Medtronic Ablation Frontiers

Panel Package

P100008

Volume 1 of 1

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FDA Questions

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PMA Voting Options

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Sponsor Executive Summary

Executive Summary of the Program

Medtronic is requesting FDA approval under PMA # P100008 for the Medtronic Cardiac Ablation System, hereafter referred to as 'the System'. The System is comprised of a multi-channel RF ablation generator, cardiac ablation catheters, system components and accessories. The System provides a treatment option for patients with drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation (AF).

Atrial Fibrillation is a growing epidemic in the United States (US). AF is a disease that progresses from short self-terminating episodes (paroxysmal AF) to longer intractable episodes (persistent AF, long-standing persistent AF and permanent AF) resulting in structural changes in the heart and increasing symptoms, decreased quality of life and significant mortality and morbidity. Therapeutic options to reduce AF burden are limited with most patients managed with rhythm control drugs, rate control drugs and/or serial cardioversion. Catheter ablation has been recently approved as a safe and effective treatment for paroxysmal AF (PAF) patients, but there is no approved ablation system for the more diseased, persistent AF population. The System was developed to meet the need for a safe and effective ablation therapy option for the drug refractory, symptomatic, persistent and long-standing persistent AF patient population.

The TTOP-AF clinical trial was a randomized controlled study to evaluate safety and effectiveness of ablation with the System in the treatment of drug refractory, symptomatic, persistent AF and long-standing persistent AF patient population as compared to medical management (persistent AF and long-standing persistent AF are hereafter referred to as 'persistent AF'). The trial demonstrated that 55.8% of patients treated with the System had a ≥90% reduction in AF/atrial flutter (AFL) burden at 6 months, a statistically significant improvement over medical management (26.4%). The effectiveness of the System remains strong (50.7%) even when applying more stringent efficacy criteria, as requested by the FDA, of no allowable 30 second or greater episode of AF. Additional analysis at 12 months suggests this positive result is maintained. Patients treated with the System had clinically relevant improvements in quality of life measures and reduction in symptom severity. The acute safety event rate of 12.3% with an upper 95% confidence bound of 19% exceeded the pre-defined performance goal of 16%. This result is not unexpected given the absence of an established benchmark for the persistent AF patient population and the conservative definition of acute safety events. The TTOP-AF trial demonstrated the effectiveness of the System while providing a reasonable assurance of safety in the treatment of adult subjects with drug refractory, symptomatic, persistent AF.

1. Clinical Need

Treatment of atrial fibrillation (AF) remains a challenge for the estimated 3.7 million patients in the United States (US) who suffer from the disease[1]. About 54% of these patients have symptomatic persistent or permanent AF[2]. Patients with AF have debilitating symptoms and reduced quality of life and it is a major risk factor for stroke and heart failure[3]. Treatment of AF incurs high personal and US healthcare cost due to increased hospitalizations, emergency room visits and mortality[3]. AF will become an even more important issue as literature suggests the incidence of AF increases with advancing age. A range of 0.4%-1.0% has been reported in the general population and increases exponentially from age 60 onwards to 8% over the age of 80[4].

AF is a progressive disease that has more deleterious effects the longer it persists. Patients with AF are clinically stratified by whether the episodes are self-terminating (paroxysmal) or non-self-terminating (persistent, long-standing persistent or permanent)[5]. The extended time in AF causes the left atrium to undergo functional changes (loss of coordinated atrial contractions), structural changes (dilation and fibrosis of the left atrium), and electrical changes (remodeling and shortening of the atrial effective refractory period). Clinically these changes can lead to increased rates of hospitalization[6], worsening heart failure[3], dementia[7], death[7, 8], ischemic disease[8], and stroke[7,9]. AF-related stroke is associated with more severe outcomes, greater disability, and higher mortality[9] when compared with non-AF related strokes and has a poor prognosis[9,10].

Reduction of AF burden and restoration and maintenance of sinus rhythm has been shown to have positive effects on symptom reduction and quality of life[3] as well as mortality benefits[11] in AF patients. Unfortunately, achieving reduction in AF burden is more difficult in the persistent patient population than in the paroxysmal (PAF) population. Therapeutic options for this patient population are limited: drugs, cardioversion, ablate and pace, and surgical ablation. Long-term effectiveness of antiarrhythmic drug therapy for AF rhythm control is usually limited due to intolerance or drug ineffectiveness over time[12] and brings with it the potential for increased mortality[13] pro-arrhythmia and toxic side effects. Serial cardioversion carries its own inherent and well documented stroke risk at approximately 0%-3% per procedure[14].

Ablate and pace improves quality of life in persistent AF patients. However, this approach does not affect the underlying AF disease and does not provide the mortality benefits associated with maintenance of sinus rhythm discussed above. Ablate and pace does not lower AF burden and, therefore cannot convey the lower risk of stroke and hospitalization rate[15,16] associated with lower AF burden. In addition, ablate and pace has been shown to have an all-cause, annual mortality rate as high as 14.7%[17].

Surgical ablation has been shown to be reasonably effective, but the highly invasive nature of the procedure limits it to a small subset of patients undergoing a concomitant surgical procedure (e.g., valve replacement, coronary artery bypass graft). Surgical ablation is also associated with a high level of operative mortality (1.2%-1.8%), peri-operative complications (10.7%-13.9%), and stroke (1.2%-1.8%) as well as lengthy hospital stays (9-12 days) for patients undergoing lone or concomitant procedures[18].

Catheter ablation is an emerging, promising therapy for treatment of symptomatic AF in patients who are refractory to antiarrhythmic drugs (AADs) and/or serial cardioversion. Electrical isolation of the pulmonary veins by catheter ablation has demonstrated success in treating the earliest stage of AF, PAF[19,20,21]. However, the technologies and procedures that have demonstrated effectiveness in the PAF population are not approved for treatment of persistent AF patients. A more extensive ablation procedure is required in these patients due to the electrical, functional and structural changes associated with the progression of the disease and even when used off-label, these technologies demonstrate lower effectiveness for the persistent patient population as compared to the PAF patient population[5].

Therefore, there is a strong clinical need for an AF treatment alternative for persistent AF patients, which is effective at reducing AF burden. The System provides a minimally invasive treatment option addressing this unmet clinical need to reduce AF burden in patients with drug refractory, symptomatic, persistent AF.

2. Medtronic Cardiac Ablation System Description

2.1. GENius Multi-Channel RF Ablation Generator

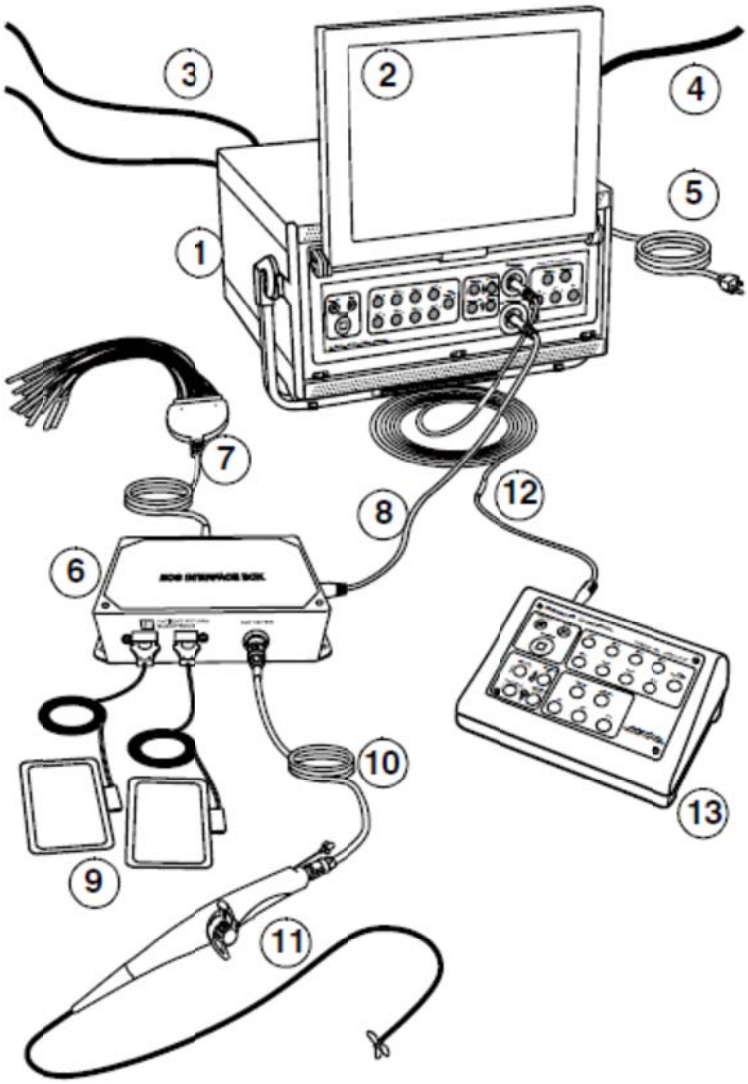
The Medtronic GENius® Multi-Channel RF Ablation Generator (the 'Generator') delivers temperature-controlled radiofrequency (RF) energy to user-selectable electrodes on the following compatible Medtronic cardiac ablation catheters:

- Pulmonary Vein Ablation Catheter® (PVAC®)
- Multi-Array Septal Catheter® (MASC®)
- Multi-Array Ablation Catheter® (MAAC®)

The generator automatically recognizes the attached cardiac ablation catheter and programs preset default temperature, ablation duration, and energy mode setting parameters. Ablation parameters including ablation duration, energy mode, target temperature, and channels (electrode pairs) can also be manually selected. A display screen monitor is available for viewing real-time system and ablation parameters. The generator features the following RF energy mode selections: bipolar only, unipolar only, and combination ratios of bipolar:unipolar energy mode selections of 1:1, 2:1, and 4:1. An ECG interface box connects the catheter with the generator, patient return electrodes, the external monitoring equipment, and pacing equipment that may be used during the procedure.

The components used with the Generator are illustrated in **Figure 1**.

Figure 1. Generator and Components



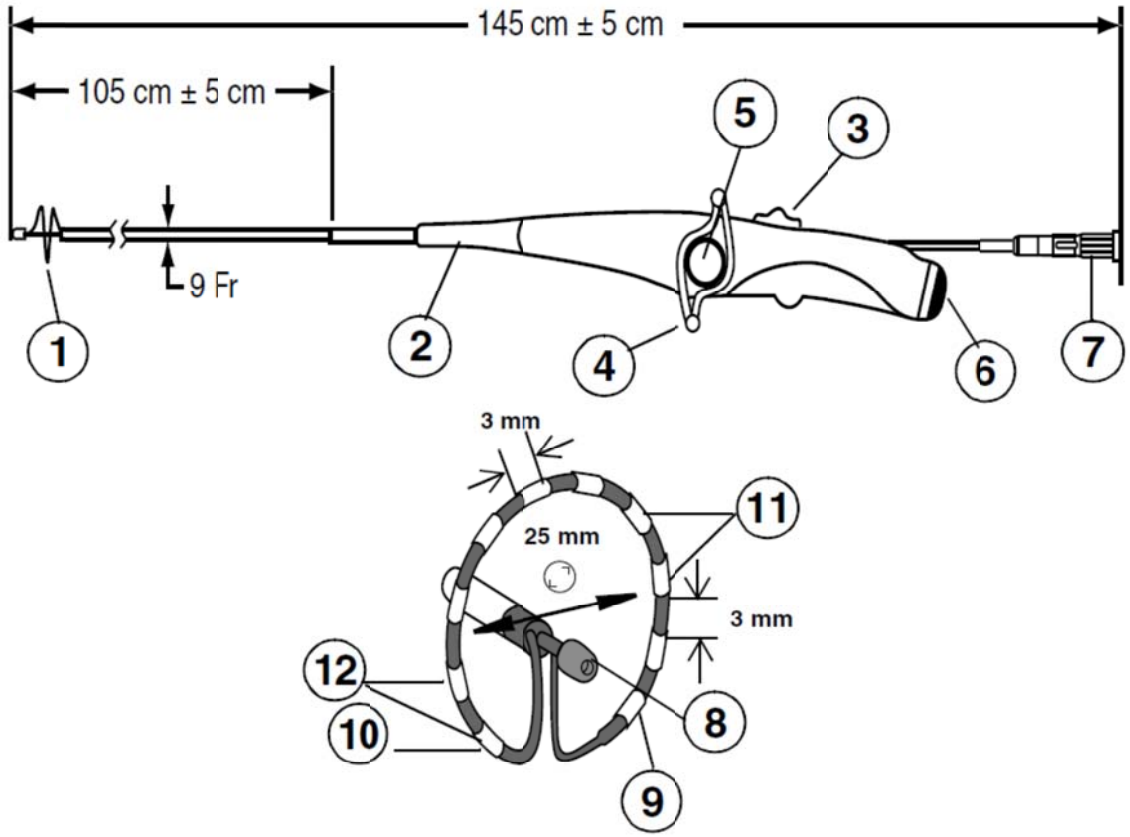
KEY:

1) GENius Multi Channel RF Ablation Generator
2) Monitor
3) VGA Monitor Cables (not included)
4) Equipotentiality (chassis ground) Cable (not included)
5) Power Cable
6) ECG Interface Box
7) Cable, Interface Box to ECG-12 Channel
8) Cable, Interface Box to the RF Generator
9) Patient Return Electrodes (2 required, not supplied)
10) Cable, Catheter Interface
11) Medtronic Cardiac Ablation Catheters
    - Pulmonary Vein Ablation Catheter (PVAC)
    - Multi-Array Septal Catheter (MASC)
    - Multi-Array Ablation Catheter (MAAC)
12) Remote Control Cable (Optional)
13) GENius Jr Remote Control (Optional)

2.2. PVAC

The PVAC is a three-dimensional, anatomically designed, multi-electrode catheter used to map, pace, and ablate the pulmonary veins (see **Figure 2**).

Figure 2. PVAC

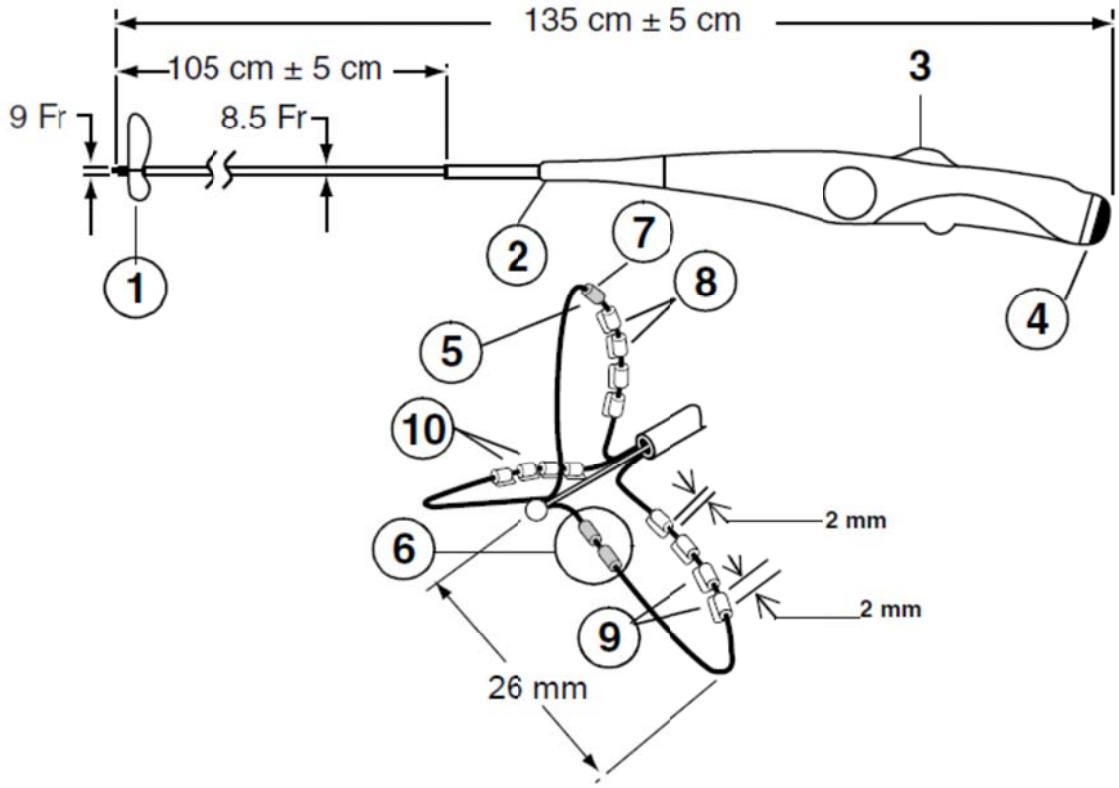


1	Spiral array	7	Proximal lumen
2	Capture device	8	Distal tip
3	Slide control knob	9	Electrode 1
4	Steering knob	10	Electrode 10
5	Tension control knob	11	Pair 2
6	Connector	12	Pair 5

2.3. MASC

The MASC is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue along the left atrial septum (see **Figure 3**).

Figure 3. MASC

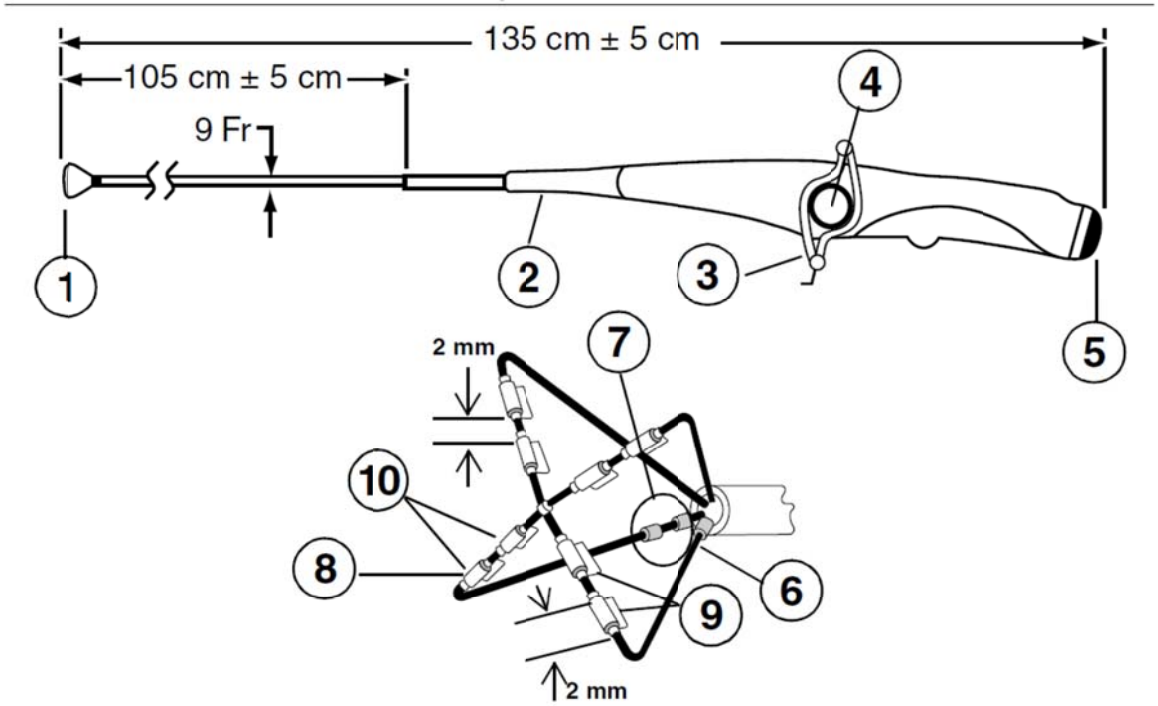


1	Array	6	Arm 2 markers
2	Capture device	7	Electrodes
3	Slide control knob	8	Pair 1
4	Connector	9	Pair 3
5	Arm 1 marker	10	Pair 5

2.4. MAAC

The MAAC is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue in the left atrial body (see **Figure 4**).

Figure 4. MAAC



1	Array	6	Arm 1 marker
2	Capture device	7	Arm 2 markers
3	Steering knob	8	Electrode
4	Tension control knob	9	Pair 1
5	Connector	10	Pair 2

3. Indications, Contraindications, and Warnings

3.1. INDICATIONS

The System is indicated for the treatment of symptomatic, drug refractory persistent atrial fibrillation (less than 1 year) with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

3.1.1. Generator

The Generator delivers temperature-controlled radiofrequency (RF) energy to user-selectable electrodes on compatible Medtronic cardiac ablation catheters, including:

- PVAC
- MASC
- MAAC

The generator automatically recognizes the attached cardiac ablation catheter and programs preset default temperature, ablation duration, and energy mode setting parameters. Ablation parameters, including ablation duration, energy mode, target temperature, and channels (electrode pairs), can also be manually selected. A display screen monitor is available for viewing real-time system and ablation parameters.

The generator features the following RF energy mode selections: bipolar only, unipolar only, and combination ratios of bipolar: unipolar energy mode selections of 1:1, 2:1, and 4:1.

An ECG interface box connects the catheter with the generator, patient return electrodes, the external monitoring equipment, and the pacing equipment that can be used during the procedure.

See the technical manual for information regarding the catheter being used.

3.1.2. PVAC

The PVAC is indicated for the treatment of symptomatic, drug refractory persistent atrial fibrillation (less than 1 year) with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The PVAC is used for mapping, pacing, and ablating pulmonary vein potentials and verifying electrical isolation of the pulmonary veins post-treatment.

3.1.3. MASC

The MASC is indicated for the treatment of symptomatic, drug refractory persistent atrial fibrillation (less than 1 year) with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The MASC is used for mapping, pacing, and ablating arrhythmogenic tissue along the left atrial septum.

3.1.4. MAAC

The MAAC is indicated for the treatment of symptomatic, drug refractory persistent atrial fibrillation (less than 1 year) with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The MAAC is used for mapping, pacing, and ablating arrhythmogenic tissue in the left atrial body.

3.2. CONTRAINDICATIONS

The following are excerpts from the Operator Manual (Generator) and Technical Manuals (Catheters) for contraindications:

3.2.1. Generator

"See the technical manual for the catheter being used."

3.2.2. Cardiac Ablation Catheters (PVAC, MASC, MAAC)

"Use of the PVAC, MASC, and MAAC are contraindicated as follows:

- Active sepsis
- Left atrial thrombus or myxoma
- Atrial Septal Patch or atrial septal defect repair with percutaneous device
- Known sensitivity to heparin
- Blood clotting abnormalities
- Venous filtering device (Greenfield Filter)

The Cardiac Ablation Catheters are not recommended for use in patients who cannot undergo standard anticoagulation protocol for a left-sided cardiac procedure, or who have had a recent coagulopathy or embolic event."

3.3. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Generator, PVAC, MASC, and MAAC labeling.

4. Clinical Study Summary

The Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) study was a prospective, randomized, controlled, multi-center clinical trial designed to assess the safety and effectiveness of the System compared to medical therapy in the drug refractory, symptomatic, persistent and long-standing persistent AF population after failing at least one Class I or III anti-arrhythmic drug (AAD). The trial was conducted over a 2.5 year period with enrollment beginning in November 2007. The last ablation procedure for the trial occurred on May 7, 2010 with the final follow-up on November 1, 2010. A total of 210 subjects were randomized at 23 sites across the United States and one site in The Netherlands. At the time of this report all subjects that did not exit the study early have completed 6-months of follow-up and have been exited from the study.

A total of 242 study candidates signed consent forms and completed screening for study participation. After informed consent, study subjects were enrolled and randomized 2:1 to Ablation Management or Medical Management. Randomization assignments were given to 210 subjects (138 Ablation Management and 72 Medical Management subjects). Medical Management treatment failures were permitted to crossover and receive an ablation, no sooner than 4 months with a target of 6 months.

See **Appendix 9** for an outline of the study protocol, inclusion and exclusion criteria, and baseline procedures.

4.1. TREATMENT REGIMEN FOR EACH ARM OF THE STUDY

4.1.1. Ablation Management Treatment

Ablation Management subjects underwent up to 2 ablation procedures for treatment of AF with the System. All 3 ablation catheters (PVAC, MASC, and MAAC) were required to be used during the initial ablation procedure in the listed order for treatment of each subject's specific source of AF. PVAC was used to map, ablate and confirm electrical isolation of the pulmonary veins. Once optimal positioning of the catheter was obtained, ablation on all channels was to be performed in a 4:1 (unipolar:bipolar) setting to a target temperature of 60°C for 60 seconds. The MASC and MAAC catheters were used to map and ablate Complex Fractionated Atrial Electrograms (CFAEs). The MASC catheter was deployed in the left atrium and the sheath retracted back to the septum toward the right atrium prior to ablation. Ablations were to occur for 60 seconds with a target temperature of 60°C using a 1:1 (unipolar:bipolar) modality setting. The MASC catheter was then rotated to identify additional CFAEs and ablation repeated. The MAAC catheter was used to map and ablate in the body of the left atrium in a similar fashion. Ablations were also to occur at 60°C for 60 seconds. However, a modality of 1:1 or 4:1 was to be used depending on the location of the ablation. Additional mapping and ablations would occur until the investigator determined that all CFAEs were eliminated. Electrical cardioversion was used during the procedure to restore sinus rhythm if the subject remained in AF. Once the subject was in sinus rhythm, the PVAC catheter was again placed to re-map any remaining

pulmonary vein potentials. All noted pulmonary vein potentials were ablated using the settings identified above, with the exception that only channels where potentials were located were to be selected.

Anticoagulation strategies were left to the discretion of the investigator. Oral anticoagulation was allowed to be discontinued and either low molecular weight heparin (LMWH) or IV heparin could be substituted for therapeutic doses of oral anticoagulation until the time of the procedure. Intravenous heparin or LMWH was to be resumed following the procedure until an INR > 2.0 was achieved. Oral anticoagulation was to be restarted for the duration of follow-up.

Recurrence of AF required additional management. If desired, the investigator could prescribe an AAD that the subject had failed prior to the ablation procedure. In addition, a single repeat ablation procedure could be performed during the follow-up period of the initial ablation procedure. The retreatment ablation procedure was to occur within 90 days of the index ablation, whenever possible. Neither AAD therapy or ablation retreatment constituted a chronic treatment failure during this period provided that the subject was off all AADs prior to the 6 month visit. If a subject required the use of an AAD after his/her ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

New onset atrial tachyarrhythmias that were exposed during or following the ablation procedure were reported as part of the follow-up management for subjects. DC cardioversion was recommended to restore sinus rhythm prior to scheduling a repeat ablation procedure.

4.1.2. Medical Management Treatment

Medical Management subjects were to receive an AAD at a previously failed dose or a new drug. Amiodarone was allowed up to a maximum allowable dosage of 200 mg/day. AAD therapy was expected to begin promptly after randomization. Changes to AAD dosage and/or changes to another drug or combination of drugs were allowed during the 6 month follow-up period when determined clinically necessary by the investigator. In addition to AAD use, subjects were expected to receive adequate anticoagulation with warfarin during the course of the study to achieve and maintain an INR level >2.0.

Direct current (DC) cardioversions to restore sinus rhythm were also allowed in the Medical Management group. Greater than 2 failed DC cardioversions (failure to convert to sinus rhythm and maintain the rhythm for at least 30 days) constituted a medical management failure.

4.2. FOLLOW-UP SCHEDULE FOR RANDOMIZED SUBJECTS

Subjects were followed for 6 months from the date of randomization for Medical Management subjects and from the date of the ablation procedure for Ablation Management subjects. If an Ablation Management subject required a repeat ablation for AF recurrence, the follow-up visit timeline would restart on the date of the retreatment ablation procedure. All study subjects were

required to have follow-up assessments at 1, 3, and 6 months for the purpose of assessing arrhythmia recurrence, use of medications (AADs and anticoagulation), and adverse event (AE) occurrence. Subjects in Ablation Management were also required to have a pre-hospital discharge visit. Office visits at 1, 3, and 6 months included history, physical examination, neurological assessment, symptom severity score, ECG, SF-36 survey, documentation of the use of medications and anticoagulation agents, the occurrence of AF interventions, and an AE review. Additionally, Ablation Management subjects had a pulmonary vein stenosis survey obtained at every follow-up visit and a CT/MRI scan performed at the 6-month visit. Forty-eight (48)-hour Holter monitoring was performed at the 6-month visit for both Ablation and Medical Management subjects.

4.3. SUBJECT ACCOUNTABILITY AND ANALYSIS POPULATIONS

The statistical methodology for the selection of subjects for the primary endpoint analyses was based on Intention-to-Treat (ITT), which require subjects' data to be analyzed with respect to their assigned randomized treatment groups (Ablation Management or Medical Management). The passive missing value imputation technique was utilized for all primary endpoint analyses. This technique assumed subjects were "failures" if their data was not available for primary endpoint analyses. Data from Medical Management subjects prior to crossover was included for endpoint analyses. However, if a Medical Management subject crossed over prior to the end of the study, data from the date of the crossover and beyond was analyzed separately.

There were 210 randomized subjects consisting of 138 Ablation Management subjects and 72 Medical Management subjects (**Table 1**). Thirteen (13) Ablation Management and 6 Medical Management subjects were withdrawn or lost to follow-up during the study. One death occurred in the study for a subject in Ablation Management. The number of subjects that completed the study and who were available for the primary effectiveness endpoint analysis was 124 Ablation Management subjects and 66 Medical Management subjects (23 subjects who completed the study using medical therapy and 43 subjects who crossed over to receive an ablation). The 43 Medical Management subjects that crossed over to receive an ablation were all considered failures for the primary effectiveness endpoint analysis. Of the 43 Medical Management Crossover subjects, 39 completed the study after receiving up to 2 ablations, but the data obtained after crossing over were not included in the primary effectiveness endpoint analysis for Ablation Management (**Table 2**).

Table 1. Subject Accountability and Disposition through 6 Month Follow-up

Subject Disposition	Subjects
Total number of subjects randomized	210
Subjects randomized to Ablation Management	**138**
Subjects who underwent a procedure to have an ablation	133
Subjects who underwent an ablation with the study catheters	132
Subjects that had a retreatment ablation	48
Lost to follow-up	0
Withdrawn	13
Death	1
Subjects that completed the study	**124**
Subjects randomized to Medical Management	**72**
Subjects that used an AAD after randomization	67
Lost to follow-up	1
Withdrawn	5
Subjects that completed the study using medical therapy	23
Subjects who completed the study and crossed over	43
Total Medical Mgmt. subjects that completed the study	**66**

Table 2. Accountability for Medical Management Subject after Crossing Over

Subject Disposition	Subjects
Medical Management Crossover Subjects	**43**
Crossover subjects requiring a retreatment ablation procedure	12
Withdrawn	4
Crossover subjects that completed the study after receiving an ablation	**39**

All randomized subjects (210) were included in the safety endpoint evaluations. However, once a Medical Management subject crossed over to receive an ablation, the safety events that occurred during the procedure or in the 6 months following the procedure were reported and analyzed separately. The total number of ablation procedures (both index and retreatment) that were evaluated for Acute Safety for Ablation Management subjects was 183 procedures (**Table 3**). Another 56 index and retreatment procedures were performed in Medical Management Crossover subjects (not included in the ITT acute safety endpoint analysis). The total number of ablation procedures that were performed within the pivotal portion of the TTOP-AF trial was 239.

Table 3. Procedures Performed for All Ablated Subjects

Procedure Description	Number of Procedures
Ablation Management Subjects (N=138)	
Index ablation procedures attempted	134
Index ablation procedures aborted prior to ablation	2[a]
Retreatment ablation procedures attempted	49
Retreatment ablation procedures aborted prior to ablation	1[b]
Total procedures (successful and aborted) in Ablation Management subjects	183
Medical Management Crossover Subjects (N=43)	
Crossover index procedures	43
Crossover retreatment procedures attempted	13[c]
Crossover retreatment procedures aborted	1[c]
Total procedures	**239**

[a] One subject had an aborted procedure upon discovery of a hemizygous vein and was withdrawn; one subject received two index procedures since the first index procedure was aborted due to the occurrence of cardiac tamponade after the transseptal puncture prior to insertion of investigational catheters.
[b] One subject had an aborted retreatment ablation procedure prior to investigational catheter deployment due to a drop in the subject's blood pressure and the appearance of ST elevation. This subject never had a second retreatment procedure and continued follow-up visits for the index procedure.
[c] One crossover subject had an aborted retreatment procedure due to patent foramen ovale and a clot that was found in the femoral sheath prior to investigational catheter deployment.

Chronic safety consisted of serious adverse events that occurred from the date of randomization through 6 months of follow-up (prior to crossover) for the 72 Medical Management subjects. All serious safety events for 138 Ablation Management subjects were reported through study completion and included serious and device and/or procedure related events whether they occurred after an index or retreatment procedure. However, serious adverse events that occurred ≤7 days after any ablation procedure were reported as acute safety and not chronic safety events.

4.4. EFFECTIVENESS ENDPOINT ANALYSIS AND OUTCOMES

The primary endpoint for chronic effectiveness was the evaluation of the proportion of ITT subjects (excluding data obtained from Medical Management subjects after they crossed over) with treatment success computed at the 6-month visit. There were a total of 138 subjects randomized to Ablation Management and 72 subjects to Medical Management.

4.4.1. Primary Effectiveness Analysis and Outcome

The primary effectiveness endpoint was defined by the following criteria:

1. Both Ablation and Medical Management subjects were required to achieve a ≥90% reduction in clinically significant AF/AFL based on a 48-hour Holter recording obtained at baseline and 6 months post-treatment. Clinically significant AF/AFL was defined as a sustained (symptomatic or asymptomatic) AF/AFL episode lasting ≥10 consecutive minutes in duration. The cumulative time of AF/AFL episodes lasting 10-minutes or longer as detected on a 6-month Holter were evaluated for ≥90% reduction when compared to the baseline Holter.

2. Ablation Management subjects were also required to be off all Class I or III AADs at the 6 month follow-up. If a subject required the use of an AAD after their ablation procedure, the

AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

3. Ablation Management subjects were also required to have acute procedure success (both index and retreatment). An Ablation Management subject was considered acutely successful if all of the following were true:

a. Medtronic ablation catheters were used to achieve procedural success.
b. All accessible pulmonary veins were isolated.
c. CFAEs were mapped and eliminated using Medtronic ablation catheters.
d. Sinus rhythm was achieved upon leaving the electrophysiology lab (± direct current cardioversion).

4.4.2. Outcome

The proportion of subjects considered primary efficacy treatment successes (meeting all success criteria) was 55.8% (77 of 138 subjects) for the Ablation Management arm and 26.4% (19 of 72 subjects) for the Medical Management arm, yielding an absolute percentage point difference of 29.4% that was statistically significant ($p<0.0001$, Chi-Squared test) to meet the primary effectiveness objective (**Table 4**). The passive imputation technique requires that missing endpoints be counted as failures.

If analyzed using only subjects receiving an ablation (excluding the 6 subjects not receiving ablation and excluded from the analysis), the proportion of subjects considered treatment successes was 58.3% (77 of 132 subjects).

Table 4. Primary Effectiveness Outcome: The Proportion of Subjects with Treatment Success at 6-Months, ITT Population

Chronic Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)	Medical Mgmt. N=72 n (%)	p-value for H_0: $P_A \leq P_M$[a]
Subjects receiving an ablation with the System	132 (95.7%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	
Subject off all AADs at 6 month follow-up[b]	95 (68.8%)	N/A	
≥90% reduction in clinically significant AF[c]	93 (67.4%)	19 (26.4%)	
Subjects meeting all success criteria	**77 (55.8%)**	**19 (26.4%)**	**<0.0001**
Number of Missing Endpoints[d]	17	15	

[a] Chi-Squared test
[b] Clinically significant AF was defined as a sustained AF/AFL episode lasting longer than 10 consecutive minutes in duration.
[c] Ablation Management success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording to be considered for treatment success.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

4.4.3. Additional Effectiveness Outcome Analyses Requested by FDA

Although the primary efficacy endpoint at 6 months was met using protocol-defined success criteria, the FDA requested additional efficacy outcome analyses as well:

- TTOP-AF effectiveness for those subjects who had **no episodes** of continuous AF/AFL ≥30 seconds at 6 months.
- TTOP-AF effectiveness for those subjects at 12 months who were 6-month treatment successes including crossovers.

4.4.4. Outcome for 6-Month Effectiveness Using the Absence of Any 30 Second AF/AFL Episode

Effectiveness was evaluated for those subjects who had no episodes of continuous AF/AFL ≥30 seconds (**Table 5**). If an episode of AF/AFL on a 48-hour Holter lasted ≥30 seconds, the subject was considered an efficacy failure. Using this criteria, 70 (50.7%) Ablation Management subjects versus 19 (26.4%) Medical Management subjects were considered treatment successes. The resulting 24.3% difference in favor of Ablation Management was clinically significant (p=0.0007, Chi-Squared test).

If analyzed using only subjects receiving an ablation (excluding the 6 subjects not receiving ablation and excluded from the analysis), the proportion of subjects considered treatment successes was 53.0% (70 of 132 subjects).

Table 5. The Proportion of Subjects with Treatment Success at 6 Months Using the Absence of Any 30-Second AF/AFL Episodes, ITT Population

Chronic Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)	Medical Mgmt. N=72 n (%)	p-value[a]
Subjects receiving an ablation with the System	132 (95.7%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	
Subject off all AADs at 6 month follow-up[b]	95 (68.8%)	N/A	
No 30 second AF episodes	85 (61.6%)	19 (26.4%)	
Subjects meeting all success criteria	**70 (50.7%)**	**19 (26.4%)**	**0.0007**
Number of Missing Endpoints[c]	17	15	

[a]Chi-Squared test
[b] Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording in order to be considered successful.
[c] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

4.4.5. Outcome for 12-Month Effectiveness of 6-Month Treatment Successes

The FDA requested 12-month efficacy data for all subjects considered 6-month treatment successes. During the course of the TTOP-AF trial, 43 Medical Management subjects crossed over to receive an ablation. Although these subjects were 6-month treatment failures for the

Medical Management effectiveness determination (calculated prior to crossover), 12-month data was obtained from the ablated Crossover subjects and analyzed with the 12-month data obtained from Ablation Management subjects for determination of 12-month effectiveness. There were a total of 173 subjects who received an ablation or crossover ablation using the System (this excluded 3 subjects whose procedures were aborted prior to deployment of the System). Of the 173 subjects, 99 were treatment successes at 6 months. Twelve-month Holters were collected on 62 of the 6-month treatment successes. Twelve (12) of the 19 subjects who were 6-month treatment successes in Medical Management provided Holters at 12-months for evaluation of efficacy. The same 6-month primary effectiveness endpoint methodology (defined in Section 4.4.1) was used to evaluate 12-month effectiveness.

Of the ablated subjects that were treatment successes at 6 months, 50 of the 62 ablated subjects met the effectiveness endpoint criteria at 12-months (**Table 6**). All 12 subjects who were treated with medical therapy were treatment successes at 12-months.

Table 6. The Proportion of Subjects with Treatment Success at 12-Months Using 12-Month Reduction of Cumulative 10-Minute AF/AFL Episodes for 6-Month Treatment Successes

Efficacy Success Criteria	Ablation Management Subjects (N=48)	Ablated Crossover Subjects (N=14)	All Ablated Subjects (Ablation Mgmt. + Crossovers) (N=62)	Subjects Not Ablated (Medical Mgmt.) (N=12)
≥90% reduction of 10-minute AF episodes without AAD	39 (81.3%)	11 (78.6%)	50 (80.6%)	N/A
≥90% reduction of 10-minute AF episodes with AAD	N/A	N/A	N/A	12 (100%)

The proportion of subjects considered treatment successes at 6 months for the combined Ablation Management and Medical Management Crossover population was 57.2% (99/173 subjects). Of the 62 ablated subjects with 12-month data, 50 were considered treatment successes without an AAD. The extrapolated 12-month efficacy result for ablated subjects was 46.1% (50/62 x 99/173). In comparison, the extrapolated 12-month success rate for Medical Management was maintained at 26.4% (same as the 6 month treatment success rate) since 100% of the Medical Management subjects were treatment successes at 12 months (12/12 x 19/72). Although the extrapolated 12-month success rate demonstrated a slight drop in efficacy from the 6-month rate, these results are impressive considering the significant AF burden (100% continuous AF) these subjects had at baseline.

4.4.6. Additional Effectiveness Evaluations

Medtronic understands that the efficacy results for catheter ablation in the persistent AF patient population is relatively unknown. As this was the first randomized, controlled clinical trial using

ablation in the persistent AF population, Medtronic conducted ad hoc analyses, in addition to those requested by FDA. The impact on Quality of Life (QoL) was also evaluated.

The efficacy evaluations explored in this section include:

- The effectiveness outcome results for 6-month treatment successes using reduction of cumulative 30-second AF/AFL episodes.
- The effectiveness outcome at 12-months for all subjects who provided 12-month data.
- The effectiveness of ablation in conjunction with the use of AADs at 6 and 12 months.
- The effect on QoL using AF Symptom Severity Scores and QoL Measures.

4.4.7. Outcome for 6-Month Treatment Effectiveness Using ≥90% Reduction of Cumulative 30-Second AF/AFL Episodes

The efficacy of the System for treating drug refractory, symptomatic, persistent AF was just as effective at reducing AF/AFL burden based on 30-second AF/AFL episodes as it was at reducing burden based on 10-minute AF/AFL episodes (**Table 7**). Ablation treatment was 29.4% absolute percentage points more effective over treatment with medical therapy, with 77 of 138 Ablation Management subjects (55.8%) achieving Treatment Success over 6 months of follow-up, compared to 19 of 72 Medical Management subjects (26.4%) ($p<0.0001$, Chi-Squared test).

Table 7. The Proportion of Subjects with Treatment Success at 6-Months Using Cumulative 30-Second AF/AFL Episodes, ITT Population

Chronic Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)	Medical Mgmt. N=72 n (%)	p-value[a]
Subjects receiving an ablation with the System	132 (95.7%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	
Subject off all AADs at 6 month follow-up[c]	95 (68.8%)	N/A	
≥90% reduction in clinically significant AF/AFL[b]	93 (67.4%)	19 (26.4%)	
Subjects meeting all success criteria	**77 (55.8%)**	**19 (26.4%)**	**<0.0001**
Number of Missing Endpoints[d]	17	15	

[a] Chi-Squared test
[b] Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording in order to be considered successful.
[c] Clinically significant AF was defined as a sustained AF/AFL episode lasting ≥30 consecutive seconds in duration.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

4.4.8. Outcome for 12-Month Effectiveness Evaluated with All 12-Month Data

Although the TTOP-AF protocol defined a 6 month follow-up and effectiveness endpoint, the FDA requested efficacy analysis based on 12-month data. At FDA's request, every attempt was made to obtain 12-month follow-up data for all TTOP-AF pivotal subjects. All TTOP-AF randomized subjects were asked to consent to a 12-month visit and provide a 48-hour Holter for efficacy evaluation.

The outcome of the Holter requests at 12 months is summarized in **Table 8**. A total of 95 Holters were obtained at 12 months from subjects that had been ablated during the TTOP-AF study, consisting of 71 Holters from Ablation Management subjects and 24 Holters from Medical Management subjects that crossed over to receive an ablation. Another 12 Holters were obtained from Medical Management subjects that did not crossover to receive an ablation and continued treatment with AADs and DC cardioversions within the 6 to 12 month period. The remaining 103 subjects either withdrew from the study (23 subjects), refused to participate or the site refused to participate (67 subjects), or a 12 month visit was completed but no Holter obtained (13 subjects). Although 210 subjects participated in the TTOP-AF pivotal portion of the trial, 107 subjects were willing to undergo the required testing for evaluation of 12-month efficacy.

Table 8. Outcome of 12-Month Holter Requests

Outcome of Holter Request	Ablation Mgmt. (Ablated) N=138	Medical Mgmt. Crossovers (Ablated) N=43	Medical Mgmt. (No Crossovers) N=29	Total N=210
Subjects withdrawn	13	4	6	23
Subject/Site Refusal	46	12	9	67
Visit done, Holter not completed	8	3	2	13
Holters Completed	**71**	**24**	**12**	**107**

Long-term efficacy for the TTOP-AF trial was evaluated from all data obtained at 12 months. A total of 67 ablated subjects had a ≥90% reduction in cumulative time of ≥ 10 minute AF/AFL episodes and who were off all AADs at 12 months (regardless of their status at 6 months) (**Table 9**). This resulted in a 70.5% (67/95 subjects) 12-month effectiveness success rate, which was 13.3% absolute percentage points higher than the 6-month effectiveness rate for the combined Ablation Management and Crossover population (57.2%).

All 12 subjects that were treated with medical therapy during TTOP-AF and the post-study period achieved ≥90% reduction in clinically significant AF/AFL at 12-months. Therefore, the 12-month success rate remained at 100% of subjects who were successes at 6 months (12 subjects). This high rate of efficacy is not truly reflective of the 12 month success rate since the majority of subjects (59.7%) that failed Medical Management crossed over to receive an ablation (43 of 72 Medical Management subjects) and are unable to be evaluated for success with medical therapy at 12 months since they were treated by ablation. The 6-month success rate (26.4%) was maintained for those subjects treated with medical therapy during the 6 to 12 month post-study period, which resulted in a 33.3% absolute percentage point difference when compared to the effectiveness of ablation at 12 months.

Table 9. The Proportion of Subjects with Treatment Success at 12-Months

	Ablation Subjects (Ablation Mgmt.+Crossovers) with 12-Month Data Obtained…					Medical Management Subjects with 12-Month Data Obtained…		
Chronic Efficacy Success Criteria at 12 months	And also 6 Month Treatment Successes N=62			And also 6 Month Treatment Failures N=33	All 12-Month Successes[a] N=95 n (%)	And also 6 Month Treatment Successes N=12	And also 6 Month Treatment Failures N=0	All 12-Month Successes N=12 n(%)
	Randomized (n=48)	Crossover (n=14)	Total (n=62)					
Without AAD	39	11	50 (80.6%)	17	67 (70.5%)	0	0	0
With AAD						12	0	12 (100%)

[a] The "All 12-Month Successes" consists of those subjects who were treatment successes at 12 months regardless of their treatment status (success or failure) at 6-months.

4.4.9. Effectiveness of Ablation in Conjunction with AADs

Although not considered a treatment success for endpoint analysis, the benefit of using an AAD to manage AF/AFL recurrence for ablated subjects was analyzed since all TTOP-AF subjects were drug refractory at enrollment (**Table 10**). Sixteen (16) subjects achieved ≥90% reduction of the cumulative time for both 10-minute and 30-second AF/AFL episodes, with the help of an AAD at 6 months. If these 16 additional subjects were now considered successes and added to the 77 subjects considered treatment successes without the use of an AAD, a total of 93 of 138 (67.4%) Ablation Management subjects benefited from ablation regardless of whether 10-minute or 30-second AF/AFL episodes were used to evaluate efficacy. If analyzed in using only subjects receiving an ablation, the proportion of subjects considered treatment successes was 70.4% (93/132 excluding the 6 subjects who did not receive an ablation using the Medtronic catheters).

TTOP-AF effectiveness was also evaluated for those subjects who had no episodes of AF/AFL ≥30 seconds at 6 months. Another 15 subjects had **no** ≥30 second AF/AFL episodes with the help of an AAD at 6 months. If these 15 additional subjects were now considered successes and added to the 70 subjects considered treatment successes without the use of an AAD, a total of 85 of 138 (61.6%) Ablation Management subjects benefited from ablation. Although these 15 subjects did not meet the primary effectiveness criteria for the study, they benefited from ablation as an AAD was now effective in managing their AF.

If analyzed using only subjects receiving an ablation (excluding the 6 subjects not receiving ablation and excluded from the analysis), the proportion of subjects considered treatment successes was 64.4% (85/132).

Finally, the benefit of using an AAD on the effectiveness outcome was evaluated at 12-months. Another 8 ablated subjects could effectively manage their AF when using an AAD at 12-months to achieve ≥90% reduction in the cumulative time of ≥10-minute episodes of AF/AFL. If these

subjects were also considered successes, the resulting efficacy rate at 12-months was 78.9% (75/95 subjects).

Although ablated subjects using an AAD to help manage their AF were not considered treatment successes for determination of the TTOP-AF primary effectiveness endpoint, subjects clearly benefited from the use of an AAD no matter which endpoint measurement was used for determination of effectiveness. These data are strong efficacy results considering the advanced state of AF and the drug refractory status at enrollment for this subject population.

Table 10. The Proportion of Subjects with Treatment Success for Ablated Subjects with and without the Use of an AAD Using Multiple Endpoint Criteria at 6 and 12 Months

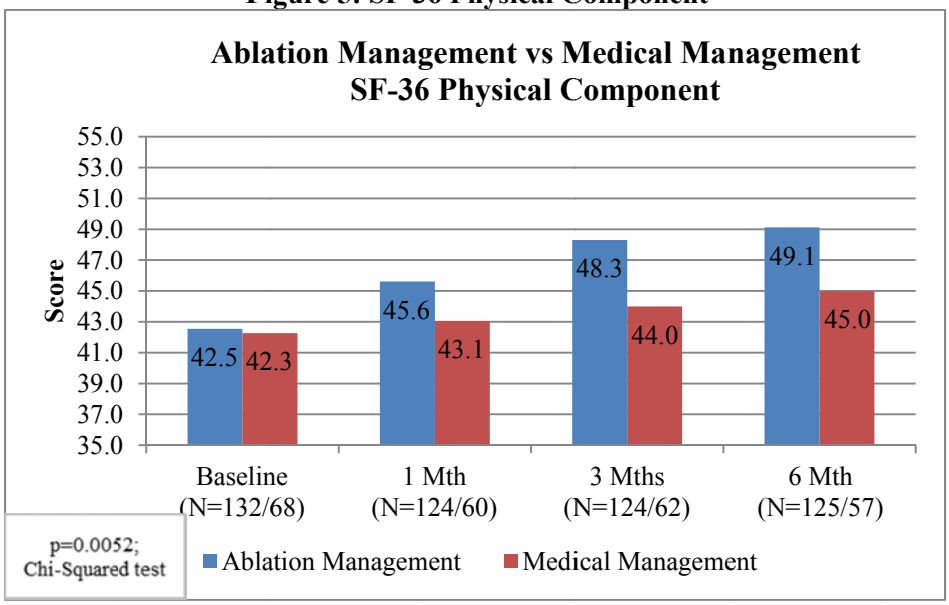
Effectiveness Endpoint Criteria	Number of Treatment Successes without an AAD	Number of Treatment Successes with an AAD	Total Treatment Successes (± AAD)	Total Treatment Successes (± AAD) for Only Subjects Treated with the System
Effectiveness at 6 months, N=138				**N=132**
≥90% reduction of cumulative 10-minute AF/AFL episodes	77	16	93 (67.4%)	93 (70.4%)
≥90% reduction of cumulative 30-second AF/AFL episodes	77	16	93 (67.4%)	93 (70.4%)
No ≥30 second AF episodes	70	15	85 (61.6%)	85 (64.4%)
Effectiveness at 12 months N=95				
≥90% reduction of cumulative 10-minute AF/AFL episodes	67	8	75 (78.9%)	

AF Symptom Severity and Quality of Life Outcomes

The SF-36 QoL questionnaire is an accepted instrument to measure the impact of therapy on a subject's physical and mental well-being. Validation of the SF-36 QoL has demonstrated that a change of 5 points or more is clinically meaningful and indicative of a positive impact by a given treatment[22]. The TTOP-AF trial utilized the SF-36 QoL questionnaire to determine the impact of Ablation Management or Medical Management of persistent AF on the physical and mental well-being of randomized subjects.

