF patients. Included are published literature where the search criteria include publications of large multi-centered studies where the therapy was the use of catheter ablation (RF ablation, cryoablation, or VGLB ablation) for a PVI-only approach for paroxysmal AF. The summary includes study results published as manuscripts in peer reviewed medical journals. Varying rates in 12-month effectiveness have been observed. Similarly, variations in definitions of primary effectiveness and variations in arrhythmia monitoring have been utilized. The proposed PULSED AF study design has an aggressive definition of primary paroxysmal AF effectiveness (requiring acute success; and disallowing reablations after the 90-day blanking period, AAD dose increase from the historic maximum ineffective dose, or initiation of new AAD) and a more rigorous study design (requiring weekly patient activated ambulatory monitoring through 12 months). The average 12-month effectiveness rate of the recent studies is 73.2%. Due to the more aggressive monitoring of study data in this study, it is expected (for sample size calculation purposes) that the 12-month effectiveness rate in this population treated by the PulseSelect™ PFA System will be approximately 5% lower, or 68%.

Table 16: Summary of Published Literature on Catheter Ablation for Paroxysmal AF

Reference	Design	Sites	Subjects (Ablation Type)	Subject Monitoring (When/How)	Effectiveness Endpoint Assessment	Acute Procedural Success	6M Effectiveness [i, ii]	12M Effectiveness [i]
STOP AF PAS P100010/R017 "STOP AF PAS Final Report".[24]	prospective, single arm	39	354 cryo	ECG @ 3M, 6M, 12M; 24hr Holter @ 6M; 48hr Holter @ 12M; Symptomatic event recorder for 30 days	AF/AFL/AT > 30s; Intervention for AF	98.0%	89% (85-92)	80% (75-84)
FIRE AND ICE Kuck KH, et al. N Engl J Med. 2016; 374:2235-45.[25]	randomized (RF and cryo), noninferiority	16	374 cryo	ECG and 24hr Holter @ 3M, 6M, 12M; Weekly and symptomatic TTM	AF/AFL/AT > 30s; AAD use; Reablation	98.9%	81% (77-85)	65% (60-70)
Squara F, et al. Europace. 2015;17:718-24.[26]	Consecutive, non-randomized, ambidirectional (prospective and retrospective)	4	178 cryo	ECG and 24hr Holter @ 1M, 3M, 6M, 9M, 12M; Symptomatic 24hr Holter	AF/AFL/AT >30s	100%	88% (82-92)	82% (76-87)
Schmidt M, et al. Int J Cardiol 2013;167:114-120.[27]	Consecutive patients	3	124 cryo	ECG and 72hr Holter @ 1M, 3M, 6M, 9M, 12M; Symptomatic event recorder	AF or Flutter >30s	100%	86% (79-92)	66% (57-74)
Providencia R, et al. Europace. 2017;19:48-57.[28]	Consecutive, prospective, non-randomized	6	393 cryo	ECG and 24hr Holter @ 1M, 3M, 6M, 9M, 12M; Symptomatic ECG and 24hr Holter	Any AF/AT >30s; AAD use	99.0%	89% (85-92)	82% (78-86)
FIRE AND ICE Kuck KH, et al. N Engl J Med. 2016; 374:2235-45.[25]	randomized (RF and cryo), noninferiority,	16	376 RF	ECG and 24hr Holter @ 3M, 6M, 12M; Weekly and symptomatic TTM	AF/AFL/AT > 30s; AAD use; Reablation	97.9%	82% (78-86)	64% (59-69)
Squara F, et al. Europace. 2015;17:718-24.[26]	Consecutive, non-randomized, ambidirectional (prospective and retrospective)	4	198 RF	ECG and 24hr Holter @ 1M, 3M, 6M, 9M, 12M; Symptomatic 24hr Holter	AF/AFL/AT >30s	100%	89% (84-93)	84% (78-89)
Providencia R, et al. Europace. 2017;19:48-57.[28]	Consecutive, prospective, non-randomized	6	467 RF	ECG and 24hr Holter @ 1M, 3M, 6M, 9M, 12M; Symptomatic ECG and 24hr Holter	Any AF/AT >30s; AAD use	97.6%	82% (78-85)	73% (69-77)
HeartLight Dukkipati S, et al. J Am Coll Cardiol. 2015;66:1350-60.[29]	Randomized (RF and VGLB), prospective	19	167 VGLB	ECG @ 1M, 3M, 6M, 9M, 12M; 24hr Holter @ 6M, 12M; Symptomatic and weekly TTM	AF >1 min; Atypical/unknown AFL/AT; AAD use	97.7%	75% (68-81)	61% (53-68)
Weighted average (weights based on study sample sizes)							**84.5%**	**73.2%**

[i] Confidence interval calculated with binomial Fisher's exact method

[ii] 6-month effectiveness rates are estimated from survival curves published in literature

Rationale for Performance Criteria (Persistent)

The choice of acceptable effectiveness performance criteria for persistent AF with 12-month follow-up data is selected based on the 2017 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, which provides recommendations for success rates in clinical trials. The recommendation for evaluating the effectiveness of a treatment for persistent AF is as follows: "*If minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for persistent AF at 12-month follow-up is 40%.*"[3] Therefore, using a one-sided test, the null hypothesis for the persistent arm is that the probability of success is less than or equal to 40%.

Table 17 displays a summary of published literature where the search criteria were publications of large multi-centered studies where the therapy was the use of catheter ablation (RF ablation or cryoablation) for a PVI-only approach for persistent AF. The summary includes study results published as manuscripts in peer reviewed medical journals. Varying rates in 12-month effectiveness have been observed. Similarly, variations in definitions of primary effectiveness and variations in arrhythmia monitoring have been utilized. The PULSED AF study design has an aggressive definition of primary persistent AF effectiveness (requiring acute success; and disallowing reablations after the 90-day blanking period, AAD dose increase from the historic maximum ineffective dose, or initiation of new AAD) and a more rigorous study design (requiring weekly patient activated ambulatory monitoring through 12 months). The average 12-month effectiveness rate of the studies is 59.5%. Due to the more aggressive monitoring of study data in this study, it is expected (for sample size calculation purposes) that the 12-month effectiveness rate in this population treated by the PulseSelect™ PFA System will be approximately 5% lower, or 54%.

Table 17: Summary of Published Literature on Catheter Ablation for Persistent AF

Reference	Design	Sites	Subjects (Ablation Type)	Subject Monitoring (When/How)	Effectiveness Endpoint Assessment	Acute Procedural Success	6M Effectiveness [i, ii]	12M Effectiveness [i]
CRYO4PERSISTENT AF Boveda S, et al. J Am Coll Cardiol. [Epub ahead of print].[30]	prospective, single-arm, interventional post-market clinical study	11	101 cryo	ECG @ 3M, 6M, 12M and 48hr Holter @ 6M, 12M	AF/AFL/AT > 30s; Reablation	98.0%	81% (72-88)	61% (51-71)
1STOP Tondo C, et al. Heart Rhythm. 2017;15:363-368.[31]	Prospective, single-arm	35	434 cryo	ECG and Holter @ 3M, 6M, 9M, 12M	AF > 30s; Reablation	98.5%	81% (77-84)	64% (59-69)
Aryana et al. Heart Rhythm. 2018;15:1121–1129.[32]	Consecutive, double-arm non-randomized	≤7	168 cryo (PVI only)	ECG @ 3M, 6M, 12M; 2-week TTM @ 6 weeks and 3–6 months	AF/AFL/AT > 30s	99.3%	67% (59-74)	47% (39-55)
STAR AF II Verma A, et al. N Engl J Med. 2015; 372: 1812-1822.[13]	Prospective, triple-arm randomized,	48	67 RF (PVI only)	ECG and 24hr Holter @ 3M, 6M, 9M, 12M; Weekly and symptomatic TTM	AF > 30s; Reablation	97.0%	81% (70-90)	60% (47-72)
Weighted average (weights based on study sample size)							**77.9%**	**59.5%**

[i] Confidence interval calculated with binomial Fisher's exact method

[ii] 6-month effectiveness rates are estimated from survival curves published in literature, with the exception of the CRYO4PERSISTENT manuscript, which reported the 6-month effectiveness rate

Determination of Subjects/Data for Analysis

All Primary Analysis Cohort subjects will be included.

Sample Size Calculation

Given the separation of primary effectiveness objectives for paroxysmal AF and persistent AF, the study sample size is powered independently for paroxysmal AF and persistent AF arms.

For both arms, the sample size was computed using a simulation program. Given the assumptions below, the program ran through 10,000 simulations of this study for each potential sample size. The lowest sample size (going by units of 5 subjects) where at least 9000 studies were successful (i.e., power >90%) was chosen as the sample size for that arm.

The simulation program took into account the [redacted] alpha boundaries, the enrollment rate, and other assumptions listed below. Where percentages are assumed, it gave each simulated subject that chance of the event occurring (e.g., each simulated subject had a 2% chance of having an acute failure). It performed the primary effectiveness objective's analysis as stated above on each simulated study to determine whether that study would have been successful [redacted]

Assumptions (Paroxysmal Arm)

- The overall alpha will be 0.025, [redacted]
- Power=90%
- The number of Primary Analysis Cohort subjects enrolled per month will average 5 (1st month), 7 (2nd month), 11, 24, 35, 43, 51, 56, 60, 60, 60…
- Daily enrollments follow a Poisson distribution with an average of x/30, where x is the average number of enrollments in that month. This allows multiple ablation procedures in a day.
- 50% of enrollments are persistent AF subjects, and the other 50% are paroxysmal AF subjects
- 12-month effectiveness rate = 68% (A weighted average 12-month effectiveness was calculated at the bottom of the Table 16, resulting in an average effectiveness rate of 73.2%. Only three of the studies utilized weekly TTMs (similar to the weekly patient activated ambulatory monitoring requirement), so due to the additional arrhythmia monitoring and a more stringent endpoint definition in PULSED AF, the 12-month paroxysmal AF effectiveness point estimate for this study has been set to 68%.)
- 6-month effectiveness rate = 79% (based on past studies (Table 16), the 6-month rate is approximately 11% higher than 12-month rate)
- 2% of patients will have an acute failure and these will occur on the first day post-ablation procedure
- Chronic failures (AF recurrence) occur either in the 3-6 month period or in the 6-12 month period, based on the assumed 68% and 79% numbers above.
- A patient with a chronic failure in the 3-6 month period has an equal chance of that failure occurring any day between 91 and 182 days post-ablation procedure
- A patient with a chronic failure in the 6-12 month period has an equal chance of that failure occurring any day between 184 and 364 days post-ablation procedure
- 5% attrition from ablation (drop out) procedure to 12 months
- Attrition occurs uniformly from 1-364 days post-ablation procedure
- [redacted]

Given the above assumptions, for the Paroxysmal AF arm of the study, a sample size of 90 Primary Analysis Cohort subjects is required.

To ensure proper characteristics of the study, especially alpha-level, the simulation program was rerun with all of the above assumptions (including a sample size of 150 subjects, which was chosen based on other objectives) the same, except that the assumed 12-month effectiveness rate was set to the null hypothesis rate of 50% (and 6-month effectiveness rate to 61%). [redacted] This meets the goal of having overall alpha being less than 2.5%.

Assumptions (Persistent Arm)

- The overall alpha will be 0.025, [redacted]
- Power=90%
- The number of Primary Analysis Cohort subjects enrolled per month will average 5 (1st month), 7 (2nd month), 11, 24, 35, 43, 51, 56, 60, 60, 60…
- Daily enrollments follow a Poisson distribution with an average of x/30, where x is the average number of enrollments in that month. This allows multiple ablation procedures in a day.
- 50% of enrollments are persistent AF subjects, and the other 50% are paroxysmal AF subjects
- 12-month effectiveness rate = 54% (A weighted average 12-month effectiveness was calculated at the bottom of Table 17, resulting in an average effectiveness rate of 59.5%. Due to the additional arrhythmia monitoring and more stringent endpoint definition in PULSED AF, the 12-month persistent AF effectiveness point estimate for this study has been set to 54%.)
- 6-month effectiveness rate = 72% (based on past studies (Table 17), the 6-month rate is approximately 18% higher than 12-month rate)
- 2% of patients will have an acute failure and these will occur on the first day post-ablation procedure
- Chronic failures (AF recurrence) occur either in the 3-6 month period or in the 6-12 month period, based on the assumed 54% and 72% numbers above.
- A patient with a chronic failure in the 3-6 month period has an equal chance of that failure occurring any day between 91 and 182 days post-ablation procedure
- A patient with a chronic failure in the 6-12 month period has an equal chance of that failure occurring any day between 184 and 364 days post-ablation procedure
- 5% attrition from ablation (drop out) procedure to 12 months
- Attrition occurs uniformly from 1-364 days post-ablation procedure
- [redacted]

Given the above assumptions, for the Persistent AF arm of the study, a sample size of 150 Primary Analysis Cohort subjects is required.

To ensure proper characteristics of the study, especially alpha-level, the simulation program was rerun with all of the above assumptions (including the sample size of 150 subjects) the same, except that the assumed 12-month effectiveness rate was set to the null hypothesis rate of 40% (and 6-month to 58%). [redacted] This meets the goal of having overall alpha being less than 2.5%.

12.2.4. Overall Study Sample Size Rationale

For the persistent arm, the sample size of 150 required for the primary effectiveness objective is higher than the 138 required for the primary safety objective, therefore, to have adequate power for both objectives, the higher value, 150 subjects treated with the PulseSelect™ PFA System (not including Roll-in subjects) is the sample size for the persistent arm.

For the paroxysmal arm, the calculated sample sizes were 90 for the primary effectiveness objective, and 138 for the primary safety objective. To ensure adequate power for both objectives, at least 138 subjects are needed. Rounding up, and to match the persistent arm's sample size, 150 subjects treated with the PulseSelect™ PFA System (not including Roll-in subjects) is the sample size for the paroxysmal arm. Increasing the sample size from 138 to 150 will also help to ensure adequate opportunity for enrollment into the [redacted] PV stenosis assessments.

Overall, up to 495 subjects will be enrolled to ensure there are up to 40 Pilot Phase subjects, up to 96 Pivotal Phase roll-in subjects, and 300 Pivotal Phase primary analysis subjects treated with the PulseSelect™ PFA System, and to account for subjects not treated prior to exit.

12.3. Secondary Objective

The secondary objective will be evaluated to gain additional information about the performance of the PulseSelect™ PFA System. The secondary objective will be reported separately by paroxysmal AF and persistent AF.

Within each arm, testing for the two QOL hypothesis tests will be performed if the primary effectiveness and primary safety objectives are met. A Hochberg multiple testing procedure will be utilized to maintain an overall type I error rate of 0.025.

The Hochberg procedure is a stepwise procedure and will be implemented as follows:

The two null hypotheses will be defined as H(1) (AFEQT) and H(2) (EQ-5D). For each of the hypotheses, p-values will be calculated and sorted $p(1) < p(2)$. The decision rule to accept or reject each hypothesis will follow the step-up algorithm, where $\alpha=0.025$:

Step 1: If $p(2) \geq \alpha$, accept H(2) and go to Step 2, otherwise reject both hypotheses and stop

Step 2: If $p(1) < \alpha/2$ reject H(1); otherwise accept H(1)

12.3.1. Secondary Objective: Quality of Life

Assess changes in quality of life from baseline through 12 months after the index ablation procedure

This objective has two parts, the AFEQT questionnaire, and the EQ-5D questionnaire.

12.3.1.1. Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

Hypothesis

The following hypothesis will be tested:

Ho: ΔAFEQT = 0

Ha: ΔAFEQT > 0

Where ΔAFEQT is the mean change in AFEQT score from baseline to 12 months.

Endpoint Definition

The AFEQT questionnaire will be utilized for this objective. The questionnaire is an atrial fibrillation specific health-related quality of life questionnaire to assess the impact of AF on a subject's life. The overall score ranges from 0 – 100, with 0 corresponding to complete disability and 100 corresponding to no disability.

The endpoint for each subject is change in AFEQT score, which is the AFEQT score at 12 months minus the AFEQT score at baseline.

Analysis Methods

The mean change in AFEQT score will be calculated, along with a two-sided 95% confidence interval. The hypothesis will be tested using the one-sample t-test.

[redacted] The p-value based on the final dataset will be compared to the Hochberg alpha level (Section 12.3) to determine significance.

Additionally, summary statistics (e.g. mean, SD) will be used to summarize the change in AFEQT scores from baseline through 12 months, including values collected at 6 months.

Performance criteria

If the p-value from the one-sample t-test is less than the Hochberg-criteria alpha level, then the objective will be considered met.

Determination of Subjects/Data for Analysis

Primary Analysis Cohort subjects who have completed baseline and 12-month follow-up questionnaires will be included.

Additional Analyses

The AFEQT questionnaire has three subscale scores, Daily Activities Subscale, Treatment Concern, and Treatment satisfaction. Each subscale ranges from 0 – 100, where 0 corresponds to low quality-of-life and 100 corresponds to high quality of life. An additional analysis will be conducted to summarize these subscales through 12 months.

Change in AFEQT subscale score is defined as 12-month AFEQT subscale score minus baseline AFEQT subscale score. A two-sided 95% confidence interval will be calculated based on the t-distribution.