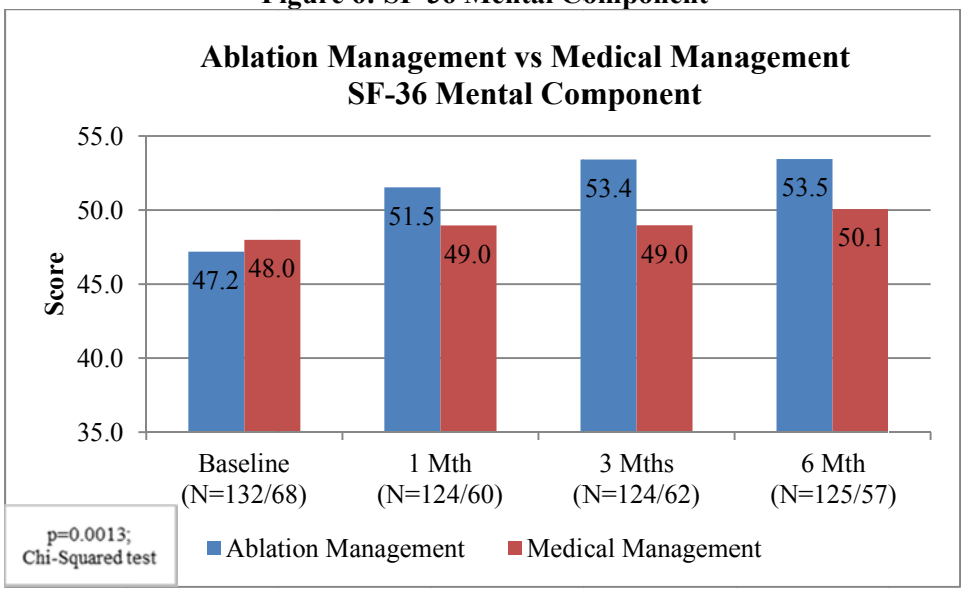
The Ablation Management subjects had clinically meaningful changes in their physical well-being (6.6 point improvement) as opposed to the Medical Management subjects (2.7 point improvement) (**Figure 5**).

Figure 5: SF-36 Physical Component



Similar results were seen in the mental component of the SF-36 QoL in the Ablation Management subjects (6.3 point improvement) compared to Medical Management subjects (2.1 point improvement) (**Figure 6**).

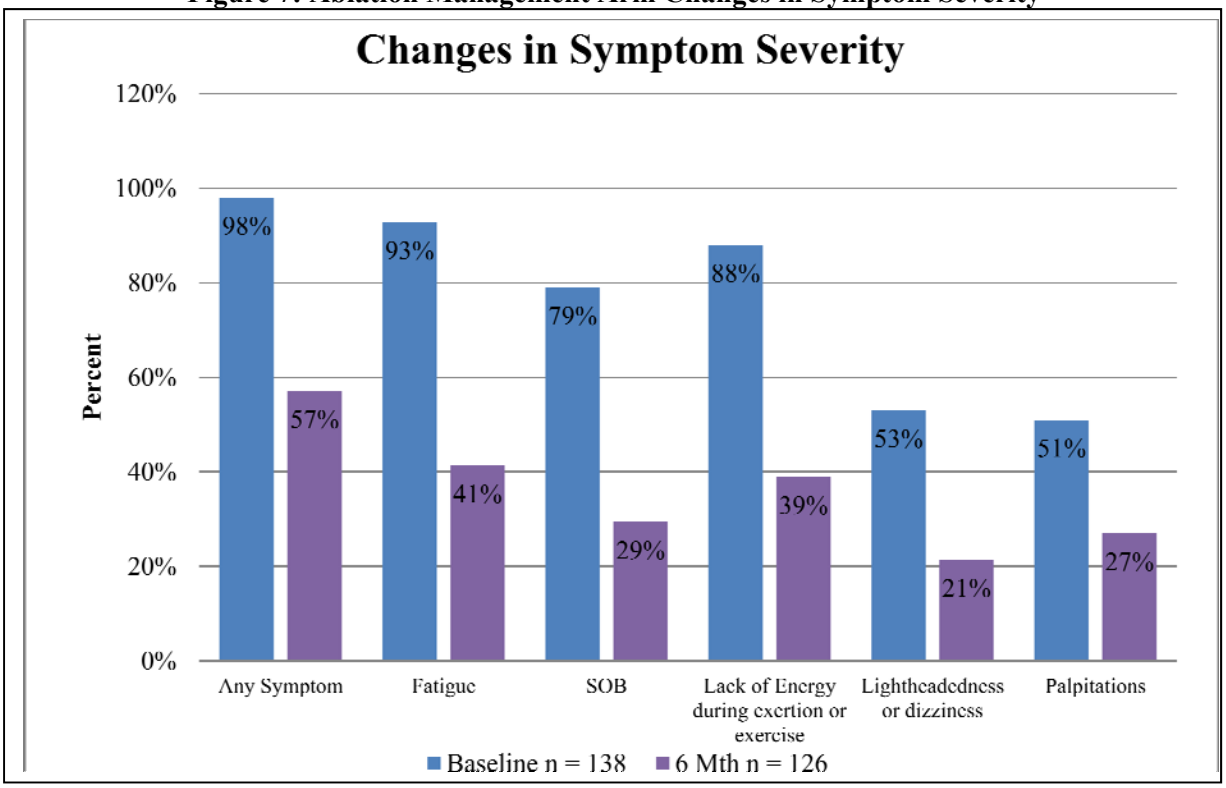
Figure 6: SF-36 Mental Component



These data demonstrate that the Ablation Management subjects had clinically improved physical and mental well-being due to Ablation Management unlike the Medical Management group that did not demonstrate a clinical improvement in physical or mental well-being.

The SF-36 QoL scores are corroborated by the changes in symptoms related to AF. **Figure 7** below illustrates the changes in symptoms from baseline compared to 6 months for the Ablation Management subjects. Nearly all Ablation Management subjects reported an AF related symptom (98%) at baseline and at 6-months the proportion of Ablation Management subjects with an AF symptom had been reduced to 57%, which was statistically significant (p<0.0001).

Figure 7: Ablation Management Arm Changes in Symptom Severity



4.5. Safety Endpoint Analysis and Outcomes

The safety of treating subjects with persistent AF using the System was studied in the TTOP-AF pivotal trial using two Primary Safety Outcome measures, Acute and Chronic Safety.

4.5.1. Acute Safety Analysis and Outcome

Acute safety was the proportion of subjects with at least one serious procedure and/or device-related adverse event (AE) reported within 7 days of an ablation procedure for subjects randomized to the Ablation Management arm.

The primary endpoint for acute safety was a success/failure variable calculated for each subject in Ablation Management at the 7-day post-procedure time point. Any subject with at least one AE adjudicated by the Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB) as both serious and either probably or definitely procedure and/or device-related occurring within 7 days of the ablation procedure was considered an acute safety failure, regardless of whether the event occurred following the index or retreatment ablation procedure.

The statistical analysis of the acute safety endpoint consisted of a comparison of the proportion of Ablation Management subjects failing to complete the 7-day post-procedure period without a serious adverse device and/or procedure related event and a historical control serious AE rate. An acceptable safety endpoint target value was based on a review of literature (dated between 2001 and 2006) consisting of a meta-analysis evaluating safety associated with left atrial AF ablation and on review of approved ablation procedures for right-sided atrial flutter. Using the information obtained from the literature review, a historical control maximum rate for serious AEs was defined at 16%, as this was the highest approved one-sided 95% confidence bound allowed for a right-sided and PAF procedures.

The acute safety objective was determined with a protocol-specified ITT analysis using an exact, one-sample binomial test at a one-sided α=0.025 level of significance. The hypothesis was that the proportion of acute safety failures in Ablation Management would be statistically significantly lower than the objective performance criterion of 16%:

$$H_o: p_A \geq 0.16 \text{ vs. } H_a: p_A < 0.16$$

where pA = the proportion of acute safety failures in Ablation Management.

Outcome: The proportion of Ablation Management subjects with one or more acute serious procedure and/or device-related AEs was 12.3% (17/138 subjects) (**Table 11**). There were 6 subjects who did not receive ablation treatment. The upper bound of the two-sided, 95% confidence interval was 19.0%, which exceeded the pre-specified performance goal of 16% (p=0.1427, Exact Binomial). Therefore, the Acute Safety objective was not met.

Table 11. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial confidence Interval	(7.3%, 19.0%)
p-value[a] of H_0: Rate ≥16%	0.1427

[a] One-sided p-value for exact one-sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

There were a total of 21 serious AEs experienced by 17 Ablation Management subjects that were adjudicated and classified by the CEC/DSMB (**Table 12**). All 21 events were adjudicated as being probably or definitely related to the procedure. No acute events were adjudicated as being probably or definitely related to the investigation devices.

Table 12. Acute Safety Serious Adverse Events for Ablation Management

Description of Events	Number of Primary Acute AEs N=138 n (%)
Probably or Definitely Related to the System	
No events	0 (0.0%)
Probably or Definitely Related to the Procedure	
Stroke	4 (2.9%)
Heart failure[a]	2 (1.4%)
Cardiac tamponade	2 (1.4%)
Pseudoaneurysm	2 (1.4%)
Pulmonary infiltrates with fever	2 (1.4%)
Drop in Hct secondary to ablation	1 (0.7%)
Anesthesia reaction	1 (0.7%)
UTI with prolonged hospitalization	1 (0.7%)
Hypotension secondary to cardiac tamponade	1 (0.7%)
Hypotension/cardiogenic shock	1 (0.7%)
Pneumonia	1 (0.7%)
Acute respiratory failure	1 (0.7%)
Retroperitoneal bleed with right ureter obstruction	1 (0.7%)
Post-procedure pericarditis	1 (0.7%)

[a] One of the heart failure subjects succumbed to death within 24 hours of receiving a retreatment ablation procedure. No investigational catheters were deployed during the procedure.

4.5.2. Relevant Acute Safety Comparator

During the development of the TTOP-AF study little was known about acute safety procedure event rates for the persistent AF population. The acute safety performance criterion of 16% was determined based on a literature review of right-sided ablation and ablation of PAF. This comparator may underestimate the safety events that could be expected in the TTOP-AF study for two reasons: 1) TTOP-AF was designed to include all serious procedure and device related adverse events within 7 days of procedure as opposed to a pre-specified list of events. 2) The persistent AF population is at higher risk of events than the PAF population due to the complexity of the procedures and the advanced disease state.

4.5.3. Chronic Safety Analysis and Outcome

The TTOP-AF trial was designed knowing that chronic safety would be difficult to assess due to the anticipated demand for subjects in Medical Management to cross over to receive an ablation in order to obtain relief from symptoms associated with AF and/or its treatment. Given the disparity in the length of time at risk, the Chronic Safety endpoint was not statistically powered as the Medical Management subjects were allowed to cross over to receive an ablation as early as 4 months.

Although not statistically powered, every attempt was made to obtain chronic safety events for all subjects in both treatment arms. All serious adverse events adjudicated by the CEC/DSMB are shown in **Table 13**. There were 10 serious AEs adjudicated as either probably or definitely related to the procedure and/or device observed in 10 Ablation Management. There were

3 events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the AADs, or events related to AF in 3 Medical Management subjects who did not crossover. Another 4 serious AEs occurred in 4 Medical Management Crossover. Recall that chronic adverse events exclude the first 7 days after an index or retreatment ablation procedure for Ablation Management subjects as these events were reported as an acute safety event. Acute events related to crossover ablations are captured in **Appendix 10**.

Table 13. Serious Chronic Safety Events–Ablation Management

Description of Event	Ablation Mgmt. Events (N = 138) n	Medical Mgmt. Events (Non-Crossover (N = 29) n	Medical Mgmt. Crossover Events (N = 43) n
Pulmonary vein stenosis	5	0	2
Stroke	1	0	0
TIAs	0	0	0
Pulmonary vein narrowing	1	0	0
Persistent ASD secondary to septal puncture	1	0	0
Pericardial effusion	1	0	0
Chest pain secondary to pericarditis	1	0	0
GI bleed	0	2	0
AF with rapid ventricular response	0	1	0
Events related to recurrent AF	0	0	1
Hyperesthesia in right leg and neuropathy	0	0	1
Total Events	**10**	**3**	**4**

Medtronic recognizes that specific chronic safety events associated with the ablation procedure need to be understood to enable physicians and patients to make informed risk/benefit decisions. As demonstrated in other randomized, controlled clinical trials in AF ablation, the significant chronic events associated with ablation consist of atrio-esophageal fistula, pulmonary vein stenosis, stroke, transient ischemic attacks (TIAs), and phrenic nerve injury. There were no observed instances of atrio-esophageal fistula or phrenic nerve injury. Pulmonary vein stenosis, stroke, and transient ischemic attacks (TIAs) are discussed further in **Section 4.5.4.**

4.5.4. Additional Safety Outcome Analyses

Additional information is provided for significant safety events that occurred for all enrolled subjects. There were a total of 72 subjects initially randomized to Medical Management. The

total number of subjects that underwent an ablation procedure (or ablation attempt) was 176 subjects (133 Ablation Management and 43 Medical Management Crossover subjects). Rates per procedure are also provided (the total number of ablation procedures was 239).

Death

One death occurred in a 63 year old male randomized to the Ablation Management arm during the course of the TTOP-AF trial. After meeting initial inclusion criteria the index procedure was performed 3 months later despite a significantly depressed LVEF of 10-15%. The procedure resulted in acute procedural success after receiving one cardioversion during the procedure. At the one month follow up exam, the subject was determined to be in NYHA Class III heart failure presenting with moderate palpitations, severe fatigue, moderate SOB, mild lightheadedness, chest pains, tachycardia, irregular heart rate, AF, positive S3 on auscultation, and severe exercise intolerance. The subject was subsequently scheduled for a retreatment ablation procedure.

Prior to the retreatment ablation 11 days later, a TEE was repeated and showed that the LVEF had increased to 30-35% with moderate mitral insufficiency. After obtaining venous and transseptal access, heparin (5000 units IV) was administered. The first investigational catheter was inserted into the sheath, but before it was advanced or deployed into any cardiac structure, the patient developed acute heart failure with significant hypotension. The subject was intubated, placed on mechanical ventilation and required multiple vasopressor agents to maintain his blood pressure. The following morning during transfer to a tertiary care center for placement of a left ventricular assist device the patient expired. The cause of death was determined to be congestive heart failure. An autopsy was not conducted per the family's request. This event was adjudicated by the CEC/DSMB as definitely related to the procedure but not device-related.

The death rate in ablated subjects in the TTOP-AF trial was 1 in 176 (0.6%).

Procedure-Related Strokes

A total of 5 subjects had strokes which were adjudicated as being related to the procedure during the TTOP-AF trial. Four (4) of the 5 strokes occurred within the first 7 days post-ablation (acute safety event) and one of the 5 strokes developed neuroembolic symptoms approximately 1 month after a retreatment ablation within the chronic period of the study.

Acute Strokes

There were a total of 4 (2.3%, 4/176 subjects) strokes that occurred within the acute period (≤7 days) after an ablation procedure. All 4 subjects who experienced a stroke developed symptoms within 18 hours of the ablation. Two (2) of the 4 subjects had complete resolution of symptoms within the 6-month follow-up period. The other 2 subjects had minor residual effects from the stroke. One subject had unresolved diplopia and disconjugate gaze as of May 2010. The other

subject had slight speech impairment as of March 2010. The acute procedural stroke rate was 1.7% (4/239 procedures).

Baseline AF characteristics were compared for those subjects experiencing an Acute Stroke (n=4) compared to the Non-Stroke subjects (n=133) to determine if a difference in underlying demographic factors existed between the two groups. In order to evaluate the risk factors associated with these strokes, the baseline AF characteristics (**Table 14**), and procedural variables of the patients with and without acute strokes were compared (**Table 15** and **Table 16**). Although there was no statistical difference between the two groups there was a trend for the stroke patients to have higher $CHADS_2$ scores, lower procedural INRs, greater left atrial diameter, and longer procedure times. The key parameters for the 4 acute stroke patients are shown in **Table 17**.

Table 14. Subject Characteristics for Acute Stroke and Non-Stroke Subjects – Ablation Management

Demographics Variable	Ablation Management N=138 Mean ± SD Median (Min, Max)	
	Non-Stroke Subjects N=133[a]	Acute Stroke Subjects N=4
Gender: Male, n (%)	110 (82.7%)	4 (100%)
Age (yrs)	59.6 ± 8.3 61.2 (35.5, 73.4)	58.1 ± 7.7 57.9 (49.1, 67.7)
LVEF (%)	54.5 ± 7.0 55.0 (40.0, 75.0)	61.5 ± 5.1 62.5 (55.0, 66.0)
$CHADS_2$ Score	0.8 ± 0.7 1.0 (0, 3)	1.3 ± 0.5 1.0 (1, 2)
LAD (cm)	4.5 ± 0.5 4.5 (3.2, 5.5)	5.0 ± 0.5 5.0 (4.4, 5.5)

[a] The one subject with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 15. Procedural Anticoagulation for Non-Stroke and Acute Stroke Subjects

Anticoagulation Parameter	Non-Stroke N=133[a] Mean ± SD Median (Min, Max)	Acute Stroke N=4 Mean ± SD Median (Min, Max)
Procedure INR Values (Index Procedure Only)	1.6 ± 0.6 1.3 (0.9, 3.8)	1.2 ± 0.2 1.2 (1.1, 1.5)
Procedure INR Values (Retreatment Procedure Only) N=48	1.6 ± 0.6 1.4 (1.0, 3.7)	N/A
ACT Values During Left Atrial Access (All Procedures)	332.9 ± 35.2 328 (239, 499)	324.9 ± 26.6 319 (302, 360)

[a] The with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 16. Ablation Procedure Dwell Times for Non-Stroke and Stroke Subjects

Ablation Procedure Times	Non-Stroke Subjects N=133[a] Mean ± SD Median (Min, Max)	Acute Stroke Subjects N=4 Mean ± SD Median (Min, Max)
Left Atrial Dwell Time (hrs:min)	2:42 ± 0:48 2:41 (0:20, 5:11)	3:46 ± 1:09 3:38 (2:34, 5:17)
Procedure Time (hrs:min)	3:16 ± 0:53 3:15 (1:18, 5:51)	4:12 ± 1:12 4:04 (2:54, 5:46)

[a] The one subject with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 17. Key Parameters for the Subjects with Acute Stroke

Parameter	Acute Stroke Subject Number			
	1	2	3	4
$CHADS_2$ Score	1	1	2	1
LVEF-Baseline	65%	66%	55%	60%
LAD – Baseline	5.5 cm	5.0 cm	4.9 cm	4.4 cm
Procedure INRs	1.5	1.1	1.2	1.1
Stroke Resolution	Recovered	Unresolved[a]	Unresolved[b]	Recovered

had unresolved diplopia and disconjugate gaze as of May 2010.
had slight speech impairment as of March 2010.

The risk profile of each of the acute stroke patients makes them more susceptible to a thromboembolic event. Apart from the risk factors illustrated in **Table 17**, there are other factors that may also have contributed to these neuroembolic events. They are:

1. *Subject population in TTOP-AF*: All subjects in the TTOP-AF subject population had persistent AF and this could have contributed to observed rate of embolic complications. Such rates have been observed in persistent AF patients undergoing ablation. A large study with

retrospective analysis of 3060 patients indicated a stroke rate of 1.8% in ablated patients with persistent AF or long-standing persistent AF as compared to 0.2% in patients with PAF[24].

2. *Learning curve*: As noted with acute safety (see **Section 5** below)**,** the stroke incidence was higher for the first few subjects undergoing an ablation procedure rather than for subjects enrolled later at each site. Three (3) of the 4 acute strokes occurred during the first 5 procedures for each investigator. As was seen with the overall procedural complications, these data may suggest that increased operator technical experience with using the System may decrease the overall stroke rate.

3. *Anticoagulation*: Case report data suggests that 2 of the 4 patients may not have had adequate anticoagulation coverage during their "bridging". It is important to ensure that subjects are protected with Lovenox or IV heparin during the period when warfarin is discontinued and reinitiated. Recent publications indicate that a strategy of uninterrupted warfarin may confer even more protection against thromboembolic events, especially in the post ablation period when most patients are vulnerable while waiting to achieve therapeutic INRs[25,26].

Chronic Stroke:

One stroke occurred within the follow-up period for an Ablation Management subject. This subject underwent an acutely successful ablation and a retreatment ablation 3 months later due to AF recurrence. One month after retreatment, the subject complained of diminished bilateral peripheral vision. The subject had an extensive history of eye complaints related to his diabetes. As the subject continued to experience symptoms, an MRI scan was completed on June 8, 2009 which showed an old infarct in the left occipital region and chronic changes suggestive of small vessel ischemia. Although this was reported as a chronic event one cannot rule out the possibility of an acute event, which would place the subject acute event rate at 5 in 176 (2.8%). This event was adjudicated as being probably related to the ablation procedure and possibly related to the device.

TIAs

Although two TIAs occurred in Medical Management Crossover subjects during the trial, only one (0.6%, 1/176) was adjudicated as device/procedure-related.. This subject developed numbness in the corner of his mouth within 72 hours of the procedure. The numbness resolved without treatment after 72 hours of initial symptoms. The procedural TIA rate was 0.4% (1/239 procedures). The FDA considers the second TIA as probably or definitely procedure-related although it was previously adjudicated by the CEC/DSMB as related to underlying disease.

Cardiac Tamponade

There were 3 (1.7%, 3/176 subjects) instances of cardiac tamponade reported during the course of the study. Two (2) of the tamponade events occurred in Ablation Management subjects within the acute period, while the third event occurred in a Medical Management Crossover subject. One of the Ablation Management tamponade events happened after the sheaths were placed and the transseptal puncture was completed without difficulty. When the RSPV was injected as part

of pulmonary vein venography, there was the appearance of staining and contrast in the pericardial space. An echocardiogram demonstrated a growing pericardial effusion and the procedure was terminated. The second tamponade event in an Ablation Management subject occurred during the transseptal puncture. There were documented blood pressure changes when performing the transseptal puncture, a cardiac tamponade was diagnosed and the ablation procedure was aborted. Note that these 2 Ablation Management subjects did not have an investigational catheter deployed during these events and they fully recovered shortly after the procedures. Both tamponade events were adjudicated as being definitely related to the procedure.

The third subject (Medical Management Crossover) had an acutely successful ablation procedure, but experienced hypotension several hours after the ablation procedure. After draining the pericardial effusion, the subject remained stable and was discharged 9 days post-ablation. This event was adjudicated as being definitely related to the procedure and possibly related to the device.

The overall procedural tamponade rate was 1.3% (3/239 procedures).

Pulmonary Vein Stenosis

CT/MRI imaging was used to detect pulmonary vein stenosis in the TTOP-AF trial. Baseline and 6 month post ablation procedure scans were compared to assess for pulmonary narrowing (50% - 70% reduction in PV diameter) or stenosis (>70% in PV diameter). Pulmonary vein stenosis was noted in 7 (4.0%, 7/176) subjects involving one vein. Five (5) of the 7 subjects were in Ablation Management and the remaining 2 were Medical Management Crossover subjects. Only 1 of the stenosis subjects experienced symptoms and required an intervention. The remaining 6 subjects were asymptomatic. The procedural stenosis rate was 2.9% (7/239 procedures).

Esophageal Perforation, Atrio-Esophageal Fistula, Phrenic Nerve Injury

There were no reported instances of esophageal perforation, atrio-esophageal fistula or phrenic nerve injury noted during the study.

5. Risk / Benefit Assessment

The TTOP-AF pivotal clinical trial was undertaken to assess the safety and effectiveness of the System compared to medical management. The results of the TTOP-AF trial demonstrate that the System consisting of the GENius generator and 3 ablation catheters (PVAC, MAAC, and MASC) met the protocol-specified effectiveness endpoint with an acceptable safety profile. It provides significant reduction in AF burden and therefore "rhythm control" as compared to medical management to treat drug-refractory, symptomatic persistent AF patients who have poor quality of life and are at increased risk for stroke[8], hospitalizations[17], dementia[7], and death[7,11].

Benefits:
All patients in the study had 100% continuous AF at the beginning of the trial. 55.8% of the ablated subjects had ≥90% reduction in burden at six months as opposed to 26.4% patients treated with medical management. This difference was statistically significant. Importantly, the key concern of this patient group is their poor quality of life and symptoms as reflected by their baseline data. Presently this is the primary justification for conducting AF ablation. There was clinically significant improvement in mental and physical "quality of life" of the ablated subjects from baseline as the difference was greater than 5 points at six months. The symptoms of the ablated patients improved as well from baseline and this difference was significant.

Although not investigated in this study, the long term benefit of maintaining rhythm control has been well discussed in the literature[4,13]. The AFFIRM data indicates that sinus rhythm was associated with significant reduction in mortality whereas the use of antiarrhythmic drugs increases mortality by 49%. The beneficial antiarrhythmic effect of the drugs in maintaining sinus rhythm is offset by their adverse effects. The DIAMOND trial also showed that the presence of sinus rhythm was associated with improved survival[4]. Therefore, the antiarrhythmic drugs not only provide insufficient short term improvements in QoL and symptoms as our data indicates, they have the potential for long term harm in this patient population.

Risks:
As with most invasive cardiac procedures, there are risks associated with this ablation procedure. There was higher than hypothesized acute adverse event rate including 4 acute strokes. Two of the 4 strokes have had complete resolution of their symptoms.

The higher stroke rates may be due to the following factors:

(a) Persistent and long-standing AF: As mentioned in **Section 4.5.4,** all subjects in the TTOP-AF patient population had persistent or long standing persistent AF and this could have contributed to the higher rate of embolic complications as compared to patients ablated for PAF. A large study with retrospective analysis of 3060 patients indicated a

stroke rate of 1.8% in ablated patients with long-standing persistent AF as compared to 0.2% in patients with PAF[28]. In their multivariate analysis, long-standing persistent AF was the only predictor of cerebral thromboembolic events with a hazard ratio 3.7.

(b) Learning curve: An assessment of the occurrence of procedure or device related serious adverse events at each site for the first 5 subject's versus 6 or more subjects revealed that 14 of the 17 (82.4%) events were experienced by the first 5 subjects treated at each site. Only 3 of the 17 events (17.7%) occurred after the first 5 subjects were treated. This data indicates that there may be a learning curve associated with using the System. As this is a new technology being used by the physicians, we believe that with more comprehensive training, it may be possible to favorably impact this outcome.

(c) The statistical threshold for acute safety outcomes was based on previous trials on PAF and may have been low. Given that this is a patient population which requires a more extensive ablation procedure and has more comorbidities, it is not unreasonable to expect a higher rate of acute safety events.

Based on the data presented, we conclude that the clinical benefits delivered by the System for treatment of drug refractory, symptomatic, persistent and long-standing persistent AF outweigh the risks associated with the use of the device.

Other technology options and their Risk/Benefit:
The other alternatives available to patients with persistent AF are "Ablate and Pace", surgical ablation and off-label catheter ablation. None of these therapies have been studied in randomized trials that were approved by the FDA. Most data with these techniques is based on non-randomized trials.

Ablate and Pace: A frequently used method for management of persistent AF patients that facilitates rate control. It has a high procedural efficacy rate and provides significant improvement in QoL and reduces symptoms as compared to drug management. However, it is associated with sudden death and life threatening arrhythmias early after the procedure [4,17]. In one study, the early complication rate (<30 days) was 4.5% with a late complication rate of 5.1% within the first year. There was a 2.6% stroke rate and an all-cause mortality rate within the first year was 14.7%[17]. Long term, ablate and pace can also reduce LV ejection fraction and cause progressive heart failure.

Surgical ablation: This is used very infrequently in patients with persistent AF unless the patients are undergoing surgery for some other primary reason, e.g. CABG, heart valve etc. This is because of the high mortality and morbidity associated with surgical ablation. The 30-day mortality rate has been reported to be 2.1-4.2%. Stroke and TIA rates between 0.5-1.6% have also been reported.

Off-label use of approved ablation technologies: Off-label use of transvenous systems approved for ablation of PAF has also been reported. Multiple procedure success of 37-77% has been reported with stroke/TIA rates between 0.65 and 2.4%[27,28].

In conclusion, given the higher acute mortality rate with ablate and pace and surgical ablation as well as high morbidity/mortality long term. Medtronic believes that the risk/benefit associated with the System is very favorable as compared to other options available to these patients.

Micro-embolism

There have been recent publications of an increased incidence of silent cerebral micro-embolism with phased RF technology which has raised some concerns about patient safety. It is important to note that none of these ablated patients with micro-embolic lesions had any neurological consequences. A discussion of micro-embolism is included as **Appendix 1** and covers the following:

- Micro-embolism is not a new observation in invasive cardiac procedures or AF ablation and occurs with all ablation technologies.
- Micro-embolism related acute lesions detected on DW-MRI have not been correlated with neurologic deficit or cognitive decline following AF ablation.
- The acute cerebral micro-emboli tend to be small in volume and have not been associated with neurologic deficit or neurocognitive decline with various cardiac procedures.
- When MRI scans are done chronically in AF ablation patients, the acute lesions have been shown to reverse in many patients.

Cerebral micro-embolism lesions have not been associated with any clinical AEs and therefore would not impact the safety endpoint of the TTOP-AF trial.

Risk / Benefit Conclusion

The data in this PMA application supports safety and effectiveness of the System. Medtronic concludes that the clinical benefits delivered by the System for the treatment of drug refractory, symptomatic, persistent AF outweigh the risks of the device when used within the indicated patient population.

Medtronic believes that physician training will improve the safety profile and this will be investigated in the post approval study.

6 Proposed Physician Training Program

Medtronic is experienced in developing effective physician training programs, and will introduce the System with a curriculum designed to ensure safe and effective use. Medtronic will also train allied health professionals (AHP) to support physicians using the System.

Intended for physicians already performing AF ablation, the training program will help operators:

- Understand the technology, theory of operation, and procedure
- Appropriately select patients
- Properly set-up and use the System within approved labeling
- Avoid device and procedural related complications
- Use the technology in challenging anatomy

Refer to **Section 6.1** (of the Executive Summary) and **Table 18** for details on learning objectives & the proposed training plan, which follows a two-step process shown in **Figure 8**.

Medtronic also believes that safety and effectiveness observed in the TTOP-AF trial can be improved by incorporating the latest System-specific practices, as well as recent guidance for AF ablation procedures, into the training curriculum. This information was not available at the time of the trial. The proposed program will address:

Improved Procedure Efficiency

The curriculum will transfer knowledge gained by highly-experienced international operators (100+ cases) to new users. Published data has demonstrated a "learning curve" that is associated with increased device experience that results in (1) reduced procedure and fluoroscopy time, (2) reduced number of RF applications, and (3) increased effectiveness (refer to **Appendix 6**). Specifically, the training program will incorporate:

- Standardized procedure approaches
- Techniques for challenging anatomy
- Interpretation of electrograms unique to the System

Transseptal sheath management to avoid air embolism

Per the HRS Expert Consensus Statement (**Appendix 7**, p 840), the curriculum will incorporate the following training items:

- Vigilantly monitor the transseptal sheath for air ingress
- Insert & withdraw ablation catheters slowly
- Regularly aspirate and flush the transseptal sheath

Peri-procedural anticoagulation to avoid thromboembolic events

Per the HRS Expert Consensus Statement (**Appendix 7**, p 828-829) and 2006 ACC Guidelines (**Appendix 8**, p 861), the curriculum will incorporate:

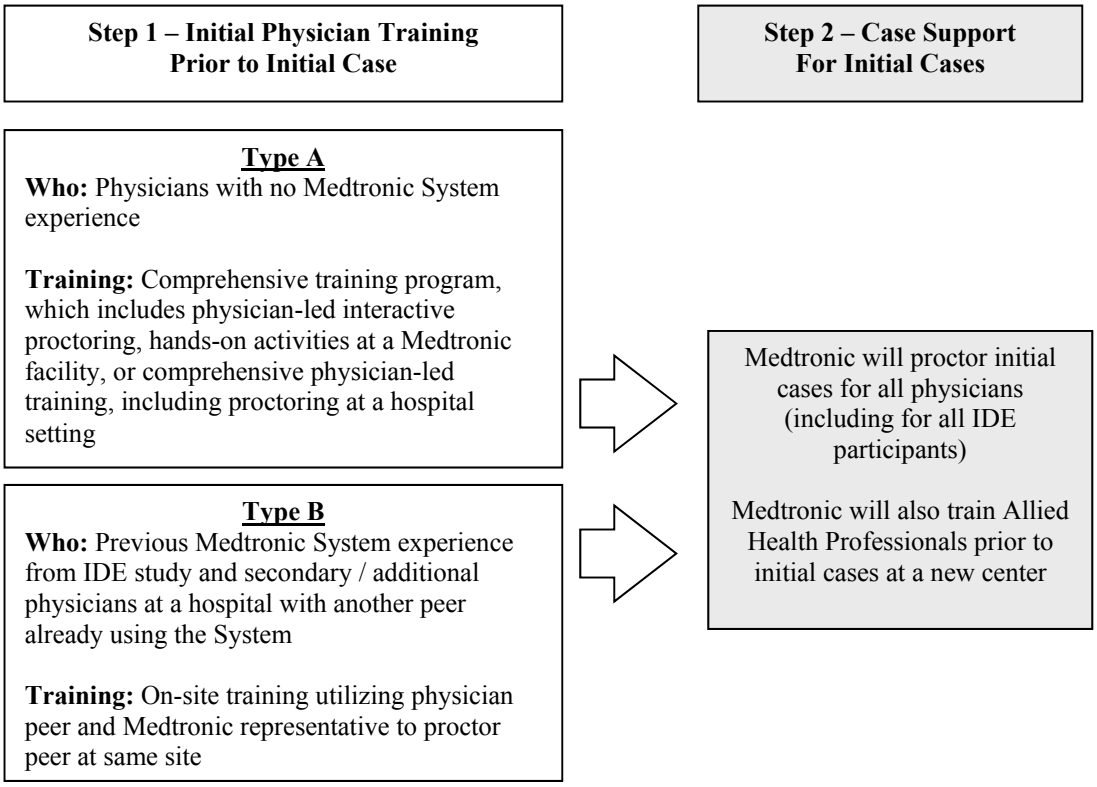
- Transseptal punctures should not be performed prior to achieving an activated clotting time (ACT) of 350s
- Maintain ACT values above 350s during the procedure, with frequent measurement (every 15-30 mins)
- Maintain therapeutic oral anticoagulation prior to, during, and after the ablation procedure

Verification of catheter/electrode position & contact to avoid thrombus formation and inadvertent RF delivery within pulmonary veins (PV)

The curriculum will incorporate that the operator:

- Maintain catheter contact with cardiac tissue by holding the catheter during the ablation.
- Does not reposition, rotate, slide, drag or otherwise intentionally disengage while ablating.
- Avoids RF delivery within a pulmonary vein, by delivering power only at the pulmonary vein antrum.

Figure 8. Medtronic Cardiac Ablation System Physician Training Program



AHP staff that support physician operators will also receive training. Prior to the first procedure, and as needed/requested thereafter, a Medtronic representative will conduct an in-service for AHPs that provides detailed information about their role in supporting physician operators.

Following the initial procedures, ongoing case support will be provided, as needed, by a Medtronic representative.

Throughout this two-part training program, physicians will learn how to safely and effectively use the System as they adopt it into their existing ablation practice.

6.1 Additional Training Program Detail

6.1.1 Qualifications of the Trainers

Physician Trainers:

Medtronic will partner with experienced physicians to help train new physician users. These physician trainers will be experienced with AF ablation procedures, as defined by the HRS Expert Consensus Statement.

In order to qualify, physician trainers must demonstrate proficiency with the System to a Medtronic representative in accordance with all warnings, precautions and instructions for use (IFU). At a minimum, these physicians will have completed 25 cases to have gained the requisite proficiency.

Physicians with extensive System experience from international regions will train new users and US-based trainers. Physicians who participated in the TTOP-AF study, and meet the 25-case minimum, may be targeted as early trainers. As device experience grows, the network of qualified physician trainers will expand.

Medtronic Representatives:

Each Medtronic representative will receive product and procedure training prior to providing case support or in-servicing.

6.1.2 Learning Objectives

The initial physician training program will be constructed around the learning objectives outlined in **Table 18**. During training, physicians will observe the key components of a procedure and participate in a didactic presentation and discussion.

Table 18. Learning Objectives for the System Training Program

Learning Objective	Details
1. Understand the principles of duty cycled phased RF ablation	• Review the differences between standard unipolar ablation versus the unipolar/bipolar duty cycled phased RF operation of the System
2. Understand the theory of operation and procedural overview	• How does the System function and how is it used in a procedure as outlined in the product labeling (IFU) • Emphasis will be placed on the equipment setup, as well as the recommended energy mode settings for pulmonary vein isolation and for ablating complex fractionated atrial electrograms
3. Understand appropriate patient selection	• As per product labeling (IFU) and the HRS Expert Consensus Statement on AF Ablation
4. Reinforce appropriate AF ablation procedural techniques	• As per product labeling (IFU), HRS Expert Consensus Statement, and the 2006 ACC Guidelines. • Attention will be placed on administering peri-procedural anticoagulation to minimize thromboembolic events • Attention will be placed on appropriate sheath management practices, including catheter insertion, deployment, and removal, as well as frequent aspiration and flushing to reduce the risk of air embolism
5. Understand how to properly use the System	• This will be demonstrated according to the product labeling (IFU) by observing key components of the procedure and case review • This will focus on the techniques for mapping, ablating and pacing with the catheters, including catheter placement and interpretation of atrial electrograms • Discussion will also include how to handle challenging anatomy and problem solve a challenging case
6. Understand how to avoid device and procedural complications	• As per product labeling (IFU) and the HRS Expert Consensus Statement • Attention will be placed on appropriate catheter and electrode position/contact, as well as correctly programming the RF generator • Adverse Events that occurred in the TTOP-AF study and international post-market experience will be reviewed, with attention placed on techniques that can minimize thromboembolic events and PV stenosis
7. Understand how to problem-solve the System	• How to manage System messages will be discussed and demonstrated according to the product labeling (IFU or Technical Manual)

Post Approval Study

Medtronic will conduct a Post Approval Study (PAS) to evaluate acute and chronic safety as well as long-term effectiveness, of the System for treating persistent AF. A summary of the PAS is provided in **Section 6** of the panel pack.

Summary and Conclusions

Persistent AF patients have significant symptoms requiring numerous interactions with the healthcare system. In addition persistent AF carries with it a five times greater risk for stroke and two times greater risk for death compared to a normal population.

Persistent AF patients have physiologically different hearts from those in sinus rhythm or paroxysmal AF. As the disease progresses and AF becomes sustained, functional, structural, and electrical changes take place in the heart. These changes complicate efforts to restore and maintain sinus rhythm.

Persistent AF patients need new treatment options. Drug therapy often does not provide adequate rhythm control and brings with it the potential for pro-arrhythmia and toxic side effects. Surgical ablation, while reasonably effective, is highly invasive and usually only prescribed as a concomitant procedure. Ablate and Pace is associated with high mortality rates and renders a patient pacemaker dependent, thus increasing the risk of heart failure.

With the limitations of available options, there is a strong clinical need for effective treatment of persistent AF. The Medtronic System provides effective treatment with an acceptable risk profile.

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Proposed SSED

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I. GENERAL INFORMATION

Device Generic Name:

Medtronic Cardiac Ablation System

Device Trade Names:

Medtronic Cardiac Ablation System (the 'System'), including:
GENius® Multi-Channel RF Ablation Generator (the 'Generator'), and components,
Cardiac Ablation Catheters (the 'Catheters'), including:
Pulmonary Vein Ablation Catheter®, (PVAC®),
Multi-Array Septal Catheter®, (MASC®), and
Multi-Array Ablation Catheter®, (MAAC®).

Table 1. GENius Multi-Channel RF Ablation Generator and Components - Model Numbers

Model Name	Model Number
GENius Multi Channel RF Ablation Generator	990018
Generator Power Cable	990025
ECG Interface Box	990028
Catheter Interface Cable	990004
ECG Amplifier Cable	990020
ECG Interface Box Cable	990027
GENius Jr Remote Control	990029
Remote Control Cable (15' or 25' length options)	990041 (15Ft Cable) 990042 (25Ft Cable)

Table 2. Cardiac Ablation Catheters - Model Numbers

Model Name	Model Number
Pulmonary Vein Ablation Catheter, (PVAC)	990030
Multi-Array Septal Catheter, (MASC)	990001
Multi-Array Ablation Catheter, (MAAC)	990000

Applicant's Name and Address:

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Date of Panel Recommendation: October 27, 2011

Premarket Approval Application (PMA) Number: P100008

Date of FDA Notice of Approval: TBD

Expedited: Yes

II. INDICATIONS FOR USE

The System is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

GENius Multi-Channel RF Ablation Generator

The Generator delivers temperature-controlled radiofrequency (RF) energy to user-selectable electrodes on compatible Medtronic cardiac ablation catheters, including:

- Pulmonary Vein Ablation Catheter (PVAC)
- Multi-Array Ablation Catheter (MAAC)
- Multi-Array Septal Catheter (MASC)

The generator automatically recognizes the attached cardiac ablation catheter and programs preset default temperature, ablation duration, and energy mode setting parameters. Ablation parameters, including ablation duration, energy mode, target temperature, and channels (electrode pairs), can also be manually selected. A display screen monitor is available for viewing real-time system and ablation parameters.

The generator features the following RF energy mode selections: bipolar only, unipolar only, and combination ratios of bipolar: unipolar energy mode selections of 1:1, 2:1, and 4:1.

An ECG interface box connects the catheter with the generator, patient return electrodes, the external monitoring equipment, and the pacing equipment that can be used during the procedure.

See the technical manual for information regarding the catheter being used.

Pulmonary Vein Ablation Catheter (PVAC)

The PVAC is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The PVAC is used for mapping, pacing, and ablating pulmonary vein potentials and verifying electrical isolation of the pulmonary veins post-treatment.

Multi-Array Septal Catheter (MASC)

The MASC is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The MASC is used for mapping, pacing, and ablating arrhythmogenic tissue along the left atrial septum.

Multi-Array Ablation Catheter (MAAC)
The MAAC is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent atrial fibrillation (1 to 4 years).

The MAAC is used for mapping, pacing, and ablating arrhythmogenic tissue in the left atrial body.

III. CONTRAINDICATIONS

The following are excerpts of the Operator Manual (Generator) and Technical Manuals (Catheters) for contraindications.

GENius Multi-Channel RF Ablation Generator
"See the technical manual for the catheter being used."

Cardiac Ablation Catheters (PVAC, MASC, MAAC)
"Use of the PVAC, MASC, and MAAC are contraindicated as follows:

- Active sepsis
- Left atrial thrombus or myxoma
- Atrial Septal Patch or atrial septal defect repair with percutaneous device
- Known sensitivity to heparin
- Blood clotting abnormalities
- Venous filtering device (Greenfield Filter)

The Cardiac Ablation Catheters are not recommended for use in patients who cannot undergo standard anticoagulation protocol for a left-sided cardiac procedure, or who have had a recent coagulopathy or embolic event."

IV. WARNINGS AND PRECAUTIONS

A list of warnings and precautions can be found in the Generator (Operator's Manual), PVAC, MASC, and MAAC labeling (Technical Manuals).

V. DEVICE DESCRIPTION

GENius Multi-Channel RF Ablation Generator

The Generator delivers temperature-controlled RF energy to user-selectable electrodes on the following compatible Medtronic cardiac ablation catheters:

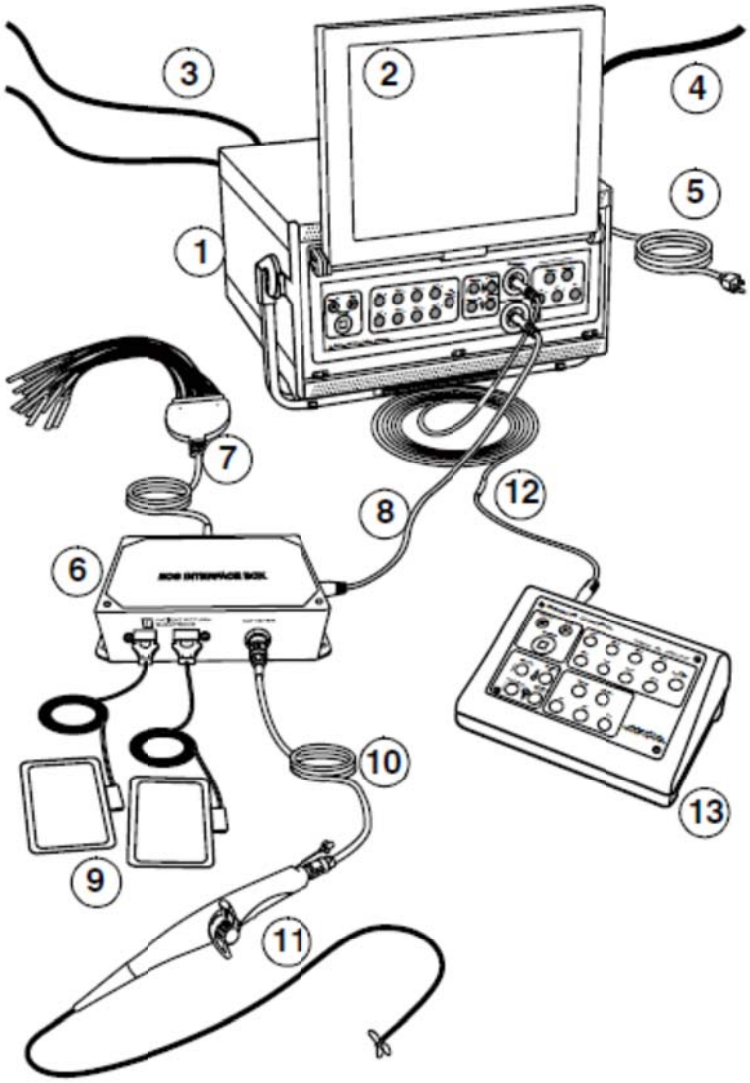
- Pulmonary Vein Ablation Catheter (PVAC)
- Multi-Array Septal Catheter (MASC)
- Multi-Array Ablation Catheter (MAAC)

The Generator automatically recognizes the attached cardiac ablation catheter and programs preset default temperature, ablation duration, and energy mode setting parameters. Ablation parameters including ablation duration, energy mode, target temperature, and channels (electrode pairs) can also be manually selected. A display screen monitor is available for viewing real-time system and ablation parameters. The generator features the following RF energy mode selections: bipolar only, unipolar only, and combination ratios of bipolar: unipolar energy mode selections of 1:1, 2:1, and 4:1. An ECG interface box connects the catheter with the Generator, patient return electrodes, the external monitoring equipment, and pacing equipment that may be used during the procedure.