12.3.1.2. EQ-5D Questionnaire

Hypothesis

The following hypothesis will be tested:

Ho: ΔEQ-5D = 0

Ha: ΔEQ-5D > 0

Where ΔEQ-5D is the change in mean composite EQ-5D score from baseline to 12 months.

Endpoint Definition

The Euroqol EQ-5D questionnaire (5L version) will be utilized for this objective. The EQ-5D questionnaire is a standardized instrument for measuring generic health status. The EQ-5D has two sections. The first section is a descriptive section where the subject checks a box by the most appropriate statement. The second section is a visual analog scale. Composite scores will be indexed against a US reference population. (Shaw, Johnson and Coons 2004).

The endpoint for each subject is change in EQ-5D composite score, which is the EQ-5D composite score at 12 months minus the EQ-5D composite score at baseline.

Analysis Methods

The mean change in EQ-5D composite score and a two-sided 95% confidence interval will be calculated based on the t-distribution.

[redacted] The p-value based on the final dataset will be compared to the Hochberg alpha level (Section 12.3) to determine significance.

Summary statistics (e.g. mean, SD) will be used to summarize the change in EQ-5D composite scores from baseline through 12 months, including values collected at 6 months. In addition, the visual analog scale of the EQ-5D will be summarized through 12 months using summary statistics.

Performance criteria

If the p-value from the one-sample t-test is less than the Hochberg-criteria alpha level, then the objective will be considered met.

Determination of Subjects/Data for Analysis

Primary Analysis Cohort subjects who have completed baseline and 12-month follow-up questionnaires will be included.

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13. Ethics

13.1. Statement(s) of Compliance

The study will be conducted in compliance with international ethical and scientific quality standards, known as good clinical practice (GCP). GCP includes review and approval by an independent Ethics Board/Institutional Review Board (IRB)/Research Ethics Board (REB)/Medical Ethics Committee (MEC)/Head of Medical Institution (HOMI)/Human Research and Ethics Committee (HREC) before initiating a study, continuing review of an ongoing study by an Ethics Board, and obtaining and documenting the freely given informed consent of a subject before initiating the study. The term Ethics Committee will henceforth be used collectively in reference to an Institutional Review Board (IRB)/Medical Ethics Committee (MEC)/Human Research Ethics Committee (HREC)/Research Ethics Board (REB)/Head of Medical Institution (HOMI) unless otherwise stated.

The study was designed to reflect the GCP principles outlined in ISO 14155:2011 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 standard, 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. 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. Adverse Event and Device Deficiency handling in this study is ISO 14155:2011 compliant for all participating geographies.

The study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. For all geographies, the principles of the Declaration of Helsinki have been implemented through the patient informed consent (IC) process, Ethics Committee approval, study training, clinical trial registration, preclinical testing, risk-benefit assessment and publication policy.

Ultimately, all sites in all geographies will follow and comply with:

- Principles of Declaration of Helsinki (including privacy and data protection laws), or the laws and regulations of each participating country, whichever affords greater protection for the study subjects
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The procedures described within this CIP
- Local Ethics Committee requirements
- The Clinical Trial Agreement

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In Australia, local laws will be complied with and below will be followed:
  - Declaration of Helsinki 2013 and ISO 14155:2011
- In Canada, the below will be followed:
  - Medical Devices Regulations, 1998 (SOR/98-282), 59(1), 59(2), 60(1), and the Canadian Regulatory Guidelines for Mandatory Medical Device Problem Reporting for Medical Devices, 2011.
- In Europe, the study will be conducted in compliance with:
  - Declaration of Helsinki 2013, the Competent Authority requirements, the Medical Device Directive (MDD) 93/42/EEC and ISO 14155:2011
- In Japan, the study will be conducted in compliance with:
  - MHLW Ordinance No. 36, 2005 and related laws and regulations
- In the United States, the study will be conducted under an FDA Investigational Device Exemption (IDE) in compliance with US FDA 21 CFR Parts:
  - 50: Protection of Human subjects, 56: Institutional Review Boards and 812: Investigational Device Exemptions

Any additional requirements imposed by an Ethics Committee or regulatory authority shall be followed, if appropriate. All participating geographies will make study data available to the regulatory body such as FDA, Health Canada or competent authority if the regulatory body deems an onsite inspection necessary. The regulatory body will be able to inspect records at clinical study sites around the world to resolve any uncertainties about whether the study was conducted in accordance with good clinical practice.

The study will be publicly registered prior to first enrollment in accordance with the 2007 Food and Drug Administration Amendments Act (FDAAA) and Declaration of Helsinki on http://clinicaltrials.gov (PL 110-85, Section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the Clinical Investigation Plan (CIP) is required from the following groups prior to any study procedures at a study site:

- Medtronic
- Principal Investigators (where required by local law)
- An independent Ethics Committee
- Geography-specific regulatory authorities (if regulatory approval is required)

Similarly, approval of subsequent revisions to the CIP is required from the above-mentioned groups prior to implementation of the revised CIP at the study sites.

14. Study Administration

14.1. Monitoring

It is the responsibility of Medtronic to ensure proper monitoring of this clinical study. Trained Medtronic personnel or delegates appointed by Medtronic may perform study monitoring at the study site in order to ensure that the study is conducted in accordance with the CIP, the Clinical Trial Agreement, and applicable regulatory and local requirements. Medtronic, or delegates, must therefore be allowed direct access to the subjects' case histories (clinic and hospital records, and other source data/documentation) upon request as per the IC Form, Research Authorization (where applicable) and Clinical Trial Agreement. The Principal Investigator should also be available during monitoring visits.

Frequency of monitoring visits may be based upon subject enrollment, duration of the study, study compliance, number of adverse events, number of deviations, findings from previous monitoring visits and any suspected inconsistency in data that requires investigation. Regulatory documents may be reviewed at each study site. Monitoring for the study may include, but is not limited to, site qualification visits, site initiation visits, interim monitoring visits, and closeout visits, and will be done in accordance to the study-specific monitoring plan. Visits may be conducted remotely.

Monitoring visits may be conducted periodically to assess site study progress, the Investigator's adherence to the CIP, regulatory compliance including but not limited to Ethics Committee approval and review of the study, maintenance of records and reports, and review of source documents against subject CRFs. Monitors review regulatory and study compliance of study sites by identifying findings of non-compliance and communicating those findings along with recommendations for preventative/corrective actions to site personnel. Monitors may work with study personnel to determine appropriate corrective action recommendations and to identify trends within the study or at a particular site.

14.2. Data Management

Data will be collected using an electronic data management system for clinical studies. eCRF data will be stored in a secure, password-protected database which will be backed up nightly. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution.

Data collected by Holters, Patient Activated Ambulatory Monitors and ECGs will be managed and over-read by a core lab. Final classification of recurrent AF/AT/AFL will be stored in the study database.

Study management reports may be generated to assess data quality and study progress. At the end of the study, the data will be frozen and will be retained per Medtronic standards and applicable regulations.

All records and other information about subjects participating in the study will be treated as confidential. Data will be transferred and processed by Medtronic or a third party designated by Medtronic in a key coded form, unless it's impossible to make it anonymous, for instance, where the subject's name cannot be removed from the data carrier, such as fluoroscopy images. In the case that de-identifying is impossible or involves a disproportionate effort, files containing personal data of subjects shall only be made accessible to authorized persons (secured role-based access).

Procedures in the CIP require source documentation. Source documentation will be maintained at the study site. Source documents, which may include worksheets, quality of life questionnaires, subject medical records, must be created and maintained by the investigational site team.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. The eCRF may be considered source for the following data collection elements:

- Database generated subject reference ID
- Esophageal temperature
- Investigator assessment of adverse event relatedness and seriousness
- Date site became aware of an adverse event, non-subject adverse event, device deficiency or death
- Reason for study deviation
- Investigator's assessment of conduction block

When copies or printouts of the source documents are made, site personnel must ensure that all copies or printouts of original source documents are certified copies (i.e., signed and dated including a statement of true reproduction).

The sponsor or a regulatory authority may audit or inspect the study site to evaluate the conduct of the study. The clinical Investigator(s)/institution(s) shall allow study related monitoring, audits, Ethics Committee review and regulatory inspection by providing direct access to source data/documents.

Copies of source documents will be requested to support event adjudication by the Clinical Events Committee. In Japan, availability of source documentation may be limited due to hospital policies. If a specific source document is not available, necessary information may be transcribed onto the relevant CRF page.

14.3. Confidentiality

All records and other information about subjects participating in the study will be treated as confidential. See Section 14.2 for further information.

14.4. Liability

Australia: Medtronic Australasia Pty Ltd is an indirectly owned subsidiary of Medtronic, Inc., which maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Study insurance statement/certificate will be provided to the Ethics Committee.

Canada: Medtronic Canada ULC is an indirectly owned subsidiary of Medtronic, Inc., which maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the Ethics Committee.

Europe: Medtronic Bakken Research Center B.V. is an indirectly owned subsidiary of Medtronic, Inc., which maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the Ethics Committee and/or Competent Authority (CA).

Japan: Medtronic Japan Co. Ltd. Maintains appropriate clinical trial liability insurance coverage as required under applicable laws and regulations. Documentation explaining compensation to the subjects in the event of study-related injuries will be submitted to Ethics Board. Information regarding insurance, warranty and compensation will be provided under separate cover.

US: Medtronic, Inc. maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable law and custom concerning specific insurance coverage. If required, a Clinical Trial Insurance statement/certificate will be provided to the IRB.

The study is conducted in multiple countries; therefore, reimbursement and indemnification will be addressed on a country specific basis in the study documents and site Clinical Trial Agreements.

14.5. CIP Amendments

Approval of subsequent revisions to the CIP is required at each study site from the following groups prior to implementation of the revised CIP at the site:

- Medtronic
- Principal Investigators (where required by local law)
- Geography-specific regulatory authorities (if regulatory approval is required)
- An independent Ethics Committee

If a CIP amendment occurs, site personnel will need to be re-trained as necessary, and will need to submit any changes to their Ethics Committee as required by the committee.

14.6. Record Retention and Reports

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

14.6.1. Investigator Records

The Investigator, or in Japan, the record keeping manager at the study site, is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and eCRFs, should be kept in the Investigator Site File (i.e., the study binder provided to the Investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study.

The following records are subject to inspection and must be retained for a period of two years (or longer as local law, regulations, or hospital administration requires) after the date on which the investigation is terminated or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the Ethics Committee, sponsor, monitor, local regulatory agencies and the Investigator that pertains to the investigation, including required reports
- Subject's case history records, including:
  - IC Form signed and dated by subject
    - In Australia, Europe and Japan, personally signed by subject and Investigator.
    - In Japan, it is acceptable to retain only the signature page with the version number of the IC Form.)
  - Observations of adverse events and device deficiencies
  - Medical history
  - Procedure and follow-up data
  - Documentation of the dates and rationale for any deviation from the CIP
- Reports of adverse events

- Electronically signed and dated CRFs
- Blank case report forms (Australia and Europe only)
- Subject screening logs and subject identification logs
- List of investigation sites
- Financial disclosure of Investigators
- Device Disposition Logs
- Shipping records of investigational devices
- Investigational device accountability logs
- All approved versions of the CIP, IC, and Investigator's Brochure
- Signed and dated Clinical Trial Agreement and Investigator Statement
- Current signed and dated curriculum vitae of:
  - Investigators (all countries/geographies)
  - Key members of investigation site team (Australia and Europe only)
- Documentation of delegated tasks
- Ethics Committee approval documentation. Written information that the Investigator or other study staff, when member of the Ethics Committee, did not participate in the approval process. Approval documentation must include the Ethics Committee composition, in Europe and where required per local law.
- Regulatory authority notification, correspondence and approval, where required per local law
- Study training records for site staff
- Insurance certificates (where requested by the Ethics Committee or CA)
- Any other records that FDA or local regulatory agencies require to be maintained
- Final Study Report including the statistical analysis

14.6.2. Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events, device deficiencies, deaths, and any deviations from the CIP. If any action is taken by an Ethics Committee with respect to this clinical 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.

The Investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section and per local regulations.

Table 18: Investigator Reports Applicable for All Geographies per Medtronic Requirements

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor and Relevant Authorities	The Investigator must report a withdrawal of approval by the reviewing Ethics Committee of the Investigator's part of the investigation within 5 working days.
Study deviations	Sponsor, Ethics Committee and Relevant Authorities	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. **Australia:** Report any suspected breaches to the sponsor and confirmed serious breaches to their institution (research governance office) within 72 hours of being aware or notified of the same; provide any follow up information as required and work with the institution or sponsor, as appropriate, to implement any corrective and preventative actions.
Final report	Sponsor, Ethics Committee and Relevant Authorities	This report must be submitted per local requirements.
Refer to Section 10 for adverse event, complaint, and device deficiency reporting.		

Table 19: Additional Investigator Reports Applicable to Australia

Report	Submit to	Description/Constraints
Progress Report	Sponsor and Ethics Committee	Per HREC requirements, but at least annually.
Other	Sponsor and Ethics Committee	Provide any other reports if required by local law or Ethics Committee.

Table 20: Additional Investigator Reports Applicable to Europe

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and Ethics Committee/CA	Provide if required by local law or Ethics Committee / CA.
Study Deviations	Sponsor and Ethics Committee	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, competent authorities or the appropriate regulatory bodies should be informed. *(ISO 14155:2011)*
Failure to obtain informed consent	Sponsor and Ethics Committee	Informed consent shall be obtained in writing and documented before a subject is enrolled into the clinical investigation. *(ISO 14155:2011)*

Table 21: Additional Investigator Reports Applicable to Japan

Report	Submit to	Description/Constraints
Co-Investigator/ Clinical Trial Collaborator List	HOMI	When the principal Investigator assigns important parts of the clinical trial duties to co-Investigators and/or clinical trial collaborators, he or she shall prepare a list of the assigned duties and the individual performing the assigned duties, submit the list to the HOMI on the list, and receive the appointments of such individuals. (MHLW Ordinance 36, 2005 Article 63)
Study Deviations	Sponsor and HOMI	The Investigator may implement a deviation from, or a change in, the protocol to eliminate an immediate hazard(s) to study subjects without prior Ethics Board approval. In this case, the Investigator shall immediately submit to the sponsor, the HOMI, and to the Ethics Board via the HOMI, the description and reason for the deviation and the proposed revision to the protocol, if one is necessary, to receive agreement. All deviations, regardless of the reason, shall be submitted to the sponsor. (MHLW Ordinance 36, 2005 Article 66)
Summary of the Clinical Study Status	HOMI	The principal Investigator shall submit a summary of the clinical study status to the HOMI in writing once a year, or more frequently if requested by the Ethics Board, to receive the continuation review by the institutional review board. (MHLW Ordinance 36, 2005 Article 68)
Premature Termination or Suspension of the Clinical Investigation	HOMI	When the principal Investigator discontinues or suspends the clinical study, he or she shall promptly notify the HOMI thereof in writing, and explain in detail in writing the discontinuation or suspension. (MHLW Ordinance 36, 2005 Article 69)
Completion of the Clinical Investigation	HOMI	When the clinical study is completed, the principal Investigator shall notify the HOMI thereof in writing and report on a summary of the clinical study results in writing. (MHLW Ordinance 36, 2005 Article 69)

Table 22: Additional Investigator Reports Applicable to the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Sponsor	The Investigator must report a withdrawal of approval by the reviewing Ethics Committee of the Investigator's part of the investigation within 5 working days. *(21 CFR 812.150(a)(2))*
Progress report	Sponsor and Ethics Committee	The Investigator must submit this report to the sponsor and Ethics Committee at regular intervals, but in no event less than yearly. *(21 CFR 812.150 (a)(3))*.
Study deviations	Sponsor and Ethics Committee	Notice of deviations from the CIP to protect the life or physical wellbeing 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. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by Medtronic, the Ethics Committee, and the FDA/applicable regulatory authorities. If the deviation does not affect these issues, then only Medtronic must approve it. *(21 CFR 812.150(a)(4))*
Failure to obtain informed consent prior to investigational device use	Sponsor and Ethics Committee	If an Investigator uses a device without obtaining a signed Informed Consent Form, the Investigator shall report such use within 5 working days after device use. *(21 CFR 812.150(a)(5))*
Final report	Sponsor, Ethics Committee, and Relevant Authorities	This report must be submitted within 3 months of study completion or termination of the investigation or the Investigator's part of the investigation. *(21 CFR 812.150(a)(6))*
Other	Ethics Committee and FDA	An Investigator shall, upon request by a reviewing Ethics Committee, FDA or any other regulatory agency, provide accurate, complete, and current information about any aspect of the investigation. *(21 CFR 812.150(a)(7))*

14.6.3. Sponsor Records

Medtronic shall maintain the following accurate, complete, and current records:

- All correspondence which pertains to the investigation
- Investigational Device Disposition Logs
- Signed Clinical Trial Agreements, financial disclosure of Investigators, & delegated task list
- Current signed and dated curriculum vitae of
  - Investigators (all countries/geographies)
  - Key members of the investigation site team (Australia and Europe only)
- All approved versions of the IC Form, and other information provided to the subjects and advertisements, including translations
- All approved versions of the Clinical Investigation Plan, study related reports, and Investigator's Brochure
- All case report forms and supporting documentation submitted by investigator, samples of Informed Consent Forms, and other information provided to the subjects
- Subject screening logs
- Copies of all Ethics Committee approval letters and relevant Ethics Committee correspondence and Ethics Committee voting list/roster/letter of assurance
- Names of the institutions in which the clinical study will be conducted
- Regulatory authorities' correspondence, notifications and approvals as required by national legislation
- Insurance certificates (where requested by the Ethics Committee)
- Shipping records of investigational devices
- Investigational device accountability logs
- Names/contact addresses of monitors
- Monitoring visit reports and follow-up letters
- Forms for reporting any adverse events and adverse device effects
- Statistical analyses and underlying supporting data
- Final report of the clinical investigation
- Study training records for site personnel and Medtronic personnel involved in the study
- Any other records that local regulatory agencies require to be maintained

14.6.4. Sponsor Reports

Medtronic shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, Medtronic shall, upon request of reviewing Ethics Committee, regulatory agency or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data reporting requirements are listed in Section 10.