The following components are used with the Generator (**Figure 1**):

- Generator Power Cable, Model 990025
- ECG Interface Box, Model 990028
- ECG Interface Box cable, Model 990020
- ECG amplifier cable, Model 990027
- Catheter interface cable, Model 990004 (supplied sterile)
- Two Valleylab™ Patient Return Electrodes, Model E7506 (required, but not supplied)
- GENius Jr. Remote Control, Model 990029 (optional)
- Remote control cable, 15 ft, Model 990041(optional)
- Remote control cable, 25 ft, Model 990042 (optional)

Figure 1. Illustration of the Medtronic GENius Multi-Channel RF Ablation Generator and its Components



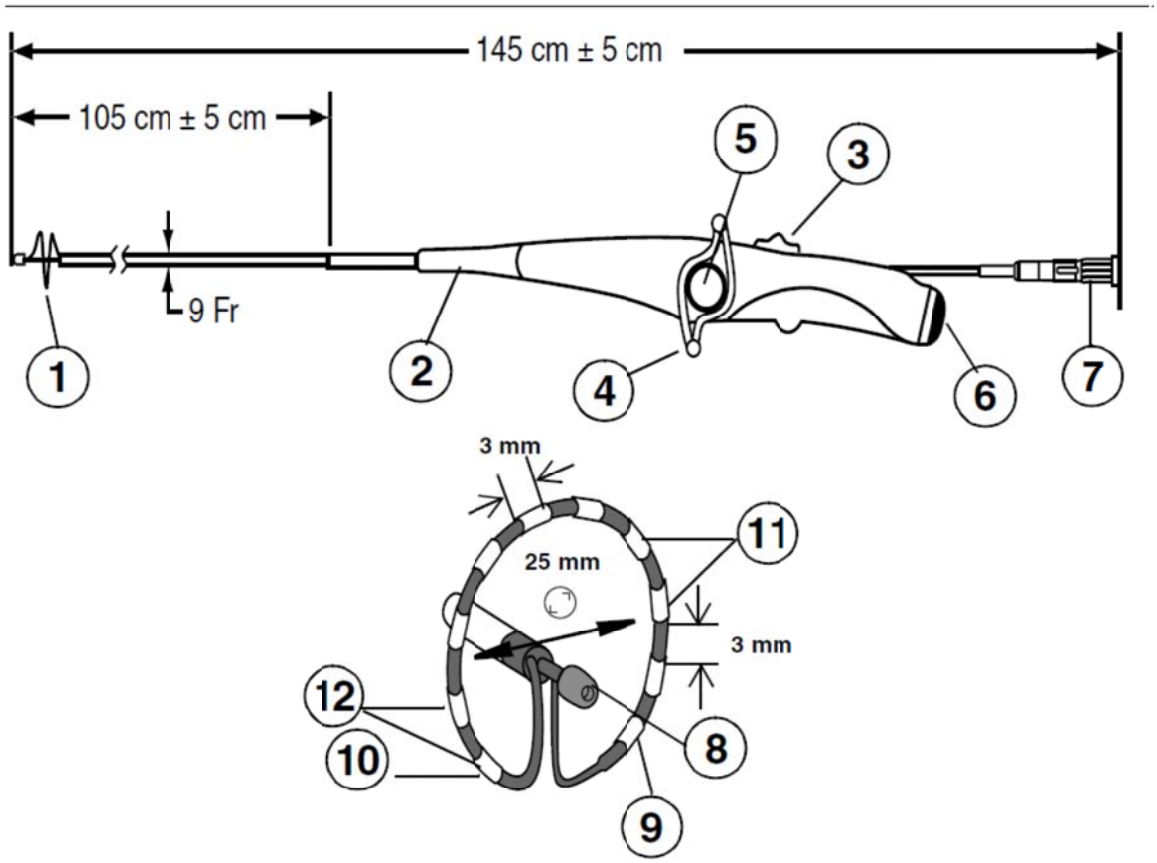
KEY:

1) GENius Multi Channel RF Ablation Generator
2) Monitor
3) VGA Monitor Cables (not included)
4) Equipotentiality (chassis ground) Cable (not included)
5) Power Cable
6) ECG Interface Box
7) Cable, Interface Box to EKG-12 Channel
8) Cable, Interface Box to the RF Generator
9) Patient Return Electrodes (2 required, not supplied)
10) Cable, Catheter Interface
11) Medtronic Cardiac Ablation Catheters
    - Pulmonary Vein Ablation Catheter (PVAC)
    - Multi-Array Septal Catheter (MASC)
    - Multi-Array Ablation Catheter (MAAC)
12) Remote Control Cable (Optional)
13) GENius Jr Remote Control (Optional)

Pulmonary Vein Ablation Catheter (PVAC)

The PVAC is a three-dimensional, anatomically designed, multi-electrode catheter used to map, pace, and ablate the pulmonary veins (**Figure 2**).

Figure 2. Illustration of PVAC

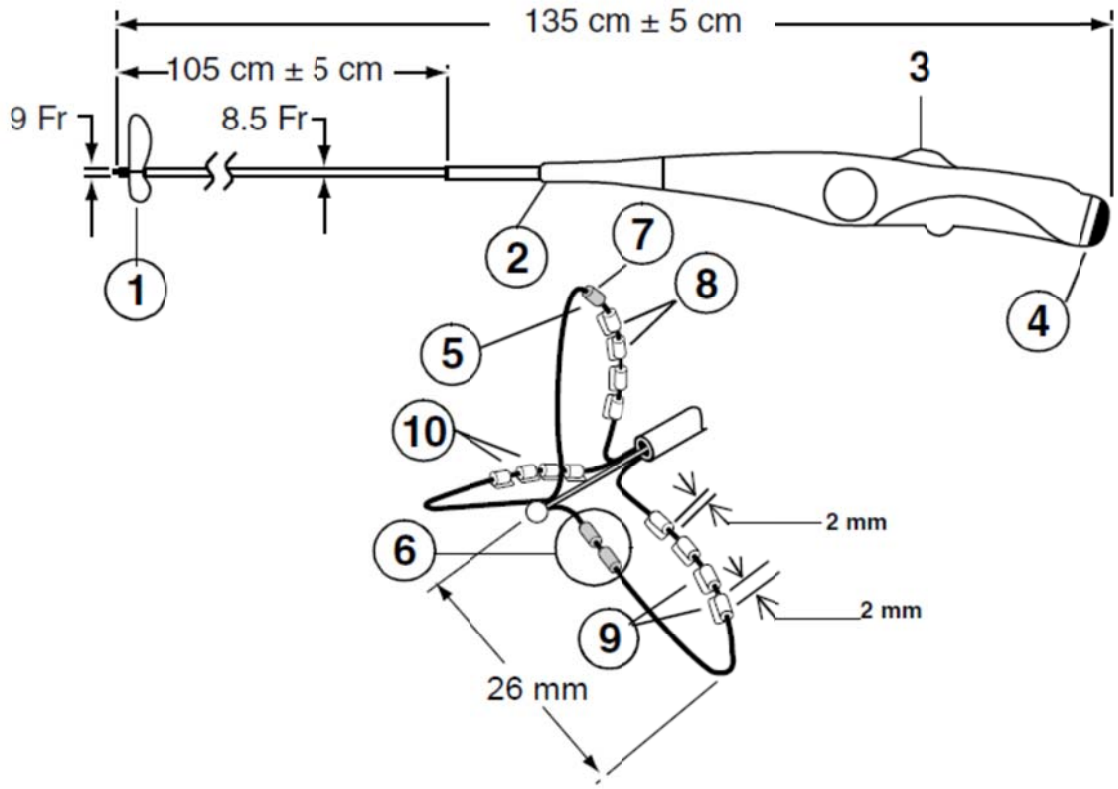


1	Spiral array	7	Proximal lumen
2	Capture device	8	Distal tip
3	Slide control knob	9	Electrode 1
4	Steering knob	10	Electrode 10
5	Tension control knob	11	Pair 2
6	Connector	12	Pair 5

Multi-Array Septal Catheter (MASC)

The MASC is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue along the left atrial septum (**Figure 3**).

Figure 3. Illustration of MASC

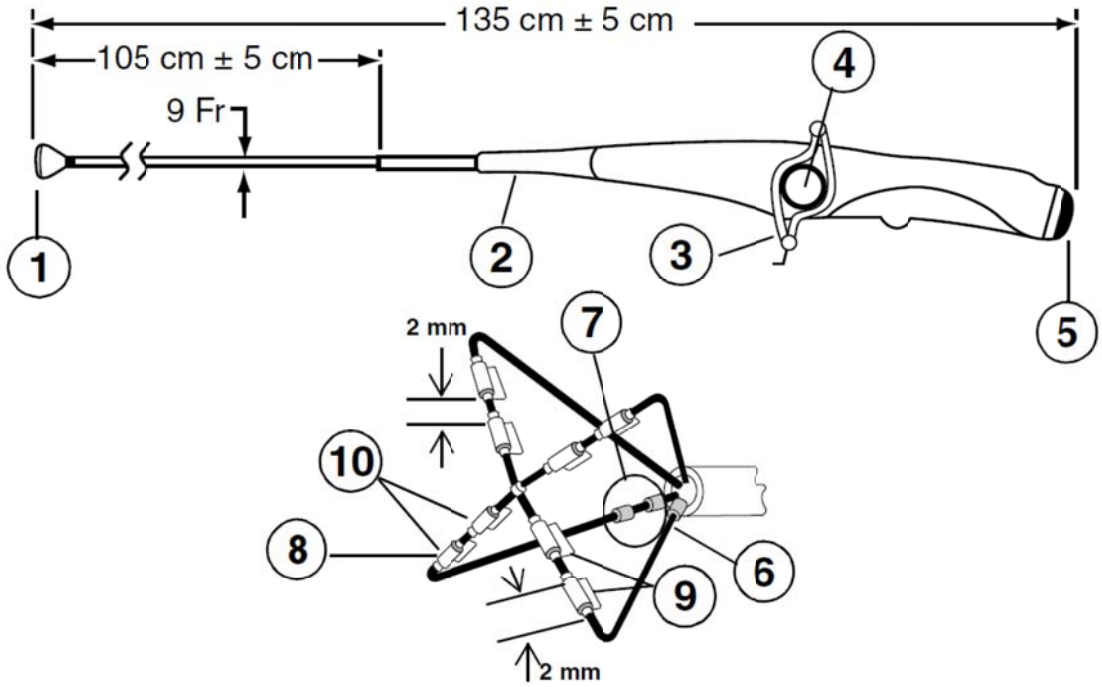


1	Array	6	Arm 2 markers
2	Capture device	7	Electrodes
3	Slide control knob	8	Pair 1
4	Connector	9	Pair 3
5	Arm 1 marker	10	Pair 5

Multi-Array Ablation Catheter (MAAC)

The MAAC is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue in the left atrial body (**Figure 4**).

Figure 4. Illustration of MAAC



1	Array	6	Arm 1 marker
2	Capture device	7	Arm 2 markers
3	Steering knob	8	Electrode
4	Tension control knob	9	Pair 1
5	Connector	10	Pair 2

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Several other alternatives for the treatment of s symptomatic, non-self-terminating, persistent and long-standing persistent states of atrial fibrillation (AF) exist, including the following:

- Pharmacological therapy for rate and/or rhythm control
- Electrical or pharmacologic cardioversion
- Surgical intervention to create atrial lesions (i.e. Cox-MAZE procedure)
- Implantable devices to control heart rates

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

GENius Multi-Channel RF Ablation Generator

The Generator and its accessories are marketed in the following economic region and countries: European Union, Norway, Switzerland, Canada, Australia, Hong Kong, Malaysia, South Korea and South Africa. Dates of when the Generator was first approved in these geographies are listed in **Table 3**.

Pulmonary Vein Ablation Catheter (PVAC)

The PVAC is marketed in the following economic region and countries: European Union, Norway, Switzerland, Canada, Hong Kong, Malaysia, South Korea and South Africa. Dates of when the PVAC was first approved in these geographies are listed in **Table 3**.

Multi-Array Septal Catheter (MASC)

The MASC is marketed in the following economic region and countries: European Union, Norway, Switzerland, Hong Kong, Malaysia, South Korea and South Africa. Dates of when the MASC was first approved in these geographies are listed in **Table 3**.

Multi-Array Ablation Catheter (MAAC)

The MAAC is marketed in the following economic region and countries: European Union, Norway, Switzerland, Hong Kong, Malaysia, South Korea and South Africa. Dates of when the MAAC was first approved in these geographies are listed in **Table 3**.

Table 3. Years of First Device Approval in Each Geography

Geography	GENius Generator	PVAC	MASC	MAAC
EU	2006	2006	2006	2006
Switzerland	2007	2007	2007	2007
Norway	2007	2007	2007	2007
Canada	2010	2010	NA	NA
Australia	2010	NA	NA	NA
Hong Kong	2008	2008	2008	2008
Malaysia	2008	2008	2008	2008
South Korea	2011	2011	2011	2011
South Africa	2008	2008	2008	2008

NA = Not Approved

The System has been withdrawn from the market in any country for any reason related to the safety or effectiveness of the system.

VIII. POTENTIAL ADVERSE EVENTS

Potential adverse events (in alphabetical order) associated with cardiac catheter ablation procedures include, but are not limited to, the following conditions shown in **Table 4**.

Table 4. Potential Adverse Events

Potential Adverse Events	
Allergic reaction to x-ray contrast media	Hypotension/hypertension
Anesthesia reactions	Infections
Arrhythmias, proarrhythmia	Myocardial infarction or ischemia
AV fistula	Nerve injury or nerve damage
Bleeding related to anticoagulation	Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system
Body temperature elevation	Pericarditis or endocarditis
Bradycardia	Pleural or pericardial effusion
Cardiac perforation of the heart or other organs during transseptal puncture or other procedures	Pneumonia
Cardiac tamponade	Pneumothorax
Cardiac thromboembolism	Pulmonary embolism
Cerebrovascular accident (CVA) or transient ischemic attack (TIA)	Pulmonary infiltrates
Chest discomfort	Pulmonary vein narrowing or stenosis
Chronic cough	Pseudoaneurysm in groin
Component damage to ICD or implanted pacemaker	Radiation injury or damage and late malignancy
Death	Respiratory depression
Dislodgement of implantable cardioverter defibrillator (ICD) or permanent pacing leads	Retroperitoneal bleed
Heart failure	Skin burns
Hematoma	Thrombolic or embolic events
Hemoptysis	Unintended complete or incomplete atrioventricular sinus node, or other heart block or damage
High creatinine phosphokinase or troponin level	Valvular insufficiency or damage
	Vasovagal reaction

For the specific adverse events that occurred in the clinical studies, please see **Section XIII** below.

IX. SUMMARY OF PRECLINICAL STUDIES

Pre-clinical testing of the System included verification and validation testing (device level, system level and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies. Performance testing was conducted to demonstrate design integrity. All tests performed were based on the Product Specification requirements, which were identified in standards or guidance documents. In the tests described below, the System was manufactured by trained manufacturing operators utilizing validated manufacturing processes. “Pass” as used below denotes that the devices and system met established product specifications and/ or performance criteria, or were in conformance with the requirements of the testing standards. Testing results confirmed that the System met the Product Specifications.

Aging studies and design validation were tested on final product. Process verification, process validation, and design verification may not have been tested on final product. All testing would have been tested against the production-revision, controlled release devices at the time, but it may not have been final product. Some tests were performed on subassembly devices built specifically for that test in order to isolate a specific joint or a feature; otherwise, that feature may not be testable.

A. Laboratory Studies

Cardiac Ablation Catheters Performance Testing

Medtronic performed mechanical and electrical performance testing on the Catheters. Catheters were pre-conditioned prior to testing. **Table 5** summarizes the mechanical and electrical performance testing for the Catheters.

Table 5. Cardiac Ablation Catheter Performance Testing

Test	Sample Size	Acceptance Criteria	Results
Array Collar to Distal Shaft	22	≥5.0lbf	Pass
Array to Proximal Bond	36	≥5.0lbf	Pass
Catheter Shaft Tensile Strength	24 / 13*	≥8.0lbf	Pass
Center Post to Distal Collar	30	≥3.0lbf	Pass
Center Post to Hypotube	36	≥10.0lbf	Pass
Center Post to Slide	36	≥10.0lbf	Pass
Distal to Proximal Shaft	24 / 30*	≥4.0lbf	Pass
Distal Slide Band to Hypotube	24	≥10.0lbf	Pass
Electrode to Arm	30	≥0.50lbf	Pass
Electrode to Spiral Array	30	≥0.5lbf	Pass
Hub to Guide Wire Tubing	24	≥3.0lbf	Pass
Hypotube to Guide Wire Lumen	10	≥3.0lbf	Pass
Proximal Shaft to Handle	24 / 36*	≥5.0lbf	Pass
Proximal Slide Band to Hypotube	24	≥10.0lbf	Pass
Spiral Array to Proximal Bond	24	≥5.0lbf	Pass
Steering Wire to Termination Coupling	24	≥10.0lbf	Pass
Temperature Accuracy	59	Within ± 2°C per product specification	Pass
Temperature Response	1 of each catheter	Temperature response <1 second	Pass
Tip Deflection	29	Tip must deflect a minimum of 180°	Pass
Torque Transmission	3	Device will transfer torque from the proximal end to the distal end	Pass
Torsional Rigidity	22	Catheter shaft shall withstand two rotations while tip is held constant without mechanical failure	Pass

*Two assessments were run for this test parameter. The first number represents the sample size for PVAC and MAAC, the second for MASC only; PVAC and MAAC were combined during testing as they are manufactured using the same shaft.

Generator/ System Level Testing

Table 6 summarizes the system level testing of the Generator, performed on a sample size of one.

Table 6. Generator Performance Testing

Test	Acceptance Criteria	Results
Operating Temperature and Humidity	Shall operate between +10°C to + 40°C and between 30% to 75% relative humidity noncondensing	Pass
Electrical Safety Requirements	Shall meet the requirements of EN60601-1 and EN60601-2-2	Pass
Electrical Transient Requirements	Shall meet the requirements of EN61000-3-2 and EN61000-3-3	Pass
Lightning Surge Immunity	Shall meet the requirements of EN61000-4-5	Pass
Voltage Requirements	Shall operate on power input of 120V±10% 60Hz and 220-240V 50Hz	Pass
Frequency Requirement	Shall be designed to deliver RF energy at a nominal frequency of 470 Khz	Pass
EMC/ EMI Requirement (with catheters as an integrated system)	Shall meet the requirements of IEC60601-1-1: 2001	Pass
Conducted Emissions Requirement	Shall meet the requirements of EN55011	Pass
Radiated Emissions Requirement	Shall meet the requirements of EN55011	Pass
Electrostatic Discharge (ESD) Requirement	Shall meet the requirements of IEC60601-4-2	Pass

Software

The Generator was developed and tested in accordance with Medtronic software and development procedures. These procedures incorporate the use of software development life cycle processes, including the development of Software Requirement Specifications, hazard analysis and verification testing plans. Testing was determined to be acceptable and demonstrated reliable operation of the software.

Biocompatibility

The Generator is not intended for direct patient contact; therefore no biocompatibility testing was required.

The Catheters are designed for contact with circulating blood for a limited duration, (the device shall be able to remain indwelling for up to four (4) hours) per specifications. The Catheters are provided sterile, as a single use device that has a polymeric catheter torque shaft, integral handle and a flexible, metallic mapping/ ablation array at the distal tip.

All materials used in the Catheters have been assessed for biocompatibility, per ISO 10993-1: 1993. A summary of the biocompatibility testing performed is summarized in **Table 7**. ‘Pass’ as used in the table denotes that the product specifications/ performance were in conformance with the requirements of the standard to which it was tested.

Table 7. Summary of Biocompatibility Testing for the Medtronic Cardiac Ablation Catheters

Biocompatibility	Test Report Results (MAAC/MASC)	Test Report Results (PVAC)
Cytotoxicity	Pass	Pass
Sensitization	Pass	Pass
Irritation or Intracutaneous Reactivity	Pass	Pass
Acute Systemic Toxicity	Pass	Pass
Hemocompatibility	Pass	Pass
Recalcification	Pass	Pass
Thromboresistance	Pass	Not Required

B. Animal Studies

The safety and performance of the System was evaluated in an animal study. A GLP study was performed using 3 swine where each animal underwent a minimum of two ablations with each of the three catheters. Ablations occurred in the left atrium and Superior Vena Cava (SVC) in each animal. All electrodes that made contact with the tissue were used to ablate during each positioning of the catheters. Each catheter was used for multiple ablations in the same animal and corresponding ablation data was recorded. Several incidences of arrhythmia occurred; incidences of arrhythmia of this nature are not uncommon during the procedure and were anticipated as a result of the swine model used. The arrhythmias were determined not to be specifically attributed to the investigational device. There were no issues reported with the advancement, deployment, or capturing of the catheters during the study. Post ablation, all lesions were evaluated as per the animal study protocol.

C. Additional Studies

Sterilization, Packaging and Shelf Life

The Generator is not provided sterile. The Catheter Interface Cable, a required component for the Generator, is provided EtO-sterile, and has been validated for steam resterilization.

The Pelican Case packaging utilized to maintain integrity of the generator during transport was subjected to shipping and storage testing, including vibration, drop, temperature and humidity conditions. The Generator passed both functional and visual inspection thereafter.

The Catheters are supplied as sterile, single use medical devices, ready for use. The Catheters are sterilized using an E-beam sterilization process. Routine validation is performed in accordance with ‘Sterilization of Medical Devices – Validation and routine control of sterilization by irradiation’, (BS EN 552: 1994).

Bioburden testing was conducted during the validation of the sterilization cycle for the process, and pyrogen testing was performed for the cardiac ablation catheters.

The packaging utilized to maintain integrity of the sterile barrier is a Mylar/Tyvek pouch and Thermoform Tray. Catheter packaging was subjected to sterilization, ship and bubble leak testing and passed visual inspection thereafter. It was concluded that the catheter packaging demonstrated the design for shipping and 18 months accelerated aging as intended.

The Catheters are labeled with an 18 month shelf life.

X. SUMMARY OF CLINICAL STUDY

Overview

The Applicant performed the Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) clinical study to establish a reasonable assurance of safety and effectiveness of ablation with the Medtronic Cardiac Ablation System for the treatment of patients with symptomatic, drug-refractory, persistent and long-standing persistent atrial fibrillation. This study was conducted in the United States and The Netherlands under IDE# G060175. A summary of the clinical study is presented in **Table 8**.

Table 8. Summary of Clinical Study

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects
Pivotal: TTOP-AF (AFI-30)	Prospective, multi-center, randomized, controlled clinical trial	Demonstrate safe and effective use of the investigational system when used to treat persistent and long-standing persistent atrial fibrillation.	24 (23 US,1 Netherlands)	Consented:242 Enrolled: 210 Randomized: 210 (138 Ablation Management, 72 Medical Management)

A. Study Design

The TTOP-AF trial was a prospective, randomized, controlled, multicenter, pivotal clinical investigation conducted in the United States and The Netherlands. Subjects were enrolled at 23 centers across the United States and one site in The Netherlands for the pivotal phase of the TTOP-AF trial. Investigators enrolled and randomized subjects during a 19 month period between November 2007 and May 2009.

At the time of protocol development there were no catheter ablation devices approved for the treatment of persistent or long-standing persistent atrial fibrillation. The TTOP-AF study was designed to evaluate the safety and effectiveness of the System in the treatment of drug refractory, symptomatic, persistent/long-standing persistent AF compared to

medical therapy consisting of the use of anti-arrhythmic drugs (AADs) and cardioversions. Subjects with persistent or long-standing persistent atrial fibrillation who had failed at least one Class I or Class III AAD were randomized 2:1 to either Ablation Management or Medical Management, respectively. All study subjects were required to have follow-up assessments at 1, 3, and 6 months for the purpose of assessing arrhythmia recurrence, use of medications (AADs and anticoagulation), and adverse event occurrence. Assessment of treatment success was defined as ≥90% reduction in clinically significant AF (>10 minute episodes) for all subjects at 6 months.

Minor changes were made to the protocol over the course of the clinical trial; however, there were no changes that impacted the overall approach or designed intent of the TTOP-AF study.

1. Objective

The primary objective of this trial was to demonstrate the safety and efficacy of the System for treatment of subjects with symptomatic, persistent or long-standing persistent atrial fibrillation who were refractory or intolerant to antiarrhythmic drug therapy.

2. Study Endpoints

Primary Endpoints

The ***primary endpoint for acute safety*** was a success/failure variable calculated for each subject in Ablation Management at the 7 day post-procedure time point.

The ***primary endpoint for chronic safety*** was a success/failure variable calculated for each subject at the 6 month time point.

The ***primary endpoint for chronic effectiveness*** was the evaluation of the proportion of subjects with treatment success computed at the 6 month visit.

Secondary Endpoints

The following ***secondary endpoints*** were intended to provide additional data on the System.

Secondary Efficacy Endpoints:

- Left atrial size (LAS) at 6 months post ablation procedure
- Left ventricular ejection fraction (LVEF)
- AF Symptom Severity Scores (AFSS)
- Quality of Life (SF-36)

- Acute efficacy will be determined as a treatment success/failure endpoint for each subject in the ablation management arm at the time of the ablation procedure. A subject will be considered successfully treated if:
  - An AFI catheter is used to achieve procedure success
  - Isolation of all accessible Pulmonary Veins is achieved
  - A minimum of 50% reduction of CFAEs and high frequency intracardiac electrogram amplitude is mapped and ablated with AFI catheters
  - Sinus rhythm is achieved upon leaving EP lab (± DC cardioversion)

Since subjects may have 1 additional procedure during the treatment period, both procedures must be deemed as acute successes in order for the subject to qualify as an acute efficacy success.

For LAS, LVEF, AFSS and SF-36 endpoints, change from baseline values for each subject will be computed by subtracting the baseline value for the endpoint from the 6 month time point value.

Secondary Safety Variables:
The secondary safety variables for this study are:

- All adverse events.

3. All adverse events. Success/Failure Criteria

The ***acute safety primary endpoint*** is a success/failure variable calculated for each subject in the Ablation Management arm at the one week post-procedure time point. Any subject with at least one adverse event adjudicated by the Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB) as both serious and device/procedure related occurring within 7 days of the procedure will be considered an acute safety failure, regardless of whether the event occurred following the index or the retreatment ablation procedure (for those subjects that require a second ablation procedure).

The ***primary endpoint for chronic safety*** was a success/failure variable calculated for each subject at the 6 month time point. Any subject that had at least one adverse event (AE) that met designated seriousness and relatedness criteria for the particular treatment group as adjudicated by the CEC/DSMB was considered a chronic safety failure. The AEs in Ablation Management that were acute (≤7 days) were not included in the calculation of the chronic safety primary endpoint.

The definitions of AEs that characterized a subject as a chronic safety failure were as follows:

- Ablation Management – Events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the ablation procedure and/or the device during the 6 month follow-up period (excluding the first 7 days post-procedure).
- Medical Management – Events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the AADs, or events related to AF during the 6 month follow-up period.

The occurrence of a new arrhythmia such as atrial flutter or atrial tachycardia, or hospital admission to treat these arrhythmias was not considered an AE.

The ***primary endpoint for chronic effectiveness*** was the evaluation of the proportion of subjects with treatment success computed at the 6 month visit. In order to be classified as a chronic success, both the Ablation and Medical Management subjects were required to achieve a 90% or greater reduction in clinically significant AF by the 6-month visit based on a 48-hour Holter recording. Clinically significant AF was defined as a sustained (symptomatic or asymptomatic) AF episode lasting for longer than (or equal to) 10 consecutive minutes in duration.

Subjects in Ablation Management were also required to meet the following endpoints to be classified as Chronic Treatment Successes:

- The subject was off all Class I or III AADs at the 6 month follow-up.
- All procedures (index and retreatment) conducted on a subject during the treatment period were deemed acutely successful (defined under acute efficacy in the secondary analyses subsection above).

4. Pre-specified Statistical Plan

Analyses were performed according to the Clinical Protocol, the Statistical Analysis Plan, and supplemental documents outlining any post hoc analyses. Standard analytic methods were used throughout utilizing SAS, SPSS, Cytel, Statistica and NCSS software. The statistical analysis of all primary endpoints was on an intention-to-treat (ITT) basis with passive missing value imputations, where all missing endpoint data were considered a treatment failure for each respective arm. Subjects were designated ITT once randomized. Descriptive statistics were calculated for each quantitative and qualitative assessment.

Acute Safety

The statistical analysis of the ***acute safety endpoint*** consisted of a comparison of the proportion of Ablation Management subjects failing to complete the 7-day post-procedure period without a serious adverse device and/or procedure related event

(SADE) and a historical control serious AE rate. An acceptable safety endpoint target value was based on a review of literature (dated between 2001 and 2006) consisting of a meta-analysis evaluating safety associated with left atrial AF ablation and on review of approved ablation procedures for right-sided atrial flutter. Using the information obtained from the literature review, a historical control maximum rate for SADEs was defined at 16%, as this was the highest approved one-sided 95% confidence bound allowed for a right-sided procedure.

The acute safety objective was determined with a protocol-specified ITT analysis using an exact, one-sample binomial test at a one-sided α=0.025 level of significance. The hypothesis was that the proportion of acute safety failures in Ablation Management was statistically significantly lower than the objective performance criterion of 16%:

$$H_o: p_A \geq 0.16 \text{ vs. } H_a: p_A < 0.16$$

where pA = the proportion of acute safety failures in Ablation Management. Passive missing value imputation was used in the computation of the test statistic.

Chronic Safety

The TTOP-AF trial was designed knowing that ***chronic safety*** would be difficult to assess due to the anticipated demand of subjects in Medical Management to cross over to receive an ablation in order to obtain relief from symptoms associated with AF and/or its treatment. Given the disparity in the length of time at risk, the Chronic Safety endpoint was not statistically powered and the Medical Management subjects were allowed to cross over to receive an ablation as early as 4 months.

Although not statistically powered, every attempt was made to obtain chronic safety events for all subjects in both treatment arms.

Chronic Efficacy

The primary endpoint for chronic effectiveness was the evaluation of the proportion of ITT subjects (excluding data obtained from Medical Management subjects after they crossed over) with treatment success computed at the 6-month visit. There were a total of 138 subjects randomized to Ablation Management and 72 subjects to Medical Management.

Chronic Effectiveness Endpoint

The chronic effectiveness endpoint was defined by the following criteria:

1. Both Ablation and Medical Management subjects were required to achieve a ≥90% reduction in clinically significant AF/AFL based on a 48-hour Holter recording obtained at baseline and 6 months post-treatment. Clinically significant AF/AFL was

defined as a sustained (symptomatic or asymptomatic) AF/AFL episode lasting ≥10 consecutive minutes in duration. The cumulative time of AF/AFL episodes lasting 10-minutes or longer as detected on a 6-month Holter were evaluated for ≥90% reduction when compared to baseline Holters.

2. Ablation Management subjects were also required to be off all Class I or III AADs at the 6 month follow-up. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

3. Ablation Management subjects were also required to have acute procedure success (both index and retreatment). An Ablation Management subject was considered acutely successful if all of the following were true:

a. Medtronic ablation catheters were used to achieve procedural success.
b. All accessible pulmonary veins were isolated.
c. CFAEs were mapped and eliminated using Medtronic ablation catheters.
d. Sinus rhythm was achieved upon leaving the electrophysiology lab (± direct current cardioversion).

Acute Safety Endpoint

For the acute safety endpoint, the goal was to verify that the proportion of subjects experiencing SADEs immediately after treatment in Ablation Management was lower than historical rates of SADEs. Based on the results of previous studies, the maximum rate of subjects observing SADEs was 16%. In order to have an 80% chance of showing that the acute SADE rate in Ablation Management is 8%, a sample size of n=135 subjects was required. This sample size calculation was based on a two-sided α=0.05 level of significance and assumed the response data was from a binominal distribution.

Overall Sample Size

In order to ensure adequate power for both the chronic effectiveness and acute safety hypotheses, with a 2-to-1 treatment group allocation, the sample sizes were increased to 140 subjects in the Ablation Management arm and 70 subjects in the Medical Management arm.

<u>Method for Handling Missing Data</u>

The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation, in which all missing success/failure endpoints were assumed failures for both treatment groups.

5. *External Evaluation Groups*

A Scientific Advisory Board was responsible for providing input on endpoints and in defining the subject population. An independent Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB) was responsible for the review and adjudication of all adverse events and adjudication of all trial endpoints, and for overseeing the conduct of the trial.

Two core laboratories were utilized for this clinical trial. One core laboratory was responsible for reading pulmonary vein dimension from CT/MRI imaging utilizing blinded, independent assessment. The Holter core laboratory was responsible for analyzing all study Holter recordings.

6. *Study Design Discussion*

When the TTOP-AF study was being designed, there were no catheters approved for ablation of AF in the United States and the 2007 HRS Consensus Statement[1] had not been written. Study design was based on available literature at the time, which was very limited regarding left-sided atrial ablation in the persistent AF population. The 2004 FDA Guidance for Industry and Staff regarding "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation"[2] which described the FDA's current thinking regarding clinical study designs for catheter ablation of AF at the time was used as a reference for TTOP-AF study design. Many recommendations outlined in the guidance document were incorporated into the protocol, including the 2:1 randomization scheme, allowance of crossovers to the ablation arm after a pre-specified period of time, reduction of AF burden in the absence of AADs as an endpoint determination, allowance of one repeat ablation, and imaging assessment of pulmonary vein stenosis at specified follow-up periods.

During the 2.5 year period that the TTOP-AF study was conducted, the field of catheter ablation rapidly evolved, as well as the peri-procedural parameters regarding standard of care for ablation of AF. The 2007 HRS Consensus Statement[1] on Catheter and Surgical Ablation of AF was published which defined recommendations regarding the study design and endpoint evaluation for clinical trials. For example, rather than reduction of AF burden, the occurrence of any 30 second episode of AF, atrial flutter, or atrial tachycardia were to be deemed treatment failures. Standard of care regarding anticoagulation practices changed as well. In addition, the body of literature on AF ablation advanced significantly from the time TTOP-AF was designed and initiated. The results from TTOP-AF in the persistent and long-standing persistent AF population will contribute to this body of knowledge as well.

7. *Clinical Inclusion and Exclusion Criteria*

Enrollment in the TTOP-AF study was limited to subjects who met the following selection criteria **Table 9**.

Table 9. Inclusion and Exclusion Criteria for Clinical Study

Inclusion:	**Exclusion:**

History of symptomatic, continuous AF defined as:
• Continuous AF lasting greater than 1 year but less than 4 years OR
• Nonself-terminating AF, lasting greater than 7 days but no more than 1 year, with at least one failed DC cardioversion.
  ▪ A failed cardioversion was defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond 7 days.
 	
AF symptoms defined as :
  ▪ Palpitations
  ▪ Fatigue
  ▪ Exertional dyspnea
  ▪ Exercise intolerance (Increased intolerance to routine activities)
	Structural heart disease of clinical significance including:
	• Previous cardiac surgery (excluding coronary artery bypass graft and mitral valve repair)
	• Symptoms of congestive heart failure including, but not limited to, NYHA Class III or IV congestive heart failure and/or documented ejection fraction <40% measured by acceptable cardiac testing
	• Left atrial diameter >55 mm
	• Moderate to severe mitral or aortic valvular heart disease
	• Stable/unstable angina or ongoing myocardial ischemia
	• Myocardial infarction (MI) within 3 months of enrollment
	• Congenital heart disease (not including atrial septal defect or patent foramen ovale without a right to left shunt) where the underlying abnormality increases the risk of an ablative procedure
	• Prior atrial septal defect of patent foramen ovale closure with a device using a percutaneous approach
	• Hypertrophic cardiomyopathy (left ventricular septal wall thickness >1.5 cm)
	• Pulmonary hypertension (mean or systolic pulmonary artery pressure >50 mm Hg on Doppler echo)

Age between 18 and 70 years	Any prior ablation for AF
Failure of at least one Class I or III rhythm control drug	Enrollment in any other ongoing arrhythmia study
Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study.	Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
	Active infection or sepsis
	Any history of cerebral vascular disease including stroke or transient ischemic attacks

	Pregnancy or lactation
	Left atrial thrombus at the time of ablation Untreatable allergy to contrast media
	Any diagnosis of AF secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
	History of blood clotting (bleeding or thrombotic) abnormalities
	Known sensitivities to heparin or warfarin
	Severe chronic obstructive pulmonary disease (defined as FEV1 <1)
	Severe co-morbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e. other disease processes, mental capacity, substance abuse, shortened life expectancy, etc.)

8. Summary of Treatment and Follow-Up Protocols

Ablation Management subjects underwent up to 2 ablation procedures for treatment of AF with the System. All 3 ablation catheters (PVAC, MASC, and MAAC) were required to be used during the initial ablation procedure in the listed order for treatment of each subject's specific source of AF. PVAC was used to map, ablate and confirm electrical isolation of the pulmonary veins. Once optimal positioning of the catheter was obtained, ablation on all channels was to be performed in a 4:1 (unipolar:bipolar) setting to a target temperature of 60°C for 60 seconds. The MASC and MAAC catheters were used to map and ablate Complex Fractionated Atrial Electrograms (CFAEs). The MASC catheter was deployed in the left atrium and the sheath retracted back to the septum toward the right atrium prior to ablation. Ablations were to occur for 60 seconds with a target temperature of 60°C using a 1:1 (unipolar:bipolar) modality setting. The MASC catheter was then rotated to identify additional CFAEs and ablation repeated. The MAAC catheter was used to map and ablate in the body of the left atrium in a similar fashion. Ablations were also to occur at 60°C for 60 seconds. However, a modality of 1:1 or 4:1 was to be used depending on the location of the ablation. Additional mapping and ablations would occur until the investigator determined that all CFAEs were eliminated. Electrical cardioversion was used during the procedure to restore sinus rhythm if the subject remained in AF. Once the subject was in sinus rhythm, the PVAC catheter was again placed to re-map any remaining pulmonary vein potentials. All noted pulmonary vein potentials were ablated using the settings identified above, with the exception that only channels where potentials were located were to be selected.

Anticoagulation strategies were left to the discretion of the investigator. Oral anticoagulation was allowed to be discontinued and either low molecular weight heparin

(LMWH) or IV heparin could be substituted for therapeutic doses of oral anticoagulation until the time of the procedure. Intravenous heparin or LMWH was to be resumed following the procedure until an INR > 2.0 was achieved. Oral anticoagulation was to be restarted for the duration of follow-up.

Recurrence of AF required additional management. If desired, the investigator could prescribe an AAD that the subject had failed prior to the ablation procedure. Alternatively, a repeat ablation procedure could be performed during the follow-up period of the initial ablation procedure, which was to occur within 90 days of the index ablation, whenever possible. The ablation retreatment followed the same procedure and follow-up assessments as for the index ablation, except that all 3 catheters were not required to be used. Neither AAD therapy or ablation retreatment constituted a chronic treatment failure during this period provided that the subject was off all AADs prior to the 6-month visit. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

Medical Management subjects were to receive an AAD at a previously failed dose or a new drug. Amiodarone was allowed up to a maximum allowable dosage of 200 mg/day. AAD therapy was expected to begin promptly after randomization. Changes to AAD dosage and/or changes to another drug or combination of drugs were allowed during the 6 month follow-up period when determined clinically necessary by the investigator. In addition to AAD use, subjects were expected to receive adequate anticoagulation with warfarin during the course of the study to achieve and maintain an INR level >2.0.

Direct current (DC) cardioversions to restore sinus rhythm were also allowed in the Medical Management group. Greater than 2 failed DC cardioversions (failure to convert to sinus rhythm and maintain the rhythm for at least 30 days) constituted a medical management failure.

All study subjects were required to have follow-up assessments at 1, 3, and 6 months for the purpose of assessing arrhythmia recurrence, the use of medications (AADs and anticoagulation), and AE occurrence (**Table 10**).

Ablation Management subjects were required to complete a baseline and 6 month CT or MRI scan for the identification of pulmonary vein changes post-ablation. All CT/MRI images were read by a blinded independent core laboratory for the purpose of assessing for pulmonary vein narrowing or stenosis. Pulmonary vein changes were recorded as "stenosis" if the vein diameter change from baseline was greater than 70% and "narrowing" if the vein change was 50-70% .

Table 10. Follow-up Schedule and Evaluations

Testing	Baseline	Pre-Discharge	1 Month	3 Month	6 Month
History, Physical Exam, Neurological Evaluation and Medication History	A, M	A	A, M	A, M	A, M
12 lead ECG (Baseline = within 6 months of screening)	A, M	A	A, M	A, M	A, M
Echocardiogram (TTE) (Baseline = within 6 months of ablation procedure or screening for medical management arm)	A, M	-	-	-	A, M
Transesophageal Echocardiogram (TEE) (Baseline = within 72 hours of ablation procedure)	A	-	-	-	-
Symptom Severity Score	A, M	-	A, M	A, M	A, M
PV Stenosis Survey	A	-	A	A	A
SF-36 Quality of Life (QOL) Survey	A, M	-	A, M	A, M	A, M
48-hour Holter	A, M	-	-	-	A, M
CT Scan or MRI	A	-	-	-	A
Adverse Events	N/A	A, M - Collected as Reported			

Key: A=Ablation Management Arm; M=Medical Management Arm; N/A=not applicable, (-) = test not required per protocol

Note: Subjects randomized to the Medical Management arm and crossed over to receive an ablation procedure followed the same data collection and visit schedule as subjects randomized to the Ablation Management arm.

XI. ACCOUNTABILITY OF PMA COHORT

The TTOP-AF trial was conducted over a 2.5 year period with enrollment beginning in November 2007. The last ablation procedure for the trial occurred on May 7, 2010 with the final follow-up on November 1, 2010. Enrollment and accountability are summarized in **Table 11** and **Table 12.**

Randomization assignments were given to 210 subjects (Ablation Management = 138, Medical Management = 72).. A total of 132 subjects underwent an index ablation procedure (5 subjects were screen failures after randomization and one subject was withdrawn prior to using the investigational devices upon discovery of a hemizygous vein). All 210 subjects were used in the Primary Effectiveness and Safety Outcomes

analyses and in all additional secondary safety and effectiveness analyses as the ITT population.

Table 11. Subject Accountability and Disposition through 6-month Follow-up

Subject Disposition	Subjects
Total number of subjects randomized	210
Subjects randomized to Ablation Management	**138**
Subjects who underwent a procedure to have an ablation	133
Subjects who underwent an ablation with the System	132
Subjects that had a retreatment ablation	48
Lost to follow-up	0
Withdrawn	13
Death	1
Subjects that completed the study	**124**
Subjects randomized to Medical Management	**72**
Subjects that used an AAD after randomization	67
Lost to follow-up	1
Withdrawn	5
Subjects that completed the study using medical therapy	23
Subjects who completed the study and crossed over	43
Total Medical Mgmt. subjects that completed the study	**66**

Table 12. Table Accountability for Medical Management Subject after Crossing Over

Subject Disposition	Subjects
Medical Management Crossover Subjects	**43**
Crossover subjects requiring a retreatment ablation procedure	12
Withdrawn	4
Crossover subjects that completed the study after receiving an ablation	**39**

The statistical methodology for the selection of subjects for the primary endpoint analyses was based on Intention-to-Treat (ITT), which require subjects' data to be analyzed with respect to their assigned randomized treatment groups (Ablation Management or Medical Management). The passive missing value imputation technique was utilized for all primary endpoint analyses. This technique assumed subjects were "failures" if their data was not available for primary endpoint analyses. Data from Medical Management subjects prior to crossover was included for endpoint analyses. However, if a Medical Management subject crossed over prior to the end of the study, data from the date of the crossover and beyond was analyzed separately.

There were 210 randomized subjects consisting of 138 Ablation Management subjects and 72 Medical Management subjects. Thirteen (13) Ablation Management and 6

Medical Management subjects were withdrawn or lost to follow-up during the study. One death occurred in the study for a subject in Ablation Management. The number of subjects that completed the study and who were available for the primary effectiveness endpoint analysis was 124 Ablation Management subjects and 66 Medical Management subjects (23 subjects who completed the study using medical therapy and 43 subjects who crossed over to receive an ablation). The 43 Medical Management subjects that crossed over to receive an ablation were all considered failures for the primary effectiveness endpoint analysis. Of the 43 Medical Management Crossover subjects, 39 completed the study after receiving up to 2 ablations, but the data obtained after crossing over were not included in the primary effectiveness endpoint analysis for Ablation Management.

All randomized subjects (210) were included in the safety endpoint evaluations. However, once a Medical Management subject crossed over to receive an ablation, the safety events that occurred during the procedure or in the 6 months following the procedure were reported and analyzed separately. The total number of ablation procedures (both index and retreatment) that were evaluated for Acute Safety for Ablation Management subjects was 183 procedures. Another 56 index and retreatment procedures were performed in Medical Management Crossover subjects (not included in the ITT acute safety endpoint analysis). The total number of ablation procedures that were performed within the pivotal portion of the TTOP-AF trial was 239.

XII. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

The baseline characteristics of both Ablation and Medical Management subjects were comparable as summarized in **Table 13**.

Table 13. Baseline Subject Demographics

Variable	Ablation Management N=138	Medical Management N=72
Age, years		
Mean ± SD	59.6 ± 8.3	60.7 ± 8.9
Median	61.2	60.8
Range	(35.5 – 73.4)	(31.3 – 75.2)
Gender		
Male, n (%)	115 (83.3%)	60 (83.3%)
Female, n (%)	23 (16.7%)	12 (16.7%)
Ethnicity		
Caucasian, n (%)	133 (96.4%)	70 (97.2%)
African American, n (%)	3 (2.2%)	1 (1.4%)
Other (Hispanic, Asian), n (%)	2 (1.4%)	1 (1.4%)

There were no significant differences in the presence of heart disease or cardiovascular risk factors between the two treatment arms (**Table 14**).

Table 14. Baseline Medical History

Characteristic	All Subjects % (n / N)	Ablation Management Subjects % (n / N)	Medical Management Subjects % (n / N)
Diabetes Mellitus	14.3% (30/210)	15.9% (22/138)	11.1% (8/72)
Coronary Artery Disease	19.0% (40/210)	20.3% (28/138)	16.7% (12/72)
Congestive Heart Failure	7.6% (16/210)	5.8% (8/138)	11.1% (8/72)
Hypertension	59.0% (124/210)	60.9% (84/138)	55.6% (40/72)
Cardiomyopathy	9.0% (19/210)	6.5% (9/138)	13.9% (10/72)
Valvular Disease	7.1% (15/210)	5.1% (7/138)	11.1% (8/72)
Congenital Heart Disease	0.5% (1/210)	0.7% (1/138)	0% (0/72)
PFO or ASD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)
Pacemaker or ICD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)

The TTOP-AF pivotal trial population achieved its intended target population of subjects with frequent, symptomatic, persistent / long-standing persistent AF into two highly comparable study groups with no significant health differences.

A. Atrial Fibrillation Status and Treatment History

All subjects enrolled in the TTOP-AF study were required to have continuous AF for either greater than 1 year (long-standing persistent AF) or less than 1 year plus the inability to maintain sinus rhythm beyond 7 days (persistent AF) with at least one failed DC cardioversion. Due to the known difficulty in treating long-standing AF [1, 3, 7], it was important to verify the distribution of subjects with persistent and long-standing persistent AF across treatment groups. Persistent AF was present in 96 (69.9%) Ablation Management subjects and 57 (79.2%) Medical Management subjects (**Table 15**). The number of subjects with long-standing persistent AF was also similar between treatment arms (30.4% Ablation Management subjects compared to 20.8% Medical Management subjects). The number of years since AF was first diagnosed also did not differ between both groups (Ablation Management 0.9 ± 0.9; Medical Management 0.7 ± 0.8)

(**Table 16**). The differences in the proportions of subjects with persistent and long-standing persistent AF were not statistically significant (p=0.1375, Chi-square test).

Table 15. Baseline Atrial Fibrillation Status

AF Burden:	Ablation Management N=138 n (%)	Medical Management N=72 n (%)	p-value*
Persistent AF[1]	96 (69.9%)	57 (79.2%)	0.1375
Long-standing Persistent AF[2]	42 (30.4%)	15 (20.8%)	

*Chi-squared test.
[1]Persistent AF was continuous AF lasting >7 days but less than 1 year.
[2]Long-standing persistent AF was continuous AF lasting >1 year.

Table 16. Baseline AF Cardioversion and AAD History

Variable	Ablation Mgmt. N=138 Mean ± SD Median (Min, Max)	Medical Mgmt. N=72 Mean ± SD Median (Min, Max)	p-value**
Years Since First AF Diagnosis	0.9 ± 0.9 0.6 (0.0, 4.1)	0.7 ± 0.8 0.5 (0.0, 3.9)	0.15
Number of DC Cardioversions in Past 4 Years / Subject	2.0 ± 1.1 2.0 1.0 – 6.0	2.4 ± 3.5 2.0 1.0 – 30.0†	0.24
Years Since First DC Cardioversion	1.3 ± 2.0 0.5 0.0 – 11.4	1.5 ± 2.3# 0.5 0.0 – 13.0	0.47
Years Since First Prescribed Class I or III AAD	2.1 ± 3.3^ 0.6 0.0 – 18.6	2.5 ± 4.1^ 0.8 0.0 –18.6	0.49
Number of Failed AADs* / Subject	1.4 ± 0.9 1.0 (1, 6)	1.1 ± 0.5 1.0 (0, 2)	0.02

*Failed AAD refers to a drug that was either ineffective or not tolerated by the subject.
†Subject with 30 cardioversions was cardioverted via implantable cardioverter defribrillator
#N=71 for Medical Management
^N=137 for Ablation Management; N=71 for Medical Management
**Two-sided, α=0.05 level significance tests

As a requisite for randomization, all subjects were required to demonstrate 48 hours of continuous AF on a baseline Holter recording **(Table 17)**. All subjects in both arms demonstrated good compliance with wearing the Holter monitor, with an average total time of 48':25'' ± 1':18''. In addition, all subjects demonstrated a single continuous episode of AF (100% AF) on their Holter recordings with no significant differences between Ablation Management and Medical Management (p= 0.64).

Eight (8) of the 210 pivotal subjects did not use a study 48-hour Holter provided by CoreLab Partners. Instead, a recent baseline Holter recording performed at each subject's institution was used for the study. Professor Helmut Klein, an independent cardiologist and a member of the DSMB, reviewed and verified each of the independent Holter recordings. Professor Klein determined that all 8 subjects were in 100% AF at baseline and the data was used for the study.

Table 17. Baseline 48-Hour Holter Data

Characteristic	Ablation Management N=138 Mean ± SD Median (Min, Max)	Medical Management N=72 Mean ± SD Median (Min, Max)	All Subjects N=210 Mean ± SD Median (Min, Max)	T-test p-value†
Total Time on Monitor* (hrs:min)	48:23 ± 1:25 48:13 (36:25, 50:00)	48:28 ± 1:04 48:11 (42:22, 49:58)	48:25 ± 1:18 48:12 (36:25, 50:00)	0.64
Clinically Significant AF Time (hrs:min)	48:25 ± 1:25 48:15 (36:27, 50:00)	48:30 ± 1:04 48:13 (42:24, 50:00)	48:27 ± 1:18 48:14 (36:27, 50:00)	0.64
Number of AF Episodes^	2.0 ± 0.54 2.0 (1,8)	1.9 ± 0.23 2.0 (1,2)	2.0 ± 0.46 2.0 (1,8)	0.29

*Note: Total time on monitor in AF was slightly longer than total time on monitor due to converting recording time from seconds to minutes.
†Two-sided t-test
^Study Holter recordings were read in two 24 hour periods. Therefore, each subject that used a study Holter will have a minimum of two 10-minute AF episodes. However, the 8 subjects that used non-study Holters will have a minimum of 1 10-minute AF episode (one 48 hour reading).