Table 23: Sponsor Reports for Australia

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical study	Investigators, Ethics Committee, and relevant authorities	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee, and relevant authorities	Notification as per local requirements in Australia.
Study deviation	Investigators, Ethics Committee, and relevant authorities	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to Investigators per local requirements. Serious breaches should be reported to the reviewing HREC and PI within 7 calendar days of confirming a serious breach has occurred and provide follow-up reports when required.

Table 24: Sponsor Reports for Canada

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, Health Canada, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and device disposition	Investigators, Ethics Committee, Health Canada	Notification as per local requirements in Canada.
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to Investigators periodically.
Final report	Investigators, Ethics Committee, Health Canada	A final report will be submitted to Health Canada, Investigators, and Ethics Committees after completion or termination of this study.

Table 25: Sponsor Reports for Europe

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	Investigators, Ethics Committee, relevant authorities	Provide prompt notification of termination or suspension and reason(s). (ISO 14155:2011)
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, relevant authorities	Investigators, other Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Withdrawal of CA approval	Investigators, Ethics Committee, relevant authorities	Investigators, Ethics Committees and relevant authorities will be notified only if required by local laws or by the Ethics Committee.
Progress Reports	Ethics Committee and regulatory authorities	This will be submitted to the Ethics Committee and regulatory authorities only if required by local laws or by the Ethics Committee.
Final report	Investigators, Ethics Committee, and regulatory authorities upon request	For sites complying with ISO 14155: • The Investigator shall have the opportunity to review and comment on the final report. • If a clinical Investigator does not agree with the final report, his/her comments shall be communicated to the other Investigator(s). • The coordinating Investigator shall sign the report. If no coordinating Investigator is appointed, then the signature of the principal Investigator in each center should be obtained. (ISO 14155:2011)
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Site specific study deviations will be submitted to Investigators periodically.

Table 26: Sponsor Reports for Japan

Report	Submit to	Description/Constraints
Premature termination or suspension of the clinical investigation	HOMI PMDA	When the sponsor suspends or discontinues the clinical trial, he or she shall promptly notify the heads of all the medical institutions and regulatory authorities thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32)
Suspension of development of investigational device	HOMI PMDA	When the sponsor decides not to attach the documents concerning clinical trial records collected in the clinical trial to the authorization application, he or she shall promptly notify the heads of all the medical institutions other facilities engaged in the clinical trial thereof and the detailed reason therefor in writing. (MHLW Ordinance 36, 2005 Article 32)
Investigator List	HOMI PMDA	The sponsor shall beforehand submit the list of Investigators to PMDA and HOMI. (MHLW Ordinance 36, 2005 Article 32) The sponsor shall submit the list of Investigators to PMDA and HOMI when making any changes in the list. (MHLW Ordinance 36, 2005 Article 32)
Important information concerning the quality, effectiveness, and safety of the investigational device	Investigators HOMI PMDA	When new, important information is obtained, the sponsor shall revise the Investigator's brochure. In addition, prior to revising the Investigator's brochure, the sponsor shall report the information to the principal Investigator, HOMI, and regulatory authorities. (MHLW Ordinance 36, 2005 Article 28)
Clinical Trial Report	PMDA upon request	The sponsor shall prepare, according to the procedure, a clinical study report that summarizes the results, etc., of a clinical study when it is completed or discontinued. (MHLW Ordinance 36, Article 33)
Study deviation	Investigators HOMI as necessary	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. (ISO 14155:2011) Site specific study deviations will be submitted to Investigators quarterly. When the monitor confirms deviation as a result of monitoring, the monitor shall notify the principal Investigator and, as necessary, the HOMI thereof. The monitor shall also request for appropriate measures to be taken to prevent such deviation in the future. (MHLW Ordinance 36, 2005 Article 30)

Table 27: Sponsor Reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of Ethics Committee approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA approval	Investigators, Ethics Committee, FDA, and relevant authorities	Notification within five working days. (21 CFR 812.150(b)(3))
Investigator List	FDA	Submit at 6-month intervals, a current list of the names and addresses of all Investigators participating in the investigation. (21 CFR 812.150(b)(4))
Progress Reports	Ethics Committee and FDA	Progress reports will be submitted at least annually. (21 CFR 812.150(b)(5), 812.36(f)
Recall and device disposition	Investigators, Head of Institution, Ethics Committee, FDA, and relevant authorities	Notification within 30 working days and will include the reasons for any request that an Investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))
Failure to obtain Informed Consent Form	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))
Final report	Investigators, Ethics Committee, Regulatory authorities upon request, and FDA	Medtronic will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, Investigators, and IRBs/ECs within six months after completion or termination of this study. (21 CFR 812.150(b)(7))
Study deviation	Investigators	Ensure that all deviations from the Clinical Investigation Plan are reviewed with the appropriate clinical Investigator(s), are reported on the case report forms and the final report of the clinical investigation. Site specific study deviations will be submitted to Investigators periodically.
Other	Ethics Committee, and FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))

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 the study.

After closure of the study Medtronic will archive records and reports per Medtronic standards and applicable regulations.

14.7. Publication and Use of Information

Publications from the study will be handled according to Medtronic Global Standard Operating Procedures and as indicated in the Clinical Trial Agreement.

Publication Committee

Medtronic may form the PULSED AF Publication Committee from the Steering Committee and/or study Investigators. Medtronic personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The Publication Committee will develop the final Publication Plan as a separate document.

The Publication Committee's role is to: 1) manage elements addressed in the publication plan as outlined in this section, 2) develop the final Publication Plan under separate cover, 3) execute the Publication Plan, 4) oversee the publication of primary, secondary and ancillary study results, 5) review and prioritize publication proposals, 6) provide input on publication content, and 7) determine authorship. In addition, the committee will apply and reinforce the authorship guidelines set forth in the Publication Plan.

Membership in the Publication Committee does not guarantee authorship. The committee will meet as needed.

Management of Primary, Secondary and Ancillary Publications

The Publication Committee reviews, prioritizes, and manages all publications including primary, secondary and ancillary publications. Primary and secondary publications are those that address analyses of any or all primary objectives or secondary objectives, respectively, as specified in the Clinical Investigation Plan.

An ancillary publication is any publication that does not address the study objectives identified in the Clinical Investigation Plan. They include publications proposed and developed by other Medtronic departments or entities, clinicians participating in this clinical study, and clinicians not participating in this clinical study. The committee will work with Medtronic to ensure that requests do not present conflicts with other proposals, are not duplicative, and to determine which ancillary publication proposals, if any, will be supported.

The committee may decide that no publications, including abstracts, will be published prior to the end of the study or with individual site data. Requests for publications on study objectives utilizing subset data (e.g., regional) will be evaluated for scientific validity and the ability of Medtronic to provide resources.

Criteria for Determining Authorship

Publications will adhere to authorship criteria defined by the International Committee of Medical Journal Editors (ICMJE, Uniform requirements for manuscripts submitted to biomedical journals, www.icmje.org). Individual authorship criteria defined by the target journal or conference will be followed when it differs from ICMJE criteria.

Authors, including Medtronic personnel, must at a minimum meet all of the conditions below:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Decisions regarding authorship and contributor-ship will be made by the committee. The selected authors will be responsible for drafting the publication. All selected authors must fulfill the authorship conditions stated above to be listed as authors, and all contributors who fulfill the conditions must be listed as authors.

All Investigators not listed as co-authors will be acknowledged as the "Medtronic PULSED AF Study Investigators" and will be individually listed according to the guidelines of the applicable scientific journal when possible and affiliation. Any other contributors will be acknowledged by name with their specific contribution indicated.

Transparency

Transparency of study results will be maintained by the following means:

- A final report, describing the results of all objectives and analysis, will be distributed to all Investigators, Ethics Committees and Regulatory Authorities of participating countries when required by local law
- Registering and posting the study results on public registries (e.g., ClinicalTrials.gov, UMIN) based on the posting rules stipulated, as required by local law
- Submitting for publication the primary study results after the study ends

- Disclosing conflicts of interest (e.g., financial) of the co-authors of publications according to the policies set forth by the corresponding journals and conferences
- Making an individual site's study data accessible to the corresponding Investigator after the completion of the study, if requested

14.8. Investigator / Site Selection

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation.