XIII. SAFETY AND EFFECTIVENESS RESULTS

A. Safety Results

The safety of treating subjects with persistent and long-standing persistent AF using the Medtronic Cardiac Ablation System was studied in the TTOP-AF pivotal trial using two safety outcomes.

Acute Safety Outcome

The Primary Acute Safety Outcome study objective for the proportion of Ablation Management subjects free of serious procedure and/or device-related adverse events (SAEs) within 7 days of the ablation procedure was not met.

The analysis of safety was based on the Ablation Management ITT cohort of 138 subjects for the 6 month evaluation. The key safety outcomes for this study are presented in **Table 18**. There were 6 subjects who were randomized to the Ablation Management arm and either exited prior to receiving a procedure or had their procedure aborted. These subjects are counted as failures per the passive ITT method for this analysis.

Additionally, 17 of the 138 Ablation Management subjects (12.3%) had one or more procedure and/or device related SAEs occurring within 7 days of the ablation procedure. The upper bound of the two-sided, 95% confidence interval was 19.0%, which exceeded the pre-specified performance goal of 16%.

Table 18. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial confidence Interval	(7.3%, 19.0%)
p-value[a] of H_0: Rate ≥16%	0.1427

[a] One-sided p-value for exact one-sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

There were a total of 21 SAEs experienced by 17 Ablation Management subjects that were adjudicated and classified by the CEC/DSMB (**Table 19**).

Table 19. Acute Safety Serious Adverse Events – Ablation Management

Description of Events	Number of Primary Acute AEs N=138 n (%)
Probably or Definitely Related to the System	
No events	0 (0.0%)
Probably or Definitely Related to the Procedure	
Stroke	4 (2.9%)
Heart failure[a]	2 (1.4%)
Cardiac tamponade	2 (1.4%)
Pseudoaneurysm	2 (1.4%)
Pulmonary infiltrates with fever	2 (1.4%)
Drop in Hct secondary to ablation	1 (0.7%)
Anesthesia reaction	1 (0.7%)
UTI with prolonged hospitalization	1 (0.7%)
Hypotension secondary to cardiac tamponade	1 (0.7%)
Hypotension/cardiogenic shock	1 (0.7%)
Pneumonia	1 (0.7%)
Acute respiratory failure	1 (0.7%)
Retroperitoneal bleed with right ureter obstruction	1 (0.7%)
Post-procedure pericarditis	1 (0.7%)

[a] One of the heart failure subjects succumbed to death within 24 hours of receiving a retreatment ablation procedure. No investigational catheters were deployed during the procedure.

The Primary Acute Safety endpoint was not met for Ablation Management using the pre-specified 16% SADE historical rate. At the time the trial was designed, no benchmark existed for left-sided AF ablation, thus the pre-specified endpoint was developed based on right-sided ablations (a less complicated procedure). Right-sided ablations generally

occur in a less complicated arrhythmia population (paroxysmal AF) and were the only known comparator group when the TTOP-AF trial was initiated in November 2007. Considering the disease state of the subjects studied, the pre-specified objective may have underestimated the true expected event rate for catheter ablation in this population.

During the development of the TTOP-AF study little was known about acute safety procedure event rates for the persistent AF population. The acute safety performance criterion of 16% was determined based on a literature review of right-sided ablation and ablation of PAF. This comparator may underestimate the safety events that could be expected in the TTOP-AF study for two reasons: 1) TTOP-AF was designed to include all serious procedure and device related adverse events within 7 days of procedure as opposed to a pre-specified list of events. 2) The persistent AF population is at higher risk of events than the PAF population due to the complexity of the procedures and the advanced disease state.

Chronic Safety Outcome:

Although not statistically powered, every attempt was made to obtain chronic safety events for all subjects in both treatment arms. All serious adverse events adjudicated by the CEC/DSMB are shown in **Table 20**. There were 10 serious AEs adjudicated as either probably or definitely related to the procedure and/or device observed in 10 Ablation Management. There were 3 events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the AADs, or events related to AF in 3 Medical Management subjects who did not crossover. Another 4 serious AEs occurred in 4 Medical Management Crossover. Recall that chronic adverse events exclude the first 7 days after an index or retreatment ablation procedure for Ablation Management subjects as these events were reported as an acute safety event.

Table 20. Serious Chronic Safety Events – Ablation Management

Description of Event	Ablation Mgmt. Events (N = 138) n	Medical Mgmt. Events (Non-Crossover) (N=29) n	Medical Mgmt. Crossover Events (N=43) n
Description of Event	5	0	2
Pulmonary vein stenosis	1	0	0
Stroke	0	0	0
TIAs	1	0	0
Pulmonary vein narrowing	1	0	0
Persistent ASD secondary to septal puncture	1	0	0
Pericardial effusion	1	0	0
Chest pain secondary to pericarditis	0	2	0
GI bleed	0	1	0
AF with rapid ventricular response	0	0	1
Events related to recurrent AF	0	0	1
Hyperesthesia in right leg and neuropathy	**10**	**3**	**4**

[a] Only these safety events are considered significant primary events in other randomized, controlled clinical trials for AF ablation.

Medtronic recognizes that specific chronic safety events associated with the ablation procedure need to be understood to enable physicians and patients to make informed risk/benefit decisions. As demonstrated in other randomized, controlled clinical trials in AF ablation, the significant chronic events associated with ablation consist of atrio-esophageal fistula, pulmonary vein stenosis, stroke, transient ischemic attacks (TIAs), and phrenic nerve injury. There were no observed instances of atrio-esophageal fistula or phrenic nerve injury. Pulmonary vein stenosis, stroke, and transient ischemic attacks (TIAs) are discussed further below.

B. Additional Safety Outcome Analyses

Additional safety information is provided for significant safety events that occurred for all enrolled subjects. There were a total of 72 subjects initially randomized to Medical

Management. The total number of subjects that underwent an ablation procedure (or attempt) was 176 subjects (133 Ablation Management and 43 Medical Management Crossover subjects). Rates per procedure are also provided (the total number of ablation procedures was 239).

1. Serious Adverse Events Related to the Procedure and/or Device

Results for adjudicated serious AEs related to the procedure and/or device are summarized below.

a) Deaths

One death occurred in a 63 year old male randomized to the Ablation Management arm during the course of the TTOP-AF trial. After meeting initial inclusion criteria the index procedure was performed 3 months later despite a significantly depressed LVEF of 10-15%. The procedure resulted in acute procedural success after receiving one cardioversion during the procedure.
At the one month follow up exam, the subject was determined to be in NYHA Class III heart failure presenting with moderate palpitations, severe fatigue, moderate SOB, mild lightheadedness, chest pains, tachycardia, irregular heart rate, AF, positive S3 on auscultation, and severe exercise intolerance. The subject was subsequently scheduled for a retreatment ablation procedure.

Prior to the retreatment ablation 11 days later, a TEE was repeated and showed that the LVEF had increased to 30-35% with moderate mitral insufficiency. After obtaining venous and transseptal access, heparin (5000 units IV) was administered. The first investigational catheter was inserted into the sheath, but before it was advanced or deployed into any cardiac structure, the patient developed acute heart failure with significant hypotension. The subject was intubated, placed on mechanical ventilation and required multiple vasopressor agents to maintain his blood pressure. The following morning during transfer to a tertiary care center for placement of a left ventricular assist device the patient expired. The cause of death was determined to be congestive heart failure. An autopsy was not conducted per the family's request. This event was adjudicated by the CEC/DSMB as definitely related to the procedure but not device-related.

The death rate in ablated subjects in the TTOP-AF trial was 1 in 176 (0.6%).

b) Procedure-related strokes

A total of 5 subjects had strokes which were adjudicated as being related to the procedure during the TTOP-AF trial. Four (4) of the 5 strokes occurred within the first 7 days post-ablation (acute safety event) and one of the 5 strokes developed neuroembolic symptoms approximately 1 month after a retreatment ablation within the chronic period of the study.

(1) Acute Strokes

There were a total of 4 (2.3%, 4/176 subjects) strokes that occurred within the acute period (≥7 days) after an ablation procedure. All 4 subjects who experienced a stroke developed symptoms within 18 hours of the ablation. Two (2) of the 4 subjects had complete resolution of symptoms within the 6-month follow-up period. The other 2 subjects had minor residual effects from the stroke. One subject had unresolved diplopia and disconjugate gaze as of May 2010. The other subject had slight speech impairment as of March 2010. The acute procedural stroke rate was 1.7% (4/239 procedures).

Baseline AF characteristics were compared for those subjects experiencing an Acute Stroke (n=4) compared to the Non-Stroke subjects (n=133) to determine if a difference in an underlying demographic factors existed between the 2 groups. In order to evaluate the risk factors associated with these strokes, the baseline AF characteristics (**Table 21**), and procedural variables of the patients with and without acute strokes were compared (**Table 22** and **Table 23**). Although there was no statistical difference between the two groups there was a trend for the stroke patients to have higher CHADS2 scores, lower procedural INRs, greater LA diameter, and longer procedure times. The key parameters for the 4 acute stroke patients are shown in **Table 24**.

Table 21. Subject Characteristics for Acute Stroke and Non-Stroke Subjects – Ablation Management

Demographics Variable	Ablation Management N=138 Mean ± SD Median (Min, Max)	
	Non-Stroke Subjects N=133[a]	Acute Stroke Subjects N=4
Gender: Male, n (%)	110 (82.7%)	4 (100%)
Age (yrs)	59.6 ± 8.3 61.2 (35.5, 73.4)	58.1 ± 7.7 57.9 (49.1, 67.7)
LVEF (%)	54.5 ± 7.0 55.0 (40.0, 75.0)	61.5 ± 5.1 62.5 (55.0, 66.0)
$CHADS_2$ Score	0.8 ± 0.7 1.0 (0, 3)	1.3 ± 0.5 1.0 (1, 2)
LAD (cm)	4.5 ± 0.5 4.5 (3.2, 5.5)	5.0 ± 0.5 5.0 (4.4, 5.5)

[a] The one subject with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 22. Procedural Anticoagulation for Non-Stroke and Acute Stroke Subjects

Anticoagulation Parameter	Non-Stroke N=133[a] Mean ± SD Median (Min, Max)	Acute Stroke N=4 Mean ± SD Median (Min, Max)
Procedure INR Values (Index Procedure Only)	1.6 ± 0.6 1.3 (0.9, 3.8)	1.2 ± 0.2 1.2 (1.1, 1.5)
Procedure INR Values (Retreatment Procedure Only) N=48	1.6 ± 0.6 1.4 (1.0, 3.7)	N/A
ACT Values During Left Atrial Access (All Procedures)	332.9 ± 35.2 328 (239, 499)	324.9 ± 26.6 319 (302, 360)

[a] The one subject with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 23. Ablation Procedure Dwell Times for Non-Stroke and Stroke Subjects

Ablation Procedure Times	Non-Stroke Subjects N=133[a] Mean ± SD Median (Min, Max)	Acute Stroke Subjects N=4 Mean ± SD Median (Min, Max)
Left Atrial Dwell Time (hrs:min)	2:42 ± 0:48 2:41 (0:20, 5:11)	3:46 ± 1:09 3:38 (2:34, 5:17)
Procedure Time (hrs:min)	3:16 ± 0:53 3:15 (1:18, 5:51)	4:12 ± 1:12 4:04 (2:54, 5:46)

[a] The with chronic stroke is described separately and not included in the Non-Stroke subject data.

Table 24. Key Parameters for the Subjects with Acute Stroke

Parameter	Acute Stroke Subject Number			
	1	2	3	4
$CHADS_2$ Score	1	1	2	1
LVEF-Baseline	65%	66%	55%	60%
LAD – Baseline	5.5 cm	5.0 cm	4.9 cm	4.4 cm
Procedure INRs	1.5	1.1	1.2	1.1
Stroke Resolution	Recovered	Unresolved[a]	Unresolved[b]	Recovered

had unresolved diplopia and disconjugate gaze as of May 2010.
had slight speech impairment as of March 2010.

(2) Acute Strokes, Discussion:

The risk profile of each of the acute stroke patients makes them more susceptible to a thromboembolic event. Apart from the risk factors illustrated in **Table 24**, there are other factors that may also have contributed to these neuroembolic events. They are:

1. *Patient population in TTOP*: All subjects in the TTOP-AF patient population had persistent AF and this could have contributed to observed rate of embolic complications. Such rates have been observed in persistent AF patients undergoing ablation. A large study with retrospective analysis of 3060 patients indicated a stroke rate of 1.8% in ablated patients with persistent AF or long-standing persistent AF as compared to 0.2% in patients with paroxysmal AF[7].

2. *Learning curve*: As noted with acute safety, the stroke incidence was higher for the first few subjects undergoing an ablation procedure rather than for subjects enrolled later at each site. Three (3) of the 4 acute strokes occurred during the first 5 procedures for each investigator. As was seen with the overall procedural complications, these data may suggest that increased operator technical experience with using the System may decrease the overall stroke rate.

3. *Anticoagulation*: Case report data suggests that 2 of the 4 patients may not have had adequate anticoagulation coverage during their "bridging". It is important to ensure that the patient is protected with Lovenox or IV heparin during the period when warfarin is discontinued and reinitiated. Recent publications indicate that a strategy of uninterrupted warfarin may confer even more protection against thromboembolic events, especially in the post ablation period when most patients are vulnerable while waiting to achieve therapeutic INRs[8,9].

(3) Narrative for chronic stroke:

One stroke occurred within the follow-up period for an Ablation Management subject. This subject underwent an acutely successful ablation and a retreatment ablation 3 months later due to AF recurrence. One month after retreatment, the subject complained of diminished bilateral peripheral vision. The subject had an extensive history of eye complaints related to his diabetes. As the subject continued to experience symptoms, an MRI scan was completed, which showed an old infarct in the left occipital region and chronic changes suggestive of small vessel ischemia. Although this was reported as a chronic event one cannot rule out the possibility of an acute event, which would place the subject acute event rate at 5 in 176 (2.8%). This event was adjudicated as being probably related to the ablation procedure and possibly related to the device.

2. TIAs

One (0.6%, 1/176) adjudicated, device/procedure-related TIA occurred in a Medical Management Crossover subject during the trial. This subject developed numbness in the corner of his mouth within 72 hours of the procedure. The numbness resolved without treatment after 72 hours of initial symptoms. The procedural TIA rate was 0.4% (1/239 procedures). **Note**: The FDA considers a second TIA as probably or definitely procedure related that was previously adjudicated by the CEC/DSMB as related to underlying disease.

3. Cardiac Tamponade

There were 3 (1.7%, 3/176 subjects) instances of cardiac tamponade reported during the course of the study. Two (2) of the tamponade events occurred in Ablation Management subjects within the acute period, while the third event occurred in a Medical Management Crossover subject. One of the Ablation Management tamponade events happened after the sheaths were placed and the transseptal puncture was completed without difficulty. When the RSPV was injected as part of pulmonary vein venography, there was the appearance of staining and contrast in the pericardial space. An echocardiogram demonstrated a growing pericardial effusion and the procedure was terminated. The second tamponade event in an Ablation Management subject occurred during the transseptal puncture. There were documented blood pressure changes when performing the transseptal puncture, a cardiac tamponade was diagnosed and the ablation procedure

was aborted. Note that the 2 Ablation Management subjects did not have an investigational catheter deployed during these events and they fully recovered shortly after the procedures. Both tamponade events were adjudicated as being definitely related to the procedure. One of the events was also adjudicated as being possibly related to the device and the other was not related to the device.

The third subject (Medical Management Crossover) had an acutely successful ablation procedure, but experienced hypotension several hours after the ablation procedure. After draining the pericardial effusion, the subject remained stable and was discharged 9 days post-ablation. This event was adjudicated as being definitely related to the procedure and possibly related to the device. The overall procedural tamponade rate was 1.3% (3/239 procedures).

4. Pulmonary Vein Stenosis

CT/MRI imaging was used to detect pulmonary vein stenosis in the TTOP-AF trial. Baseline and 6 month post ablation procedure scans were compared to assess for pulmonary narrowing (50% -70% reduction in PV diameter) or stenosis (>70% in PV diameter). Pulmonary vein stenosis was noted in 7 (4.0%, 7/176) subjects involving one vein. Five (5) of the 7 subjects were in Ablation Management and the remaining 2 were Medical Management Crossover subjects. Only 1 of the stenosis subjects experienced symptoms and required an intervention. The remaining 6 subjects were asymptomatic. The procedural stenosis rate was 2.9% (7/239 procedures).

5. Esophageal Perforation, Atrio-Esophageal Fistula, Phrenic Nerve Injury

There were no reported instances of esophageal perforation, atrio-esophageal fistula or phrenic nerve injury noted during the study.

C. Effectiveness Results

The primary endpoint for chronic effectiveness evaluating the proportion of ITT subjects with treatment success computed at the 6 month visit was met.

The proportion of subjects considered primary efficacy treatment successes (meeting all success criteria) was 55.8% (77 of 138 subjects) for the Ablation Management arm and 26.4% (19 of 72 subjects) for the Medical Management arm, yielding an absolute percentage point difference of 29.4% that was statistically significant ($p<0.0001$) to meet the primary effectiveness objective (**Table 25**). The passive imputation technique requires that missing endpoints be counted as failures. The proportion of subjects receiving an ablation that were treatment successes was 58.3% (77 of 132 subjects).

Table 25. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Success at the 6-Month Follow-Up Visit

Chronic Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)	Medical Mgmt. N=72 n (%)	p-value for H_0: $P_A \leq P_M$[a]
Subjects receiving an ablation with device	132 (95.7%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	
Subject off all AADs at 6 month follow-up[b]	95 (68.8%)	N/A	
≥90% reduction in clinically significant AF[c]	93 (67.4%)	19 (26.4%)	
Subjects meeting all success criteria	**77 (55.8%)**	**19 (26.4%)**	**<0.0001**
Number of Missing Endpoints[d]	17	15	

[a] Chi-Squared test
[b] Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
[c] Ablation Management success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording to be considered for treatment success.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

D. Additional Effectiveness Results

Medtronic understands that the efficacy results for catheter ablation in the persistent AF patient population is relatively unknown. As this was the first randomized, controlled clinical trial in the persistent AF population, multiple ad hoc analyses were performed. In addition, the impact of the significant reduction in AF burden that occurred for subjects receiving an ablation on their quality of life was also evaluated.

The efficacy evaluations explored in this section include:

- The effectiveness outcome at 12-months for all subjects who provided 12-month data.
- The effectiveness of ablation in conjunction with the use of AADs at 6 and 12 months.
- The impact of ablation effectiveness for persistent AF patients as reported using AF Symptom Severity Scores and Quality of Life Measures.

1. Outcome for 12-Month Effectiveness Evaluated with All 12-Month Data

Although the TTOP-AF protocol defined a 6 month follow-up and effectiveness endpoint, the FDA requested efficacy analysis based on 12-month data. At FDA's request, every attempt was made to obtain 12-month follow-up data for all TTOP-AF pivotal subjects. All TTOP-AF randomized subjects were asked to consent to a 12-month visit and provide a 48-hour Holter for efficacy evaluation.

The outcome of the Holter requests at 12 months is summarized in **Table 26**. A total of 95 Holters were obtained at 12 months from subjects that had been ablated during the TTOP-AF study, consisting of 71 Holters from Ablation Management subjects and 24 Holters from Medical Management subjects that crossed over to receive an ablation. Another 12 Holters were obtained from Medical Management subjects that did not crossover to receive an ablation and continued treatment with AADs and DC cardioversions within the 6 to 12 month period. The remaining 103 subjects either withdrew from the study (23 subjects), refused to participate or the site refused to participate (67 subjects), or a 12 month visit was completed but no Holter obtained (13 subjects). Although 210 subjects participated in the TTOP-AF pivotal portion of the trial, 107 subjects were willing to undergo the required testing for evaluation of 12-month efficacy.

Table 26. Outcome of 12-Month Holter Requests

Outcome of Holter Request	Ablation Mgmt. (Ablated) N=138	Medical Mgmt. Crossovers (Ablated) N=43	Medical Mgmt. (No Crossovers) N=29	Total N=210
Subjects withdrawn	13	4	6	23
Subject/Site Refusal	46	12	9	67
Visit done, Holter not completed	8	3	2	13
Holters Completed	**71**	**24**	**12**	**107**

Long-term efficacy for the TTOP-AF trial was evaluated from all data obtained at 12 months. A total of 67 ablated subjects had a ≥90% reduction of the sum of cumulative time ≥ 10 minute AF/AFL episodes and who were off all AADs at 12 months (regardless of their status at 6 months) (**Table 27**). This resulted in a 70.5% (67/95 subjects) 12-month effectiveness success rate, which was 13.3% absolute percentage points higher than the 6-month effectiveness rate for the combined Ablation Management and Crossover population (57.2%).

All 12 subjects that were treated with medical therapy during TTOP-AF and the post-study period achieved ≥90% reduction in clinically significant AF at 12-months. Therefore, the 12-month success rate remained at 100% (12 subjects). This high rate of efficacy is not truly reflective of the 12 month success rate since the majority of subjects (59.7%) that failed Medical Management crossed over to receive an ablation (43 of 72 Medical Management subjects) and are unable to be evaluated for success with medical therapy at 12 months since they were treated by ablation after 6 months. The 6-month success rate (26.4%) was maintained for those subjects treated with medical therapy during the 6 to 12 month post-study period, which resulted in a 33.3% absolute percentage point difference when compared to the effectiveness of ablation at 12 months.

Table 27. Treatment Success Evaluated at 12-Months

	Ablation Subjects (Ablation Mgmt.+Crossovers) with 12-Month Data Obtained…					Medical Management Subjects with 12-Month Data Obtained…		
Chronic Efficacy Success Criteria at 12 months	And also 6 Month Treatment Successes N=62			And also 6 Month Treatment Failures N=33	All 12-Month Successes[a] N=95 n (%)	And also 6 Month Treatment Successes N=12	And also 6 Month Treatment Failures N=0	All 12-Month Successes N=12 n(%)
	Randomized (n=48)	Crossover (n=14)	Total (n=62)					
Without AAD	39	11	50 (80.6%)	17	67 (70.5%)	0	0	0
With AAD						12	0	12 (100%)

[a] The "All 12-Month Successes" consists of those subjects who were treatment successes at 12 months regardless of their treatment status (success or failure) at 6-months.

2. Effectiveness of Ablation in Conjunction with AADs

Although not considered a treatment success for endpoint analysis, the benefit of using an AAD to manage AF/AFL recurrence for ablated subjects was analyzed since all TTOP-AF subjects were drug refractory at enrollment (**Table 28**). Sixteen (16) subjects achieved ≥90% reduction of the cumulative time for both 10-minute and 30-second AF/AFL episodes, with the help of an AAD at 6 months. If these 16 additional subjects were now considered successes and added to the 77 subjects considered treatment successes without the use of an AAD, a total of 93 (67.4%) Ablation Management subjects benefited from ablation regardless of whether 10-minute or 30-second AF/AFL episodes were used to evaluate efficacy. When the 6 subjects who did not receive an ablation using the Medtronic catheters are excluded from the analysis, the ablation effectiveness was 93/132 (70.4%).

TTOP-AF effectiveness was also evaluated for those subjects who had no episodes of AF/AFL ≥30 seconds at 6 months. Another 15 subjects had **no** ≥30 second AF/AFL episodes with the help of an AAD at 6 months. If these 15 additional subjects are now considered successes and added to the 70 subjects considered treatment successes without the use of an AAD, a total of 85 (61.6%) Ablation Management subjects benefited from ablation. Although these 15 subjects did not meet the primary effectiveness criteria for the study, they benefited from ablation as an AAD was now effective at managing their AF. When the 6 subjects who did not receive an ablation using the Medtronic catheters are excluded from the analysis, the ablation effectiveness was 85/132 (64.4%).

Finally, the benefit of using an AAD on the effectiveness outcome was evaluated at 12-months. Another 8 ablated subjects could effectively manage their AF when using an AAD at 12-months to achieve ≥90% reduction in the cumulative time of ≥10-minute

episodes of AF/AFL. If these subjects were also considered successes, the resulting efficacy rate at 12-months is 78.9% (75/95 subjects).

Although ablated subjects using an AAD to help manage their AF were not considered treatment successes for determination of the TTOP-AF primary effectiveness endpoint, subjects clearly benefited from the use of an AAD no matter which endpoint measurement was used for determination of effectiveness. These data are strong efficacy results considering the advanced state of AF and the drug refractory status at enrollment for this subject population.

Table 28. Treatment Success for Ablated Subjects with and without the Use of an AAD Using Multiple Endpoint Criteria at 6 and 12 Months

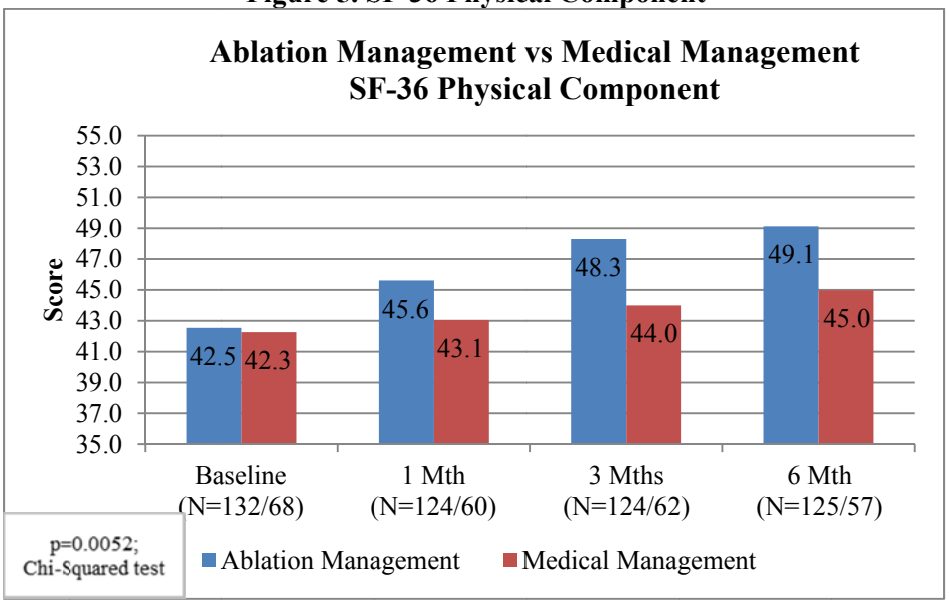
Effectiveness Endpoint Criteria	Number of Treatment Successes without an AAD	Number of Treatment Successes with an AAD	Total Treatment Successes (± AAD)	Total Treatment Successes (± AAD) for Only Subjects Treated with the System
Effectiveness at 6 months, N=138				**N=132**
≥90% reduction of cumulative 10-minute AF/AFL episodes	77	16	93 (67.4%)	93 (70.4%)
≥90% reduction of cumulative 30-second AF/AFL episodes	77	16	93 (67.4%)	93 (70.4%)
No ≥30 second AF episodes	70	15	85 (61.6%)	85 (64.4%)
Effectiveness at 12 months N=95				
≥90% reduction of cumulative 10-minute AF/AFL episodes	67	8	75 (78.9%)	

3. AF Symptom Severity and Quality of Life Outcomes

The SF-36 QOL questionnaire is an accepted instrument to measure the impact of therapy on a subject's physical and mental well-being. Validation of the SF-36 QOL has demonstrated that a change of 5 points or more is clinically meaningful and indicative of a positive impact by a given treatment[10]. The TTOP AF trial utilized the SF-36 QOL questionnaire to determine the impact of ablation management or medical management of persistent AF on the physical and mental well-being of randomized subjects.

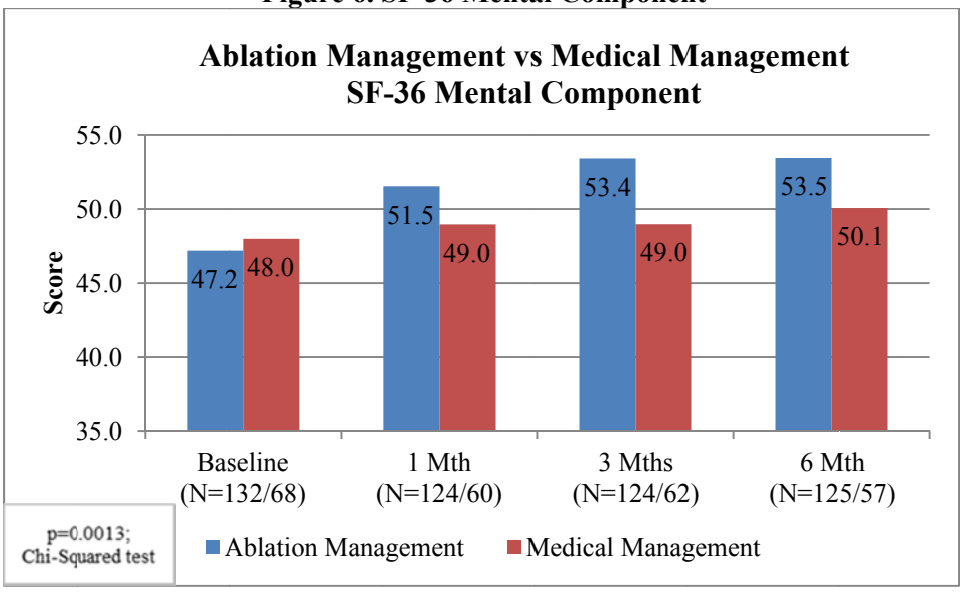
The ablation management subjects had clinically meaningful changes in their physical well-being (6.6 point improvement) as opposed to the medical management subjects (2.7 point improvement) (**Figure 5**).

Figure 5. SF-36 Physical Component



Similar results were seen in the mental component of the SF-36 QoL in the Ablation Management subjects (6.3 point improvement) compared to Medical Management subjects (2.1 point improvement) (**Figure 6**).

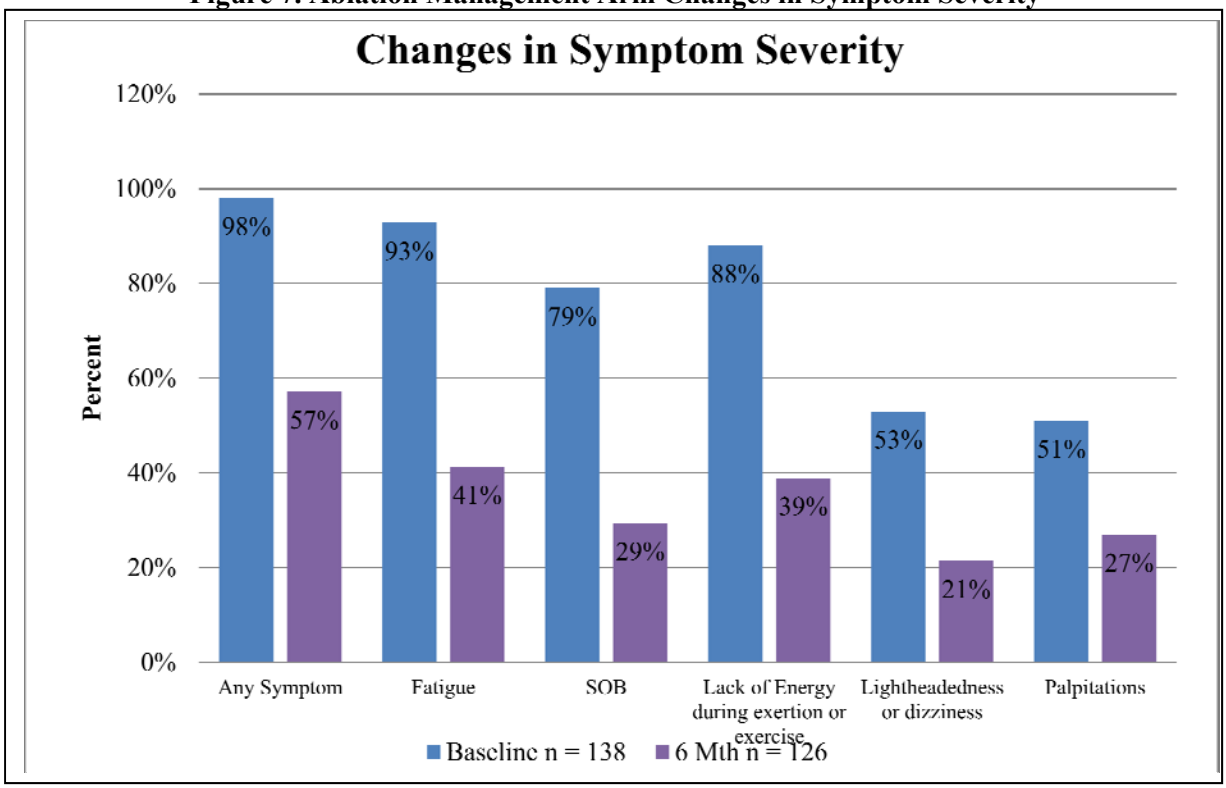
Figure 6. SF-36 Mental Component



These data demonstrate that the Ablation Management subjects had clinically improved physical and mental well-being due to Ablation Management unlike the Medical Management group that did not demonstrate a clinical improvement in physical or mental well-being.

The SF-36 QoL scores are corroborated by the changes in symptoms related to AF. **Figure 7** below illustrates the changes in symptoms from baseline compared to 6 months for the Ablation Management subjects. Nearly all Ablation Management subjects reported an AF related symptom (98%) at baseline and at 6-months the proportion of Ablation Management subjects with an AF symptom had been reduced to 57%, which was statistically significant (p<0.0001).

Figure 7. Ablation Management Arm Changes in Symptom Severity



E. Overall Conclusion from Clinical Data

The results of the TTOP-AF pivotal trial demonstrate that the Medtronic Cardiac Ablation System consisting of the GENius generator and 3 ablation catheters (PVAC, MAAC, and MASC) met the protocol specified effectiveness endpoint with an acceptable safety profile.

Pre-Clinical Testing

Pre-clinical testing of the Cardiac Ablation System included verification and validation testing (device level, system level, and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies. The results of this testing confirmed that when used in accordance to the intended use, the benefits in

using the Medtronic Cardiac Ablation System to treat persistent and long-standing persistent AF outweighs the risks to the patient.

TTOP-AF Clinical Trial

The overall safety profile of the Medtronic Cardiac Ablation System is comparable to other treatment alternatives that currently exist for the persistent/long-standing persistent AF population. In addition, ablation provides an alternative therapy choice for subjects in whom AADs are intolerable or ineffective, and/or require serial cardioversions or in whom invasive procedures such as open heart surgical treatment or permanent rate control (ablate and pace) are an unwanted consideration.

The data in this application support the reasonable assurance of safety and effectiveness of the devices when used in accordance with the indications for use. Ablated subjects demonstrated statistically better effectiveness and overall improvement in their quality of life compared to medical management of AF. The risks associated with the device were acceptable and consistent with alternative treatments. In conclusion, the clinical benefits of ablation using the Medtronic Cardiac Ablation System for the treatment of persistent/long-standing persistent AF, exceeds the clinical risks associated with the procedure and alleviates the increased risk for stroke[11,13], dementia,[13] and death[12,13] that is associated with untreated persistent and long-standing persistent atrial fibrillation.

XIV. Implied Claims

TBD

XV. SSED vs. Device Labeling

"Off-Label" Use

TBD

Contraindications Based on Clinical Trial Data

TBD

Special Patient Populations

TBD

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Proposed Labeling

LABELING

Relevant product manuals for the Medtronic Cardiac Ablation System (the 'System') are provided in this Section of the Panel Pack.

Clinical Study Summary sections in the Technical Manuals for the PVAC, MASC, and MAAC do not contain final data. These Clinical Study Summary sections are provided to show the structure of the labeling only; when FDA and Medtronic determine final data that should be included, the Manuals will be updated accordingly.

MANUALS

Table 1 provides a listing of the manuals provided in this Section of the Panel Pack.

Table 1: Manuals for the Medtronic Cardiac Ablation System

Document Title	Attachment(s)
GENius Multi-Channel RF Ablation Generator Operator's Manual	1
Pulmonary Vein Ablation Catheter (PVAC) Technical Manual	2
Multi-Array Septal Catheter (MASC) Technical Manual	3
Multi-Array Ablation Catheter (MAAC) Technical Manual	4

Attachment 1: Generator Manual

Medtronic

990018 GENius™ Multi-Channel RF Ablation Generator

Operator's Manual

Caution: Federal Law (USA) restricts this device to sale by or on the order of a physician.

990018 GENius™ Multi-Channel RF Ablation Generator

Operator's Manual

A guide for setting up and using the 990018 generator and its components.

The following list includes trademarks or registered trademarks of Medtronic in the United States and possibly in other countries. All other trademarks are the property of their respective owners.

Ablation Frontiers, GENius, Medtronic, Multi-Array Ablation Catheter, MAAC, Multi-Array Septal Catheter, MASC, Pulmonary Vein Ablation Catheter, and PVAC

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Explanation of symbols

Refer to the package label and the product to see which symbols apply. The symbols that immediately follow appear on packaging.

SN	Serial number
REF	Reorder number
!	Caution
LOT	Lot number
	Keep dry
	Manufacturer
STERILE EO	Sterilized using ethylene oxide
	Use by
EC REP	Authorized representative in the European Community
	Package contents
	GENius Multi-Channel RF Ablation Generator
	GENius Jr. Remote Control
	ECG Interface Box
	Cable
	Power cord

Operator's Manual

	Consult instructions for use
	Product documentation
− XX °C − XX °F + XX°C + XX°F	Temperature limitations
XX% XX%	Humidity limitations

The symbols that follow appear on the generator or its components.

	Duration up
	Duration down
	Temperature up
	Temperature down
	Equipotentiality (chassis ground)
	Output power (non-ionizing electromagnetic radiation)
	Alternating current
XXX XXXX	Caution: use only fuse rated at the indicated voltage, current, operating speed, and breaking capacity
	Defibrillation Proof Type CF applied part
F	Patient return electrode
	Start button

	Stop button
	Standby button
! USA	For US audiences only
	Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.
	Do not use if package is damaged
	Nationally Recognized Testing Laboratory; Certification to electrical safety requirements of CAN/CSA-C22.2 No. 601-1-M90 and UL 60601-1:2003.

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Description and intended use

The Model 990018 Medtronic GENius Multi-Channel RF Ablation Generator delivers temperature-controlled radiofrequency (RF) energy to user-selectable electrodes on compatible Medtronic multi-electrode cardiac ablation catheters.

The generator automatically recognizes the attached cardiac ablation catheter and programs preset default temperature, ablation duration, and energy mode setting parameters. Ablation parameters, including ablation duration, energy mode, target temperature, and channels (electrode pairs), can also be manually selected. A display screen monitor is available for viewing real-time system and ablation parameters.

The generator features the following RF energy mode selections: bipolar only, unipolar only, and combination ratios of bipolar:unipolar energy mode selections of 1:1, 2:1, and 4:1.

An ECG interface box connects the catheter with the generator, patient return electrodes, the external monitoring equipment, and the pacing equipment that can be used during the procedure.

Warnings

Note: For catheter-specific warnings, refer to the technical manual for the catheter being used.

X-ray and fluoroscopic exposure – Minimize x-ray and fluoroscopic exposure. Due to the x-ray beam intensity and the duration of the fluoroscopic imaging during ablation procedures, patients and laboratory staff may be subjected to acute radiation injury and increased risk for somatic and genetic effects. Take all appropriate measures to minimize x-ray exposure to both patients and clinical staff. The long-term effects of protracted fluoroscopy have not been established.

High electrode temperatures – Only use catheters as recommended, maintain catheter contact with cardiac tissue during ablation, and monitor the displayed electrode temperatures and power delivery, in order to avoid high instantaneous electrode temperatures. Temperatures above 80 °C during ablation may increase the patient's risk of thromboembolic events (formation of coagulum), steam pops, and cardiac perforation, depending on catheter type used.

- Only use catheter in the recommended anatomical location.
- Maintain catheter contact with cardiac tissue by holding the catheter during the ablation.
- Do not reposition, rotate, slide, drag or otherwise intentionally disengage and then re-engage the catheter electrodes with cardiac tissue while ablating. Stop ablation prior to performing any of these actions.
- Monitor the displayed electrode temperature and power delivery during ablation. For Medtronic's APVAC, PVAC, MAAC, and MASC, deselect the affected electrode pair or discontinue ablation in any of the following cases:
  - If the electrode does not reach 50 °C and is receiving maximum power delivery.
  - If the electrode is not at target temperature and the power is not at maximum (based on selected energy mode).
  - If power and temperature levels are continuously fluctuating.

Use of RF energy near implanted devices – Implantable devices, such as pacemakers and implantable cardioverter-defibrillators (ICDs), may be inhibited or otherwise affected by RF energy. Since RF ablation therapy may affect implantable devices:

- Have temporary pacing and defibrillation equipment available.
- Program pacemaker sensing parameters to VOO or DOO to ensure that RF energy is not sensed as an intrinsic event.
- Program ICD detection parameters to OFF or MONITOR to ensure that the RF energy is not sensed and inappropriately treated as a ventricular fibrillation episode.
- Monitor surface and/or intracardiac electrograms and/or vital signs during RF energy delivery to assess for device interaction. Take appropriate action if any interaction is detected.
- Reprogram and confirm all parameters of implantable devices after an RF ablation procedure.
- Exercise extreme caution when delivering ablation energy in close proximity to implanted leads.
- Refer to the appropriate implantable device technical manual for additional information.

Electrical isolation during ablation – Do not allow the patient to contact grounded equipment that might produce electrical current leakage during ablation or DCCV (Direct Current Cardioversion). Electrical current leakage may induce arrhythmias that may result in the patient's death.

Placement of monitoring electrodes – Place all physiological monitoring electrodes as far away as possible from the patient return electrodes and their leads to avoid RF interference affecting the ability to interpret patient electrocardiograms (ECGs).

Generator settings or equipment failure – Do not increase target temperature or ablation duration settings before checking for obvious defects or misapplication, as patient injury may occur. Apparent low power output or failure of the equipment to function correctly at normal settings may indicate faulty application of the patient return electrodes or failure of an electrical lead.

Electromagnetic interference (EMI) radiated – The generator emits RF energy during ablation at a frequency level that may cause EMI with unshielded electronic equipment. To minimize EMI, the generator should be moved away from any other electronic device. If EMI is apparent during the application of RF energy, EMI may be reduced by repositioning the generator or other equipment.

Electromagnetic interference (EMI) susceptibility – The generator has been designed to minimize electromagnetic interference (EMI). If interference should occur, move the generator away from the device generating the interference or place the generator at a different angle.

Cable positioning – Position all cables associated with the generator so they do not come in contact with the patient or other leads. RF interference may affect the ability to interpret patient ECGs.

Leakage current from connected devices – Use only isolated amplifiers, pacing equipment, and ECG equipment (IEC 60601-1 Type CF equipment, or equivalent), as patient injury or death may occur. Do not allow leakage current from any connected devices to the patient to exceed 10 microamperes (µA) under any circumstances.

Equipment modification – Do not modify this equipment. Modifications may reduce system effectiveness and impact safety.

Flammable materials – Do not allow flammable material in the area where RF ablation procedures are performed. The risk of igniting flammable gases, flammable agents used for cleaning or disinfecting, or other materials is inherent in the application of RF energy.

Long-term risk – The long-term risks of lesions created by RF ablation have not been established. In particular, the long-term effects of lesions in proximity to the specialized conduction system or coronary vasculature are unknown.

No direct skin contact during system testing – Do not test the operation of the ablation system through direct contact with the electrodes. Testing through direct skin contact may cause damage to healthy tissue.

EP recording systems – Use only high-frequency, current-limiting EP recording systems or patient injury may occur.

Equipment stability during use – Do not disturb or move the generator, ECG interface box, or cables while the catheter is positioned within the patient, as patient injury may occur.

System compatibility – Use only the following components with the Medtronic GENius Multi-Channel RF Ablation Generator: the supplied Medtronic ECG interface box and cable, GENius Jr. Remote Control and cable, compatible Medtronic multi-electrode cardiac ablation catheters, compatible Medtronic catheter interface cables, the supplied Medtronic ECG amplifier cable, and Valleylab Patient Return Electrodes (Model E7506, two required). The safety and use of the system with other catheters or components have not been tested.

Proper use of patient return electrodes – Use only the designated Valleylab Patient Return Electrodes (Model E7506, two required) when operating the ablation system. Prepare the area where the patient return electrodes are attached in accordance with the patient return electrode manufacturer documentation. For best contact, avoid areas with adipose tissue, bony prominences, fluid invasion, scar tissue, and excess hair (shave the patient if necessary). Incorrect use of the patient return electrodes may reduce efficacy and patient safety during ablation.

Grounded wall outlet – To avoid the risk of electric shock, this equipment must only be connected to supply mains with protective earth (grounded receptacle).

Unintentional power output – Failure of the ablation equipment can result in an unintentional power output increase. An unintentional power output increase may impact patient safety.

Stimulation equipment – Certain stimulation equipment may alter the RF energy waveform, which may trigger atrial fibrillation on rare occasions. To eliminate the influence of stimulation equipment during ablation, disconnect the stimulation equipment while ablating.

Precautions

Related product literature – Do not attempt to operate this Medtronic cardiac ablation system prior to completely reading and understanding the GENius Multi-Channel RF Generator operator's manual and the technical manual of the compatible Medtronic cardiac ablation catheter.

Required use environment – Cardiac ablation procedures should be performed only in a fully equipped electrophysiology laboratory.

Qualified users – This equipment should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this Medtronic multi-channel RF ablation generator and compatible catheters.

Regular inspection – Regularly inspect reusable cables for visual evidence of damage.

Disposal of system components – Contact Medtronic for the return of non-disposable components. The following components are considered non-disposable: generator, ECG interface box, remote control, and cables.

Generator placement – Place the generator on a level surface. Do not place other equipment on top of the generator. Do not place the generator on top of other equipment.

Overheating the generator – Do not place the generator near heat-generating equipment. Do not block cooling inlets or outlets on the generator.

Fluid incursion – The generator may not function correctly if the electronic circuitry or the connectors are wet:

- Do not allow any fluid or moisture into the generator, the ECG interface box, or the cables.
- Do not hang fluids above the generator.
- Do not immerse the cables into fluids.

Indications

See the technical manual for the catheter being used.

Contraindications

See the technical manual for the catheter being used.

Potential adverse events

See the technical manual for the catheter being used.

Compatible components

The following components are used with the generator. For more details, see Appendix A: GENius generator components on page 59.

- ECG Interface Box, Model 990028
- ECG Interface Box Cable, Model 990020
- ECG Amplifier Cable, Model 990027
- Catheter Interface Cable, Model 990004 (supplied sterile)
- Two Valleylab Patient Return Electrodes (Model E7506) (required but not supplied)
- Compatible Medtronic cardiac ablation catheters (not supplied)
- GENius Jr. Remote Control, Model 990029 (optional)
- Remote Control Cable, 15 ft (4.57 m), Model 990041(optional)
- Remote Control Cable, 25 ft (7.62 m), Model 990042 (optional)

Generator controls and connections 2

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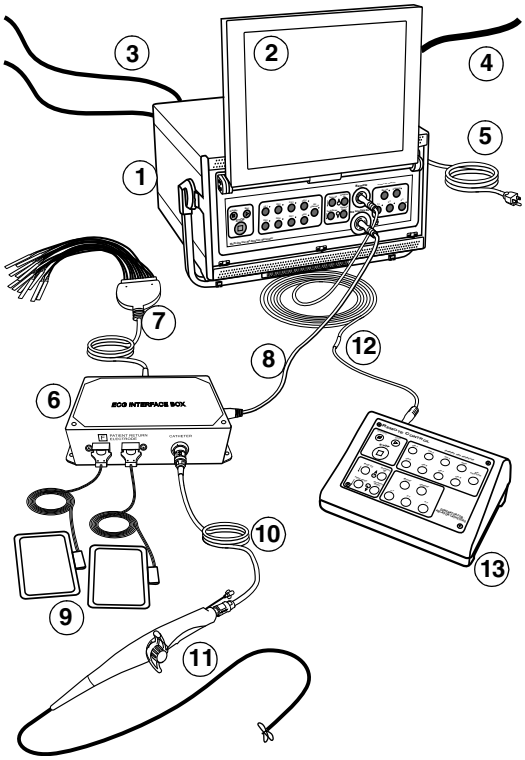
System overview

Figure 2-1 shows connections among the generator, its components, the patient return electrodes, and a compatible catheter.



1 GENius cardiac ablation generator
2 Monitor
3 VGA monitor cables (not included)
4 Equipotentiality (chassis ground) cable (not included)
5 Power cord
6 ECG interface box
7 ECG amplifier cable
8 ECG interface box cable
9 Patient return electrodes (not included)
10 Catheter interface cable
11 Catheter (not included)
12 (Optional) Remote control cable
13 (Optional) GENius Jr. remote control

Figure 2-1. The generator, its components, patient return electrodes, and catheter

Operating modes

The GENius Multi-Channel RF Ablation Generator incorporates three separate modes of operation: Setup, Standby, and Ablation.

Setup mode

The Setup mode is used to set the following parameters prior to initiating an ablation:

- Channels (system default is Off)
- Duration (system default is 60 seconds)
- Target temperature (system default is 60 °C)
- Energy mode (system default provided for each catheter) - see “Energy mode power limits” on page 45

Standby mode

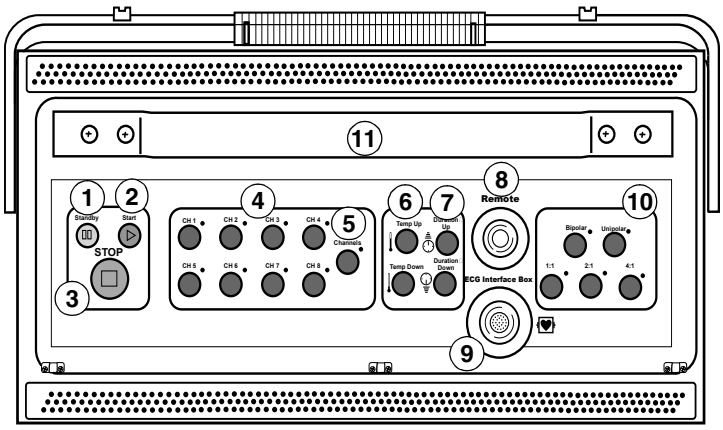
The Standby mode displays electrode temperature information for all selected channels.