The minimum required criteria for a Principal Investigator and proposed investigational center are listed below:

- Principal investigator has an MD degree, or equivalent, with a Fellowship in Electrophysiology and a minimum of 2 years of experience treating atrial fibrillation in patients using endocardial techniques.
- Principal Investigator must participate in a Medtronic physician engagement event with hands on use of the Pulsed Field Ablation System, prior to enrolling a subject.
- Principal Investigator has adequate time and resources to conduct the study throughout the duration of the study, including, as applicable, facilities, and qualified staff.
- Principal Investigator has access to an adequate number of subjects in the study specific patient population to enroll 1-2 subjects per month.
- Principal Investigator has the ability to comply with the Clinical Investigation Plan, and applicable REB/EC/IRB and regulatory requirements.
- Principal Investigator is not debarred, disqualified or working under sanctions.

14.9. Site Activation

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

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

- Ethics Committee approval (and membership roster/voting list) of the current version of the CIP, Informed Consent Form, subject facing materials, Investigator Brochure as required by local laws and other materials, as necessary.
- Regulatory authority approval or notification (as required per local law)
- Fully executed Clinical Trial Agreement (CTA) and Investigator Statement where applicable
- Financial Disclosure of Investigators

- Curriculum Vitae (CV) of Investigators and key members of the investigation site team (as required by local law) (in Australia and Europe, CVs are required for the Principal Investigator and all site personnel who have been delegated tasks)
- Documentation of delegated tasks
- Documentation of study training (including CIP, IB if available, informed consent process, data collection tools, regulations and product training)

Documentation of delegated tasks must be completed prior to any person other than the Principal Investigator performing study activities.

Additional requirements imposed by the Ethics Committee and regulatory authority shall be followed.

Medtronic contracts with participating institutions/investigators through a Clinical Trial Agreement that defines the scope and responsibilities and associated compensation related to carrying out the obligations under a clinical study sponsored by Medtronic.

In addition, all participating site staff must be trained on the current version of the CIP and must be delegated by the Principal Investigator to perform study related activities.

Medtronic will provide each study site with documentation of study site/Investigator readiness in the form of a site readiness letter; this letter must be received prior to subject enrollment. Additional site personnel included after the initial activation will be notified when all requirements have been completed.

14.10. Suspension or Early Termination

14.10.1. Early Termination or Suspension

Early termination is the closure of a clinical study that occurs prior to meeting defined endpoints. This is possible for the whole study or a single site. Suspension is a temporary postponement of study activities related to enrollment. This is possible for the whole study or a single site. If suspension is lifted, the Investigator shall assess whether or not to continue the clinical study at their site.

14.10.2. Study-wide Termination or Suspension

Possible reasons for considering study termination or suspension of the study include but are not limited to:

- Adverse events associated with the system or product under investigation which might endanger the safety or welfare of the subject
- Observed/suspected performance different from the product's design intent
- Decision by Medtronic or regulatory body (where the study is operating under regulatory body authority)
- Technical issues during the manufacturing process

14.10.3. Investigator/Center Termination or Suspension

Possible reasons for clinical Investigator or center/site termination or suspension include but are not limited to:

- Failure to obtain Ethics Committee annual renewal of the study
- Persistent non-compliance to the Clinical Investigation Plan (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per visit schedule)
- Lack of enrollment
- Noncompliance to regulations and the terms of the Clinical Trial Agreement (e.g. failure to submit data in a timely manner, failure to resolve data queries and monitoring findings in a timely manner)
- Ethics Committee suspension of the site
- Fraud or fraudulent misconduct is discovered (as defined by local law and regulations)
- Investigator request (e.g. no longer able to support the study)

14.10.4. Procedures for Termination or Suspension

14.10.4.1. Medtronic-Initiated and Regulatory Authority-Initiated

- Medtronic will promptly inform the clinical Investigators, or in Japan the HOMI, of the termination or suspension and the reasons and inform the regulatory authority(ies) where required.
- In the case of study termination or suspension for reasons other than a temporary Ethics Committee approval lapse, the Investigator will promptly inform the Ethics Committee. In Japan, the HOMI will promptly inform the Investigator and Ethics Board.
- In the case of study termination, the Investigator must inform the subjects and may inform the personal physician of the subjects to ensure appropriate care and follow-up is provided
- In the case of a study suspension, subject enrollment must stop until the suspension is lifted by Medtronic.
- In the case of a study suspension, enrolled subjects should continue to be followed out of consideration of their safety, rights and welfare.

14.10.4.2. Investigator-Initiated

- The Investigator will inform Medtronic and provide a detailed written explanation of the termination or suspension. In Japan, the Investigator will promptly inform the HOMI and the HOMI will inform Medtronic in writing.
- The Investigator will promptly inform the institution (where required per regulatory requirements).
- The Investigator will promptly inform the Ethics Committee.
- The Investigator will promptly inform the regulatory authorities (where required per regulatory requirements).
- The Investigator will promptly inform the subjects and/or the personal physician of the subjects to ensure appropriate care and follow-up is provided.
- In the case of a study suspension, subjects enrolled should continue to be followed out of consideration of their safety, rights and welfare.

14.10.4.3. Ethics Committee-Initiated

- The Investigator, or in Japan the HOMI, will inform Medtronic and provide a detailed written explanation of the termination or suspension within 5 business days. In Japan, HOMI will also inform the Investigator.
- Subject enrollment must stop until the suspension is lifted.
- Subjects already enrolled should continue to be followed in accordance with Ethics Committee policy or its determination if an overriding safety concern or ethical issue is involved.
- The Investigator will inform his/her institution (where required per local requirements).
- The Investigator will promptly inform the subjects and/or the personal physician of the subjects, with the rationale for the study termination or suspension.
- The Investigator will promptly inform the regulatory authorities (where required per regulatory requirements).

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16. Appendices

Appendix A: Study-Specific Requirements by Country

Regulations for the conduct of clinical trials vary by country. Study-specific requirements in each country not outlined in the Clinical Investigational Plan will be provided under separate cover.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Appendix C: Foreseeable Adverse Events

The information provided in this section pertains to foreseeable adverse events that may be observed in study subjects and may collectively assist in identifying those events for a given device or therapy that are unexpected in nature.

The PVI ablation procedure involves surgery, therefore, standard adverse events associated with a surgical procedure may be experienced (e.g. anesthesia complications, injury, infections, bleeding, exacerbation of pre-existing conditions, healing complications). The focus of this section is to specifically address in more detail, those events that are foreseeable due to the use, performance, and/or presence of the PulseSelect™ PFA System under investigation.

Treatment required for procedure and/or PulseSelect™ PFA System related adverse events that are experienced may include medication or other surgical and medical remedies. The adverse events associated with the use of the PulseSelect™ PFA System include but are not limited to those in Table C- 1.

Table C- 1: Foreseeable Adverse Events

Adverse Event/Risk	Definition
Access site complications (e.g. bruising, ecchymosis, AV fistula, hematoma, pseudoaneurysm)	Complications at catheter insertion site in the groin
Allergic reaction to x-ray contrast media	Moderate to severe symptoms (for example: nausea, vomiting, hives, swelling, anaphylaxis) due to infusion of iodinated contrast media via IV
Anesthesia reactions	Moderate to severe side effects due to general anesthesia use, e.g. prolonged fatigue, transient confusion or memory loss, dizziness, urinary retention, nausea, vomiting, chills, and sore throat. In older patients, this can also include persistent confusion, memory loss, heart attack, pneumonia, thromboembolism and cerebrovascular accident.
Anemia	Deficiency of red blood cells or of hemoglobin in the blood resulting in weariness
Arrhythmias, proarrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)	Disruption of normal heart rate or rhythm
Back pain	Pain felt in the lower or upper back
Bleeding, possibly requiring transfusion	Loss of blood, including loss resulting in transfusion
Body temperature elevation	Sustained or continued fever, e.g. increase in body's set point temperature greater than 1°C above normal diurnal body temperature