Ablation mode

The Ablation mode starts the ablation sequence according to the front panel settings.

Front panel

Figure 2-2 shows the front panel of the generator, where controls are available for operation. The panel also provides receptacles for the ECG interface box and the optional remote control.



1 Standby button
2 Start button
3 STOP button
4 Channel buttons
5 All Channels button
6 Target temperature adjustment buttons
7 Ablation duration adjustment buttons
8 Remote control cable receptacle
9 ECG interface box cable receptacle
10 Energy mode buttons
11 Monitor handle

Figure 2-2. Generator front panel and monitor handle

Standby button

After the catheter has been positioned for ablation and prior to initiating an ablation, the **Standby** button is used to display electrode temperature information for all selected channels. **Standby** is also used to reset the Cumulative RF usage display (see “Cumulative RF usage display” on page 35).

Note: Press and hold the **Standby** button for 3 seconds to reset the Cumulative RF usage display.

Start button

The **Start** button begins energy delivery according to the front panel settings. During the ablation, a continuous audible tone is emitted, indicating that energy is being delivered. When complete, an end-of-ablation audible tone (beep) sounds.

STOP button

The **STOP** button can be pressed anytime during an ablation sequence to immediately stop energy delivery. When the **STOP** button is pressed, the end-of-ablation audible tone (beep) sounds and the generator enters Setup mode.

Channel buttons

While in Setup mode, with the catheter connected, channels (electrode pairs) can selectively be turned On or Off for ablation. Each channel button (channels 1–6) corresponds to a pair of electrodes and includes an indicator that is illuminated when selected. Channels 7 and 8 are non-functional.

All Channels button

The **All Channels** button is available to select or de-select all channels with a single press. Channels can be de-selected during ablation. The default setting for channel selection is all electrode channels off.

Target temperature adjustment buttons

The target temperature can be adjusted (set) during Setup mode or Ablation mode. Push the **Temp Up** button to increase the target temperature and **Temp Down** button to decrease target temperature. Adjustments can be made from 50 °C to 70 °C in increments of 1 °C.

Ablation duration adjustment buttons

The value (in seconds) for ablation duration can be selected during Setup mode. Adjustments can be made from 45 to 120 seconds in 5-second increments.

Remote control cable receptacle

This receptacle accepts the connector from the optional remote control cable.

ECG interface box cable receptacle

This receptacle accepts the connector from the ECG interface box cable.

Energy mode buttons

The generator features these RF energy mode selections: bipolar only, unipolar only, and combination energy mode selections of 1:1, 2:1, and 4:1. The first number of the combined energy mode selection refers to the bipolar component, and the second number refers to the unipolar component. For example, in the 1:1 energy mode, both bipolar and unipolar are equally distributed over time. The generator also employs a software power limit based on the energy mode selected.

Bipolar button

The **Bipolar** button is used to select bipolar energy delivery. When selected, its indicator is illuminated.

Unipolar button

The **Unipolar** button is used to select unipolar energy delivery. When selected, its indicator is illuminated.

1:1 button

The **1:1** button is used to select bipolar-to-unipolar energy at a 1:1 ratio. When selected, its indicator is illuminated.

2:1 button

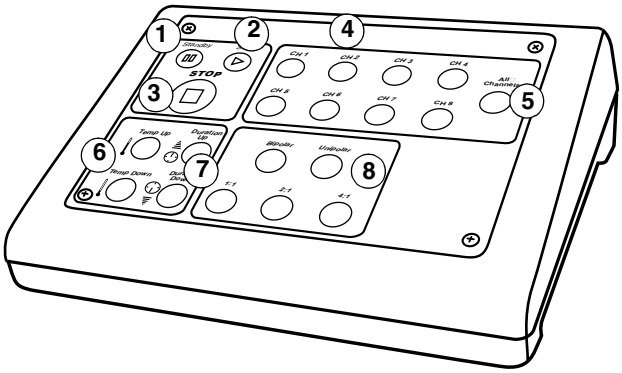
The **2:1** button is used to select bipolar-to-unipolar energy at a 2:1 ratio. When selected, its indicator is illuminated.

4:1 button

The **4:1** button is used to select bipolar-to-unipolar energy at a 4:1 ratio. When selected, its indicator is illuminated.

Remote control panel

If used, the remote control provides the same ablation controls as the front panel (see “Front panel” on page 22). Figure 2-3 shows the layout of the remote control panel.

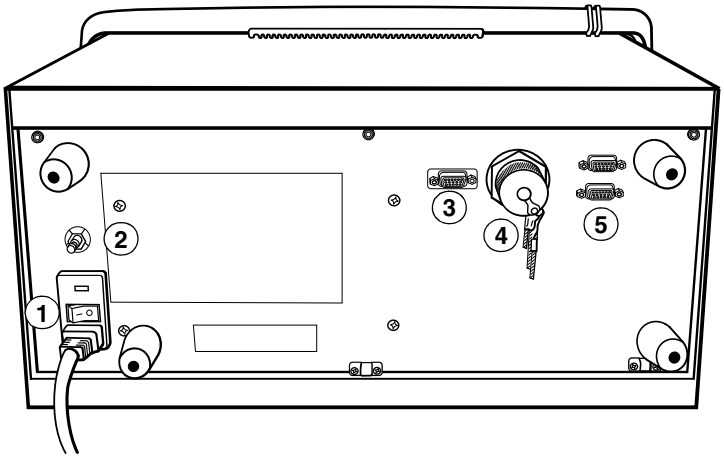


1 Standby button
2 Start button
3 STOP button
4 Channel buttons
5 All Channels button
6 Target temperature adjustment buttons
7 Ablation duration adjustment buttons
8 Energy mode buttons

Figure 2-3. Remote control panel

Rear panel

The rear panel of the generator provides the following receptacles and connectors:



1 Power input receptacle
2 Equipotential (chassis ground) receptacle
3 RS-232
4 USB connector
5 VGA Out connectors

Power input receptacle

The power input receptacle accepts the connector from the hospital-grade power cord (supplied) and includes the main On/Off switch.

Equipotential (chassis ground) receptacle

This single contact receptacle provides a positive connection to the generator chassis. Connecting a ground wire cable to this receptacle is recommended.

RS-232 connector

The RS-232 connector is for use by Medtronic personnel only.

USB connector

This covered USB connector is for use by Medtronic personnel only.

VGA Out connector (2)

These two receptacles are used for connection to the IEC 60601-1 approved external VGA monitors.

Display screens 3

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Sample system message display 36

The generator provides information on screens to assist with setup and give real-time information during the Ablation and Standby modes.

Language selection instruction display

Upon startup, the generator displays a splash screen with multilingual instructions for selecting from available languages (Figure 3-1). Selection determines the language in which system messages and other text are displayed.

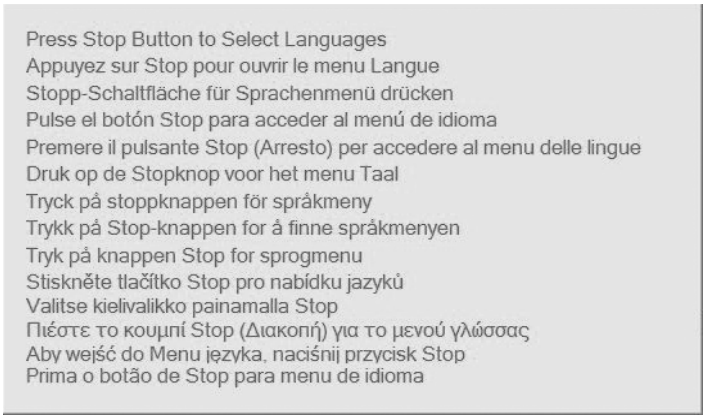


Figure 3-1. Language selection instruction display

After the user follows on-screen instructions to press STOP, the generator displays a key to available languages (Figure 3-2).

CH1 = Danish CH5 = Polish
CH2 = Czech CH6 = Portuguese
CH3 = Finnish
CH4 = Greek
Press Stop Button for Language Menu
Appuyez sur Stop pour ouvrir le menu Langue
Stopp-Schaltfläche für Sprachenmenü drücken
Pulse el botón Stop para acceder al menú de idioma
Premere il pulsante Stop (Arresto) per accedere al menu delle lingue
Druk op de Stopknop voor het menu Taal
Tryck på stoppknappen för språkmeny
Trykk på Stop-knappen for å finne språkmenyen
Tryk på knappen Stop for sprogmenu
Stiskněte tlačítko Stop pro nabídku jazyků
Valitse kielivalikko painamalla Stop
Πιέστε το κουμπί Stop (Διακοπή) για το μενού γλώσσας
Aby wejść do Menu języka, naciśnij przycisk Stop
Prima o botão de Stop para menu de idioma

Figure 3-2. Language selection key display

Instructions direct the user to press the corresponding Channel button to select a language, or to press STOP for more languages.

These screens are displayed at startup only.

Patient return electrode placement image

Prior to ablation, the display indicates patient electrode placement (see Figure 3-3).

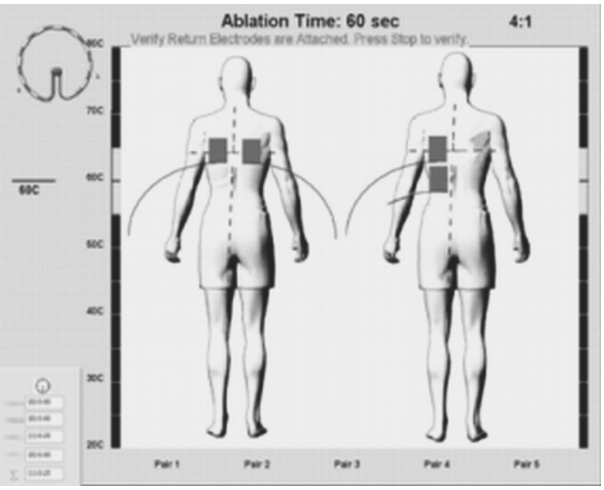


Figure 3-3. Patient electrode return placement image

Operator's Manual

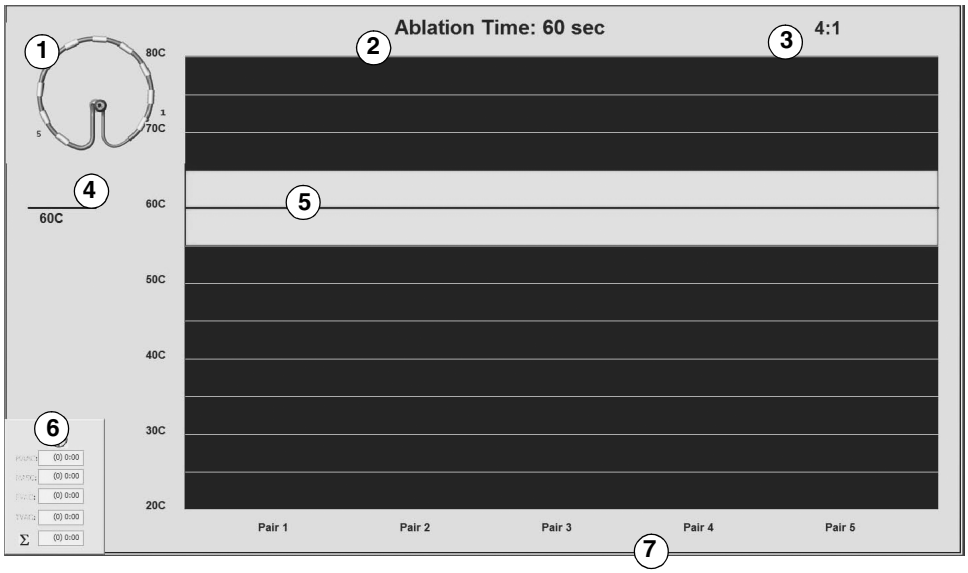
This screen is displayed:

- After the generator has successfully initialized and after the language selection screen has timed out.
- After the Cumulative RF usage display has been reset.
- After one hour with no generator use.

Patient return electrode placement can be verified by pressing the STOP button.

Setup Screen

In Setup mode, the Setup screen allows for the selection of ablation settings, as shown in Figure 3-4.



1 Catheter image
2 Ablation Time; starts incrementing after the initiation of ablation and counts up to the selected value for ablation duration
3 Energy mode identifier
4 Target temperature in °C
5 Target temperature range (±5 °C of the target temperature)
6 Cumulative RF usage display – data may vary
7 Selectable channels (pairs)

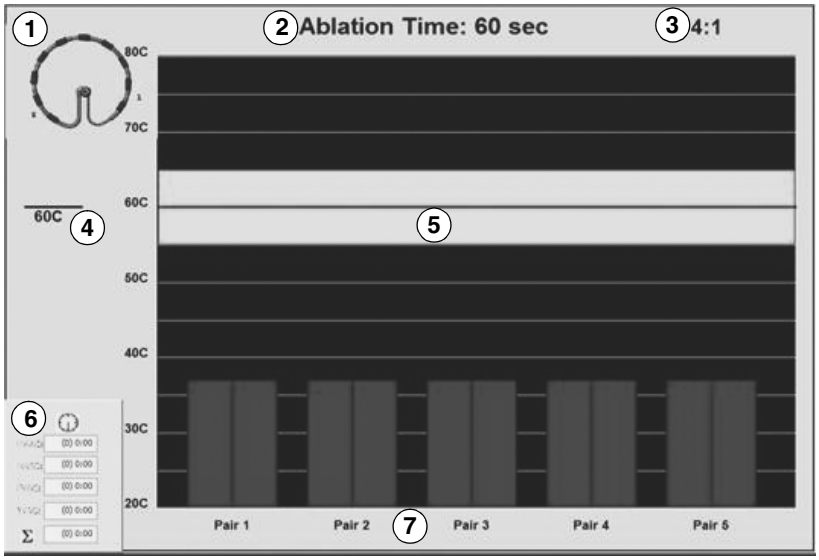
Figure 3-4. Setup Screen

This screen is displayed:

- Upon initialization, if no error conditions are detected and after the patient return electrode placement image has been dismissed
- Immediately after an ablation sequence
- When the STOP button is pressed

Standby Screen

In Standby mode, the Standby Screen (Figure 3-5) displays the following information.



1 Catheter image showing selected pairs registering in blue
2 Ablation Time
3 Energy mode identifier
4 Target temperature
5 Target temperature range (±5 °C of the target temperature)
6 Cumulative RF usage display – data may vary
7 Temperature readings for each selectable electrode in a channel (pair)

Figure 3-5. Standby Screen

This screen is displayed:

- After the Standby button is pressed on the front panel or remote control box, if used.

Ablation Screen

During ablation, the Ablation Screen (Figure 3-6) displays the following information.

1 Catheter image with color-coded temperature indicators for each electrode
2 Ablation Time (increments up to preset time during ablation)
3 Area for system status, user prompts, and system messages
4 Energy delivery mode identifier
5 Target temperature in °C
6 Target temperature range (±5 °C of the target temperature)
7 Temperature readings for each electrode in a selected pair (channel)
8 Real-time power output data (watts) for each selected electrode within a channel
9 Real-time ablation duration at target temperature

Figure 3-6. Sample Ablation screen

Note: The temperature readings for each electrode provide a 1-second running average that is calculated based on 8 temperature readings per second.

This screen is displayed:

- Throughout ablation. It is displayed when the Start button has been pressed on the front panel or the remote control, if no error conditions are detected.

Temperature color-code key

The channel bars and catheter image use the following colors to provide temperature information:

Color	Significance
Blue	Temperatures below the target temperature range
Green	Temperatures within ±5 °C of the target temperature
Yellow	Temperatures that are above the target temperature range
Red	Temperatures that are +10 °C or higher than the target temperature

Cumulative RF usage display

The Cumulative RF usage display is displayed following each ablation.

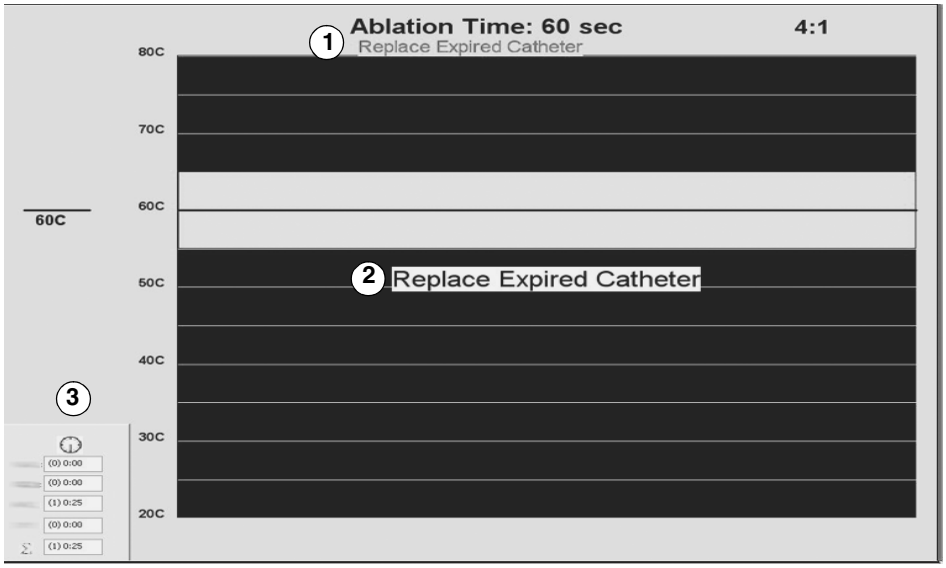
The Cumulative RF usage display is located in the bottom left corner of the Setup and Standby screens. It increments the accumulated RF time for each catheter used for a patient. The sum symbol $\sum$ at the bottom of the timer indicates the accumulated time in seconds since the Cumulative RF usage display was last reset.

To reset the Cumulative RF usage display to zero, press and hold the **Standby** button for 3 seconds, or turn off the generator.

If no ablations occur following a one-hour period, the generator will automatically reset the Cumulative RF usage display.

Sample system message display

The generator is able to detect error conditions and identifies them on the display. (See “System messages” on page 48 for a complete list.)



1 Area for system status, user prompts, and system messages

2 Message popup

3 Cumulative RF usage display – data may vary

Figure 3-7. Sample system message display

A screen similar to this may be displayed when an error condition is detected.

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Connecting non-sterile cables 39

Connecting the remote control (optional) 39

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Inspecting the system components

Prior to use, inspect all system components for visible damage. (See “Compatible components” on page 18). Replace any component if damage is found.

Ensuring the catheter interface cable is sterile

The catheter interface cable is supplied sterile and ready for use. If repeat sterilization is required, it is recommended that the catheter interface cable be sterilized using the steam method with specific parameters. For steam sterilization, rely on standard hospital practice. Alternatively, a sterile probe cover can be used.

Steam method

Resterilization parameters	
Method of sterilization	Steam
Steam cycle temperature	127 °C (260 °F)
Steam cycle time at temperature	35 ±5 minutes
Cool-down time	30 minutes minimum

If the recommended sterilization parameters are followed, the catheter interface cable can be resterilized and reused up to 10 times. Continue to inspect for damage (bent pins, cracks in jacket, etc.) before each use.

Note: Following sterilization, allow the catheter interface cable to reach ambient temperature.

Sterile probe cover

If the steam sterilization parameters cannot be followed, it is recommended that a sterile probe cover be used to fully enclose the catheter interface cable before use. If a sterile probe cover is used in place of steam sterilization, there is no restriction for reuse of the catheter interface cable.

Note: Inspect for damage (bent pins, cracks in jacket, etc.) before each use.

Connecting non-sterile cables

1. Connect the ECG interface box cable to the generator front panel receptacle labeled *ECG Interface Box*.

   To do this, align the red connector key to the 12:00 position, and then push the connector into the receptacle firmly until it stops. To disconnect, pull the connector body until it separates from the receptacle.
2. Connect the other end of the ECG interface box cable to the receptacle labeled *Generator* on the ECG interface box.
3. Connect the ECG amplifier cable to the receptacle labeled *ECG Amplifier* on the ECG interface box. Connect the other end of the ECG amplifier cable to an external recording system.

   Warning: Use only isolated amplifiers, pacing equipment, and ECG equipment (IEC 60601-1 Type CF equipment, or equivalent), as patient injury or death may occur. Do not allow leakage current from any connected devices to the patient to exceed 10 microamperes (µA) under any circumstances.

Connecting the remote control (optional)

1. If the remote control is used, connect one end of the remote control cable to the generator front panel receptacle labeled *Remote Control*.
2. **If the remote control is to be used outside the sterile field,** connect the other end of the remote control cable to the rear panel receptacle on the remote control labeled *Generator*.

If the remote control is to be used within the sterile field, use sterile technique to cover the remote control with a sterile cover and connect the remote control cable to the rear panel receptacle on the remote control labeled *Generator*.

Initializing the generator

1. Pull out the handle on the monitor until it stops, and then rotate the monitor up until it stops in the vertical position.
2. Turn the generator power switch **On** (located on the rear panel). The generator initiates a power-up/self-test routine.
3. During the self-test routine, which may take up to 2 minutes, the screen intermittently displays test information and language selection menus. Upon completion of a successful self-test, the generator enters Setup mode and all default settings are enabled.

The following default settings are enabled with no catheter attached.

Default settings (no catheter attached)	
Mode	Setup
Channels	All off (de-selected)
Target temperature	60 °C
Ablation duration	60 seconds
Energy delivery	Bipolar:Unipolar, 4:1

In the event of a power-up/self-test failure, the generator displays a system message, emits an audible tone (beep), and is locked from further use. For more information, see “System messages” on page 48.

Applying patient return electrodes

1. Apply two Valleylab Patient Return Electrodes (Model E7506) according to the manufacturer documentation. Refer to Figure 4-1 for proper placement. For best contact, avoid areas with adipose tissue, bony prominences, fluid invasion, scar tissue, and excess hair (shave the patient if necessary).

   Note: Be sure to use only Valleylab Patient Return Electrodes (Model E7506). For use instructions, refer to the manufacturer documentation.

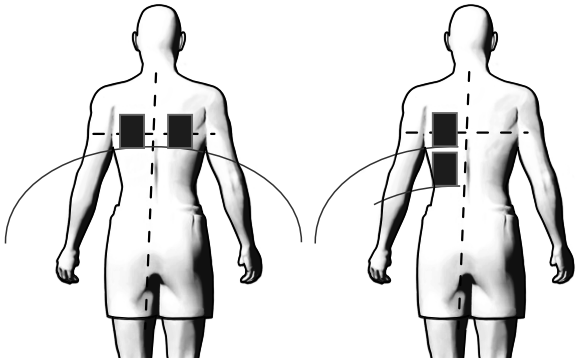

Figure 4-1. Patient return electrode placement

   For proper system operation, position the patient return electrodes according to the patient return electrode placement image (see Figure 4-1).

2. Connect the patient return electrodes to the receptacles labeled *Patient Return Electrode* on the ECG interface box.

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Attaching the catheter

Note: For catheter placement and use instructions, consult the technical manual of the compatible Medtronic cardiac ablation catheter being used.

Use sterile technique to attach the catheter to the sterile catheter interface cable.

When a compatible Medtronic cardiac ablation catheter is connected, the generator identifies the catheter (an hourglass is displayed during this process), then displays the appropriate catheter image and default system parameters.

> **Important:** After identification, the catheter can be used for up to 6 hours.

Following the attachment of a catheter, the generator begins to monitor system conditions. For information about conditions it may detect, see “System messages” on page 48.

Setting generator parameters

During Setup mode, prior to delivery of RF energy, ensure that the following parameters are set according to physician preference:

- Channels (system default is Off)
- Duration (system default is 60 seconds)
- Target temperature (system default is 60 °C)
- Energy mode (system default exists for each catheter) - also see Table 5-1 on page 45.

For information about selecting ablation options, see Chapter 2, “Generator controls and connections” on page 19.

The generator software limits power to the electrodes depending on the selected energy mode.

Table 5-1. Energy mode power limits

Selected energy mode	Power limit
Unipolar	10W
Bipolar	6W
1:1	10W
2:1	10W
4:1	8W

Performing ablation

Note: Consult the technical manual of the compatible Medtronic cardiac ablation catheter being used.

1. Verify that setup steps have been completed. (See Chapter 4, “Preparing for ablation” on page 37.)
2. Verify that the catheter has been inserted into the patient and attached to the system (see “Attaching the catheter” on page 44) and that ablation settings have been selected (see “Setting generator parameters” on page 44).
3. If necessary, press the **STOP** button on the generator to dismiss the *Verify Return Electrodes Are Attached* message and patient return electrode placement image.
4. Press the **Standby** button to automatically calibrate all thermocouples to the patient’s body temperature. No energy is delivered to the catheter while in Standby mode.

   Note: It is possible to begin ablation from Setup mode. To do so, press the Start button instead of Standby. Calibration will still occur.
5. Press the **Start** button to deliver RF energy and start the ablation sequence according to the front panel settings.

   The ablation feedback tone is enabled and sounds throughout the ablation. The Ablation Time display begins to increment.
6. Monitor the ablation readings provided on the Ablation Screen during the sequence. (See “Ablation Screen” on page 34 for more information about the display.)

Note: Target temperature can be adjusted and channel(s) de-selected during the ablation. The **STOP** button can be used at any time to end the ablation.

Following completion of the ablation sequence, the end-of-ablation beep sounds and the generator enters Setup mode. (See “Setup Screen” on page 32 for more information about the display.)

7. Change the settings prior to the next ablation, if required. If no settings are changed, the generator maintains the last settings used during ablation.
8. Repeat steps 4 and 5 to perform additional ablation sequences, if required. (See “Cumulative RF usage display” on page 35 for information about total ablation time in the current session.)

Notes:

- To prevent inaccurate temperature acquisition, the generator does not permit ablation until all electrode temperatures are below 45 °C.
- See “System messages” on page 48 for a list of possible exceptions to normal procedure, and how the generator responds.

Shutting down and disconnecting the system

1. Following the final delivery of RF energy, turn off the generator at the main’s **On/Off** switch located on the rear panel of the generator. *O* on the power switch represents Off.
2. Disconnect all cables.
3. Ensure that all connections are clean and dry. If the catheter interface cable is heavily soiled, it is recommended that the cable be discarded.
4. Clean and store the generator and components as indicated in “Storage and handling” on page 56 and in Appendix A: "GENius generator components" on page 59.

Troubleshooting 6

System messages 48

System messages

The generator may display the following system messages. Follow the steps in the Troubleshooting column in the sequence specified until the system message clears. (Some messages may require another ablation to determine if the error condition has been corrected.)

If the steps are unsuccessful, contact your Medtronic representative.

System message	Description	Occurs during	Troubleshooting
Open Circuit	An Open Circuit is detected by the system. ▪ If the condition is detected when the catheter is attached, channels cannot be selected and ablation cannot be performed. ▪ If the condition is detected during ablation, the ablation is terminated.	Setup or Ablation	1. Disconnect and reconnect both ends of the catheter interface cable and ECG interface box cable. 2. Replace catheter interface cable. 3. Replace catheter. 4. Replace ECG interface box cable. 5. Replace ECG interface box. 6. Replace generator.
Replace Expired Catheter	An expired catheter is detected by the system when the catheter is attached. If an expired catheter is detected, the system is locked from further use.	Setup	Replace catheter.

System message	Description	Occurs during	Troubleshooting
Short Circuit	A Short Circuit is detected by the system during ablation. If a Short Circuit is detected between any two electrodes, selected or not, the ablation is terminated. There are two separate conditions for Short Circuit detection: ▪ A Short Circuit is detected if any non-selected electrode reaches 50 °C or higher after the first 15 seconds of the ablation or 15 seconds after a selected electrode is deselected. This detection applies to all compatible Medtronic multi-electrode cardiac ablation catheters. ▪ A Short Circuit is detected if any selected electrode is 5 °C above the target temperature and the power on that electrode is <2 watts for more than 1 second, after the first 15 seconds of the ablation. This detection applies to any compatible Medtronic multi-electrode cardiac ablation catheter except T-VAC.	Ablation	1. Adjust catheter position or shape to ensure that no ablation electrode is in contact with another ablation electrode. 2. Press the STOP button. 3. Disconnect and reconnect both ends of the catheter interface cable. 4. Replace catheter interface cable. 5. Replace catheter. 6. Replace ECG interface box cable. 7. Replace ECG interface box. 8. Replace generator.

System message	Description	Occurs during	Troubleshooting
Channel Fault	A Channel Fault is detected by the system when a catheter is attached. If a resistive connection (poor contact) is encountered within the system connections during setup, the generator emits an error beep, displays the Channel Fault message in place of the temperature bar graph for the faulty channel, and does not allow selection of that channel.	Setup	1. Disconnect and reconnect both ends of the catheter interface cable and ECG interface box cable. 2. Replace catheter interface cable. 3. Replace catheter. 4. Replace ECG interface box cable. 5. Replace ECG interface box. 6. Replace generator.

System message	Description	Occurs during	Troubleshooting
Channel Fault	A Channel Fault is detected by the system during ablation. If a thermocouple short is detected proximal to the electrode during ablation, the generator emits an error beep, turns off both electrodes on the faulty channel, displays the Channel Fault message in place of the temperature bar graph for the faulty channel, and the ablation continues using the unaffected electrodes. Depending on catheter type, there are one or more conditions for thermocouple short detection: ▪ Any compatible Medtronic multi-electrode cardiac ablation catheter that exhibits maximum power and remains below 40 °C. ▪ Any compatible Medtronic multi-electrode cardiac ablation catheter except T-VAC that has an electrode below 40 °C while its bipolar mate is in the target temperature range.	Ablation	1. Adjust catheter position or shape to ensure that no ablation electrode is in contact with another ablation electrode. 2. Replace catheter. 3. Replace catheter interface cable. 4. Replace ECG interface box cable. 5. Replace ECG interface box. 6. Replace generator.
Power Error	A Power Error is detected by the system during ablation if the power delivery exceeds 15 watts for any compatible Medtronic multi-electrode cardiac ablation catheter except T-VAC. If a Power Error is detected by the system, the ablation is terminated.	Ablation	Replace generator.

System message	Description	Occurs during	Troubleshooting
Temperature System Failure	A Temperature System Failure is detected by the system during ablation if the temperature system malfunctions. If a Temperature System Failure occurs, the ablation is terminated.	Ablation	Replace generator.
Keypad Failure	A Keypad Failure is detected by the system during power-up/self-test if the front panel keypad malfunctions. If a Keypad Failure occurs, the system is locked from further use.	Power-up/ self test	Replace generator.
System Error	A System Error is detected by the system during power-up/self-test if the generator malfunctions. If a System Error occurs, the system is locked from further use.	Power-up/ self test	Replace generator.
Temperature Shutoff	A Temperature Shutoff occurs during ablation if any electrode reaches 80 °C or higher. If a Temperature Shutoff occurs, the generator displays the Temperature Shutoff message in place of the offending channels bar graph and the ablation continues.	Ablation	1. Reposition catheter. 2. Replace catheter. 3. Replace generator.

System message	Description	Occurs during	Troubleshooting
Verify Return Electrodes are Attached. Press STOP to Verify.	If the generator does not detect the presence of the patient return electrodes, the generator terminates the ablation, outputs the error beep, and displays the message, “Verify Return Electrodes are Attached. Press STOP to Verify.”	Ablation	1. Verify use of correct equipment: Valleylab Patient Return Electrodes (Model E7506, two required). 2. Verify that the patient return electrodes are connected to the ECG interface box. 3. Verify the patient return electrodes are correctly positioned (see “Patient return electrode placement image” on page 31). 4. Verify that the patient return electrodes are properly adhered to clean dry skin according to patient return electrode manufacturer documentation. For best contact, avoid areas with adipose tissue, bony prominences, fluid invasion, scar tissue, and excess hair (shave the patient if necessary). 5. Adjust catheter position or shape to ensure that no ablation electrode is in contact with another ablation electrode.
No MESSAGE Blue screen	Generator displays a blank blue screen.	Setup	1. Turn the generator off, then on again. 2. Replace the generator.

Generator maintenance, handling, and specifications 7

Maintenance 56

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Cleaning 56

Technical specifications of the generator 56

Maintenance

- The generator requires no adjustments, calibrations, or regularly-scheduled maintenance.
- The generator should be returned to the manufacturer for evaluation if exposed to excessive shock, vibration, or any mishandling.

Storage and handling

The GENius Multi-Channel RF Ablation Generator should be stored at normal room temperatures with relatively low humidity levels.

- Storage temperature limitations: 0 °C to 60 °C (32 °F to 140 °F)
- Storage relative humidity limitations: 15% to 95%
- Handle with care.
- Keep the generator dry.

Cleaning

Wipe off the generator with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Technical specifications of the generator

Information about catheters is not included here. See the technical manual of the compatible Medtronic cardiac ablation catheter being used.

See Appendix A: GENius generator components on page 59 for specifications for generator components.

GENius Multi-Channel RF Ablation Generator

Physical characteristics	
Weight	38 lbs (17.6 kg)
External dimensions	Height: 8.6 inches (21.8 cm) Width: 17.5 inches (44.4 cm) Depth: 17.1 inches (43.4 cm)
Features	Integral carrying handle Flat front panel Integral rubber feet Pull-out, 15-in display screen
Environmental characteristics	
Operating temperature	10 °C to 40 °C (50 °F to 104 °F)
Operating relative humidity	30% to 75% non-condensing
Storage temperature	0 °C to 60 °C (32 °F to 140 °F)
Storage humidity	15% to 95% non-condensing
Safety (Type CF) characteristics	
Safety class	Class I
System electrical leakage	≤ 10 µA
Grounding system	Floating (applied parts); integral equipotential grounding connection
Defibrillator protection	Ability to withstand 5000 VDC defibrillator pulse
Operating parameters	
Maximum output power	45 watts/channel into 100Ω (nominal)
Rated output power	45 watts/channel into 100Ω (nominal)
Rated load range	80Ω to 250Ω
Voltage output	Unipolar 300V (peak to peak) Bipolar 600V (peak to peak) Constant voltage delivery (voltage does not fluctuate with operator setting or device load)
Frequency	470 kHz

Input voltage	120 VAC, 60 Hz 220–240 VAC, 50 Hz
Input current	5 A
Temperature accuracy	± 2 °C between 37 °C and 70 °C
Power accuracy	± 20%
Degree of protection against ingress of liquid	IPXO (not protected)
Flammability	Not suitable for use in presence of flammable materials

GENius generator components

A

GENius Jr. Remote Control 60

Remote control cable 62

ECG interface box 64

ECG interface box cable 67

ECG amplifier cable 68

Catheter interface cable 70

This appendix contains detailed information about individual components supplied with the GENius generator. For information about interaction among the generator and its components, see “System overview” on page 20.

Warnings

These devices are components of the GENius generator. See “Warnings” on page 13 for important information related to the generator.

Precautions

These devices are components of the GENius generator. See “Precautions” on page 17 for important information related to the generator.

Note: Individual warnings and precautions do not appear in this components appendix.

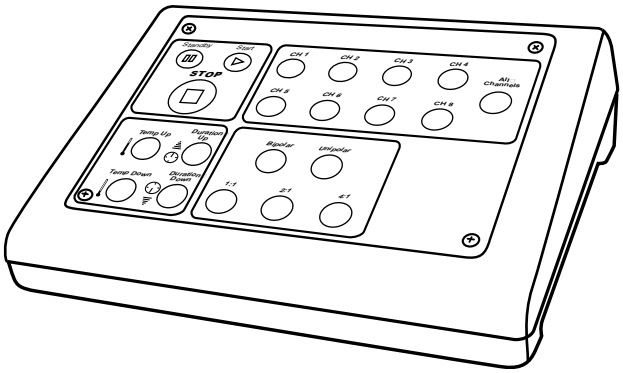
GENius Jr. Remote Control

Intended Use

The GENius Jr. Remote Control Model 990029 is designed for use with the GENius Multi-Channel RF Ablation Generator Model 990018. Its use is optional.

Description

The GENius Jr. Remote Control is available as an alternative to the front panel for selecting ablation parameters and controlling energy delivery. The generator accepts inputs from either the front panel or the remote, when the remote is installed.



The remote control is connected to either of two remote control cables that are available:

- Remote control cable Model 990041—15 ft (4.57 m)
- Remote control cable Model 990042—25 ft (7.62 m)

Instructions for Use

1. Ensure that the generator is turned Off (recommended).
2. If the remote control is used, connect one end of the remote control cable to the generator front panel receptacle labeled Remote Control.
3. **If the remote control is to be used outside the sterile field**, connect the other end of the remote control cable to the rear panel receptacle on the remote control labeled *Generator*.

If the remote control is to be used within the sterile field, use sterile technique to cover the remote control and connect the remote control cable to the rear panel receptacle on the remote control labeled *Generator*.

Cleaning and storage

Wipe off the remote control with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Store in accordance with temperature described in technical specifications (page 62).

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Weight	1.2 lbs (0.55 kg)
External dimensions	Height: 1.75 inches (4.4 cm) Width: 8.6 inches (21.8 cm) Depth: 4.3 inches (10.9 cm)
Features	Integral rubber feet Plastic case
Environmental characteristics	
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity
Operating temperature	10 °C to 40 °C (50 °F to 104 °F)
Operating relative humidity	30% to 75% non-condensing
Operating parameters	
Degree of protection against ingress of liquid	IPXO (not protected)
Flammability	Not suitable for use in presence of flammable materials

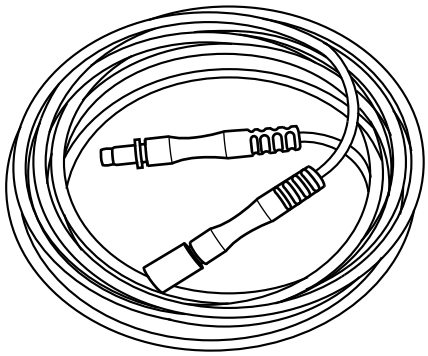
Remote control cable

Intended Use

The remote control cable Model 990041 and Model 990042 are designed for use with the GENius Multi-Channel RF Ablation Generator Model 990018 and the GENius Jr. Remote Control Model 990029. It is required only if the optional remote control is used.

Description

The remote control cable connects the remote control and the generator.



Instructions for Use

1. Ensure that the generator is turned Off (recommended).
2. Plug the remote control cable into the remote control port.
3. Plug the cable into the Remote Control Cable port on the front of the generator.

Cleaning and Storage

Wipe off the remote control cable with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Store in accordance with conditions described in technical specifications (page 64).

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Length (two lengths available)	15 ft (4.57 m) 25 ft (7.62 m)
Environmental characteristics	
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity

ECG interface box

Intended Use

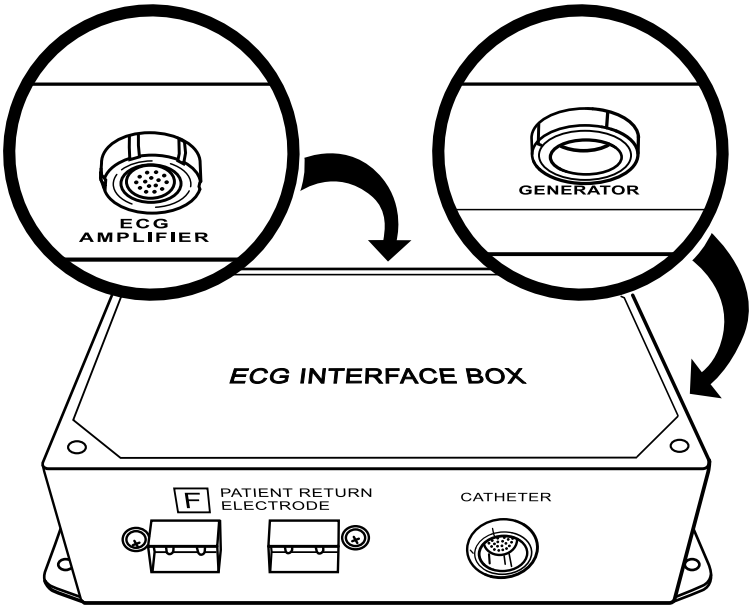
The ECG interface box is designed for use with the GENius Multi-Channel RF Ablation Generator Model 990018. The ECG interface box is required for proper system operation.

Description

The ECG interface box connects the catheter with the generator, patient return electrodes, the external monitoring equipment, and the pacing equipment that can be used during the procedure.

The ECG interface box has the following receptacles:

- **Generator receptacle** – This receptacle accepts the connector from the ECG interface box cable.
- **ECG Amplifier receptacle** – This receptacle accepts the connector from the ECG amplifier cable.
- **Catheter receptacle** – This receptacle accepts the connector from the catheter interface cable.
- **Patient Return Electrode receptacles** – These two receptacles accept the connector from the Valleylab Patient Return Electrodes (Model E7506) (not supplied).



The following cables and electrodes are used with the ECG interface box:

- **ECG Interface Box Cable Model 990020** – This cable connects the ECG Interface Box to the generator.
- **ECG Amplifier Cable Model 990027** – This cable connects the ECG Interface Box to an external recording system.
- **Catheter Interface Cable Model 990004** – This cable connects the ECG Interface Box to the ablation catheter.
- **Patient Return Electrodes** —Refer to Valleylab Patient Return Electrodes (Model E7506) manufacturer documentation for more information.

Instructions for Use

1. Ensure that the generator is turned Off (recommended).
2. Insert the connector of each interconnecting cable to the appropriate receptacle on the ECG interface box.

Cleaning and Storage

Wipe off the ECG interface box with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Store in accordance with temperature described in technical specifications (page 66).

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Weight	1.2 lbs (0.55 kg)
External dimensions	Height: 2.5 inches (6.3 cm) Width: 4.75 inches (12 cm) Depth: 7.75 inches (19.6 cm)
Environmental characteristics	
Operating temperature	10 °C to 40 °C (50 °F to 104 °F)
Operating relative humidity	30% to 75% non-condensing
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity
Safety (Type CF) characteristics	
System electrical leakage	≤ 10 µA
Grounding system	Floating (applied parts); integral equipotential grounding connection
Defibrillator protection	Ability to withstand 5000 VDC defibrillator pulse

Operating parameters	
Provides connection to:	Multi-Channel RF Ablation Generator Catheter interface cable Two (2) Valleylab Patient Return Electrodes (Model E7506) ECG amplifier cable

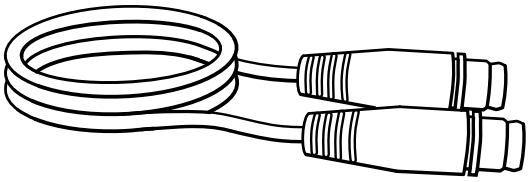
ECG interface box cable

Intended Use

The ECG Interface Box Cable Model 990020 is designed for use with the GENius Multi-Channel RF Ablation Generator Model 990018 and the ECG Interface Box Model 990028.

Description

The ECG interface box cable connects the ECG interface box with the generator.



Instructions for Use

1. Ensure that the generator is turned Off (recommended).
2. Connect the ECG interface box cable to the receptacle on the ECG interface box labeled *Generator*.
3. Connect the other end to the receptacle labeled *ECG Interface Box* on the front panel of the generator.

Cleaning and Storage

Wipe off the ECG interface box cable with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Store in accordance with temperature described in technical specifications (page 68).

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Length	6 ft (1.8 m)
Environmental characteristics	
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity

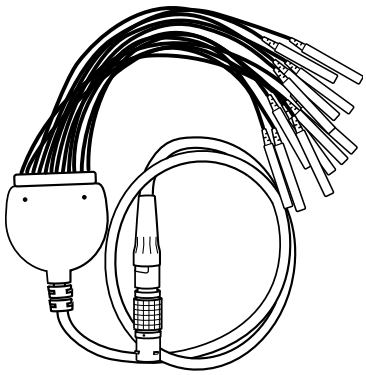
ECG amplifier cable

Intended Use

The ECG Amplifier Cable Model 990027 is designed for use with the GENius Multi-Channel RF Ablation Generator Model 990018 and the ECG Interface Box Model 990028.

Description

The ECG amplifier cable connects the ECG interface box to an external recording system.



Instructions for Use

1. Ensure that the generator is turned Off (recommended).
2. Connect the ECG amplifier cable to the receptacle labeled *ECG Amplifier* on the ECG interface box.
3. Connect the other end of the ECG amplifier cable to an external recording system.

Cleaning and Storage

Wipe off the ECG amplifier cable with a damp cloth. If necessary, use a mild detergent solution. Dry thoroughly.

Do not immerse in water.

Store in accordance with temperature described in technical specifications (page 70).

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Length	6 ft (1.8 m)
Environmental characteristics	
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity

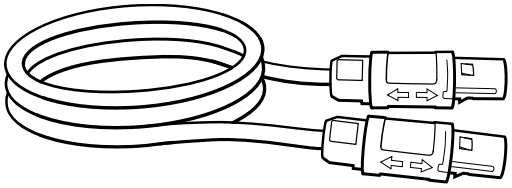
Catheter interface cable

Intended Use

The Catheter Interface Cable Model 990004 is designed for use with the GENius Multi-Channel RF Ablation Generator and with compatible Medtronic multi-electrode cardiac ablation catheters.

Description

The catheter interface cable connects the ECG interface box and the catheter. It is shipped sterile and must be resterilized or covered with a sterile cover before reuse.



Instructions for Use

1. Connect the cable to the catheter.
2. Connect the catheter interface cable to the ECG interface box, at the receptacle labeled *Catheter.*

Cleaning and Storage

The catheter interface cable is shipped sterile. After use and prior to subsequent use, the catheter interface cable must be resterilized. (Alternatively, it may be covered in a sterile fashion during reuse.) See “Resterilization” on page 71.

Do not immerse in water.

Store in accordance with temperature described in technical specifications (page 72).

Resterilization

The catheter interface cable is supplied sterile and ready for use. If repeat sterilization is required, it is recommended that the catheter interface cable be sterilized using the steam method with specific parameters. For steam sterilization, rely on standard hospital practice. Alternatively, a sterile probe cover can be used.

Steam method resterilization parameters

Resterilization parameters	
Method of sterilization	Steam
Steam cycle temperature	127 °C (260 °F)
Steam cycle time at temperature	35 ±5 minutes
Cool-down time	30 minutes minimum

If the recommended sterilization parameters are followed, the catheter interface cable can be resterilized and reused up to 10 times. Continue to inspect for damage (for example, bent connection pins, damage to jacket, etc.) before each use.

Note: Following sterilization, allow the catheter interface cable to reach ambient temperature.

Sterile probe cover

If the steam sterilization parameters cannot be followed, it is recommended that a sterile probe cover be used to fully enclose the catheter interface cable before use. If a sterile probe cover is used in place of steam sterilization, there is no restriction for reuse of the catheter interface cable.

Note: Inspect for damage (for example, bent connection pins, damage to jacket, etc.) before each use.

Disposal

Do not dispose of this product in the unsorted municipal waste stream. Dispose of this product according to local regulations. See http://recycling.medtronic.com for instructions on proper disposal of this product.

Technical Specifications

Physical characteristics	
Length	6 ft (1.8 m)
Environmental characteristics	
Storage temperature	0 °C to 60 °C (32 °F to 140 °F) non-condensing humidity

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Attachment 2: PVAC Technical Manual

Medtronic

PVAC® 990030

Pulmonary Vein Ablation Catheter®

Technical Manual

! USA **Caution:** Federal law (USA) restricts this device to sale by or on the order of a physician.

The following are trademarks or registered trademarks of Medtronic in the United States and possibly in other countries. All other trademarks are the property of their respective owners:
Medtronic, GENius, PVAC, Pulmonary Vein Ablation Catheter

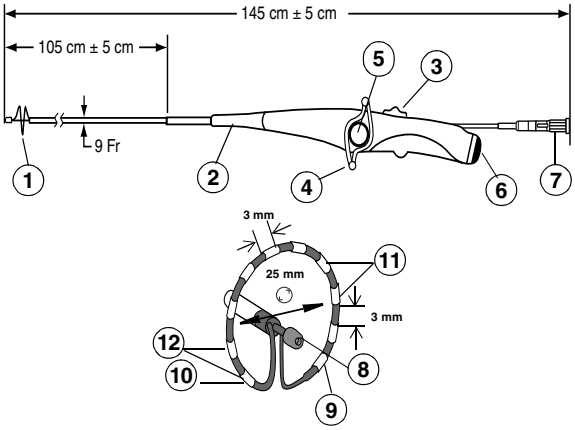
Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which of these apply to this product.

LOT	Lot number
REF	Reorder number
	Use by
STERILE R	Sterilized using irradiation
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Keep dry
	Product documentation
	Keep away from heat
	Bidirectional
	Inside diameter
! USA	For US audiences only

1 Description

The Medtronic Pulmonary Vein Ablation Catheter (PVAC) is a three-dimensional, anatomically designed, multi-electrode catheter used to map, pace, and ablate the pulmonary veins (see Figure 1).



1	Spiral array	7	Proximal lumen
2	Capture device	8	Distal tip
3	Slide control knob	9	Electrode 1
4	Steering knob	10	Electrode 10
5	Tension control knob	11	Pair 2
6	Connector	12	Pair 5

Figure 1. Pulmonary Vein Ablation Catheter

1.1 Contents of package

The package contains the following:

- 1 Pulmonary Vein Ablation Catheter
- Product documentation

Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions noted in these instructions. Failure to do so may result in less than expected outcomes.

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

2 Indications for use

The Pulmonary Vein Ablation Catheter is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent (1 to 4 years) atrial fibrillation.

The PVAC is used for mapping, pacing, and ablating pulmonary vein potentials and verifying electrical isolation of the pulmonary veins post-treatment.