Perforation of the heart or other organs during transseptal puncture or other procedures	Creation of a dissection or tear in myocardial tissue or other non-cardiac tissues during the ablation procedure that compromises hemodynamic stability
Cardiac tamponade	Pressure on the heart as a result of a significant pericardial effusion
Chest discomfort	Includes a range of feeling from sharp stabbing to dull ache in the chest
Cough	Rapid expulsion of air from the lungs
Embolism	Introduction of air, formation and dislodgement of a blood clot (thrombus) or dislodgement of cholesterol/plaque within the blood vessel, which travels downstream into small vessels, blocking blood flow and causing temporary or permanent damage to organs distal to blockage. Emboli are known to cause myocardial infarction, transient ischemic attack, stroke/cardiovascular accident, blurred vision, visual changes, paralysis, paresis, or kidney damage, peripheral ischemia and may ultimately lead to incapacitation or death. Symptomatic and non-symptomatic.
Catheter entrapment in cardiac structures requiring intervention	Tangling of the catheter with heart tissues which requires invasive intervention, including surgical repair
Cerebrovascular accident (CVA)	Blockage of blood flow, or rupture of an artery, to the brain which causes sudden death of brain cells
Transient ischemic attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), no more than 24 hours
Collateral damage to the conduction system or coronary vasculature	Coronary artery injury due to occlusion or stenosis of the coronary arteries that may require balloon dilation, nitroglycerin use, or stenting. Prolonged injury may lead to myocardial infarction. Collateral damage to the conduction system includes unintended damage to the cardiac conduction system (e.g., atrioventricular node or sinus node).
Death	Complication or deterioration of health ultimately leading to a patient's death
Esophageal damage (including atrial esophageal fistula)	Damage to the esophagus, including ulcer and atrioesophageal fistula (an abnormal passageway between the heart and esophagus)
Hemoptysis	Coughing up blood or blood-stained mucus
Hypotension	Low blood pressure
Hypertension	High blood pressure
Infections	Invasion and multiplication of microorganisms (e.g. bacteria, virus) not normally present within the body

Myocardial infarction or ischemia	Blockage of blood flow to the heart muscle (i.e. heart attack)
Nerve injury or nerve damage (e.g. phrenic nerve injury)	Phrenic Nerve Injury: Absent phrenic nerve function as assessed by diaphragmatic fluoroscopy/sniff test. Vagal Nerve Injury: an injury to the vagal nerve that results in esophageal dysmotility or gastroparesis
Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system	Collateral damage to the vascular system includes unintended damage to the peripheral vascular system (ex: superior vena cava).
Pericarditis or endocarditis	Inflammation of the sac-like tissue that surrounds the heart, or vegetative growth inside the heart.
Pleural effusion	Collection of extra fluid around the lungs
Pericardial effusion	Fluid collecting in the pericardial sac that surrounds the heart
Pneumonia	Lung infection that inflames air sacs in one or both lungs
Pneumothorax	Collapsed lung
Pulmonary vein stenosis	Shrinkage of one or more pulmonary veins that carry blood from the lungs to the left atrium of the heart.
Pulmonary edema	Excess fluid accumulation in the lungs
Radiation injury or damage and late malignancy	Delayed effect of the radiation received by the patients, including acute and subacute skin injury, malignancy, and genetic abnormalities.
Respiratory depression	Suppression of normal breathing ability.
Sore throat	Pain in throat
Unintended complete or incomplete atrioventricular node (AV-Node) or sinus node block or damage	AV block has been defined by the occurrence of a complete AV block lasting ≥3 s during either catheter manipulation or the administration of RF pulses. Sinus node dysfunction: abnormality of cardiac impulse formation that may be caused by pacemaking dysfunction of the SA node, which may manifest on an electrocardiogram as: sinus bradycardia, sinus arrest or exit block, combinations of sino-atrial and atrioventricular nodal conduction disturbances, atrial tachyarrhythmias, with symptoms of: syncope, pre-syncope, palpitations, or dizziness.
Valvular insufficiency or damage	Damage to heart valve (e.g. tricuspid, mitral), including backward flow of blood through the valve
Vasovagal reaction	Reflex of the involuntary nervous system that causes the heart to slow down and blood pressure drops; may result in fainting

Appendix D: Endpoint-Related Adverse Event Definitions

Table D- 1 describes definitions for a subset of endpoint-related adverse events that may be observed in the study.

Table D- 1: Adverse Event Definitions

Adverse Event	Definition
Atrioesophageal fistula	Connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair.
Cardiac tamponade/perforation	Development of a significant pericardial effusion during or within 30 days of undergoing the study ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Cerebrovascular accident	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Confirmed by neurology assessment and/or radiographic confirmation.
Major bleeding requiring transfusion	Bleeding that requires and/or is treated with transfusion or results in a 20% or greater fall in hematocrit.
Myocardial infarction	Presence of any one of the following criteria: 1) detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB), which persist for more than one hour; 2) development of new pathological Q waves on an ECG; 3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
Pericarditis requiring intervention	Pericardial effusion that leads to pericarditis with hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Phrenic nerve injury/diaphragmatic paralysis	Absent phrenic nerve function as assessed by diaphragmatic fluoroscopy/sniff test that is ongoing from hospital discharge. Phrenic nerve injury documented to be present 6 months or longer following ablation will be considered against the primary safety endpoint.

Pulmonary vein stenosis	Reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will be considered against the primary safety endpoint.
Transient ischemic attack	A sudden-onset focal neurological symptom or sign lasting at least 10 minutes but less than 24 hours without evidence of acute brain ischemia on diffusion-weighted MR or other imaging. Eligible symptoms include hemiplegia or hemiparesis, monoplegia or monoparesis, and a language disturbance other than isolated dysarthria. Symptoms that will not qualify as TIA include transient monocular blindness, blindness in both eyes, dysarthria, vertigo, isolated sensory symptoms, confusion, memory loss, non-specific complaints of dizziness, or syncope. No other etiology for the symptoms may be evident and the diagnosis must be confirmed by the site principal investigator.
Vagal nerve injury resulting in esophageal dysmotility or gastroparesis	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis (i.e. delayed gastric emptying) that prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following the ablation procedure
Vascular access complications requiring intervention	Development of a hematoma (excluding minor hematomas not requiring surgical treatment), AV fistula or pseudoaneurysm that requires intervention, prolongs the hospital stay, or requires hospital admission.
Systemic/pulmonary embolism requiring intervention	Systemic/pulmonary embolism that prolongs hospitalization by more than 48 hours or requires hospitalization
Pulmonary edema	Pulmonary alveolar fluid accumulation accompanied by typical symptoms (dyspnea), physical findings (rales, hypoxemia), radiologic findings, and response to diuretic therapy and requiring or prolonging hospitalization
Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours (excluding recurrent AF/AFL/AT)	Any PulseSelect™ PFA System-related or PFA procedure-related cardiovascular and/or pulmonary adverse event that prolongs or requires hospitalization for more than 48 hours. Because early recurrences of AF/AFL/AT are to be expected following AF ablation, recurrent AF/AFL/AT within 90 days that requires or prolongs a patient's hospitalization will not be considered against the primary safety endpoint.

Appendix E: Instructions For Use

Always reference the current version of the Instructions For Use (IFU) document as provided by Medtronic under separate cover.

Appendix F: Data Collection Elements (Case Report Forms)

Draft CRFs for the study will be provided under separate cover. Final CRFs will be provided to sites via the electronic data management system after the site has fulfilled all requirements for database access.

Appendix G: Informed Consent Template

The Informed Consent Template will be distributed under separate cover.

Appendix H: Participating Investigators and Institutions

A final list of participating Investigators and institutions has not been finalized prior to development of the Clinical Investigation Plan and will be distributed under separate cover.

Appendix I: IRB/REB/EC List

A final IRB/REB/EC list has not been finalized prior to development of the Clinical Investigation Plan and will be distributed under separate cover if required or upon request.

Appendix J: Pre-Clinical Testing

A summary of results from pre-clinical testing with the PulseSelect™ PFA System is provided in the Investigator's Brochure under separate cover.

Appendix K: Centers for Medicare and Medicaid Services (CMS) IDE Study Criteria

Applicability of PFA to the Medicare Population

There is a high prevalence of atrial fibrillation in the Medicare population as evidenced by the most recently available claims data for pulmonary vein isolation (PVI) ablation procedures. According to Medicare Physician/Supplier Procedure Summary data[51], there were 41,906 PVI ablation procedures performed on Medicare beneficiaries in CY2017.

Although study participation will be open to patients between the ages of 18-80, it is anticipated that approximately 50% of the patients enrolled will be age 65+. This enrollment pattern mirrors the age distribution of the general population of patients with atrial fibrillation (AF)[1,2,3,4] and therefore results from this trial may be both relevant and generalizable to the Medicare beneficiary population.