3 Contraindications

Use of the Pulmonary Vein Ablation Catheter is contraindicated as follows:

- Active sepsis
- Left atrial thrombus or myxoma
- Atrial Septal Patch or atrial septal defect repair with percutaneous device
- Known sensitivity to heparin
- Blood clotting abnormalities
- Venous filtering device (Greenfield Filter)

The catheter is not recommended for use in patients who cannot undergo standard anticoagulation protocol for a left-sided cardiac procedure, or who have had a recent coagulopathy or embolic event.

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Cable positioning – Position all cables associated with the generator so they do not come in contact with the patient or other leads. RF interference may affect the ability to interpret patient EGMs.

Catheter exchange – Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

Catheter placement – It is recommended that the application of RF energy be applied at the antrum of the pulmonary veins. Delivery of RF energy inside the pulmonary veins may result in pulmonary vein stenosis.

Disposal of catheter – Dispose of the catheter according to hospital biohazard requirements. If returning the catheter, contact your local Medtronic representative.

Electrical isolation during ablation – Do not allow the patient to contact grounded equipment that might produce electrical current leakage during ablation. Electrical current leakage may induce arrhythmias that may result in the patient's death.

Electrode contact – Avoid contact between electrodes. Contact between electrodes may create a short circuit or channel fault system error.

Electrode separation – Maintain adequate separation between all energized electrodes during ablation. Failure to maintain adequate separation may result in leading to high temperatures.

Embolism risk – Introducing any catheter or sheath into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism. Closely monitor transseptal sheaths, performing aspiration and/or flushing to prevent air ingress and/or soft clot formation.

Expiration date – Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Flammable materials – Do not allow flammable material in the area where RF ablation procedures are performed. The risk of igniting flammable gases, flammable agents used for cleaning or disinfecting, or other materials is inherent in the application of RF energy.

Fluoroscopy required for catheter placement – Use of fluoroscopy during catheter manipulation and placement is strongly advised. Manipulating the catheter without fluoroscopy may result in damage to cardiac and vascular structures.

For single use only – This device is intended only to be used once for a single patient. Do not reuse, reprocess, or resterilize this device for purpose of reuse. Reuse, reprocessing, or

resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent aspiration and flushing of the sheath – Aspirate and flush the sheath frequently to help minimize the potential for embolic events resulting from the introduction of air or the formation of clot within the sheath.

Generator settings or equipment failure – Do not increase target temperature or ablation duration settings before checking for obvious defects or misapplication, as patient injury may occur. Apparent low power output or failure of the equipment to function correctly at normal settings may indicate faulty application of the patient return electrodes or failure of an electrical lead.

High electrode temperatures – Only use catheters as recommended, maintain catheter contact with cardiac tissue during ablation, and monitor the displayed electrode temperatures and power delivery, in order to avoid high instantaneous electrode temperatures. Temperatures above 80° C during ablation may increase the patient's risk of thromboembolic events (formation of coagulum), steam pops, and cardiac perforation, depending on catheter type used.

- Only use catheter in the recommended anatomical location.
- Maintain catheter electrode contact with cardiac tissue by holding the catheter during the ablation.
- Do not reposition, rotate, slide, drag or otherwise intentionally disengage and then re-engage the catheter electrodes with cardiac tissue while ablating. Stop ablation prior to performing any of these actions.
- Monitor the displayed electrode temperature and power delivery during ablation. Deselect the affected electrode pair or discontinue ablation if the electrode does not reach 50° C and is receiving maximum power delivery.

Left-sided ablation – Closely monitor patients undergoing left-sided ablation procedures for clinical manifestations of infarction, cardiac tamponade, thromboembolism, or stroke.

Long-term risk – The long-term risks of lesions created by radiofrequency (RF) ablation have not been established. In particular, the long-term effects of lesions in proximity to the specialized conduction system or coronary vasculature are unknown.

No direct skin contact during system testing – Do not test the operation of the ablation system through direct skin contact with the electrodes. Testing through direct skin contact may cause damage to healthy tissue.

Oral anticoagulation therapy – Anticoagulation (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion and/or ablation.[1]

Placement of monitoring electrodes – Place all physiological monitoring electrodes as far away as possible from the patient return electrodes and their leads to avoid RF interference, which affects the ability to interpret patient electrograms (EGMs).

Procedural anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Qualified users – The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

Related product literature – Do not attempt to operate the Medtronic cardiac ablation system prior to completely reading and understanding the GENius Multi-Channel RF Ablation Generator Operator's Manual and the relevant cardiac ablation catheter technical manual.

Required use environment – Cardiac ablation procedures should be performed only in a fully equipped electrophysiology laboratory.

Sheath or guide catheter required – Do not attempt to advance or withdraw the catheter through the vascular bed without the use of a sheath or guide catheter, as it may result in damage to cardiac and vascular structures.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or the catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Storage conditions – Store the catheter in normal operating room temperatures and humidity levels and in a manner that protects the integrity of the package and the sterile barrier. Keep in a dry location away from heat and sunlight.

System compatibility – Use only the following components with the catheter: Medtronic GENius Multi-Channel RF Ablation Generator, its compatible Medtronic components, and Valleylab Patient Return Electrodes (Model E7506, two required). Use of the catheter with other components may cause patient harm.

Use of RF energy near implanted devices – Implantable devices, such as pacemakers and implantable cardioverter-defibrillators (ICDs), may be inhibited or otherwise affected by RF energy. Refer to the Multi-Channel RF Generator Operators Manual and the appropriate implantable device technical manual for additional information.

X-ray and fluoroscopic exposure – Minimize x-ray and fluoroscopic exposure. Due to the intensity of the x-ray beam and the duration of the fluoroscopic imaging during ablation procedures, patients and laboratory staff may be subjected to acute radiation injury and increased risk for somatic and genetic effects. Take all appropriate measures to minimize x-ray exposure to both patients and clinical staff. The long-term effects of protracted fluoroscopy have not been established.

5 Clinical Study Summary

Note: Clinical section provided to show structure only - data subject to change.

5.1 Study Purpose

Medtronic conducted a prospective multi-center, controlled, randomized clinical study to support a pre-market application (PMA) for a multi-channel, duty-cycled, phased radiofrequency (RF) generator (Medtronic GENius Multi Channel RF Ablation Generator) and three anatomically designed, multi-electrode catheters, which will be referred to as the Medtronic Cardiac Ablation System. The purpose of the Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) clinical study was to evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation (AF).

5.2 Study Scope, Design and Methods

The TTOP-AF clinical study utilized a prospective, multi-center, randomized, controlled design. After all entrance criteria were met, subjects were randomized in a 2:1 fashion to either Ablation Management or Medical Management.

Subjects in the Ablation Management arm were allowed up to 2 ablations with the investigational device, as is typical in this patient population, to achieve treatment success. All procedures (index and retreatment) consisted of intra-cardiac signal mapping and ablation of pulmonary vein potentials and complex fractionated atrial electrograms (CFAEs) with three anatomically designed, multi-electrode catheters; Pulmonary Vein Ablation Catheter (PVAC), Multi-Array Septal Catheter (MASC) and Multi-Array Ablation Catheter (MAAC). There were no requirements for 3-dimensional navigation and complex mapping systems. If AF was not terminated during an ablation procedure, subjects received a direct current (DC) cardioversion (internal or external) to restore sinus rhythm. Confirmation of pulmonary vein isolation (PVI) was then completed in sinus rhythm with the PVAC. Catheter use was consistent in retreatment procedures unless sinus rhythm restoration prevented additional signal mapping of CFAEs with the MASC and/or MAAC. Subjects were followed at pre-discharge, 1, 3 and 6 months post-ablation. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements.

The Medical Management arm subjects received antiarrhythmic drug (AAD) changes and DC cardioversions to achieve and maintain sinus rhythm. Crossover to receive an ablation

[1] Fuster, Valentin, et al. "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation - Executive Summary." Circulation 114.7 (2006): 700-52.)

procedure could occur after 4 months with documentation of continuous AF on a 48-hour Holter recording. Subjects were followed at 1, 3, and 6 months but were also required to be evaluated 30 days after any DC cardioversion.

The TTOP-AF clinical study protocol included the ability to perform an interim analysis. Interim analysis was allowed after at least 50% of the enrolled subjects reached their chronic effectiveness endpoint at 6 months and 100% of the subjects reached their acute safety endpoint. The interim analysis was conducted using a July 31, 2009 cutoff date, signifying the point in time where the interim analysis criteria specified above were met. In order to provide a more complete representation of all acute safety events in the Ablation Management arm, retreatment adverse events collected through November 24, 2009 were included in this Clinical Study Report.

Subjects were enrolled at 23 centers across the United States and one site in The Netherlands for the pivotal phase of the TTOP-AF trial. Investigators enrolled and randomized subjects during a 19 month period between November 2007 and May 2009. The first subject was randomized on November 28, 2007 and the ablation procedure for the last enrolled subject occurred on June 5, 2009. The last retreatment procedure for subjects in Ablation Management occurred on November 24, 2009. All subjects enrolled, randomized and treated in the TTOP-AF trial have completed their 6-month follow-up assessments. Subjects that completed all assessments were exited from the study per protocol requirements.

Data from all study required Holter recordings were analyzed and reviewed by an independent core lab. All safety events were adjudicated by an independent Clinical Events Committee/Data and Safety Monitoring Board (CEC/DSMB). For identification of pulmonary vein changes post-ablation, Ablation Management subjects were required to complete a baseline and 6 month CT scan or MRI. Subjects with scans demonstrating pulmonary vein diameter changes, as noted by the study site, were reviewed by a Core laboratory. Pulmonary vein changes were recorded as “stenosis” if the vein diameter change from baseline was greater than 70% and “narrowing” if the vein change was between 50% and 70%.

The statistical analysis of all primary endpoints was on an intention-to-treat basis (ITT) with passive missing value imputations, where all missing endpoint data were considered a treatment failure for each respective arm. Subjects were designated ITT once randomized.

The TTOP-AF clinical study initially enrolled 20 consecutive feasibility subjects that received an ablation procedure from May 2007 to August 2007. Successful completion of this 20 subject Feasibility phase was required before proceeding to the Pivotal phase. Enrollment of the Pivotal phase began in November 2007 and was completed in 19 months. The final index procedure occurred on June 15, 2009; the last retreatment procedure was performed on November 24, 2009.

Table 1summarizes the major study milestones and data cutoff dates for this report.

Table 1. Study Milestones

First subject randomized in the TTOP-AF clinical study	November 28, 2007
Last subject randomized in the TTOP-AF clinical study	May 20, 2009
Last index ablation procedure performed	June 15, 2009
Last retreatment procedure performed	November 24, 2009

5.3 Subject Inclusion and Exclusion Criteria

5.3.1 Inclusion Criteria

1. History of drug refractory, symptomatic, persistent/long-standing persistent atrial fibrillation defined as:
   - AF greater than 1 year but less than 4 years; OR
   - Non self-terminating AF, lasting greater than 7 days but no more than one year, with at least one failed DC cardioversion. Unsuccessful
     - DC cardioversion failure was defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond 7 days.
   - AF symptoms defined as the manifestation of:
     - Palpitations
     - Fatigue
     - Exertional dyspnea
     - Increased intolerance to routine activities (exercise intolerance)
2. Age between 18 and 70
3. Failure of at least one Class I or Class III AAD
4. Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study.

5.3.2 Exclusion Criteria

1. Structural heart disease of clinical significance including:
   - Previous cardiac surgery (excluding coronary artery bypass graft [CABG] and mitral valve repair)
   - Symptoms of congestive heart failure including, but not limited to, New York Heart Association (NYHA) Class III or IV CHF and/or documented ejection fraction < 40% measured by acceptable cardiac testing
   - Left atrial diameter of > 55mm
   - Moderate to severe mitral or aortic valvular heart disease
   - Stable/unstable angina or ongoing myocardial ischemia
   - Myocardial infarction (MI) within three months of enrollment
   - Congenital heart disease (not including atrial septal defect [ASD] or patent foramen ovale [PFO] without a right to left shunt) where the underlying abnormality increases the risk of an ablation procedure
   - Prior ASD or PFO closure with a device using a percutaneous approach
   - Hypertrophic cardiomyopathy (defined as left ventricular septal wall thickness > 1.5 cm)
   - Pulmonary hypertension (defined as mean or systolic pulmonary artery pressure > 50mm Hg on Doppler echo)
2. Any prior ablation for atrial fibrillation
3. Enrollment in any other ongoing arrhythmia study protocol
4. Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
5. Active infection or sepsis
6. Any history of cerebral vascular disease including stroke or transient ischemic attacks (TIAs)
7. Pregnancy or lactation
8. Left atrial thrombus at the time of ablation
9. Untreatable allergy to contrast media
10. Any diagnosis of atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
11. History of blood clotting (bleeding or thrombotic) abnormalities
12. Known sensitivities to heparin or warfarin
13. Severe COPD (defined as an Forced Expiratory Volume in One Second (FEV_1) <1)
14. Severe co morbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e., other disease processes, mental capacity, substance abuse, shortened life expectance, etc.)

5.4 Results

5.4.1 Subject demographics

A total of 242 study candidates signed an informed consent, with 210 randomized in a 2:1 fashion to the Ablation Management or Medical Management arms (Figure 2). Thirty-two

(32) subjects signed informed consent but withdrew before being randomized for the following reasons:

- Subject did not have 100% atrial fibrillation on the 48-hour Holter recording (n=12)
- Subject did not meet other entrance criteria (n=12)
- Subject withdrew consent (n=6)
- Subject was withdrawn per the Sponsor (n=1)
- Other: Enrollment was closed prior to completion of screening (n=1)

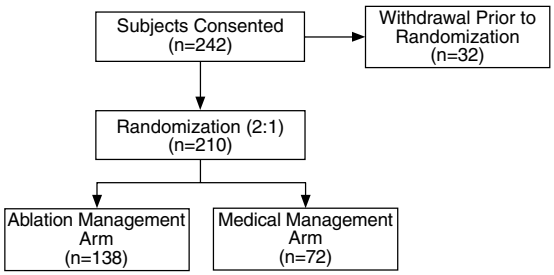


Figure 2. Study Enrollment

As shown in Table 2, the subject characteristics were similar in the Ablation Management and Medical Management arms. The average age of subjects in the Ablation Management arm was 59.6 years and in the Medical Management arm 60.7 years. Over 80% of the subjects enrolled in the study were male despite efforts of the study coordinators to identify eligible female participants. Gender and ethnicity were equally matched between randomized arms.

Information was obtained through medical records, referring physician notes, and subject interviews to verify the duration of AF burden prior to enrollment. The average time in years that each subject was initially diagnosed with AF, was 0.9 years for Ablation Management and 0.7 years for Medical Management, which was not statistically different. Subjects in both arms had an average of 2 DC cardioversions (2.0 for Ablation Management and 2.4 for Medical Management) in the previous 4 years.

Therapy with Class I or III antiarrhythmic drugs began, on average, 2.1 years prior to enrollment for subjects in the Ablation Management arm and 2.5 years prior for subjects in the Medical Management arm.

Left atrial diameter at baseline (average of 4.5 cm for Ablation Management and 4.6 for Medical Management) was enlarged compared to the paroxysmal patient population but comparable between treatment arms. Likewise, left ventricular ejection fraction, as measured by a screening transthoracic echocardiogram, was also comparable (average of 54.7% for Ablation Management and 54.9% for Medical Management).

Table 2. Subject Characteristics

Variable	Ablation Management Arm (n=138) Mean ± SD Median (Min, Max)	Medical Management Arm (n=72) Mean ± SD Median (Min, Max)	p-value[a]
Age, years	59.6 ± 8.3 61.2 (35.5, 73.4)	60.7 ± 8.9 60.8 (31.3, 75.2)	0.37
Gender			
Male (%)	115 (83.3%)	60 (83.3%)	1.00
Female (%)	23 (16.7%)	12 (16.7%)	
Ethnicity			
Caucasian (%)	133 (96.4%)	70 (97.2%)	0.92
African American (%)	3 (2.2%)	1 (1.4%)	
Other (Hispanic, Asian) (%)	2 (1.4%)	1 (1.4%)	
Years Since First Atrial Fibrillation Diagnosis	0.9 ± 0.9 0.6 (0.0, 4.1)	0.7 ± 0.8 0.5 (0.0, 3.9)	0.15
Years Since First DC Cardioversion	1.3 ± 2.0 0.5 (0.0, 11.4)	2.1 ± 3.3[b] 0.5 (0.0, 13.0)	0.47
Years Since First Prescribed Class I or III AAD	2.1 ± 3.3[c] 0.6 (0.0, 18.6)	2.5 ± 4.1[c] 0.8 (0.0, 18.6)	0.49
Approximate Number of DC Cardioversions in Last 4 Years/ Subject	2.0 ± 1.1 2.0 (1.0, 6.0)	2.4 ± 3.5 2.0 (1.0, 30.0)[d]	0.24
Left atrial diameter, cm	4.5 ± 0.5 4.6 (3.2, 5.5)	4.6 ± 0.5 4.7 (3.0, 5.5)	0.33
Left Ventricular Ejection Fraction,%	54.7 ± 7.1 55.0 (40.0, 75.0)	54.9 ± 6.6 55.0 (40.0, 69.0)	0.83

[a] Two-sided α=0.05 level significance
[b] N=71 for Medical Management
[c] N=137 for Ablation Management; N=71 for Medical Management
[d] Subject with 30 cardioversions was cardioverted via implanted cardioverter defibrillator.

Table 3 details the baseline medical history for the Ablation Management and Medical Management arms. There were no significant differences in baseline medical history between arms.

Table 3. Baseline Medical History

Characteristic	All Subjects % (n / N)	Ablation Management Subjects % (n / N)	Medical Management Subjects % (n / N)	Pearson Chi-square p-value
Diabetes Mellitus	14.3% (30/210)	15.9% (22/138)	11.1% (8/72)	0.34
Coronary Artery Disease	19.0% (40/210)	20.3% (28/138)	16.7% (12/72)	0.53
Congestive Heart Failure	7.6% (16/210)	5.8% (8/138)	11.1% (8/72)	0.17
Hypertension	59.0% (124/210)	60.9% (84/138)	55.6% (40/72)	0.46
Cardiomyopathy	9.0% (19/210)	6.5% (9/138)	13.9% (10/72)	0.08
Valvular Disease	7.1% (15/210)	5.1% (7/138)	11.1% (8/72)	0.11
Congenital Heart Disease	0.5% (1/210)	0.7% (1/138)	0% (0/72)	0.47
PFO or ASD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63
Pacemaker or ICD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63

Pertinent baseline physical examination findings are found in Table 4. Heart rate at the time of baseline evaluation was statistically different but not clinically relevant in the Ablation Management arm compared to the Medical Management arm. Blood pressure was comparable among the treatment arms. In order to quantify the risk of stroke in the TTOP-AF clinical study population, a $CHADS_2$ score was retrospectively calculated using parameters

collected at baseline. The $CHADS_2$ score was determined by assigning 1 point each for the presence of **C**ongestive heart failure, **H**ypertension, **A**ge 75 years or older, and **D**iabetes mellitus and by assigning 2 points for history of **S**troke or transient ischemic attack.[1] There were no differences in $CHADS_2$ scores between treatment arms at baseline.

Table 4. Baseline Physical Examination Measurements and $CHADS_2$ Score

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value[a]
Heart rate (bpm)	79.0 ± 15.4 79.5 (43, 129)	77.3 ± 14.9 78.0 (43, 119)	82.4 ± 15.9 83.0 (50, 129)	0.02
Systolic BP (mm Hg)	124.3 ± 15.3 124.5 (88, 165)	124.1 ± 15.5 125.0 (88, 165)	124.8 ± 15.0 124.5 (90, 164)	0.77
Diastolic BP (mm Hg)	77.5 ± 10.01[b] 79.0 (50, 118)	77.8 ± 9.95 80.0 (50, 118)	76.8 ± 10.16[c] 78.0 (50, 102)	0.47
$CHADS_2$ Score	0.81 ± 0.72 1 (0, 3)	0.83 ± 0.74 1 (0, 3)	0.79 ± 0.69 1 (0,2)	Not calculated

[a] Two-sided t-test
[b] The total number of subjects for diastolic BP is N=209, due to the one subject (26-305) that was missing a diastolic BP reading.
[c] One subject was missing diastolic BP recording (Subject 25-305), so there is only an N=71for diastolic BP in Medical Management

As a requisite for randomization, all subjects were required to demonstrate 48 hours of continuous atrial fibrillation on a baseline Holter recording. All subjects in both arms demonstrated a single episode of continuous atrial fibrillation. Table lists the baseline Holter recordings from the Ablation Management and Medical Management arms.

Table 5. Baseline 48-hour Holter Recording

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value
Total Time on Monitor (Hours:Minutes)	48:25 ± 1:18 48:12 (36:25, 50:00)	48:23 ± 1:25 48:13 (36:25, 50:00)	48:28 ± 1:04 48:11 (42:22, 49:58)	0.64
Total Time on Monitor in Atrial Fibrillation (Hour:Minutes)	48:27 ± 1:18 48:14 (36:27, 50:00)	48:25 ± 1:25 48:15 (36:27, 50:00)	48:30 ± 1:04 48:13 (42:24, 50:00)	0.64

Note: Total time on monitor in atrial fibrillation was slightly longer than total time on monitor due to converting recording time from seconds to minutes.

5.4.2 Persistent and long-standing persistent AF Patient Summary

Key medical history and clinical findings of the study population included:

- Overall, all randomized subjects were diagnosed with AF on average 0.8 years prior to enrollment.
- Overall, the first documented DC cardioversion occurred on average 1.4 years prior to enrollment for all randomized subjects with > 2 DC cardioversions on average performed for each subject in the previous 4 years.
- The first time an AAD was prescribed for all randomized subjects was > 2 years prior to enrollment. On average, at least one AAD was discontinued due to failure to sustain long-term sinus rhythm and/or due to intolerance.
- Each subject had a baseline Holter recording demonstrating 48-hours of continuous AF.
- The left atrial diameter ranged from 3.0 to 5.5 cm for all subjects and the left ventricular ejection fraction ranged from 40 to 75% as measured by transthoracic echo.
- Coumadin was prescribed for thrombus prevention in 98.6% of subjects. Other anticoagulants being taken by subjects was aspirin (30.0% of subjects) and Plavix (3.3% of subjects).

5.4.3 Study Population

The following section defines the interventions performed within the Ablation management and Medical Management arms.

Ablation Management Arm

Subjects randomized to the Ablation Management arm underwent an ablation procedure. One hundred thirty-eight (138) subjects were randomized to the Ablation Management arm (intention-to-treat) and 132 of these subjects received an index ablation procedure in which the Medtronic catheters were used. The remaining 6 subjects were not treated with ablation for the following reasons:

- Insurance denials (n=2)
- Underlying medical conditions discovered with pre-procedure testing (n=2)
- Atypical anatomy preventing access to the left atrium (n=2)
- If a subject converted back to AF after the index ablation procedure, the investigator could 1) initiate antiarrhythmic drug therapy (including amiodarone), 2) perform a DC cardioversion and/or, 3) opt for one additional retreatment ablation procedure. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

Forty-eight (48) of 132 subjects required a retreatment procedure resulting in (constituting a 36.4% retreatment rate). All subjects in Ablation Management who qualified for a retreatment ablation have undergone the procedure.

Table 6 lists the catheters used for index and retreatment procedures. All three investigational catheters were used in all index procedures.

Table 6. Investigational Catheter Use in Ablation Management Procedures

Type of Catheter	Index Procedure N=132 n (%)	Retreatment Procedure N=47[a] n (%)	Total Procedures N=179 n (%)
PVAC	132 (100%)	46 (97.9%)	178 (99.4%)
MASC	132 (100%)	38 (80.9%)	170 (95.0%)
MAAC	**132 (100%)**	**41 (87.2%)**	**173 (96.6%)**

[a] One subject experienced heart failure prior to using the investigational catheters and did not have a second procedure resulting in an N of 47 retreatment procedures.

The use of all three ablation catheters in retreatment procedures was not mandated but rather left to the discretion of the investigator. Since the MASC and MAAC were used for

[1] Gage, BF, Waterman, AD, Shannon, W, et al. **Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation.** JAMA. 2001; 285(22):2864-70.

mapping and ablating CFAEs, these catheters would not have been used if ablation with the PVAC restored sinus rhythm.

The times for venous access, transseptal puncture, and introduction of the ablation catheters were documented on case report forms. As shown in Table 7, procedure times averaged approximately three hours and did not differ in duration between index and retreatment procedures. Total fluoroscopy time averaged 55 minutes.

Table 7. Procedure, Ablation, and Fluoroscopy Times for Ablation

Procedure Times	Index Proc N=132 Mean ± SD Median (Min, Max)	Retreatment Proc. N=47 Mean ± SD Median (Min, Max)	All Procedures N=179 Mean ± SD Median (Min, Max)
Time from first venous access to removal of all catheters (hrs:min)	3:21 ± 0:53[a] 3:22 (1:26, 5:51)	3:11 ± 0:52 3:11 (1:25, 5:31)	3:18 ± 0:53[a] 3:19 (1:25, 5:51)
Time from insertion of Medtronic ablation catheters to all catheters removed (hrs:min)	2:30 ± 0:45[a] 2:29 (1:09, 4:58)	2:11 ± 0:44[a] 2:10 (0:44, 4:41)	2:25 ± 0:45[a] 3:22 (0:44,4:58)
Total Fluoroscopy time (hrs:min)	0:55 ± 0:25 0:53 (0:12, 2:19)	0:51 ± 0:18 0:52 (0:16, 1:36)	0:54 ± 0:23[a] 0:53 (0:12, 2:19)

[a] Complete procedure times were not obtained for one index procedure (Subject 26-318)

Medical Management Arm

The TTOP-AF clinical study allowed for aggressive management of subjects enrolled in the Medical Management arm. At the discretion of study investigators, subjects randomized to the Medical Management arm continued treatment with prescribed AAD therapy, received new AAD medications (including amiodarone), and/or were treated with DC cardioversion. In addition to drug changes, subjects in the Medical Management arm could have up to two DC cardioversions separated by 30 days. A “crossover” from Medical Management to an ablation procedure with the study device could occur after the subject completed at least 4 months of Medical Management treatment and demonstrated treatment failure (AF on 48-hour Holter recording).

Medical therapy consisting of starting new AADs, dose changes, and/or direct current cardioversions received by Medical Management subjects is summarized in Table 8. Most Medical Management subjects received optimal medical therapy over the 6 month study period.

Table 8. Treatment Interventions for Medical Management Subjects

Treatment Strategy Combination	Treatment Failures N=38 n (%)	Treatment Successes N=20 n (%)	Missing[a] N=14 n(%)	Overall N=72 n(%)
AADs started only	3 (7.9%)	2 (10.0%)	3 (21.4%)	8 (11.1%)
DC cardioversions only	1 (2.6%)	0 (0.0%)	1 (7.1%)	2 (2.8%)
ADD dose change (s) only	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.4%)
AAD(s) started and AAD dose change(s)	1 (2.6%)	2 (10.0%)	1 (7.1%)	4 (5.6%)
AAD(s) started and DC cardioversions	11 (28.9%)	6 (30.0%)	4 (28.6%)	21 (29.2%)
AAD dose change(s) and DC cardioversion(s)	2 (5.3%)	1 (5.0%)	0 (0.0%)	3 (4.2%)
AAD dose change(s) and DC cardioversion(s) and AAD(s) started	20 (52.6%)	9 (45.0%)	1 (7.1%)	30 (41.7%)
No Treatment Strategy	0 (0.0%)	0 (0.0%)	3 (21.4%)	3 (4.2%)

[a] The Missing category consists of 1 subject lost to follow-up, 4 withdrawn subjects, 1 subject that was allowed to crossover early (<1 month), and 8 subjects that did not complete a 6 month 48-hour Holter recording and/or visit.

Of the 72 subjects that were randomized to the Medical Management arm, 43 (59.7%) crossed over to receive an ablation procedure. There were two subjects that crossed over to receive an ablation procedure prior to 4 months. One subject crossed over at 1.1 months (approved by FDA) and the other at 3.7 months (approved by sponsor).

Subjects that crossed over to receive an ablation procedure were considered a Medical Management failure in the chronic effectiveness endpoint analysis. Data for Medical Management subjects that crossed over to receive an ablation were analyzed separately.

5.4.4 Primary Objectives

Chronic Effectiveness Endpoint

Objective: The primary endpoint for chronic effectiveness was a treatment success/failure measure for each subject computed at the 6 month time point. A subject was considered successfully treated for AF if all three elements of the endpoint, defined as below, were met.

- A ≥90% reduction in clinically significant AF from baseline to the 6 month time point based on a 48-hour Holter recording. Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
- The subject was off all Class I or Class III antiarrhythmic drugs at the 6 month follow-up (Ablation Management arm only). Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording in order to be considered successful.
- All procedures (index and retreatment) conducted on a subject during the treatment period were acutely successful (Ablation Management arm only).

Chronic Effectiveness Results

The primary endpoint for chronic effectiveness evaluating the proportion of ITT subjects with treatment success computed at the 6 month visit was met (Table 9). Treatment Success was achieved in 77 of 138 (55.8%) subjects in Ablation Management compared to 19 of 72 (26.4%) Medical Management subjects in the ITT population, yielding an absolute percentage point difference of 29.4% which was statistically significant (p<0.0001, one-sided Chi-square test).

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	Ablation Management Arm N=138 (n %)	Medical Management Arm N=72 (n %)	p-value for H_0: $P_A \leq P_M$[a]
≥90% reduction in clinically significant AF[b]	93 (67.4%)	20 (27.8%)	
Subject off all AADs at 6 month follow-up[c]	94 (68.1%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	Ablation Management Arm N=138 (n %)	Medical Management Arm N=72 (n %)	p-value for H_0: $P_A \leq P_M$[a]
Subjects meeting all success criteria	**77 (55.8%)**	**20 (27.8%)**	**<0.0001**
Number of missing endpoints[d]	17	14	

[a] Chi-Squared test
[b] Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
[c] Ablation Management success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording to be considered for treatment success.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

The chronic effectiveness endpoint for Ablation Management subjects was evaluated for subjects that were not taking AADs. Although not pre-defined as a success, 16 additional subjects (67.4% of total subjects) benefited from ablation in that an AAD was now effective at managing their AF when they were drug refractory at enrollment.

5.4.5 Acute Safety Endpoint

Objective: The primary endpoint for acute safety was a success/failure variable calculated for each subject in Ablation Management at the 7 day post-procedure time point.

Any subject with at least one adverse event adjudicated by the CEC/DSMB as both serious and procedure and/or device-related (SADE) was considered an acute safety failure, regardless of whether the event occurred following the index or retreatment ablation procedure.

As shown in Table 10, the TTOP-AF clinical study recorded 17 of 138 Ablation Management subjects (12.3%) with at least one SADE occurring within 7 days post-procedure (either index or retreatment). The upper bound of the two-sided, 95% confidence interval was 19.0% (p-value = 0.1427), which exceeded the 16.0% performance goal

Table 10. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial confidence Interval	(7.3%, 19.0%)
p-value[a] for H_0: $P_A \leq P_M$	0.1427

[a] One-sided p-value for exact one sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

The Medtronic Cardiac Ablation System did not statistically meet the upper bounds of the performance goal. However, considering the disease state and acuity of the subject studied, the pre-specified objective may have underestimated the true safety rate for catheter ablation in this population.

Chronic Safety Endpoint

Objective: The primary endpoint for chronic safety was a success/failure variable calculated for each subject at the 6 month time point. The definitions of adverse events that characterized a subject as a chronic safety failure were as follows:

1. **Ablation Management** - Events adjudicated by the CEC/DSMB to be both serious and related to the ablation procedure and/or device (serious adverse device effects or SADEs) and/or other characteristics unique to the Ablation Management arm during the 6 month follow-up period (excluding the first 7 days post procedure).
2. **Medical Management** - Events adjudicated by the CEC/DSMB to be both serious and related to antiarrhythmic drugs, and/or other characteristics unique to the Medical Management arm (DC cardioversion, anticoagulation) during the 6 month follow-up period (serious adverse events or SAEs).

Chronic Safety Results

The Primary Chronic Safety Outcome study objective was met (Table 11). Ten percent (11.6%) of Ablation Management subjects (16 of 138) failed to remain free of procedure- or device-related SAEs, which was not worse than 19.4% (14 of 72 subjects) of Medical Management subjects using a pre-specified 6% non-inferiority margin (p=0.0052) to meet the Chronic Safety objective.

Subjects who withdrew prior to study completion were considered endpoint failures per the intention-to-treat passive missing values imputation method (p=0.0011).

Table 11. Chronic Safety Endpoint

	Ablation Management Arm (N=138) n (%)	Medical Management Arm (N=72) n (%)
Number of Subjects with Chronic SADEs or SAEs (%)	10 (5.8%)	3 (4.2%)
p-value for H_0: $P_A \geq P_M + 6\%$ (Chi-Square test of Homogeneity)		p=0.0052

5.4.6 Secondary Endpoints and Results

Acute effectiveness, for subjects randomized to the Ablation Management arm had a pre-specified hypothesis identified in the Statistical Analysis Plan. For all other secondary endpoints no established performance criterion was identified therefore, descriptive statistics are presented.

Acute Effectiveness Endpoint

Objective: The statistical analysis of the acute effectiveness endpoint consisted of a comparison of the proportion of subjects achieving acute treatment success with the target success rate of 90% or greater. A count of successes and the proportion of successfully treated subjects were computed for the Ablation Management arm. The numerator of the proportion was the number of acutely successful subjects in the Ablation Management arm and the denominator was the number of subjects in the Ablation Management arm. Missing values were treated as described in the Statistical Analysis Plan.

Acute effectiveness was characterized for subjects randomized to the Ablation Management arm undergoing either an index or retreatment procedure. Acute effectiveness was defined as:

- Use of Medtronic catheters to achieve procedure success, and
- Isolation of all accessible pulmonary veins, and
- Elimination of mapped complex fractionated atrial electrograms (CFAEs), using Medtronic catheters, and
- Sinus rhythm up on leaving the EP laboratory (with or without the need for DC cardioversion).

Acute Effectiveness Results

Table 12 summarizes the acute effectiveness results for subjects that were randomized to Ablation Management. Required acute success components were met in 128 of 138 (92.8%) subjects with a confidence interval of (87%, 96%) using the exact approach. Overall, the mean success rate of 92.8% exceeded the 90% pre-specified hypothesis, however, the

confidence interval included the 90% pre-specified acute efficacy rate and therefore the acute procedural success rate was not shown to be statistically significantly greater than 90% (p-value = 0.1754).

Table 12. Acute Procedural Success - ITT Population

Acute Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)
Subjects that received an ablation procedure	132 (95.7%)
Medtronic Ablation catheter(s) used in each procedure	129 (93.5%)
Isolation of all pulmonary veins	129 (93.5%)
Mapped CFAEs eliminated in index procedure	131 (94.9%)
Sinus rhythm at completion of procedure	128 (92.8%)
Subjects meeting all Success Criteria	**128 (92.8%)**

Note: Exact One-sample binomial test (H0: proportion Success ≤0.90)

Of the 138 Ablation Management subjects, 132 subjects actually received an ablation procedure in which the investigational catheters were used (mITT population). Of the 132 ablated subjects, acute effectiveness was achieved in 97.7% with a resulting 95% confidence interval of (92.4%, 99.2%) which exceeded the 90% target rate to meet the Acute Efficacy objective.

Comparative Analyses between Treatment Arms at 6 Months

- **Left Atrial Size at 6 Months compared to Baseline**

  Subjects in Ablation Management demonstrated a slight reduction in mean LAD from 4.5 ± 0.53 cm to 4.4 ± 0.67 cm over 6 months compared to almost no change in mean LAD for subjects in Medical Management (4.6 ± 0.49 cm at baseline; 4.6 ± 0.56 cm at 6 months). No significant difference (p=0.35) for LAD was observed between the treatment arms at the 6 month time point.
- **Left Ventricular Ejection Fraction at 6 Months compared to Baseline**

  Improvement in LVEF was observed in both Ablation and Medical Management subjects. The difference in LVEF improvement was in favor of Ablation Management over Medical Management and approached significance (p=0.0625).
- **Symptom Severity Score at 6 Months compared to Baseline**

  Subjects were asked to rate the severity of atrial fibrillation-related symptoms (protocol-specified), on a scale from 1 (no symptoms) to 5 (most severe), during each of follow-up visit. A reduction in score denotes improvement in symptoms. There was a consistent reduction in the score in both arms at the 1 month follow-up visit. Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Quality of Life (SF-36) at 6 Months compared to Baseline**

  In a repeated-measure analysis, Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

All Adverse Events

All adverse events reported by investigational sites were adjudicated by the CEC/DSMB as being related to the 1) ablation procedure, 2) investigational ablation system, 3) antiarrhythmic drug (AAD) therapy, or 4) underlying disease.

A total of 183 ablation procedures (134 index and 49 retreatment) were performed in 180 Ablation Management subjects, including all aborted procedures for each subject. In addition, 43 subjects crossed over from Medical Management to receive an ablation procedure (43 total procedures) and 12 of those subjects required a retreatment procedure (total of 13 procedures as one subject had 2 retreatment procedures). A total of 239 ablation procedures were performed (including procedure attempts and procedure completions).

There were a total of 31 serious adverse events related to the procedure or the device reported and adjudicated for 27 Ablation Management subjects:

- 21 acute events reported for 17 subjects
- 10 chronic events reported for 10 subjects

Another 23 serious events, not related to the procedure or the device were reported in 21 Ablation Management subjects:

- 8 acute events occurred in 8 subjects
- 15 chronic events occurred in 13 subjects

Medical Management had a total of 6 serious adverse events reported and adjudicated for 6 subjects. There was no breakdown for acute and chronic events within the Medical Management treatment arm.

- 3 events were adjudicated as being related to medical therapy treatment or AF.
- Another 3 events were serious but adjudicated as not being related to treatment.

An overall total of 98 adverse events were adjudicated as being “non-serious”.

There was one procedure-related study death reported which occurred prior to deployment of the investigational device.

5.5 Overall Conclusions on the Results from TTOP-AF Clinical Study

The aim of this study was to systematically evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System utilizing multi-electrode, anatomically-designed catheters combined with a duty-cycled, phased RF energy system in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation.

The Primary Effectiveness Outcomes and associated analyses were overwhelmingly in favor of duty-cycled, phased-RF ablation compared with Medical Management treatment in subjects with symptomatic, drug-refractory persistent and long-standing persistent AF:

- **Primary Effectiveness Outcome**: Phased-RF ablation resulted in a 28.0% absolute percentage point increase in Treatment Success over treatment with AADs, with 77 Ablation Management subjects (55.8%) achieving Treatment Success over 6 months of follow-up, compared to 20 Medical Management subjects (27.8%) (p<0.0001).
- **Effectiveness Outcome of Ablation with and without the Use of AADs**: The total number of ablated subjects able to reduce their AF burden by ≥90% with and without the use of AADs was 93 subjects or 67.4% (93/138), an absolute percentage point difference of 39.6% from Medical Management (27.8%).
- **Reduced Symptoms:** Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Improved Quality of Life:** Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

The Primary Safety Outcomes and associated analyses demonstrated a favorable safety profile for treatment with duty-cycled, phased-RF ablation compared with AAD and DC cardioversion treatment in subjects with drug refractory, symptomatic, persistent and long-standing AF:

- **Primary Acute Safety Outcome**: The Primary Acute Safety endpoint was not met for Ablation Management. The upper bound of the two-sided, 95% confidence interval was 19.0%, which exceeded the pre-specified performance goal of 16%.

Primary Chronic Safety Outcome: Duty-cycled, phased-RF ablation resulted in a statistically significant lower rate of SAEs/SADEs related to AF and its treatment during the 6 months of study follow-up for Ablation Management subjects (10.0%) compared to Medical Management subjects (20.9%), to meet the Primary Chronic Safety Outcome (p=0.0011).

6 Adverse events

Potential adverse events associated with cardiac catheter ablation procedures include, but are not limited to, the following conditions:

- Allergic reaction to x-ray contrast media
- Anesthesia reactions
- Arrhythmias, proarrhythmia
- AV fistula
- Bleeding related to anticoagulation
- Body temperature elevation
- Bradycardia
- Cardiac perforation of the heart or other organs during transseptal puncture or other procedures
- Cardiac tamponade
- Cardiac thromboembolism
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Chest discomfort
- Chronic cough
- Component damage to ICD or implanted pacemaker
- Death
- Dislodgement of implantable cardioverter defibrillator (ICD) or permanent pacing leads
- Heart failure
- Hematoma
- Hemoptysis
- High creatinine phosphokinase or troponin level
- Hypotension
- Infections
- Myocardial infarction or ischemia
- Nerve injury or nerve damage
- Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system
- Pericarditis or endocarditis
- Unintended complete or incomplete atrioventricular node (AV-Node) or sinus node block or damage
- Pleural or pericardial effusion
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Pulmonary infiltrates
- Pulmonary vein narrowing or stenosis
- Pseudoaneurysm in groin
- Radiation injury or damage and late malignancy
- Respiratory depression
- Retroperitoneal bleed
- Skin burns
- Thrombotic or embolic events
- Valvular insufficiency or damage
- Vasovagal reaction

7 Instructions for use

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Note: Activated clotting times (ACT) should be checked at 10 to 15 minute intervals until therapeutic anticoagulation is achieved and then at 30 minute intervals during the case. The lower level of anticoagulation should be maintained at an ACT f at least 300-350 seconds throughout the procedure, as it has been demonstrated that less intense anticoagulation is associated with a high prevalence of in situ thrombus adherent to the transseptal sheaths. If significant atrial enlargement or spontaneous echo contrast is observed, many operators target a higher aCE range of 350 - 400.[1]

7.1 Preparing the catheter

1. Prepare and utilize the catheter under aseptic conditions.
2. Carefully remove the catheter from the packaging and inspect the catheter prior to use to verify that it has not been compromised during shipping or handling.
3. Remove the stylet from the proximal end of the guidewire luer hub on the proximal end of the handle (see Figure 2).

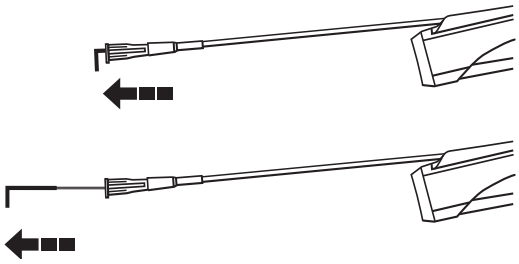


Figure 3. Removing the stylet

4. Flush the lumen and rinse the distal end of the catheter using heparinized saline.
5. Insert the proximal end of the guidewire into the distal end of the PVAC. The guidewire must exit the proximal end of the PVAC device.

   Note: The PVAC is an over-the-wire catheter designed to be used with an 0.032 inch guidewire at all times.

7.2 Preparing and managing the transseptal sheath

1. Prepare the transseptal sheath following the directions in the manufacturer's Instructions for Use (IFU).

   Note: After left atrial access, maintain anticoagulation within the sheath.
2. Perform aspiration or spontaneous bleed back from the transseptal sheath prior to insertion of the catheter into the sheath**.**

   Note: Perform this step following all catheter exchanges, preferably on the right side.
   Warning: Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

7.3 Capturing the array with the capture device

1. Rotate the steering knob until the catheter is in a straight position with the array in a neutral position.
2. Remove the capture device from the handle and slide it up to the spiral array.
3. Verify that the guidewire extends from the distal tip a minimum of 10 cm.
4. While holding the capture device against the spiral array, slowly advance the slide control knob forward, as shown in Figure 4, while advancing the capture device.

   Note: Avoid advancing the capture device beyond the end of the array.

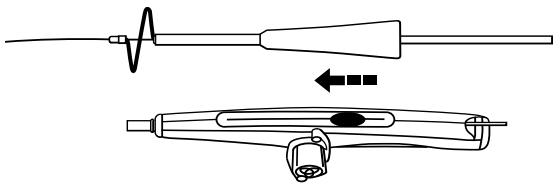


Figure 4. Advancing the capture device

5. As the capture device is advanced forward, continue to advance the slide control knob forward (see Figure 4).

[1] (Calkins, Hugh, 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 9.6 (2007): 335-79.)

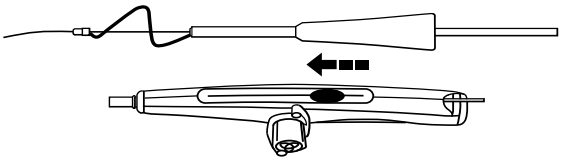


Figure 5. Advancing the slide control knob

Note: It is important to always lead the distal tip of the catheter ahead of the capture device to prevent kinking of the distal lumen.

6. Hold the slide control knob in the forward position while capturing the tip of the spiral array (see Figure 5).

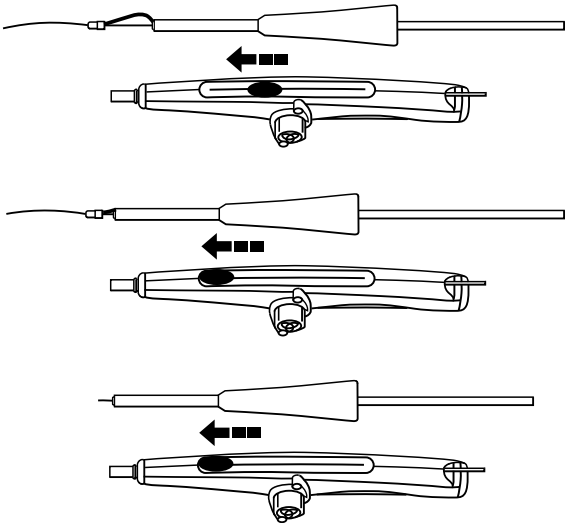


Figure 6. Capturing the array

7.4 Inserting the catheter and deploying the array

1. Retract the guidewire to the distal tip of the PVAC.
2. With the array contained, insert the capture device into the hemostasis valve and advance until the capture device is seated against the inner surface of the sheath hub.
3. Insert approximately half of the guidewire length into the transseptal sheath.
4. Advance the array portion of the catheter into the sheath before removing and placing the capture device firmly onto the handle.

   Note: Perform steps 5–9 under fluoroscopic visualization.
5. Advance the catheter through the transseptal sheath until the array enters the atrium.
6. Before fully deploying the catheter, verify that the guidewire is positioned in one of the left pulmonary veins.
7. Continue to advance the catheter until the fourth electrode on the spiral array begins to exit the sheath.
8. Slowly pull back on the slide control knob while continuing to advance the catheter forward to deploy the spiral array.
9. Retract the distal end of the transseptal sheath into the right atrium. This allows for full deflection of the distal segment of the catheter, as shown in Figure 6.

   Note: Do not attempt to steer the catheter within the sheath.

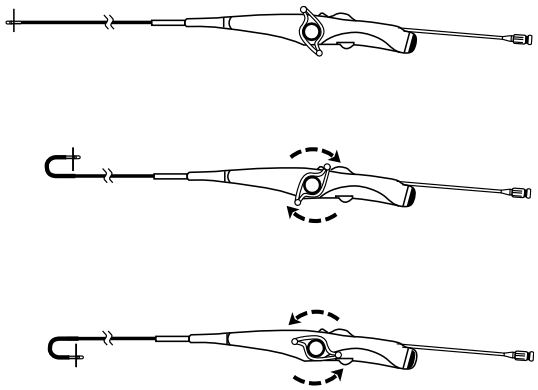


Figure 7. Deflecting the distal segment of the array

7.5 Connecting the cables

1. After insertion of the catheter, use sterile technique to connect the catheter interface cable to the connector located on the handle of the catheter.
2. Pass the other end of the catheter interface cable out of the sterile field and connect it to the ECG interface box.

   Note: The generator automatically identifies the catheter when it is connected and displays the catheter image and default system parameters.
   - Energy mode 4:1
   - Ablation duration 60 seconds
   - Target temperature 60° C

   Note: Refer to the generator operator's manual for detailed operation information.

7.6 Mapping and ablating

Note: Perform steps 1–7 under fluoroscopic visualization.

Caution: Do not allow electrodes 1 and 10 to come in contact with each other. Doing so creates a short circuit resulting in a system error condition.

1. Advance the guidewire into the selected pulmonary vein.
2. Advance the spiral array onto the antrum.

3. Map for pulmonary vein potentials.
4. Ablate
5. Pull the array back from the antrum, rotate the array 90° and advance it onto the antrum.
6. Repeat mapping and ablating applications as necessary for each pulmonary vein.
   Notes:
   – Do not attempt to steer the catheter within the sheath.
   – Use the tension control knob to maintain curve configuration.
7. To verify isolation in the pulmonary veins, perform the following steps:
   a. Retract the catheter from the ostium of the vein.
   b. Advance the slide control knob forward halfway.
   c. Advance the spiral array into the vein while rotating in a counter clockwise rotation.
   d. Retract the slide control know slightly to expand the spiral array against the inside surface of the vein.
   e. Utilize electrode 1 for pacing.
   f. Confirm isolation.
   g. Rotate the spiral array and repeat as necessary until isolation is verified.

7.7 Removing the catheter

1. Disconnect the catheter from the catheter interface cable.
   Note: Perform steps 2–6 under fluoroscopic visualization.
2. Verify the catheter is in the straight position and at least 5 cm of guidewire is inserted into one of the left pulmonary veins.
3. Slowly advance the slide control knob forward one-fourth of the travel distance and begin to pull back on the catheter shaft to retract the array into the transseptal sheath.
4. Continue to slowly advance the slide control knob while simultaneously retracting the catheter, until the spiral array is completely inside the transseptal sheath.
5. Withdraw the catheter halfway through the sheath.
6. Insert the capture device into the hemostasis valve and continue retracting the catheter until the array is located in the capture device.
7. Remove the capture device with the spiral array and the guidewire from the valve of the sheath.

8 Specifications

Overall length	145 cm ±5 cm (57.09 in ±1.97 in)
Effective length	105 cm ±5 cm (41.34 in ±1.97 in)
Array configuration	Single spiral array [25 mm (0.98 in) diameter]
Number of electrodes	10
Electrode spacing	3 mm (0.12 in)
Electrode width	3 mm (0.12 in)
Measured temperature accuracy	± 2°C (± 3.6°F)
Single use circuitry	Circuitry allows the RF ablation generator to assess “single use”
Shaft and electrode array OD	3 mm (9 French; 0.118 in) OD Withdrawal through a 3.17 mm (9.5 French; 0.12 in) sheath (minimum)

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

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MASC® 990001

Multi-Array Septal Catheter®

Technical Manual

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Medtronic, GENius, MASC, Multi-Array Septal Catheter

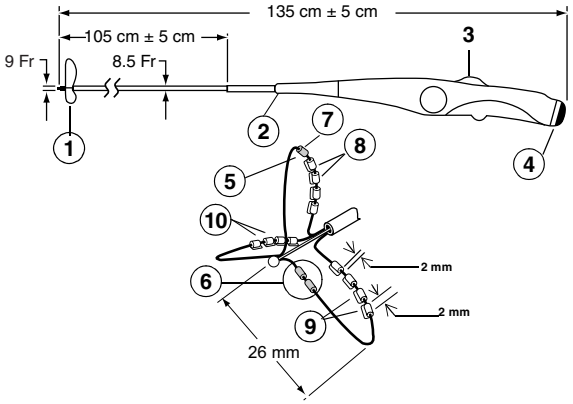
Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which of these apply to this product..

LOT	Lot number
REF	Reorder number
	Use by
STERILE R	Sterilized using irradiation
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Keep dry
	Product documentation
	Keep away from heat
! USA	For US audiences only

1 Description

The Medtronic Multi-Array Septal Catheter (MASC) is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue along the left atrial septum (see Figure 1).



1	Array	6	Arm 2 markers
2	Capture device	7	Electrodes
3	Slide control knob	8	Pair 1
4	Connector	9	Pair 3
5	Arm 1 marker	10	Pair 5

Figure 1. Multi-Array Septal Catheter

1.1 Contents of package

The package contains the following:

- 1 Multi-Array Septal Catheter
- Product documentation

Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions noted in these instructions. Failure to do so may result in less than expected outcomes.

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

2 Indications for use

The Multi-Array Septal Catheter is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent (1 to 4 years) atrial fibrillation.

The MASC is used for mapping, pacing, and ablating arrhythmogenic tissue along the left atrial septum.

3 Contraindications

Use of the Multi-Array Septal Catheter is contraindicated as follows:

- Active sepsis
- Left atrial thrombus or myxoma
- Atrial Septal Patch or atrial septal defect repair with percutaneous device
- Known sensitivity to heparin
- Blood clotting abnormalities
- Venous filtering device (Greenfield Filter)

The catheter is not recommended for use in patients who cannot undergo standard anticoagulation protocol for a left-sided cardiac procedure, or who have had a recent coagulopathy or embolic event.

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Cable positioning – Position all cables associated with the generator so they do not come in contact with the patient or other leads. RF interference may affect the ability to interpret patient EGMs.

Catheter exchange – Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

Catheter placement – It is recommended that the application of RF energy be applied at the antrum of the pulmonary veins. Delivery of RF energy inside the pulmonary veins may result in pulmonary vein stenosis.

Disposal of catheter – Dispose of the catheter according to hospital biohazard requirements. If returning the catheter, contact your local Medtronic representative.

Electrical isolation during ablation – Do not allow the patient to contact grounded equipment that might produce electrical current leakage during ablation. Electrical current leakage may induce arrhythmias that may result in the patient's death.

Electrode contact – Avoid contact between electrodes. Contact between electrodes may create a short circuit or channel fault system error.

Electrode separation – Maintain adequate separation between all energized electrodes during ablation. Failure to maintain adequate separation may result in leading to high temperatures.

Embolism risk – Introducing any catheter or sheath into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism. Closely monitor transseptal sheaths, performing aspiration and/or flushing to prevent air ingress and/or soft clot formation.

Expiration date – Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Flammable materials – Do not allow flammable material in the area where RF ablation procedures are performed. The risk of igniting flammable gases, flammable agents used for cleaning or disinfecting, or other materials is inherent in the application of RF energy.

Fluoroscopy required for catheter placement – Use of fluoroscopy during catheter manipulation and placement is strongly advised. Manipulating the catheter without fluoroscopy may result in damage to cardiac and vascular structures.

For single use only – This device is intended only to be used once for a single patient. Do not reuse, reprocess, or resterilize this device for purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent aspiration and flushing of the sheath – Aspirate and flush the sheath frequently to help minimize the potential for embolic events resulting from the introduction of air or the formation of clot within the sheath.

Generator settings or equipment failure – Do not increase target temperature or ablation duration settings before checking for obvious defects or misapplication, as patient injury may occur. Apparent low power output or failure of the equipment to function correctly at normal settings may indicate faulty application of the patient return electrodes or failure of an electrical lead.

High electrode temperatures – Only use catheters as recommended, maintain catheter contact with cardiac tissue during ablation, and monitor the displayed electrode temperatures and power delivery, in order to avoid high instantaneous electrode temperatures. Temperatures above 80° C during ablation may increase the patient's risk of thromboembolic events (formation of coagulum), steam pops, and cardiac perforation, depending on catheter type used.

- Only use catheter in the recommended anatomical location.
- Maintain catheter electrode contact with cardiac tissue by holding the catheter during the ablation.
- Do not reposition, rotate, slide, drag or otherwise intentionally disengage and then re-engage the catheter electrodes with cardiac tissue while ablating. Stop ablation prior to performing any of these actions.
- Monitor the displayed electrode temperature and power delivery during ablation. Deselect the affected electrode pair or discontinue ablation if the electrode does not reach 50° C and is receiving maximum power delivery.

Left-sided ablation – Closely monitor patients undergoing left-sided ablation procedures for clinical manifestations of infarction, cardiac tamponade, thromboembolism, or stroke.

Long-term risk – The long-term risks of lesions created by radiofrequency (RF) ablation have not been established. In particular, the long-term effects of lesions in proximity to the specialized conduction system or coronary vasculature are unknown.

No direct skin contact during system testing – Do not test the operation of the ablation system through direct skin contact with the electrodes. Testing through direct skin contact may cause damage to healthy tissue.

Oral anticoagulation therapy – Anticoagulation (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion and/or ablation.[1]

Placement of monitoring electrodes – Place all physiological monitoring electrodes as far away as possible from the patient return electrodes and their leads to avoid RF interference, which affects the ability to interpret patient electrograms (EGMs).

Procedural anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Qualified users – The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

Related product literature – Do not attempt to operate the Medtronic cardiac ablation system prior to completely reading and understanding the GENius Multi-Channel RF Ablation Generator Operator's Manual and the relevant cardiac ablation catheter technical manual.

Required use environment – Cardiac ablation procedures should be performed only in a fully equipped electrophysiology laboratory.

Sheath or guide catheter required – Do not attempt to advance or withdraw the catheter through the vascular bed without the use of a sheath or guide catheter, as it may result in damage to cardiac and vascular structures.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or the catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Storage conditions – Store the catheter in normal operating room temperatures and humidity levels and in a manner that protects the integrity of the package and the sterile barrier. Keep in a dry location away from heat and sunlight.

System compatibility – Use only the following components with the catheter: Medtronic GENius Multi-Channel RF Ablation Generator, its compatible Medtronic components, and Valleylab Patient Return Electrodes (Model E7506, two required). Use of the catheter with other components may cause patient harm.

Use of RF energy near implanted devices – Implantable devices, such as pacemakers and implantable cardioverter-defibrillators (ICDs), may be inhibited or otherwise affected by RF energy. Refer to the Multi-Channel RF Generator Operators Manual and the appropriate implantable device technical manual for additional information.

X-ray and fluoroscopic exposure – Minimize x-ray and fluoroscopic exposure. Due to the intensity of the x-ray beam and the duration of the fluoroscopic imaging during ablation procedures, patients and laboratory staff may be subjected to acute radiation injury and increased risk for somatic and genetic effects. Take all appropriate measures to minimize x-ray exposure to both patients and clinical staff. The long-term effects of protracted fluoroscopy have not been established.

5 Clinical Study Summary

Note: Clinical section provided to show structure only - data subject to change.

5.1 Study Purpose

Medtronic conducted a prospective multi-center, controlled, randomized clinical study to support a pre-market application (PMA) for a multi-channel, duty-cycled, phased radiofrequency (RF) generator (Medtronic GENius Multi Channel RF Ablation Generator) and three anatomically designed, multi-electrode catheters, which will be referred to as the Medtronic Cardiac Ablation System. The purpose of the Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) clinical study was to evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation (AF).

5.2 Study Scope, Design and Methods

The TTOP-AF clinical study utilized a prospective, multi-center, randomized, controlled design. After all entrance criteria were met, subjects were randomized in a 2:1 fashion to either Ablation Management or Medical Management.

Subjects in the Ablation Management arm were allowed up to 2 ablations with the investigational device, as is typical in this patient population, to achieve treatment success. All procedures (index and retreatment) consisted of intra-cardiac signal mapping and ablation of pulmonary vein potentials and complex fractionated atrial electrograms (CFAEs) with three anatomically designed, multi-electrode catheters; Pulmonary Vein Ablation Catheter (PVAC), Multi-Array Septal Catheter (MASC) and Multi-Array Ablation Catheter (MAAC). There were no requirements for 3-dimensional navigation and complex mapping systems. If AF was not terminated during an ablation procedure, subjects received a direct current (DC) cardioversion (internal or external) to restore sinus rhythm. Confirmation of pulmonary vein isolation (PVI) was then completed in sinus rhythm with the PVAC. Catheter use was consistent in retreatment procedures unless sinus rhythm restoration prevented additional signal mapping of CFAEs with the MASC and/or MAAC. Subjects were followed at pre-discharge, 1, 3 and 6 months post-ablation. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements.

The Medical Management arm subjects received antiarrhythmic drug (AAD) changes and DC cardioversions to achieve and maintain sinus rhythm. Crossover to receive an ablation procedure could occur after 4 months with documentation of continuous AF on a 48-hour

[1] Fuster, Valentin, et al. "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation - Executive Summary." Circulation 114.7 (2006): 700-52.)

Holter recording. Subjects were followed at 1, 3, and 6 months but were also required to be evaluated 30 days after any DC cardioversion.

The TTOP-AF clinical study protocol included the ability to perform an interim analysis. Interim analysis was allowed after at least 50% of the enrolled subjects reached their chronic effectiveness endpoint at 6 months and 100% of the subjects reached their acute safety endpoint. The interim analysis was conducted using a July 31, 2009 cutoff date, signifying the point in time where the interim analysis criteria specified above were met. In order to provide a more complete representation of all acute safety events in the Ablation Management arm, retreatment adverse events collected through November 24, 2009 were included in this Clinical Study Report.

Subjects were enrolled at 23 centers across the United States and one site in The Netherlands for the pivotal phase of the TTOP-AF trial. Investigators enrolled and randomized subjects during a 19 month period between November 2007 and May 2009. The first subject was randomized on November 28, 2007 and the ablation procedure for the last enrolled subject occurred on June 5, 2009. The last retreatment procedure for subjects in Ablation Management occurred on November 24, 2009. All subjects enrolled, randomized and treated in the TTOP-AF trial have completed their 6-month follow-up assessments. Subjects that completed all assessments were exited from the study per protocol requirements.

Data from all study required Holter recordings were analyzed and reviewed by an independent core lab. All safety events were adjudicated by an independent Clinical Events Committee/Data and Safety Monitoring Board (CEC/DSMB). For identification of pulmonary vein changes post-ablation, Ablation Management subjects were required to complete a baseline and 6 month CT scan or MRI. Subjects with scans demonstrating pulmonary vein diameter changes, as noted by the study site, were reviewed by a Core laboratory. Pulmonary vein changes were recorded as “stenosis” if the vein diameter change from baseline was greater than 70% and “narrowing” if the vein change was between 50% and 70%.

The statistical analysis of all primary endpoints was on an intention-to-treat basis (ITT) with passive missing value imputations, where all missing endpoint data were considered a treatment failure for each respective arm. Subjects were designated ITT once randomized.

The TTOP-AF clinical study initially enrolled 20 consecutive feasibility subjects that received an ablation procedure from May 2007 to August 2007. Successful completion of this 20 subject Feasibility phase was required before proceeding to the Pivotal phase. Enrollment of the Pivotal phase began in November 2007 and was completed in 19 months. The final index procedure occurred on June 15, 2009; the last retreatment procedure was performed on November 24, 2009.

Table 1summarizes the major study milestones and data cutoff dates for this report.

Table 1. Study Milestones

First subject randomized in the TTOP-AF clinical study	November 28, 2007
Last subject randomized in the TTOP-AF clinical study	May 20, 2009
Last index ablation procedure performed	June 15, 2009
Last retreatment procedure performed	November 24, 2009

5.3 Subject Inclusion and Exclusion Criteria

5.3.1 Inclusion Criteria

1. History of drug refractory, symptomatic, persistent/long-standing persistent atrial fibrillation defined as:
   - AF greater than 1 year but less than 4 years; OR
   - Non self-terminating AF, lasting greater than 7 days but no more than one year, with at least one failed DC cardioversion. Unsuccessful
     - DC cardioversion failure was defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond 7 days.
   - AF symptoms defined as the manifestation of:
     - Palpitations
     - Fatigue
     - Exertional dyspnea
     - Increased intolerance to routine activities (exercise intolerance)
2. Age between 18 and 70
3. Failure of at least one Class I or Class III AAD
4. Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study.

5.3.2 Exclusion Criteria

1. Structural heart disease of clinical significance including:
   - Previous cardiac surgery (excluding coronary artery bypass graft [CABG] and mitral valve repair)
   - Symptoms of congestive heart failure including, but not limited to, New York Heart Association (NYHA) Class III or IV CHF and/or documented ejection fraction < 40% measured by acceptable cardiac testing
   - Left atrial diameter of > 55mm
   - Moderate to severe mitral or aortic valvular heart disease
   - Stable/unstable angina or ongoing myocardial ischemia
   - Myocardial infarction (MI) within three months of enrollment
   - Congenital heart disease (not including atrial septal defect [ASD] or patent foramen ovale [PFO] without a right to left shunt) where the underlying abnormality increases the risk of an ablation procedure
   - Prior ASD or PFO closure with a device using a percutaneous approach
   - Hypertrophic cardiomyopathy (defined as left ventricular septal wall thickness > 1.5 cm)
   - Pulmonary hypertension (defined as mean or systolic pulmonary artery pressure > 50mm Hg on Doppler echo)
2. Any prior ablation for atrial fibrillation
3. Enrollment in any other ongoing arrhythmia study protocol
4. Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
5. Active infection or sepsis
6. Any history of cerebral vascular disease including stroke or transient ischemic attacks (TIAs)
7. Pregnancy or lactation
8. Left atrial thrombus at the time of ablation
9. Untreatable allergy to contrast media
10. Any diagnosis of atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
11. History of blood clotting (bleeding or thrombotic) abnormalities
12. Known sensitivities to heparin or warfarin
13. Severe COPD (defined as an Forced Expiratory Volume in One Second (FEV_1) <1)
14. Severe co morbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e., other disease processes, mental capacity, substance abuse, shortened life expectance, etc.)

5.4 Results

5.4.1 Subject demographics

A total of 242 study candidates signed an informed consent, with 210 randomized in a 2:1 fashion to the Ablation Management or Medical Management arms (Figure 2). Thirty-two (32) subjects signed informed consent but withdrew before being randomized for the following reasons:

- Subject did not have 100% atrial fibrillation on the 48-hour Holter recording (n=12)
- Subject did not meet other entrance criteria (n=12)
- Subject withdrew consent (n=6)
- Subject was withdrawn per the Sponsor (n=1)
- Other: Enrollment was closed prior to completion of screening (n=1)

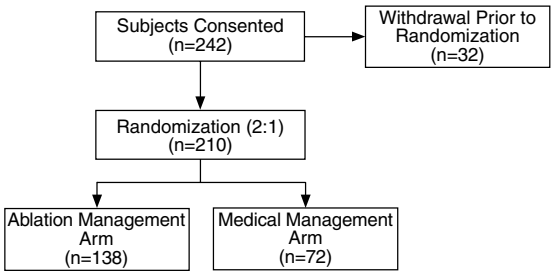


Figure 2. Study Enrollment

As shown in Table 2, the subject characteristics were similar in the Ablation Management and Medical Management arms. The average age of subjects in the Ablation Management arm was 59.6 years and in the Medical Management arm 60.7 years. Over 80% of the subjects enrolled in the study were male despite efforts of the study coordinators to identify eligible female participants. Gender and ethnicity were equally matched between randomized arms.

Information was obtained through medical records, referring physician notes, and subject interviews to verify the duration of AF burden prior to enrollment. The average time in years that each subject was initially diagnosed with AF, was 0.9 years for Ablation Management and 0.7 years for Medical Management, which was not statistically different. Subjects in both arms had an average of 2 DC cardioversions (2.0 for Ablation Management and 2.4 for Medical Management) in the previous 4 years.

Therapy with Class I or III antiarrhythmic drugs began, on average, 2.1 years prior to enrollment for subjects in the Ablation Management arm and 2.5 years prior for subjects in the Medical Management arm.

Left atrial diameter at baseline (average of 4.5 cm for Ablation Management and 4.6 for Medical Management) was enlarged compared to the paroxysmal patient population but comparable between treatment arms. Likewise, left ventricular ejection fraction, as measured by a screening transthoracic echocardiogram, was also comparable (average of 54.7% for Ablation Management and 54.9% for Medical Management).

Table 2. Subject Characteristics

Variable	Ablation Management Arm (n=138) Mean ± SD Median (Min, Max)	Medical Management Arm (n=72) Mean ± SD Median (Min, Max)	p-value[a]
Age, years	59.6 ± 8.3 61.2 (35.5, 73.4)	60.7 ± 8.9 60.8 (31.3, 75.2)	0.37
Gender			
Male (%)	115 (83.3%)	60 (83.3%)	1.00
Female (%)	23 (16.7%)	12 (16.7%)	
Ethnicity			
Caucasian (%)	133 (96.4%)	70 (97.2%)	0.92
African American (%)	3 (2.2%)	1 (1.4%)	
Other (Hispanic, Asian) (%)	2 (1.4%)	1 (1.4%)	
Years Since First Atrial Fibrillation Diagnosis	0.9 ± 0.9 0.6 (0.0, 4.1)	0.7 ± 0.8 0.5 (0.0, 3.9)	0.15
Years Since First DC Cardioversion	1.3 ± 2.0 0.5 (0.0, 11.4)	2.1 ± 3.3[b] 0.5 (0.0, 13.0)	0.47
Years Since First Prescribed Class I or III AAD	2.1 ± 3.3[c] 0.6 (0.0, 18.6)	2.5 ± 4.1[c] 0.8 (0.0, 18.6)	0.49
Approximate Number of DC Cardioversions in Last 4 Years/ Subject	2.0 ± 1.1 2.0 (1.0, 6.0)	2.4 ± 3.5 2.0 (1.0, 30.0)[d]	0.24
Left atrial diameter, cm	4.5 ± 0.5 4.6 (3.2, 5.5)	4.6 ± 0.5 4.7 (3.0, 5.5)	0.33
Left Ventricular Ejection Fraction,%	54.7 ± 7.1 55.0 (40.0, 75.0)	54.9 ± 6.6 55.0 (40.0, 69.0)	0.83

[a] Two-sided α=0.05 level significance
[b] N=71 for Medical Management
[c] N=137 for Ablation Management; N=71 for Medical Management
[d] Subject with 30 cardioversions was cardioverted via implanted cardioverter defibrillator.

Table 3 details the baseline medical history for the Ablation Management and Medical Management arms. There were no significant differences in baseline medical history between arms.

Table 3. Baseline Medical History

Characteristic	All Subjects % (n / N)	Ablation Management Subjects % (n / N)	Medical Management Subjects % (n / N)	Pearson Chi-square p-value
Diabetes Mellitus	14.3% (30/210)	15.9% (22/138)	11.1% (8/72)	0.34
Coronary Artery Disease	19.0% (40/210)	20.3% (28/138)	16.7% (12/72)	0.53
Congestive Heart Failure	7.6% (16/210)	5.8% (8/138)	11.1% (8/72)	0.17
Hypertension	59.0% (124/210)	60.9% (84/138)	55.6% (40/72)	0.46
Cardiomyopathy	9.0% (19/210)	6.5% (9/138)	13.9% (10/72)	0.08
Valvular Disease	7.1% (15/210)	5.1% (7/138)	11.1% (8/72)	0.11
Congenital Heart Disease	0.5% (1/210)	0.7% (1/138)	0% (0/72)	0.47
PFO or ASD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63
Pacemaker or ICD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63

Pertinent baseline physical examination findings are found in Table 4. Heart rate at the time of baseline evaluation was statistically different but not clinically relevant in the Ablation Management arm compared to the Medical Management arm. Blood pressure was comparable among the treatment arms. In order to quantify the risk of stroke in the TTOP-AF clinical study population, a $CHADS_2$ score was retrospectively calculated using parameters collected at baseline. The $CHADS_2$ score was determined by assigning 1 point each for the presence of **C**ongestive heart failure, **H**ypertension, **A**ge 75 years or older, and **D**iabetes

mellitus and by assigning 2 points for history of **S**troke or transient ischemic attack.[1] There were no differences in $CHADS_2$ scores between treatment arms at baseline.

Table 4. Baseline Physical Examination Measurements and $CHADS_2$ Score

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value[a]
Heart rate (bpm)	79.0 ± 15.4 79.5 (43, 129)	77.3 ± 14.9 78.0 (43, 119)	82.4 ± 15.9 83.0 (50, 129)	0.02
Systolic BP (mm Hg)	124.3 ± 15.3 124.5 (88, 165)	124.1 ± 15.5 125.0 (88, 165)	124.8 ± 15.0 124.5 (90, 164)	0.77
Diastolic BP (mm Hg)	77.5 ± 10.01[b] 79.0 (50, 118)	77.8 ± 9.95 80.0 (50, 118)	76.8 ± 10.16[c] 78.0 (50, 102)	0.47
$CHADS_2$ Score	0.81 ± 0.72 1 (0, 3)	0.83 ± 0.74 1 (0, 3)	0.79 ± 0.69 1 (0,2)	Not calculated

[a] Two-sided t-test
[b] The total number of subjects for diastolic BP is N=209, due to the one subject (26-305) that was missing a diastolic BP reading.
[c] One subject was missing diastolic BP recording (Subject 25-305), so there is only an N=71for diastolic BP in Medical Management

As a requisite for randomization, all subjects were required to demonstrate 48 hours of continuous atrial fibrillation on a baseline Holter recording. All subjects in both arms demonstrated a single episode of continuous atrial fibrillation. Table lists the baseline Holter recordings from the Ablation Management and Medical Management arms.

Table 5. Baseline 48-hour Holter Recording

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value
Total Time on Monitor (Hours:Minutes)	48:25 ± 1:18 48:12 (36:25, 50:00)	48:23 ± 1:25 48:13 (36:25, 50:00)	48:28 ± 1:04 48:11 (42:22, 49:58)	0.64
Total Time on Monitor in Atrial Fibrillation (Hour:Minutes)	48:27 ± 1:18 48:14 (36:27, 50:00)	48:25 ± 1:25 48:15 (36:27, 50:00)	48:30 ± 1:04 48:13 (42:24, 50:00)	0.64

Note: Total time on monitor in atrial fibrillation was slightly longer than total time on monitor due to converting recording time from seconds to minutes.

5.4.2 Persistent and long-standing persistent AF Patient Summary

Key medical history and clinical findings of the study population included:

- Overall, all randomized subjects were diagnosed with AF on average 0.8 years prior to enrollment.
- Overall, the first documented DC cardioversion occurred on average 1.4 years prior to enrollment for all randomized subjects with > 2 DC cardioversions on average performed for each subject in the previous 4 years.
- The first time an AAD was prescribed for all randomized subjects was > 2 years prior to enrollment. On average, at least one AAD was discontinued due to failure to sustain long-term sinus rhythm and/or due to intolerance.
- Each subject had a baseline Holter recording demonstrating 48-hours of continuous AF.
- The left atrial diameter ranged from 3.0 to 5.5 cm for all subjects and the left ventricular ejection fraction ranged from 40 to 75% as measured by transthoracic echo.
- Coumadin was prescribed for thrombus prevention in 98.6% of subjects. Other anticoagulants being taken by subjects was aspirin (30.0% of subjects) and Plavix (3.3% of subjects).

5.4.3 Study Population

The following section defines the interventions performed within the Ablation management and Medical Management arms.

Ablation Management Arm

Subjects randomized to the Ablation Management arm underwent an ablation procedure. One hundred thirty-eight (138) subjects were randomized to the Ablation Management arm (intention-to-treat) and 132 of these subjects received an index ablation procedure in which the Medtronic catheters were used. The remaining 6 subjects were not treated with ablation for the following reasons:

- Insurance denials (n=2)
- Underlying medical conditions discovered with pre-procedure testing (n=2)
- Atypical anatomy preventing access to the left atrium (n=2)
- If a subject converted back to AF after the index ablation procedure, the investigator could 1) initiate antiarrhythmic drug therapy (including amiodarone), 2) perform a DC cardioversion and/or, 3) opt for one additional retreatment ablation procedure. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

Forty-eight (48) of 132 subjects required a retreatment procedure resulting in (constituting a 36.4% retreatment rate). All subjects in Ablation Management who qualified for a retreatment ablation have undergone the procedure.

Table 6 lists the catheters used for index and retreatment procedures. All three investigational catheters were used in all index procedures.

Table 6. Investigational Catheter Use in Ablation Management Procedures

Type of Catheter	Index Procedure N=132 n (%)	Retreatment Procedure N=47[a] n (%)	Total Procedures N=179 n (%)
PVAC	132 (100%)	46 (97.9%)	178 (99.4%)
MASC	132 (100%)	38 (80.9%)	170 (95.0%)
MAAC	**132 (100%)**	**41 (87.2%)**	**173 (96.6%)**

[a] One subject experienced heart failure prior to using the investigational catheters and did not have a second procedure resulting in an N of 47 retreatment procedures.

The use of all three ablation catheters in retreatment procedures was not mandated but rather left to the discretion of the investigator. Since the MASC and MAAC were used for mapping and ablating CFAEs, these catheters would not have been used if ablation with the PVAC restored sinus rhythm.

[1] Gage, BF, Waterman, AD, Shannon, W, et al. **Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation.** JAMA. 2001; 285(22):2864-70.

The times for venous access, transseptal puncture, and introduction of the ablation catheters were documented on case report forms. As shown in Table 7, procedure times averaged approximately three hours and did not differ in duration between index and retreatment procedures. Total fluoroscopy time averaged 55 minutes.

Table 7. Procedure, Ablation, and Fluoroscopy Times for Ablation

Procedure Times	**Index Proc N=132 Mean ± SD Median (Min, Max)**	**Retreatment Proc. N=47** Mean ± SD **Median (Min, Max)**	**All Procedures N=179** Mean ± SD **Median (Min, Max)**
Time from first venous access to removal of all catheters (hrs:min)	3:21 ± 0:53[a] 3:22 (1:26, 5:51)	3:11 ± 0:52 3:11 (1:25, 5:31)	3:18 ± 0:53[a] 3:19 (1:25, 5:51)
Time from insertion of Medtronic ablation catheters to all catheters removed (hrs:min)	2:30 ± 0:45[a] 2:29 (1:09, 4:58)	2:11 ± 0:44[a] 2:10 (0:44, 4:41)	2:25 ± 0:45[a] 3:22 (0:44,4:58)
Total Fluoroscopy time (hrs:min)	0:55 ± 0:25 0:53 (0:12, 2:19)	0:51 ± 0:18 0:52 (0:16, 1:36)	0:54 ± 0:23[a] 0:53 (0:12, 2:19)

[a] Complete procedure times were not obtained for one index procedure (Subject 26-318)

Medical Management Arm

The TTOP-AF clinical study allowed for aggressive management of subjects enrolled in the Medical Management arm. At the discretion of study investigators, subjects randomized to the Medical Management arm continued treatment with prescribed AAD therapy, received new AAD medications (including amiodarone), and/or were treated with DC cardioversion. In addition to drug changes, subjects in the Medical Management arm could have up to two DC cardioversions separated by 30 days. A "crossover" from Medical Management to an ablation procedure with the study device could occur after the subject completed at least 4 months of Medical Management treatment and demonstrated treatment failure (AF on 48-hour Holter recording).

Medical therapy consisting of starting new AADs, dose changes, and/or direct current cardioversions received by Medical Management subjects is summarized in Table 8. Most Medical Management subjects received optimal medical therapy over the 6 month study period.

Table 8. Treatment Interventions for Medical Management Subjects

Treatment Strategy Combination	**Treatment Failures N=38 n (%)**	**Treatment Successes N=20 n (%)**	**Missing[a] N=14 n(%)**	**Overall N=72 n(%)**
AADs started only	3 (7.9%)	2 (10.0%)	3 (21.4%)	8 (11.1%)
DC cardioversions only	1 (2.6%)	0 (0.0%)	1 (7.1%)	2 (2.8%)
ADD dose change (s) only	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.4%)
AAD(s) started and AAD dose change(s)	1 (2.6%)	2 (10.0%)	1 (7.1%)	4 (5.6%)
AAD(s) started and DC cardioversions	11 (28.9%)	6 (30.0%)	4 (28.6%)	21 (29.2%)
AAD dose change(s) and DC cardioversion(s)	2 (5.3%)	1 (5.0%)	0 (0.0%)	3 (4.2%)
AAD dose change(s) and DC cardioversion(s) and AAD(s) started	20 (52.6%)	9 (45.0%)	1 (7.1%)	30 (41.7%)
No Treatment Strategy	0 (0.0%)	0 (0.0%)	3 (21.4%)	3 (4.2%)

[a] The Missing category consists of 1 subject lost to follow-up, 4 withdrawn subjects, 1 subject that was allowed to crossover early (<1 month), and 8 subjects that did not complete a 6 month 48-hour Holter recording and/or visit.

Of the 72 subjects that were randomized to the Medical Management arm, 43 (59.7%) crossed over to receive an ablation procedure. There were two subjects that crossed over to receive an ablation procedure prior to 4 months. One subject crossed over at 1.1 months (approved by FDA) and the other at 3.7 months (approved by sponsor).

Subjects that crossed over to receive an ablation procedure were considered a Medical Management failure in the chronic effectiveness endpoint analysis. Data for Medical Management subjects that crossed over to receive an ablation were analyzed separately.

5.4.4 Primary Objectives

Chronic Effectiveness Endpoint

Objective: The primary endpoint for chronic effectiveness was a treatment success/failure measure for each subject computed at the 6 month time point. A subject was considered successfully treated for AF if all three elements of the endpoint, defined as below, were met.

- A ≥90% reduction in clinically significant AF from baseline to the 6 month time point based on a 48-hour Holter recording. Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
- The subject was off all Class I or Class III antiarrhythmic drugs at the 6 month follow-up (Ablation Management arm only). Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording in order to be considered successful.
- All procedures (index and retreatment) conducted on a subject during the treatment period were acutely successful (Ablation Management arm only).

Chronic Effectiveness Results

The primary endpoint for chronic effectiveness evaluating the proportion of ITT subjects with treatment success computed at the 6 month visit was met (Table 9). Treatment Success was achieved in 77 of 138 (55.8%) subjects in Ablation Management compared to 19 of 72 (26.4%) Medical Management subjects in the ITT population, yielding an absolute percentage point difference of 29.4% which was statistically significant (p<0.0001, one-sided Chi-square test).

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	**Ablation Management Arm N=138 (n %)**	**Medical Management Arm N=72 (n %)**	**p-value for H_0: $P_A \leq P_M$[a]**
≥90% reduction in clinically significant AF[b]	93 (67.4%)	20 (27.8%)	
Subject off all AADs at 6 month follow-up[c]	94 (68.1%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	Ablation Management Arm N=138 (n %)	Medical Management Arm N=72 (n %)	p-value for H_0: $P_A \leq P_M$[a]
Subjects meeting all success criteria	**77 (55.8%)**	**20 (27.8%)**	**<0.0001**
Number of missing endpoints[d]	17	14	

[a] Chi-Squared test
[b] Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
[c] Ablation Management success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording to be considered for treatment success.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

The chronic effectiveness endpoint for Ablation Management subjects was evaluated for subjects that were not taking AADs. Although not pre-defined as a success, 16 additional subjects (67.4% of total subjects) benefited from ablation in that an AAD was now effective at managing their AF when they were drug refractory at enrollment.

5.4.5 Acute Safety Endpoint

Objective: The primary endpoint for acute safety was a success/failure variable calculated for each subject in Ablation Management at the 7 day post-procedure time point.

Any subject with at least one adverse event adjudicated by the CEC/DSMB as both serious and procedure and/or device-related (SADE) was considered an acute safety failure, regardless of whether the event occurred following the index or retreatment ablation procedure.

As shown in Table 10, the TTOP-AF clinical study recorded 17 of 138 Ablation Management subjects (12.3%) with at least one SADE occurring within 7 days post-procedure (either index or retreatment). The upper bound of the two-sided, 95% confidence interval was 19.0% (p-value = 0.1427), which exceeded the 16.0% performance goal

Table 10. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial confidence Interval	(7.3%, 19.0%)
p-value[a] for H_0: $P_A \leq P_M$	0.1427

[a] One-sided p-value for exact one sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

The Medtronic Cardiac Ablation System did not statistically meet the upper bounds of the performance goal. However, considering the disease state and acuity of the subject studied, the pre-specified objective may have underestimated the true safety rate for catheter ablation in this population.

Chronic Safety Endpoint

Objective: The primary endpoint for chronic safety was a success/failure variable calculated for each subject at the 6 month time point. The definitions of adverse events that characterized a subject as a chronic safety failure were as follows:

1. **Ablation Management** - Events adjudicated by the CEC/DSMB to be both serious and related to the ablation procedure and/or device (serious adverse device effects or SADEs) and/or other characteristics unique to the Ablation Management arm during the 6 month follow-up period (excluding the first 7 days post procedure).
2. **Medical Management** - Events adjudicated by the CEC/DSMB to be both serious and related to antiarrhythmic drugs, and/or other characteristics unique to the Medical Management arm (DC cardioversion, anticoagulation) during the 6 month follow-up period (serious adverse events or SAEs).

Chronic Safety Results

The Primary Chronic Safety Outcome study objective was met (Table 11). Ten percent (11.6%) of Ablation Management subjects (16 of 138) failed to remain free of procedure- or device-related SAEs, which was not worse than 19.4% (14 of 72 subjects) of Medical Management subjects using a pre-specified 6% non-inferiority margin (p=0.0052) to meet the Chronic Safety objective.

Subjects who withdrew prior to study completion were considered endpoint failures per the intention-to-treat passive missing values imputation method (p=0.0011).

Table 11. Chronic Safety Endpoint

	Ablation Management Arm (N=138) n (%)	Medical Management Arm (N=72) n (%)
Number of Subjects with Chronic SADEs or SAEs (%)	10 (5.8%)	3 (4.2%)
p-value for H_0: $P_A \geq P_M + 6\%$ (Chi-Square test of Homogeneity)		p=0.0052

5.4.6 Secondary Endpoints and Results

Acute effectiveness, for subjects randomized to the Ablation Management arm had a pre-specified hypothesis identified in the Statistical Analysis Plan. For all other secondary endpoints no established performance criterion was identified therefore, descriptive statistics are presented.

Acute Effectiveness Endpoint

Objective: The statistical analysis of the acute effectiveness endpoint consisted of a comparison of the proportion of subjects achieving acute treatment success with the target success rate of 90% or greater. A count of successes and the proportion of successfully treated subjects were computed for the Ablation Management arm. The numerator of the proportion was the number of acutely successful subjects in the Ablation Management arm and the denominator was the number of subjects in the Ablation Management arm. Missing values were treated as described in the Statistical Analysis Plan.

Acute effectiveness was characterized for subjects randomized to the Ablation Management arm undergoing either an index or retreatment procedure. Acute effectiveness was defined as:

- Use of Medtronic catheters to achieve procedure success, and
- Isolation of all accessible pulmonary veins, and
- Elimination of mapped complex fractionated atrial electrograms (CFAEs), using Medtronic catheters, and
- Sinus rhythm up on leaving the EP laboratory (with or without the need for DC cardioversion).

Acute Effectiveness Results

Table 12 summarizes the acute effectiveness results for subjects that were randomized to Ablation Management. Required acute success components were met in 128 of 138 (92.8%) subjects with a confidence interval of (87%, 96%) using the exact approach. Overall, the mean success rate of 92.8% exceeded the 90% pre-specified hypothesis, however, the

confidence interval included the 90% pre-specified acute efficacy rate and therefore the acute procedural success rate was not shown to be statistically significantly greater than 90% (p-value = 0.1754).

Table 12. Acute Procedural Success - ITT Population

Acute Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)
Subjects that received an ablation procedure	132 (95.7%)
Medtronic Ablation catheter(s) used in each procedure	129 (93.5%)
Isolation of all pulmonary veins	129 (93.5%)
Mapped CFAEs eliminated in index procedure	131 (94.9%)
Sinus rhythm at completion of procedure	128 (92.8%)
Subjects meeting all Success Criteria	**128 (92.8%)**

Note: Exact One-sample binomial test (H0: proportion Success ≤0.90)

Of the 138 Ablation Management subjects, 132 subjects actually received an ablation procedure in which the investigational catheters were used (mITT population). Of the 132 ablated subjects, acute effectiveness was achieved in 97.7% with a resulting 95% confidence interval of (92.4%, 99.2%) which exceeded the 90% target rate to meet the Acute Efficacy objective.

Comparative Analyses between Treatment Arms at 6 Months

- **Left Atrial Size at 6 Months compared to Baseline**

  Subjects in Ablation Management demonstrated a slight reduction in mean LAD from 4.5 ± 0.53 cm to 4.4 ± 0.67 cm over 6 months compared to almost no change in mean LAD for subjects in Medical Management (4.6 ± 0.49 cm at baseline; 4.6 ± 0.56 cm at 6 months). No significant difference (p=0.35) for LAD was observed between the treatment arms at the 6 month time point.
- **Left Ventricular Ejection Fraction at 6 Months compared to Baseline**

  Improvement in LVEF was observed in both Ablation and Medical Management subjects. The difference in LVEF improvement was in favor of Ablation Management over Medical Management and approached significance (p=0.0625).
- **Symptom Severity Score at 6 Months compared to Baseline**

  Subjects were asked to rate the severity of atrial fibrillation-related symptoms (protocol-specified), on a scale from 1 (no symptoms) to 5 (most severe), during each of follow-up visit. A reduction in score denotes improvement in symptoms. There was a consistent reduction in the score in both arms at the 1 month follow-up visit. Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Quality of Life (SF-36) at 6 Months compared to Baseline**

  In a repeated-measure analysis, Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

All Adverse Events

All adverse events reported by investigational sites were adjudicated by the CEC/DSMB as being related to the 1) ablation procedure, 2) investigational ablation system, 3) antiarrhythmic drug (AAD) therapy, or 4) underlying disease.

A total of 183 ablation procedures (134 index and 49 retreatment) were performed in 180 Ablation Management subjects, including all aborted procedures for each subject. In addition, 43 subjects crossed over from Medical Management to receive an ablation procedure (43 total procedures) and 12 of those subjects required a retreatment procedure (total of 13 procedures as one subject had 2 retreatment procedures). A total of 239 ablation procedures were performed (including procedure attempts and procedure completions).

There were a total of 31 serious adverse events related to the procedure or the device reported and adjudicated for 27 Ablation Management subjects:

- 21 acute events reported for 17 subjects
- 10 chronic events reported for 10 subjects

Another 23 serious events, not related to the procedure or the device were reported in 21 Ablation Management subjects:

- 8 acute events occurred in 8 subjects
- 15 chronic events occurred in 13 subjects

Medical Management had a total of 6 serious adverse events reported and adjudicated for 6 subjects. There was no breakdown for acute and chronic events within the Medical Management treatment arm.

- 3 events were adjudicated as being related to medical therapy treatment or AF.
- Another 3 events were serious but adjudicated as not being related to treatment.

An overall total of 98 adverse events were adjudicated as being “non-serious”.

There was one procedure-related study death reported which occurred prior to deployment of the investigational device.

5.5 Overall Conclusions on the Results from TTOP-AF Clinical Study

The aim of this study was to systematically evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System utilizing multi-electrode, anatomically-designed catheters combined with a duty-cycled, phased RF energy system in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation.

The Primary Effectiveness Outcomes and associated analyses were overwhelmingly in favor of duty-cycled, phased-RF ablation compared with Medical Management treatment in subjects with symptomatic, drug-refractory persistent and long-standing persistent AF:

- **Primary Effectiveness Outcome**: Phased-RF ablation resulted in a 28.0% absolute percentage point increase in Treatment Success over treatment with AADs, with 77 Ablation Management subjects (55.8%) achieving Treatment Success over 6 months of follow-up, compared to 20 Medical Management subjects (27.8%) (p<0.0001).
- **Effectiveness Outcome of Ablation with and without the Use of AADs**: The total number of ablated subjects able to reduce their AF burden by ≥90% with and without the use of AADs was 93 subjects or 67.4% (93/138), an absolute percentage point difference of 39.6% from Medical Management (27.8%).
- **Reduced Symptoms:** Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Improved Quality of Life:** Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

The Primary Safety Outcomes and associated analyses demonstrated a favorable safety profile for treatment with duty-cycled, phased-RF ablation compared with AAD and DC cardioversion treatment in subjects with drug refractory, symptomatic, persistent and long-standing AF:

- **Primary Acute Safety Outcome**: The Primary Acute Safety endpoint was not met for Ablation Management. The upper bound of the two-sided, 95% confidence interval was 19.0%, which exceeded the pre-specified performance goal of 16%.

Primary Chronic Safety Outcome: Duty-cycled, phased-RF ablation resulted in a statistically significant lower rate of SAEs/SADEs related to AF and its treatment during the 6 months of study follow-up for Ablation Management subjects (10.0%) compared to Medical Management subjects (20.9%), to meet the Primary Chronic Safety Outcome (p=0.0011).

6 Adverse events

Potential adverse events associated with cardiac catheter ablation procedures include, but are not limited to, the following conditions:

- Allergic reaction to x-ray contrast media
- Anesthesia reactions
- Arrhythmias, proarrhythmia
- AV fistula
- Bleeding related to anticoagulation
- Body temperature elevation
- Bradycardia
- Cardiac perforation of the heart or other organs during transseptal puncture or other procedures
- Cardiac tamponade
- Cardiac thromboembolism
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Chest discomfort
- Chronic cough
- Component damage to ICD or implanted pacemaker
- Death
- Dislodgement of implantable cardioverter defibrillator (ICD) or permanent pacing leads
- Heart failure
- Hematoma
- Hemoptysis
- High creatinine phosphokinase or troponin level
- Hypotension
- Infections
- Myocardial infarction or ischemia
- Nerve injury or nerve damage
- Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system
- Pericarditis or endocarditis
- Unintended complete or incomplete atrioventricular node (AV-Node) or sinus node block or damage
- Pleural or pericardial effusion
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Pulmonary infiltrates
- Pulmonary vein narrowing or stenosis
- Pseudoaneurysm in groin
- Radiation injury or damage and late malignancy
- Respiratory depression
- Retroperitoneal bleed
- Skin burns
- Thrombotic or embolic events
- Valvular insufficiency or damage
- Vasovagal reaction

7 Instructions for use

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Note: Activated clotting times (ACT) should be checked at 10 to 15 minute intervals until therapeutic anticoagulation is achieved and then at 30 minute intervals during the case. The lower level of anticoagulation should be maintained at an ACT f at least 300-350 seconds throughout the procedure, as it has been demonstrated that less intense anticoagulation is associated with a high prevalence of in situ thrombus adherent to the transseptal sheaths. If significant atrial enlargement or spontaneous echo contrast is observed, many operators target a higher aCE range of 350 - 400.[1]

7.1 Preparing the catheter

1. Prepare and utilize the catheter under aseptic conditions.
2. Carefully remove the catheter from the packaging and inspect the catheter prior to use to verify that it has not been compromised during shipping or handling.
3. Rinse the distal end of the catheter using heparinized saline.

7.2 Preparing and managing the transseptal sheath

1. Prepare the transseptal sheath following the directions in the manufacturer's Instructions for Use (IFU).

   Note: After left atrial access, maintain anticoagulation within the sheath.
2. Perform aspiration or spontaneous bleed back from the transseptal sheath prior to insertion of the catheter into the sheath**.**

   Note: Perform this step following all catheter exchanges, preferably on the right side.
   Warning: Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

7.3 Capturing the array with the capture device

1. Remove the capture device from the handle and slide it up to the array.
2. While holding the capture device against the array, advance the slide control knob on the handle completely forward.
3. Hold the slide control knob forward and slide the capture device over the distal array, as shown in Figure 2.

   Note: Avoid advancing the capture device beyond the end of the array.

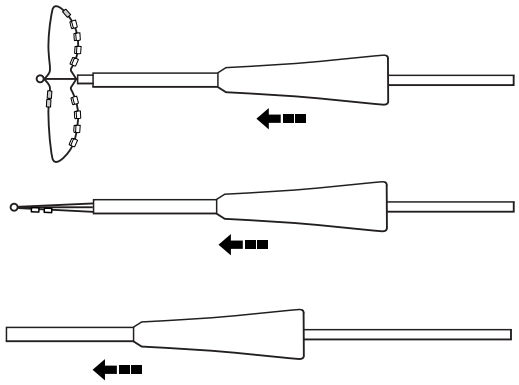


Figure 3. Capturing the array
Note: Avoid advancing the capture device beyond the end of the array.

7.4 Inserting the catheter and deploying the array

1. With the array contained, insert the capture device into the hemostasis valve and advance until the capture device is seated against the inner surface of the sheath hub.
2. Advance the catheter into the sheath approximately 15 cm (5.90 in).
3. Slide the capture device back into place on the handle.

   Note: Perform steps 4–6 under fluoroscopic visualization.
4. Advance the catheter through the remainder of the transseptal sheath until the array enters the left atrium. The distal portion of the array must exit the sheath prior to retraction of the slide control knob.
5. As the slide control knob is retracted simultaneously retract the sheath back into the right atrium
6. After the array is fully deployed into the left atrium verify the tip of the sheath does not extend into the left atrium so as to not inhibit electrode contact with the septal wall.

[1] (Calkins, Hugh, 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 9.6 (2007): 335-79.)

7.5 Connecting the cables

1. After insertion of the catheter, use sterile technique to connect the catheter interface cable to the connector located on the handle of the catheter.
2. Pass the other end of the catheter interface cable out of the sterile field and connect it to the ECG interface box.

   Note: The generator automatically identifies the catheter when it is connected and displays the catheter image and default system parameters.
   - Energy mode 1:1
   - Ablation duration 60 seconds
   - Target temperature 60 °C

   Note: Refer to the generator operator's manual for detailed operation information.

7.6 Mapping and ablating

Note: Perform steps 1–5 under fluoroscopic visualization.

1. Retract the catheter to engage the electrode array against the left atrial septum.
2. Map for arrhythmogenic tissue.
3. Ablate.
4. Repeat mapping and ablation applications as necessary
5. To relocate the array, push the array forward away from the septum, rotate the array and then retract the catheter to engage the electrodes against the septum.

7.7 Removing the catheter

1. Disconnect the catheter from the catheter interface cable.

   Note: Perform steps 2 and 3 under fluoroscopic visualization.
2. Fully advance the slide control knob and pull back on the catheter shaft to capture the array within the sheath.
3. Carefully withdraw the catheter halfway through the transseptal sheath.
4. Insert the capture device into the hemostasis valve and continue to withdraw the catheter until the array is located within the capture device.
5. Complete the withdrawal of the catheter by removing the capture device from the hemostasis valve of the sheath.

8 Specifications

Overall length	135 cm ± 5 cm (53.15 in ±1.97 in)
Effective length	105 cm ±5 cm (41.34 in ±1.97 in)
Array configuration	3 arm array
Mapping/ablation electrodes:	
Number of electrodes	12
Width	2 mm (0.08 in)
Electrode spacing	Asymmetric, 2 mm (0.08 in)
Measured temperature accuracy	± 2 °C (± 3.6 °F)
Single use circuitry	Circuitry allows the RF ablation generator to assess "single use"
Shaft and electrode array OD	2.8 mm (8.5 French; 0.11 in) OD Withdrawal through a 3.17 mm (9.5 French; 0.12 in) sheath (minimum)

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number of address listed on the back cover.

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Attachment 4: MAAC Technical Manual

Medtronic

MAAC® 990000

Multi-Array Ablation Catheter®

Technical Manual

! USA **Caution:** Federal law (USA) restricts this device to sale by or on the order of a physician.

The following are trademarks or registered trademarks of Medtronic in the United States and possibly in other countries. All other trademarks are the property of their respective owners:
Medtronic, GENius, MAAC, Multi-Array Ablation Catheter

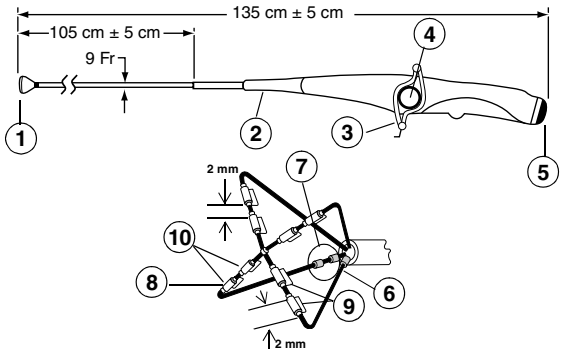
Explanation of symbols

The following list of symbols and abbreviations applies to various products. Refer to the package labels to see which of these apply to this product.