[51] Medicare Physician/Supplier Procedure Summary data. Available at: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Physician-Supplier-Procedure-Summary/index.html

17. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Clinical Research Specialist
2.0	• Updated details of study contact for Japan and monitoring contact for Europe/Australia. • Added new vendor details to Table 3. • Sections 2 and 12, and Appendix D: changed "and" to "and/or" in last bullet of each safety endpoint to clarify that the PFA system-related or PFA procedure-related AEs will be included in the endpoint if adjudicated as any of the following: cardiovascular, pulmonary, or both cardiovascular and pulmonary. • Section 2: updated Safety Assessments language to require collection of all adverse events. • Section 3.1 and Section 15: Added missing reference; Corrected broken links to references. • Section 6.1: corrected broken link to Figure 3. • Sections 6.1, 9.1, 14.6, 14.9 and Appendix J: removed references to Report of Prior Investigation (RPI) for US sites. Investigator Brochure (IB) only will be provided for this study. • Section 6.14: removed details of investigational labeling of market released components for each geography, instead referencing Appendix A where those details will be listed. • Section 10.4: removed duplicative links to Table 10 and Table 11. • Sections 10 and 12.2.2: updated language throughout to require collection of all adverse events; removed definition of "cardiovascular related" AE and instructions for Investigator to classify cardiovascular relatedness for AEs. • [redacted] • Section 13: updated to remove the language claiming an exception to the ISO14155:2011 requirement to collect all adverse events.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Clinical Research Specialist

3.0	• Updated study contact details for Worldwide Clinical Study Leader. • Added new vendor details to Table 3. • Section 12.2.3: within "rationale for performance criteria" paragraphs, clarified definitions of primary effectiveness for paroxysmal AF and persistent AF to match the primary endpoint definitions. • Sections 6.14 and 6.16: modified language for product packaging and return requirements to allow better compliance to local laws and regulations in all study countries. • Section 8.4.4: added further guidelines for PFA therapy delivery and Table 8. • Section 8.1, Table 7, Section 8.5: added physical exam at discharge, with requirement to perform cardiopulmonary exam at a minimum. • Table of Contents (adding sub-header under 8.9), Section 2, Section 5, Figure 1, Section 8.1, Table 7, Section 8.9, Table 9, Section 12.1.1, Table 14, Appendix B- Figure B-1: added 7-day telephone or office visit including an AE assessment and medication review. • Section 8.1, Table 7, Section 8.9: at the 30-day visit, added NIHSS assessment and physical exam with requirement to perform cardiopulmonary exam at a minimum. • Section 8.6: added sentence and reference to consult the 2014 Guidelines for the Management of Patients with AF for AAD prescriptions. • Sections 2, 12.1.2, 12.2.3, 12.4.1: clarified definition of acute procedural success. • Sections 9.2, 9.3, Table 10, Appendix C: added pulmonary edema as a potential risk.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Clinical Research Specialist
4.0	• Updated name of the PFA system to PulseSelect™ PFA System throughout • Table 3: removed "atrial" from duties performed by HeartCor Solutions to clarify they will review all arrhythmias. • Sections 2, 6, Figure 3, Table 6, Table 10, Table 11: updated product component information for Cardiac Trigger Monitor and accessories, and for the Catheter Interface Cable. • Sections 2, 5, 6.1, 7.2.1, 12, Figure 2: Added 8 sites and 16 roll-in subjects	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist

4.0	• Sections 2, 5, 7.2.1: clarified that roll-in subject utilization requirement is one per investigator instead of 2 per site. • Sections 2, 5, 6.1, 12.2.3, 12.2.4 (including removal of Figures 5 and 6): Adjusted the Paroxysmal AF cohort OPC and rationale to be consistent with the 2017 HRS Expert Consensus Statement recommendation; this also modified the Paroxysmal AF cohort sample size, the treatment maximum per site and the anticipated number of catheters to be used in the study. • Section 2: modified language to clarify that a neurologist will be part of the CEC. • Sections 2, 12.1.1, 12.2.2, Table 14, Appendix D: added "systemic/pulmonary embolism requiring intervention" and "pulmonary edema" to the pilot phase and pivotal phase primary safety endpoints • Sections 2, 5, 12: corrected definition of severe PV stenosis (from >70% diameter reduction to ≥70% diameter reduction) to be consistent with definition in Appendix D. • Sections 2, 8.3, 8.6, 8.7, 12.2.3: adjusted primary effectiveness endpoint such that more than one repeat PVI ablation during the blanking period will be considered a primary endpoint failure. Also modified the AAD failure portion of the paroxysmal AF primary effectiveness endpoint definition to be consistent with the persistent AF endpoint definition, which better aligns with clinical practice and allows for gradual titration of AADs which may extend past the 90-day blanking period. Previous amiodarone requirements were removed as they are not applicable under the updated endpoint definition. • Sections 2, 8.7, 12.2.3: added requirement to use entrainment maneuvers during EP testing to confirm typical right-sided cavotricuspid isthmus dependent atrial flutter. • Sections 2, 3.2, 5.3, 8.1, 8.3, 8.9, 12.2.2, Table 3, Table 7, Figure 1: added details for pulmonary vein stenosis assessment to require PV stenosis screening in a subset of Pivotal Phase subjects at the 3-month follow-up visit.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist

4.0	[redacted] [redacted] • Modified Sections 2, 4, 8.1, 8.5, 8.9, 8.11, 12, Table 7; [redacted] Patient activated ambulatory monitors will be given to subjects at discharge to begin the weekly and symptomatic transmissions rather than starting at the 3-month visit. Also added note regarding occurrence of pre-planned protocol deviation with the patient activated ambulatory monitor during the pilot phase. • Sections 2 and 7: revised inclusion criteria to require physician note confirming 2 episodes of paroxysmal AF within 6 months prior to enrollment and 1 ECG-documented AF episode within 12 months prior to enrollment. • Sections 2 and 7: revised inclusion criteria to clarify that either form of ECG documentation of persistent AF is required within 6 months prior to enrollment. • Section 5.1: extended expected total study duration. • Section 6.8: clarified that a new catheter interface cable should be used for each procedure. • Sections 7.2, 12 and 14: added language to describe screening log requirements. • Added sections 7.2.2 and 7.2.3 to clarify enrollment strategy for [redacted] PV stenosis assessments. • Section 8.1, 8.3, 8.4, 9.2, Table 7: changed the requirement for TEE to be performed in all subjects, to allow ICE and CCTA as alternative options.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist

4.0	• Section 8.4: modified recommendation for standard pulmonary vein ablation with the PFA System. • Section 8.4.5: clarified that additional left atrial ablations outside the pulmonary veins may be performed if clinically necessary, using a commercially released catheter. Applies at index and/or repeat ablation procedure. • New Section: added section 8.5.1 to require phrenic nerve injury screening prior to discharge. • Section 8.7: clarified requirements of a repeat ablation, based on whether it is performed with the PFA System or a commercially released catheter. • Section 8.9: included details for alternative methods of data collection that may be necessary in the case of extenuating circumstances, such as a global pandemic. • Section 8.10: clarified that a telehealth visit completed in place of an in-office visit may count as an unscheduled visit and ECG is not required if this occurs. • Section 8.11 and 8.17: clarified that patient activated ambulatory monitors may be sent directly to subjects as allowed and core lab data is not entered directly into the study database. • Section 8.12: clarified that only the 12-lead ECGs collected at baseline and the 3-month, 6-month, and 12-month visits will be sent to the core lab for adjudication. • Section 8.19: clarified that completion of an early study exit CRF is not required in the case of a subject death. • Section 14.1: clarified that monitoring visits may be conducted remotely. • Section 14.2: removed reference to generator log files possibly being considered source documentation. • Appendix D: modified the endpoint-related adverse event definition for TIA. • Minor formatting and grammatical corrections throughout.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist

5.0	• Table 1: updated contact details for US/Canada monitoring. • Figure 2 and Sections 2, 5, 6.1, 12.2.4: expanded study pilot phase to include up to 40 subjects at up to 8 sites. • Table 7 and Sections 8.1, 8.5, 8.9, 8.11: modified language such that weekly and symptomatic patient-activated ambulatory monitor recordings start after discharge for remaining pilot phase subjects; reverted to CIP v3.0 language for pivotal phase subjects (i.e., start weekly and symptomatic recordings after the blanking period). • Removed all CIP v4.0 changes (i.e., reverted to all CIP v3.0 language), with the following exceptions: ○ Updated name of the PFA system to PulseSelect™ PFA System throughout. ○ Sections 2, 6, Figure 3, Table 6, Table 10, Table 11: updated product component information for Cardiac Trigger Monitor and accessories, and for the Catheter Interface Cable. ○ Section 8.4: modified recommendation for standard pulmonary vein ablation with the PFA System. ○ Section 8.19: clarified that completion of an early study exit CRF is not required in the case of a subject death. ○ Section 14.1: clarified that monitoring visits may be conducted remotely. ○ Section 14.2: removed reference to generator log files possibly being considered source documentation.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist
6.0	• Added the previously removed CIP v4.0 changes, with the exception that CCTA is not added back as an alternative option to TEE in Sections 8.1, 8.3 and in Table 7.	Jeff Cerkvenik, Distinguished Statistician Josh Treadway, Senior Clinical Research Specialist