LOT	Lot number
REF	Reorder number
	Use by
STERILE R	Sterilized using irradiation
	Do not reuse
	Do not resterilize
	Do not use if package is damaged
	Package contents
	Consult instructions for use
	Keep dry
	Product documentation
	Keep away from heat
	Bidirectional
! USA	For US audiences only

1 Description

The Medtronic Multi-Array Ablation Catheter (MAAC) is a three-dimensional, anatomically designed, multi-electrode catheter designed to map, pace, and ablate arrhythmogenic tissue in the left atrial body (see Figure 1).



1	Array	6	Arm 1 marker
2	Capture device	7	Arm 2 markers
3	Steering knob	8	Electrode
4	Tension control knob	9	Pair 1
5	Connector	10	Pair 2

Figure 1. Multi-Array Ablation Catheter

1.1 Contents of package

The package contains the following:

- 1 Multi-Array Ablation Catheter
- Product documentation

Carefully read all instructions prior to use. Observe all contraindications, warnings, and precautions noted in these instructions. Failure to do so may result in less than expected outcomes.

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

2 Indications for use

The Multi-Array Ablation Catheter is indicated for the treatment of drug refractory, symptomatic, persistent atrial fibrillation with early recurrence (< 7 days) following direct current (DC) cardioversion or long-standing persistent (1 to 4 years) atrial fibrillation.

The MAAC is used for mapping, pacing, and ablating arrhythmogenic tissue in the left atrial body.

3 Contraindications

Use of the Multi-Array Ablation Catheter is contraindicated as follows:

- Active sepsis
- Left atrial thrombus or myxoma
- Atrial Septal Patch or atrial septal defect repair with percutaneous device
- Known sensitivity to heparin
- Blood clotting abnormalities
- Venous filtering device (Greenfield Filter)

The catheter is not recommended for use in patients who cannot undergo standard anticoagulation protocol for a left-sided cardiac procedure, or who have had a recent coagulopathy or embolic event.

4 Warnings and precautions

Anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Cable positioning – Position all cables associated with the generator so they do not come in contact with the patient or other leads. RF interference may affect the ability to interpret patient EGMs.

Catheter exchange – Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

Catheter placement – It is recommended that the application of RF energy be applied at the antrum of the pulmonary veins. Delivery of RF energy inside the pulmonary veins may result in pulmonary vein stenosis.

Disposal of catheter – Dispose of the catheter according to hospital biohazard requirements. If returning the catheter, contact your local Medtronic representative.

Electrical isolation during ablation – Do not allow the patient to contact grounded equipment that might produce electrical current leakage during ablation. Electrical current leakage may induce arrhythmias that may result in the patient's death.

Electrode contact – Avoid contact between electrodes. Contact between electrodes may create a short circuit or channel fault system error.

Electrode separation – Maintain adequate separation between all energized electrodes during ablation. Failure to maintain adequate separation may result in leading to high temperatures.

Embolism risk – Introducing any catheter or sheath into the circulatory system entails the risk of air or gas embolism, which can occlude vessels and lead to tissue infarction with serious consequences. Always advance and withdraw components slowly to minimize the vacuum created and therefore minimize the risk of air embolism. Closely monitor transseptal sheaths, performing aspiration and/or flushing to prevent air ingress and/or soft clot formation.

Expiration date – Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Flammable materials – Do not allow flammable material in the area where RF ablation procedures are performed. The risk of igniting flammable gases, flammable agents used for cleaning or disinfecting, or other materials is inherent in the application of RF energy.

Fluoroscopy required for catheter placement – Use of fluoroscopy during catheter manipulation and placement is strongly advised. Manipulating the catheter without fluoroscopy may result in damage to cardiac and vascular structures.

For single use only – This device is intended only to be used once for a single patient. Do not reuse, reprocess, or resterilize this device for purpose of reuse. Reuse, reprocessing, or resterilization may compromise the structural integrity of the device or create a risk of contamination of the device that could result in patient injury, illness, or death.

Frequent aspiration and flushing of the sheath – Aspirate and flush the sheath frequently to help minimize the potential for embolic events resulting from the introduction of air or the formation of clot within the sheath.

Generator settings or equipment failure – Do not increase target temperature or ablation duration settings before checking for obvious defects or misapplication, as patient injury may occur. Apparent low power output or failure of the equipment to function correctly at normal settings may indicate faulty application of the patient return electrodes or failure of an electrical lead.

High electrode temperatures – Only use catheters as recommended, maintain catheter contact with cardiac tissue during ablation, and monitor the displayed electrode temperatures and power delivery, in order to avoid high instantaneous electrode temperatures. Temperatures above 80° C during ablation may increase the patient's risk of thromboembolic events (formation of coagulum), steam pops, and cardiac perforation, depending on catheter type used.

- Only use catheter in the recommended anatomical location.
- Maintain catheter electrode contact with cardiac tissue by holding the catheter during the ablation.
- Do not reposition, rotate, slide, drag or otherwise intentionally disengage and then re-engage the catheter electrodes with cardiac tissue while ablating. Stop ablation prior to performing any of these actions.
- Monitor the displayed electrode temperature and power delivery during ablation. Deselect the affected electrode pair or discontinue ablation if the electrode does not reach 50° C and is receiving maximum power delivery.

Left-sided ablation – Closely monitor patients undergoing left-sided ablation procedures for clinical manifestations of infarction, cardiac tamponade, thromboembolism, or stroke.

Long-term risk – The long-term risks of lesions created by radiofrequency (RF) ablation have not been established. In particular, the long-term effects of lesions in proximity to the specialized conduction system or coronary vasculature are unknown.

No direct skin contact during system testing – Do not test the operation of the ablation system through direct skin contact with the electrodes. Testing through direct skin contact may cause damage to healthy tissue.

Oral anticoagulation therapy – Anticoagulation (INR 2.0 to 3.0) is recommended for at least three weeks prior to and four weeks after cardioversion and/or ablation.[1]

Placement of monitoring electrodes – Place all physiological monitoring electrodes as far away as possible from the patient return electrodes and their leads to avoid RF interference, which affects the ability to interpret patient electrograms (EGMs).

Procedural anticoagulation therapy – Administer appropriate levels of peri-procedural anticoagulation therapy for patients undergoing left-sided and transseptal cardiac procedures.

Qualified users – The catheter should be used only by or under the supervision of physicians trained in left atrial ablation procedures using this catheter and the Medtronic multi-channel RF ablation generator.

Related product literature – Do not attempt to operate the Medtronic cardiac ablation system prior to completely reading and understanding the GENius Multi-Channel RF Ablation Generator Operator's Manual and the relevant cardiac ablation catheter technical manual.

Required use environment – Cardiac ablation procedures should be performed only in a fully equipped electrophysiology laboratory.

Sheath or guide catheter required – Do not attempt to advance or withdraw the catheter through the vascular bed without the use of a sheath or guide catheter, as it may result in damage to cardiac and vascular structures.

Sterile package inspection – Inspect the sterile packaging and catheter prior to use. If the sterile packaging or the catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Storage conditions – Store the catheter in normal operating room temperatures and humidity levels and in a manner that protects the integrity of the package and the sterile barrier. Keep in a dry location away from heat and sunlight.

System compatibility – Use only the following components with the catheter: Medtronic GENius Multi-Channel RF Ablation Generator, its compatible Medtronic components, and Valleylab Patient Return Electrodes (Model E7506, two required). Use of the catheter with other components may cause patient harm.

Use of RF energy near implanted devices – Implantable devices, such as pacemakers and implantable cardioverter-defibrillators (ICDs), may be inhibited or otherwise affected by RF energy. Refer to the Multi-Channel RF Generator Operators Manual and the appropriate implantable device technical manual for additional information.

X-ray and fluoroscopic exposure – Minimize x-ray and fluoroscopic exposure. Due to the intensity of the x-ray beam and the duration of the fluoroscopic imaging during ablation procedures, patients and laboratory staff may be subjected to acute radiation injury and increased risk for somatic and genetic effects. Take all appropriate measures to minimize x-ray exposure to both patients and clinical staff. The long-term effects of protracted fluoroscopy have not been established.

5 Clinical Study Summary

Note: Clinical section provided to show structure only - data dubject to change.

5.1 Study Purpose

Medtronic conducted a prospective multi-center, controlled, randomized clinical study to support a pre-market application (PMA) for a multi-channel, duty-cycled, phased radiofrequency (RF) generator (Medtronic GENius Multi Channel RF Ablation Generator) and three anatomically designed, multi-electrode catheters, which will be referred to as the Medtronic Cardiac Ablation System. The purpose of the Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) clinical study was to evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation (AF).

5.2 Study Scope, Design and Methods

The TTOP-AF clinical study utilized a prospective, multi-center, randomized, controlled design. After all entrance criteria were met, subjects were randomized in a 2:1 fashion to either Ablation Management or Medical Management.

Subjects in the Ablation Management arm were allowed up to 2 ablations with the investigational device, as is typical in this patient population, to achieve treatment success. All procedures (index and retreatment) consisted of intra-cardiac signal mapping and ablation of pulmonary vein potentials and complex fractionated atrial electrograms (CFAEs) with three anatomically designed, multi-electrode catheters; Pulmonary Vein Ablation Catheter (PVAC), Multi-Array Septal Catheter (MASC) and Multi-Array Ablation Catheter (MAAC). There were no requirements for 3-dimensional navigation and complex mapping systems. If AF was not terminated during an ablation procedure, subjects received a direct current (DC) cardioversion (internal or external) to restore sinus rhythm. Confirmation of pulmonary vein isolation (PVI) was then completed in sinus rhythm with the PVAC. Catheter use was consistent in retreatment procedures unless sinus rhythm restoration prevented additional signal mapping of CFAEs with the MASC and/or MAAC. Subjects were followed at pre-discharge, 1, 3 and 6 months post-ablation. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements.

The Medical Management arm subjects received antiarrhythmic drug (AAD) changes and DC cardioversions to achieve and maintain sinus rhythm. Crossover to receive an ablation procedure could occur after 4 months with documentation of continuous AF on a 48-hour Holter recording. Subjects were followed at 1, 3, and 6 months but were also required to be evaluated 30 days after any DC cardioversion.

The TTOP-AF clinical study protocol included the ability to perform an interim analysis. Interim analysis was allowed after at least 50% of the enrolled subjects reached their chronic

[1] Fuster, Valentin, et al. "ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation - Executive Summary." Circulation 114.7 (2006): 700-52.)

effectiveness endpoint at 6 months and 100% of the subjects reached their acute safety endpoint. The interim analysis was conducted using a July 31, 2009 cutoff date, signifying the point in time where the interim analysis criteria specified above were met. In order to provide a more complete representation of all acute safety events in the Ablation Management arm, retreatment adverse events collected through November 24, 2009 were included in this Clinical Study Report.

Subjects were enrolled at 23 centers across the United States and one site in The Netherlands for the pivotal phase of the TTOP-AF trial. Investigators enrolled and randomized subjects during a 19 month period between November 2007 and May 2009. The first subject was randomized on November 28, 2007 and the ablation procedure for the last enrolled subject occurred on June 5, 2009. The last retreatment procedure for subjects in Ablation Management occurred on November 24, 2009. All subjects enrolled, randomized and treated in the TTOP-AF trial have completed their 6-month follow-up assessments. Subjects that completed all assessments were exited from the study per protocol requirements.

Data from all study required Holter recordings were analyzed and reviewed by an independent core lab. All safety events were adjudicated by an independent Clinical Events Committee/Data and Safety Monitoring Board (CEC/DSMB). For identification of pulmonary vein changes post-ablation, Ablation Management subjects were required to complete a baseline and 6 month CT scan or MRI. Subjects with scans demonstrating pulmonary vein diameter changes, as noted by the study site, were reviewed by a Core laboratory. Pulmonary vein changes were recorded as “stenosis” if the vein diameter change from baseline was greater than 70% and “narrowing” if the vein change was between 50% and 70%.

The statistical analysis of all primary endpoints was on an intention-to-treat basis (ITT) with passive missing value imputations, where all missing endpoint data were considered a treatment failure for each respective arm. Subjects were designated ITT once randomized.

The TTOP-AF clinical study initially enrolled 20 consecutive feasibility subjects that received an ablation procedure from May 2007 to August 2007. Successful completion of this 20 subject Feasibility phase was required before proceeding to the Pivotal phase. Enrollment of the Pivotal phase began in November 2007 and was completed in 19 months. The final index procedure occurred on June 15, 2009; the last retreatment procedure was performed on November 24, 2009.

Table 1summarizes the major study milestones and data cutoff dates for this report.

Table 1. Study Milestones

First subject randomized in the TTOP-AF clinical study	November 28, 2007
Last subject randomized in the TTOP-AF clinical study	May 20, 2009
Last index ablation procedure performed	June 15, 2009
Last retreatment procedure performed	November 24, 2009

5.3 Subject Inclusion and Exclusion Criteria

5.3.1 Inclusion Criteria

1. History of drug refractory, symptomatic, persistent/long-standing persistent atrial fibrillation defined as:
   - AF greater than 1 year but less than 4 years; OR
   - Non self-terminating AF, lasting greater than 7 days but no more than one year, with at least one failed DC cardioversion. Unsuccessful
     - DC cardioversion failure was defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond 7 days.
   - AF symptoms defined as the manifestation of:
     - Palpitations
     - Fatigue
     - Exertional dyspnea
     - Increased intolerance to routine activities (exercise intolerance)
2. Age between 18 and 70
3. Failure of at least one Class I or Class III AAD
4. Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study.

5.3.2 Exclusion Criteria

1. Structural heart disease of clinical significance including:
   - Previous cardiac surgery (excluding coronary artery bypass graft [CABG] and mitral valve repair)
   - Symptoms of congestive heart failure including, but not limited to, New York Heart Association (NYHA) Class III or IV CHF and/or documented ejection fraction < 40% measured by acceptable cardiac testing
   - Left atrial diameter of > 55mm
   - Moderate to severe mitral or aortic valvular heart disease
   - Stable/unstable angina or ongoing myocardial ischemia
   - Myocardial infarction (MI) within three months of enrollment
   - Congenital heart disease (not including atrial septal defect [ASD] or patent foramen ovale [PFO] without a right to left shunt) where the underlying abnormality increases the risk of an ablation procedure
   - Prior ASD or PFO closure with a device using a percutaneous approach
   - Hypertrophic cardiomyopathy (defined as left ventricular septal wall thickness > 1.5 cm)
   - Pulmonary hypertension (defined as mean or systolic pulmonary artery pressure > 50mm Hg on Doppler echo)
2. Any prior ablation for atrial fibrillation
3. Enrollment in any other ongoing arrhythmia study protocol
4. Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
5. Active infection or sepsis
6. Any history of cerebral vascular disease including stroke or transient ischemic attacks (TIAs)
7. Pregnancy or lactation
8. Left atrial thrombus at the time of ablation
9. Untreatable allergy to contrast media
10. Any diagnosis of atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
11. History of blood clotting (bleeding or thrombotic) abnormalities
12. Known sensitivities to heparin or warfarin
13. Severe COPD (defined as an Forced Expiratory Volume in One Second (FEV_1) <1)
14. Severe co morbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e., other disease processes, mental capacity, substance abuse, shortened life expectance, etc.)

5.4 Results

5.4.1 Subject demographics

A total of 242 study candidates signed an informed consent, with 210 randomized in a 2:1 fashion to the Ablation Management or Medical Management arms (Figure 2). Thirty-two (32) subjects signed informed consent but withdrew before being randomized for the following reasons:

- Subject did not have 100% atrial fibrillation on the 48-hour Holter recording (n=12)
- Subject did not meet other entrance criteria (n=12)
- Subject withdrew consent (n=6)
- Subject was withdrawn per the Sponsor (n=1)

- Other: Enrollment was closed prior to completion of screening (n=1)

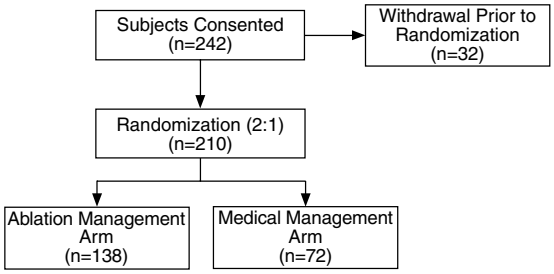


Figure 2. Study Enrollment

As shown in Table 2, the subject characteristics were similar in the Ablation Management and Medical Management arms. The average age of subjects in the Ablation Management arm was 59.6 years and in the Medical Management arm 60.7 years. Over 80% of the subjects enrolled in the study were male despite efforts of the study coordinators to identify eligible female participants. Gender and ethnicity were equally matched between randomized arms.

Information was obtained through medical records, referring physician notes, and subject interviews to verify the duration of AF burden prior to enrollment. The average time in years that each subject was initially diagnosed with AF, was 0.9 years for Ablation Management and 0.7 years for Medical Management, which was not statistically different. Subjects in both arms had an average of 2 DC cardioversions (2.0 for Ablation Management and 2.4 for Medical Management) in the previous 4 years.

Therapy with Class I or III antiarrhythmic drugs began, on average, 2.1 years prior to enrollment for subjects in the Ablation Management arm and 2.5 years prior for subjects in the Medical Management arm.

Left atrial diameter at baseline (average of 4.5 cm for Ablation Management and 4.6 for Medical Management) was enlarged compared to the paroxysmal patient population but comparable between treatment arms. Likewise, left ventricular ejection fraction, as measured by a screening transthoracic echocardiogram, was also comparable (average of 54.7% for Ablation Management and 54.9% for Medical Management).

Table 2. Subject Characteristics

Variable	Ablation Management Arm (n=138) Mean ± SD Median (Min, Max)	Medical Management Arm (n=72) Mean ± SD Median (Min, Max)	p-value[a]
Age, years	59.6 ± 8.3 61.2 (35.5, 73.4)	60.7 ± 8.9 60.8 (31.3, 75.2)	0.37
Gender			
Male (%)	115 (83.3%)	60 (83.3%)	1.00
Female (%)	23 (16.7%)	12 (16.7%)	
Ethnicity			
Caucasian (%)	133 (96.4%)	70 (97.2%)	0.92
African American (%)	3 (2.2%)	1 (1.4%)	
Other (Hispanic, Asian) (%)	2 (1.4%)	1 (1.4%)	
Years Since First Atrial Fibrillation Diagnosis	0.9 ± 0.9 0.6 (0.0, 4.1)	0.7 ± 0.8 0.5 (0.0, 3.9)	0.15
Years Since First DC Cardioversion	1.3 ± 2.0 0.5 (0.0, 11.4)	2.1 ± 3.3[b] 0.5 (0.0, 13.0)	0.47
Years Since First Prescribed Class I or III AAD	2.1 ± 3.3[c] 0.6 (0.0, 18.6)	2.5 ± 4.1[c] 0.8 (0.0, 18.6)	0.49
Approximate Number of DC Cardioversions in Last 4 Years/ Subject	2.0 ± 1.1 2.0 (1.0, 6.0)	2.4 ± 3.5 2.0 (1.0, 30.0)[d]	0.24
Left atrial diameter, cm	4.5 ± 0.5 4.6 (3.2, 5.5)	4.6 ± 0.5 4.7 (3.0, 5.5)	0.33
Left Ventricular Ejection Fraction,%	54.7 ± 7.1 55.0 (40.0, 75.0)	54.9 ± 6.6 55.0 (40.0, 69.0)	0.83

[a] Two-sided α=0.05 level significance
[b] N=71 for Medical Management
[c] N=137 for Ablation Management; N=71 for Medical Management
[d] Subject with 30 cardioversions was cardioverted via implanted cardioverter defibrillator.

Table 3 details the baseline medical history for the Ablation Management and Medical Management arms. There were no significant differences in baseline medical history between arms.

Table 3. Baseline Medical History

Characteristic	All Subjects % (n / N)	Ablation Management Subjects % (n / N)	Medical Management Subjects % (n / N)	Pearson Chi-square p-value
Diabetes Mellitus	14.3% (30/210)	15.9% (22/138)	11.1% (8/72)	0.34
Coronary Artery Disease	19.0% (40/210)	20.3% (28/138)	16.7% (12/72)	0.53
Congestive Heart Failure	7.6% (16/210)	5.8% (8/138)	11.1% (8/72)	0.17
Hypertension	59.0% (124/210)	60.9% (84/138)	55.6% (40/72)	0.46
Cardiomyopathy	9.0% (19/210)	6.5% (9/138)	13.9% (10/72)	0.08
Valvular Disease	7.1% (15/210)	5.1% (7/138)	11.1% (8/72)	0.11
Congenital Heart Disease	0.5% (1/210)	0.7% (1/138)	0% (0/72)	0.47
PFO or ASD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63
Pacemaker or ICD	3.3% (7/210)	2.9% (4/138)	4.2% (3/72)	0.63

Pertinent baseline physical examination findings are found in Table 4. Heart rate at the time of baseline evaluation was statistically different but not clinically relevant in the Ablation Management arm compared to the Medical Management arm. Blood pressure was comparable among the treatment arms. In order to quantify the risk of stroke in the TTOP-AF clinical study population, a $CHADS_2$ score was retrospectively calculated using parameters collected at baseline. The $CHADS_2$ score was determined by assigning 1 point each for the presence of **C**ongestive heart failure, **H**ypertension, **A**ge 75 years or older, and **D**iabetes

mellitus and by assigning 2 points for history of **S**troke or transient ischemic attack.[2] There were no differences in $CHADS_2$ scores between treatment arms at baseline.

Table 4. Baseline Physical Examination Measurements and $CHADS_2$ Score

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value[a]
Heart rate (bpm)	79.0 ± 15.4 79.5 (43, 129)	77.3 ± 14.9 78.0 (43, 119)	82.4 ± 15.9 83.0 (50, 129)	0.02
Systolic BP (mm Hg)	124.3 ± 15.3 124.5 (88, 165)	124.1 ± 15.5 125.0 (88, 165)	124.8 ± 15.0 124.5 (90, 164)	0.77
Diastolic BP (mm Hg)	77.5 ± 10.01[b] 79.0 (50, 118)	77.8 ± 9.95 80.0 (50, 118)	76.8 ± 10.16[c] 78.0 (50, 102)	0.47
$CHADS_2$ Score	0.81 ± 0.72 1 (0, 3)	0.83 ± 0.74 1 (0, 3)	0.79 ± 0.69 1 (0,2)	Not calculated

[a] Two-sided t-test
[b] The total number of subjects for diastolic BP is N=209, due to the one subject (26-305) that was missing a diastolic BP reading.
[c] One subject was missing diastolic BP recording (Subject 25-305), so there is only an N=71for diastolic BP in Medical Management

As a requisite for randomization, all subjects were required to demonstrate 48 hours of continuous atrial fibrillation on a baseline Holter recording. All subjects in both arms demonstrated a single episode of continuous atrial fibrillation. Table lists the baseline Holter recordings from the Ablation Management and Medical Management arms.

Table 5. Baseline 48-hour Holter Recording

Characteristic	All Subjects (n=210) Mean (SD) Median (Min, Max)	Ablation Management Subjects (n=138) Mean (SD) Median (Min, Max)	Medical Management Subjects (n=72) Mean (SD) Median (Min, Max)	T-test p-value
Total Time on Monitor (Hours:Minutes)	48:25 ± 1:18 48:12 (36:25, 50:00)	48:23 ± 1:25 48:13 (36:25, 50:00)	48:28 ± 1:04 48:11 (42:22, 49:58)	0.64
Total Time on Monitor in Atrial Fibrillation (Hour:Minutes)	48:27 ± 1:18 48:14 (36:27, 50:00)	48:25 ± 1:25 48:15 (36:27, 50:00)	48:30 ± 1:04 48:13 (42:24, 50:00)	0.64

Note: Total time on monitor in atrial fibrillation was slightly longer than total time on monitor due to converting recording time from seconds to minutes.

5.4.2 Persistent and long-standing persistent AF Patient Summary

Key medical history and clinical findings of the study population included:

- Overall, all randomized subjects were diagnosed with AF on average 0.8 years prior to enrollment.
- Overall, the first documented DC cardioversion occurred on average 1.4 years prior to enrollment for all randomized subjects with > 2 DC cardioversions on average performed for each subject in the previous 4 years.
- The first time an AAD was prescribed for all randomized subjects was > 2 years prior to enrollment. On average, at least one AAD was discontinued due to failure to sustain long-term sinus rhythm and/or due to intolerance.
- Each subject had a baseline Holter recording demonstrating 48-hours of continuous AF.
- The left atrial diameter ranged from 3.0 to 5.5 cm for all subjects and the left ventricular ejection fraction ranged from 40 to 75% as measured by transthoracic echo.
- Coumadin was prescribed for thrombus prevention in 98.6% of subjects. Other anticoagulants being taken by subjects was aspirin (30.0% of subjects) and Plavix (3.3% of subjects).

5.4.3 Study Population

The following section defines the interventions performed within the Ablation management and Medical Management arms.

Ablation Management Arm

Subjects randomized to the Ablation Management arm underwent an ablation procedure. One hundred thirty-eight (138) subjects were randomized to the Ablation Management arm (intention-to-treat) and 132 of these subjects received an index ablation procedure in which the Medtronic catheters were used. The remaining 6 subjects were not treated with ablation for the following reasons:

- Insurance denials (n=2)
- Underlying medical conditions discovered with pre-procedure testing (n=2)
- Atypical anatomy preventing access to the left atrium (n=2)
- If a subject converted back to AF after the index ablation procedure, the investigator could 1) initiate antiarrhythmic drug therapy (including amiodarone), 2) perform a DC cardioversion and/or, 3) opt for one additional retreatment ablation procedure. Retreatment ablation procedures restarted all follow-up requirements and endpoint measurements. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

Forty-eight (48) of 132 subjects required a retreatment procedure resulting in (constituting a 36.4% retreatment rate). All subjects in Ablation Management who qualified for a retreatment ablation have undergone the procedure.

Table 6 lists the catheters used for index and retreatment procedures. All three investigational catheters were used in all index procedures.

Table 6. Investigational Catheter Use in Ablation Management Procedures

Type of Catheter	Index Procedure N=132 n (%)	Retreatment Procedure N=47[a] n (%)	Total Procedures N=179 n (%)
PVAC	132 (100%)	46 (97.9%)	178 (99.4%)
MASC	132 (100%)	38 (80.9%)	170 (95.0%)
MAAC	**132 (100%)**	**41 (87.2%)**	**173 (96.6%)**

[a] One subject experienced heart failure prior to using the investigational catheters and did not have a second procedure resulting in an N of 47 retreatment procedures.

The use of all three ablation catheters in retreatment procedures was not mandated but rather left to the discretion of the investigator. Since the MASC and MAAC were used for mapping and ablating CFAEs, these catheters would not have been used if ablation with the PVAC restored sinus rhythm.

[2] Gage, BF, Waterman, AD, Shannon, W, et al. **Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation.** JAMA. 2001; 285(22):2864-70.

The times for venous access, transseptal puncture, and introduction of the ablation catheters were documented on case report forms. As shown in Table 7, procedure times averaged approximately three hours and did not differ in duration between index and retreatment procedures. Total fluoroscopy time averaged 55 minutes.

Table 7. Procedure, Ablation, and Fluoroscopy Times for Ablation

Procedure Times	**Index Proc N=132 Mean ± SD Median (Min, Max)**	**Retreatment Proc. N=47** Mean ± SD **Median (Min, Max)**	**All Procedures N=179** Mean ± SD **Median (Min, Max)**
Time from first venous access to removal of all catheters (hrs:min)	3:21 ± 0:53[a] 3:22 (1:26, 5:51)	3:11 ± 0:52 3:11 (1:25, 5:31)	3:18 ± 0:53[a] 3:19 (1:25, 5:51)
Time from insertion of Medtronic ablation catheters to all catheters removed (hrs:min)	2:30 ± 0:45[a] 2:29 (1:09, 4:58)	2:11 ± 0:44[a] 2:10 (0:44, 4:41)	2:25 ± 0:45[a] 3:22 (0:44,4:58)
Total Fluoroscopy time (hrs:min)	0:55 ± 0:25 0:53 (0:12, 2:19)	0:51 ± 0:18 0:52 (0:16, 1:36)	0:54 ± 0:23[a] 0:53 (0:12, 2:19)

[a] Complete procedure times were not obtained for one index procedure (Subject 26-318)

Medical Management Arm

The TTOP-AF clinical study allowed for aggressive management of subjects enrolled in the Medical Management arm. At the discretion of study investigators, subjects randomized to the Medical Management arm continued treatment with prescribed AAD therapy, received new AAD medications (including amiodarone), and/or were treated with DC cardioversion. In addition to drug changes, subjects in the Medical Management arm could have up to two DC cardioversions separated by 30 days. A "crossover" from Medical Management to an ablation procedure with the study device could occur after the subject completed at least 4 months of Medical Management treatment and demonstrated treatment failure (AF on 48-hour Holter recording).

Medical therapy consisting of starting new AADs, dose changes, and/or direct current cardioversions received by Medical Management subjects is summarized in Table 8. Most Medical Management subjects received optimal medical therapy over the 6 month study period.

Table 8. Treatment Interventions for Medical Management Subjects

Treatment Strategy Combination	**Treatment Failures N=38 n (%)**	**Treatment Successes N=20 n (%)**	**Missing[a] N=14 n(%)**	**Overall N=72 n(%)**
AADs started only	3 (7.9%)	2 (10.0%)	3 (21.4%)	8 (11.1%)
DC cardioversions only	1 (2.6%)	0 (0.0%)	1 (7.1%)	2 (2.8%)
ADD dose change (s) only	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.4%)
AAD(s) started and AAD dose change(s)	1 (2.6%)	2 (10.0%)	1 (7.1%)	4 (5.6%)
AAD(s) started and DC cardioversions	11 (28.9%)	6 (30.0%)	4 (28.6%)	21 (29.2%)
AAD dose change(s) and DC cardioversion(s)	2 (5.3%)	1 (5.0%)	0 (0.0%)	3 (4.2%)
AAD dose change(s) and DC cardioversion(s) and AAD(s) started	20 (52.6%)	9 (45.0%)	1 (7.1%)	30 (41.7%)
No Treatment Strategy	0 (0.0%)	0 (0.0%)	3 (21.4%)	3 (4.2%)

[a] The Missing category consists of 1 subject lost to follow-up, 4 withdrawn subjects, 1 subject that was allowed to crossover early (<1 month), and 8 subjects that did not complete a 6 month 48-hour Holter recording and/or visit.

Of the 72 subjects that were randomized to the Medical Management arm, 43 (59.7%) crossed over to receive an ablation procedure. There were two subjects that crossed over to receive an ablation procedure prior to 4 months. One subject crossed over at 1.1 months (approved by FDA) and the other at 3.7 months (approved by sponsor).

Subjects that crossed over to receive an ablation procedure were considered a Medical Management failure in the chronic effectiveness endpoint analysis. Data for Medical Management subjects that crossed over to receive an ablation were analyzed separately.

5.4.4 Primary Objectives

Chronic Effectiveness Endpoint

Objective: The primary endpoint for chronic effectiveness was a treatment success/failure measure for each subject computed at the 6 month time point. A subject was considered successfully treated for AF if all three elements of the endpoint, defined as below, were met.

- A ≥90% reduction in clinically significant AF from baseline to the 6 month time point based on a 48-hour Holter recording. Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
- The subject was off all Class I or Class III antiarrhythmic drugs at the 6 month follow-up (Ablation Management arm only). Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording in order to be considered successful.
- All procedures (index and retreatment) conducted on a subject during the treatment period were acutely successful (Ablation Management arm only).

Chronic Effectiveness Results

The primary endpoint for chronic effectiveness evaluating the proportion of ITT subjects with treatment success computed at the 6 month visit was met (Table 9). Treatment Success was achieved in 77 of 138 (55.8%) subjects in Ablation Management compared to 19 of 72 (26.4%) Medical Management subjects in the ITT population, yielding an absolute percentage point difference of 29.4% which was statistically significant (p<0.0001, one-sided Chi-square test).

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	**Ablation Management Arm N=138 (n %)**	**Medical Management Arm N=72 (n %)**	**p-value for H_0: $P_A \leq P_M$[a]**
≥90% reduction in clinically significant AF[b]	93 (67.4%)	20 (27.8%)	
Subject off all AADs at 6 month follow-up[c]	94 (68.1%)	N/A	
Acute success of all ablation procedures	128 (92.8%)	N/A	

Table 9. Primary Effectiveness Outcome: The Proportion of ITT Subjects with Treatment Successes at the 6-Month Follow-up Visit

Chronic Efficacy Success Criteria	Ablation Management Arm N=138 (n %)	Medical Management Arm N=72 (n %)	p-value for H_0: $P_A \leq P_M$[a]
Subjects meeting all success criteria	**77 (55.8%)**	**20 (27.8%)**	**<0.0001**
Number of missing endpoints[d]	17	14	

[a] Chi-Squared test
[b] Clinically significant AF was defined as a sustained AF episode lasting longer than 10 consecutive minutes in duration.
[c] Ablation Management success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording to be considered for treatment success.
[d] The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation.

The chronic effectiveness endpoint for Ablation Management subjects was evaluated for subjects that were not taking AADs. Although not pre-defined as a success, 16 additional subjects (67.4% of total subjects) benefited from ablation in that an AAD was now effective at managing their AF when they were drug refractory at enrollment.

5.4.5 Acute Safety Endpoint

Objective: The primary endpoint for acute safety was a success/failure variable calculated for each subject in Ablation Management at the 7 day post-procedure time point.

Any subject with at least one adverse event adjudicated by the CEC/DSMB as both serious and procedure and/or device-related (SADE) was considered an acute safety failure, regardless of whether the event occurred following the index or retreatment ablation procedure.

As shown in Table 10, the TTOP-AF clinical study recorded 17 of 138 Ablation Management subjects (12.3%) with at least one SADE occurring within 7 days post-procedure (either index or retreatment). The upper bound of the two-sided, 95% confidence interval was 19.0% (p-value = 0.1427), which exceeded the 16.0% performance goal

Table 10. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial confidence Interval	(7.3%, 19.0%)
p-value[a] for H_0: $P_A \leq P_M$	0.1427

[a] One-sided p-value for exact one sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

The Medtronic Cardiac Ablation System did not statistically meet the upper bounds of the performance goal. However, considering the disease state and acuity of the subject studied, the pre-specified objective may have underestimated the true safety rate for catheter ablation in this population.

Chronic Safety Endpoint

Objective: The primary endpoint for chronic safety was a success/failure variable calculated for each subject at the 6 month time point. The definitions of adverse events that characterized a subject as a chronic safety failure were as follows:

1. **Ablation Management** - Events adjudicated by the CEC/DSMB to be both serious and related to the ablation procedure and/or device (serious adverse device effects or SADEs) and/or other characteristics unique to the Ablation Management arm during the 6 month follow-up period (excluding the first 7 days post procedure).
2. **Medical Management** - Events adjudicated by the CEC/DSMB to be both serious and related to antiarrhythmic drugs, and/or other characteristics unique to the Medical Management arm (DC cardioversion, anticoagulation) during the 6 month follow-up period (serious adverse events or SAEs).

Chronic Safety Results

The Primary Chronic Safety Outcome study objective was met (Table 11). Ten percent (11.6%) of Ablation Management subjects (16 of 138) failed to remain free of procedure- or device-related SAEs, which was not worse than 19.4% (14 of 72 subjects) of Medical Management subjects using a pre-specified 6% non-inferiority margin (p=0.0052) to meet the Chronic Safety objective.

Subjects who withdrew prior to study completion were considered endpoint failures per the intention-to-treat passive missing values imputation method (p=0.0011).

Table 11. Chronic Safety Endpoint

	Ablation Management Arm (N=138) n (%)	Medical Management Arm (N=72) n (%)
Number of Subjects with Chronic SADEs or SAEs (%)	10 (5.8%)	3 (4.2%)
p-value for H_0: $P_A \geq P_M + 6\%$ (Chi-Square test of Homogeneity)		p=0.0052

5.4.6 Secondary Endpoints and Results

Acute effectiveness, for subjects randomized to the Ablation Management arm had a pre-specified hypothesis identified in the Statistical Analysis Plan. For all other secondary endpoints no established performance criterion was identified therefore, descriptive statistics are presented.

Acute Effectiveness Endpoint

Objective: The statistical analysis of the acute effectiveness endpoint consisted of a comparison of the proportion of subjects achieving acute treatment success with the target success rate of 90% or greater. A count of successes and the proportion of successfully treated subjects were computed for the Ablation Management arm. The numerator of the proportion was the number of acutely successful subjects in the Ablation Management arm and the denominator was the number of subjects in the Ablation Management arm. Missing values were treated as described in the Statistical Analysis Plan.

Acute effectiveness was characterized for subjects randomized to the Ablation Management arm undergoing either an index or retreatment procedure. Acute effectiveness was defined as:

- Use of Medtronic catheters to achieve procedure success, and
- Isolation of all accessible pulmonary veins, and
- Elimination of mapped complex fractionated atrial electrograms (CFAEs), using Medtronic catheters, and
- Sinus rhythm up on leaving the EP laboratory (with or without the need for DC cardioversion).

Acute Effectiveness Results

Table 12 summarizes the acute effectiveness results for subjects that were randomized to Ablation Management. Required acute success components were met in 128 of 138 (92.8%) subjects with a confidence interval of (87%, 96%) using the exact approach. Overall, the mean success rate of 92.8% exceeded the 90% pre-specified hypothesis, however, the

confidence interval included the 90% pre-specified acute efficacy rate and therefore the acute procedural success rate was not shown to be statistically significantly greater than 90% (p-value = 0.1754).

Table 12. Acute Procedural Success - ITT Population

Acute Efficacy Success Criteria	Ablation Mgmt. N=138 n (%)
Subjects that received an ablation procedure	132 (95.7%)
Medtronic Ablation catheter(s) used in each procedure	129 (93.5%)
Isolation of all pulmonary veins	129 (93.5%)
Mapped CFAEs eliminated in index procedure	131 (94.9%)
Sinus rhythm at completion of procedure	128 (92.8%)
Subjects meeting all Success Criteria	**128 (92.8%)**

Note: Exact One-sample binomial test (H0: proportion Success ≤0.90)

Of the 138 Ablation Management subjects, 132 subjects actually received an ablation procedure in which the investigational catheters were used (mITT population). Of the 132 ablated subjects, acute effectiveness was achieved in 97.7% with a resulting 95% confidence interval of (92.4%, 99.2%) which exceeded the 90% target rate to meet the Acute Efficacy objective.

Comparative Analyses between Treatment Arms at 6 Months

- **Left Atrial Size at 6 Months compared to Baseline**

  Subjects in Ablation Management demonstrated a slight reduction in mean LAD from 4.5 ± 0.53 cm to 4.4 ± 0.67 cm over 6 months compared to almost no change in mean LAD for subjects in Medical Management (4.6 ± 0.49 cm at baseline; 4.6 ± 0.56 cm at 6 months). No significant difference (p=0.35) for LAD was observed between the treatment arms at the 6 month time point.
- **Left Ventricular Ejection Fraction at 6 Months compared to Baseline**

  Improvement in LVEF was observed in both Ablation and Medical Management subjects. The difference in LVEF improvement was in favor of Ablation Management over Medical Management and approached significance (p=0.0625).
- **Symptom Severity Score at 6 Months compared to Baseline**

  Subjects were asked to rate the severity of atrial fibrillation-related symptoms (protocol-specified), on a scale from 1 (no symptoms) to 5 (most severe), during each of follow-up visit. A reduction in score denotes improvement in symptoms. There was a consistent reduction in the score in both arms at the 1 month follow-up visit. Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Quality of Life (SF-36) at 6 Months compared to Baseline**

  In a repeated-measure analysis, Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

All Adverse Events

All adverse events reported by investigational sites were adjudicated by the CEC/DSMB as being related to the 1) ablation procedure, 2) investigational ablation system, 3) antiarrhythmic drug (AAD) therapy, or 4) underlying disease.

A total of 183 ablation procedures (134 index and 49 retreatment) were performed in 180 Ablation Management subjects, including all aborted procedures for each subject. In addition, 43 subjects crossed over from Medical Management to receive an ablation procedure (43 total procedures) and 12 of those subjects required a retreatment procedure (total of 13 procedures as one subject had 2 retreatment procedures). A total of 239 ablation procedures were performed (including procedure attempts and procedure completions).

There were a total of 31 serious adverse events related to the procedure or the device reported and adjudicated for 27 Ablation Management subjects:

- 21 acute events reported for 17 subjects
- 10 chronic events reported for 10 subjects

Another 23 serious events, not related to the procedure or the device were reported in 21 Ablation Management subjects:

- 8 acute events occurred in 8 subjects
- 15 chronic events occurred in 13 subjects

Medical Management had a total of 6 serious adverse events reported and adjudicated for 6 subjects. There was no breakdown for acute and chronic events within the Medical Management treatment arm.

- 3 events were adjudicated as being related to medical therapy treatment or AF.
- Another 3 events were serious but adjudicated as not being related to treatment.

An overall total of 98 adverse events were adjudicated as being “non-serious”.

There was one procedure-related study death reported which occurred prior to deployment of the investigational device.

5.5 Overall Conclusions on the Results from TTOP-AF Clinical Study

The aim of this study was to systematically evaluate the effectiveness and safety of the Medtronic Cardiac Ablation System utilizing multi-electrode, anatomically-designed catheters combined with a duty-cycled, phased RF energy system in the treatment of drug refractory, symptomatic, persistent and long-standing persistent atrial fibrillation.

The Primary Effectiveness Outcomes and associated analyses were overwhelmingly in favor of duty-cycled, phased-RF ablation compared with Medical Management treatment in subjects with symptomatic, drug-refractory persistent and long-standing persistent AF:

- **Primary Effectiveness Outcome**: Phased-RF ablation resulted in a 28.0% absolute percentage point increase in Treatment Success over treatment with AADs, with 77 Ablation Management subjects (55.8%) achieving Treatment Success over 6 months of follow-up, compared to 20 Medical Management subjects (27.8%) (p<0.0001).
- **Effectiveness Outcome of Ablation with and without the Use of AADs**: The total number of ablated subjects able to reduce their AF burden by ≥90% with and without the use of AADs was 93 subjects or 67.4% (93/138), an absolute percentage point difference of 39.6% from Medical Management (27.8%).
- **Reduced Symptoms:** Ablation Management subjects had a statistically significant reduction from baseline to 6 months in AF symptomatic burden after phased-RF ablation compared to Medical Management (p<0.0001).
- **Improved Quality of Life:** Ablation Management subjects showed a clinically and statistically significant improvement in SF-36 quality of life scores through 6 months of follow-up for both Physical and Mental Health Component Scores compared to Medical Management (Physical Component, p=0.0052; Mental Component p=0.0013).

The Primary Safety Outcomes and associated analyses demonstrated a favorable safety profile for treatment with duty-cycled, phased-RF ablation compared with AAD and DC cardioversion treatment in subjects with drug refractory, symptomatic, persistent and long-standing AF:

- **Primary Acute Safety Outcome**: The Primary Acute Safety endpoint was not met for Ablation Management. The upper bound of the two-sided, 95% confidence interval was 19.0%, which exceeded the pre-specified performance goal of 16%.
- **Primary Chronic Safety Outcome**: Duty-cycled, phased-RF ablation resulted in a statistically significant lower rate of SAEs/SADEs related to AF and its treatment during the 6 months of study follow-up for Ablation Management subjects (10.0%) compared to Medical Management subjects (20.9%), to meet the Primary Chronic Safety Outcome (p=0.0011).

6 Adverse events

Potential adverse events associated with cardiac catheter ablation procedures include, but are not limited to, the following conditions:

- Allergic reaction to x-ray contrast media
- Anesthesia reactions
- Arrhythmias, proarrhythmia
- AV fistula
- Bleeding related to anticoagulation
- Body temperature elevation
- Bradycardia
- Cardiac perforation of the heart or other organs during transseptal puncture or other procedures
- Cardiac tamponade
- Cardiac thromboembolism
- Cerebrovascular accident (CVA) or transient ischemic attack (TIA)
- Chest discomfort
- Chronic cough
- Component damage to ICD or implanted pacemaker
- Death
- Dislodgement of implantable cardioverter defibrillator (ICD) or permanent pacing leads
- Heart failure
- Hematoma
- Hemoptysis
- High creatinine phosphokinase or troponin level
- Hypotension
- Infections
- Myocardial infarction or ischemia
- Nerve injury or nerve damage
- Obstruction, perforation, damage, or spasm of the vascular system including the coronary circulation system
- Pericarditis or endocarditis
- Unintended complete or incomplete atrioventricular node (AV-Node) or sinus node block or damage
- Pleural or pericardial effusion
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Pulmonary infiltrates
- Pulmonary vein narrowing or stenosis
- Pseudoaneurysm in groin
- Radiation injury or damage and late malignancy
- Respiratory depression
- Retroperitoneal bleed
- Skin burns
- Thrombotic or embolic events
- Valvular insufficiency or damage
- Vasovagal reaction

7 Instructions for use

Caution: Inspect the sterile packaging and catheter prior to use. If the sterile packaging or catheter exhibits damage, do not use the catheter. Contact your local Medtronic representative.

Caution: Check to verify that the catheter is within its expiration date. Do not use if the product date has expired.

Note: Activated clotting times (ACT) should be checked at 10 to 15 minute intervals until therapeutic anticoagulation is achieved and then at 30 minute intervals during the case. The lower level of anticoagulation should be maintained at an ACT f at least 300-350 seconds throughout the procedure, as it has been demonstrated that less intense anticoagulation is associated with a high prevalence of in situ thrombus adherent to the transseptal sheaths. If significant atrial enlargement or spontaneous echo contrast is observed, many operators target a higher aCE range of 350 - 400.[3]

7.1 Preparing the catheter

1. Prepare and utilize the catheter under aseptic conditions.
2. Carefully remove the catheter from the packaging and inspect the catheter prior to use to verify that it has not been compromised during shipping or handling.
3. Rinse the distal end of the catheter using heparinized saline.

7.2 Preparing and managing the transseptal sheath

1. Prepare the transseptal sheath following the directions in the manufacturer's Instructions for Use (IFU).

   Note: After left atrial access, maintain anticoagulation within the sheath.
2. Perform aspiration or spontaneous bleed back from the transseptal sheath before inserting the catheter into the sheath.

   Note: Perform this step following all catheter exchanges, preferably on the right side.
   Warning: Avoid unnecessary catheter exchanges to minimize sheath-related embolic events.

7.3 Capturing the array with the capture device

1. Remove the capture device from the handle and slide it up to the array.
2. Begin sliding the capture device forward to capture the array, as shown in Figure 3.

   Note: Avoid advancing the capture device beyond the end of the array.

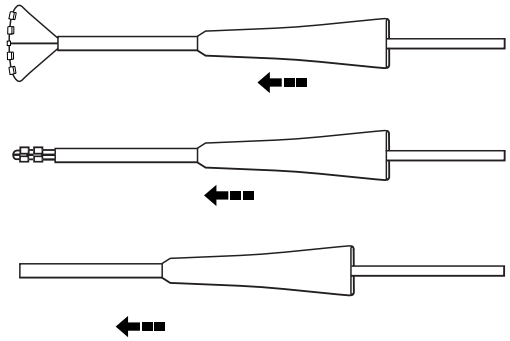


Figure 3. Capturing the array

7.4 Inserting the catheter and deploying the array

1. With the array contained, insert the capture device into the hemostasis valve and advance until the capture device is seated against the inner surface of the sheath hub.
2. Advance the catheter approximately 15 cm.
3. Remove the capture device and replace it firmly onto the catheter handle.

   Note: Perform steps 4 and 5 under fluoroscopic visualization.
4. Advance the catheter through the transseptal sheath until it enters the left atrium.
5. As the array exits the distal end of the sheath, begin the process of advancing the catheter and retracting the sheath into the right atrium to enable full deflection of the distal segment of the catheter.

7.5 Connecting the cables

1. After insertion of the catheter is achieved, use sterile technique to connect the catheter interface cable to the connector located on the handle of the catheter.
2. Pass the other end of the catheter interface cable out of the sterile field and connect it to the ECG interface box.

   Note: The generator automatically identifies the catheter when it is connected and displays the catheter image and default system parameters.
   – Energy mode 1:1

[3] (Calkins, Hugh, 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 9.6 (2007): 335-79.)

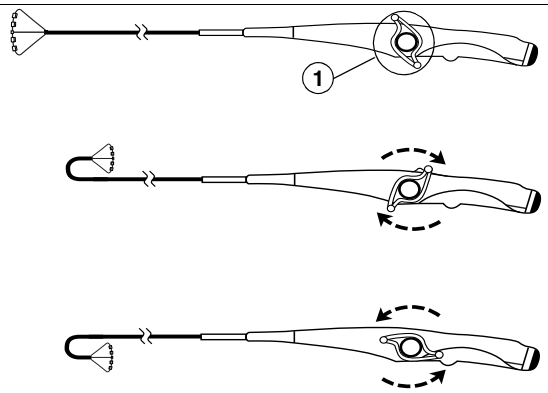
– Ablation duration 60 seconds
– Target temperature 60 °C

Note: Refer to the generator operator's manual for detailed operation information.

7.6 Mapping and ablating

Note: Perform steps 1–6 under fluoroscopic visualization.

1. Using the steering knob, deflect the tip in the direction of interest within the atrium for mapping and ablation (see Figure 4).



1 Neutral position

Figure 4. Deflecting the tip of the catheter within the atrium

2. Push the array forward to engage the electrodes against the left atrial wall.
3. Map for arrhythmogenic tissue.
4. Ablate.
5. Repeat mapping and ablating applications as necessary.
6. To reposition the array, pull the array back from the atrial wall, rotate and then push the array forward to engage the electrodes against the atrial wall.
   – Do not attempt to steer the catheter within the sheath.
   – Use the tension control knob to maintain curve configuration.

7.7 Removing the catheter

1. Disconnect the catheter from the catheter interface cable.

   Note: Perform steps 2–4 under fluoroscopic visualization.
2. Advance the distal end of the sheath into the left atrium.
3. Ensure the catheter is straight and the steering knob is in the neutral position (Figure 4).
4. Slowly retract the catheter into the sheath to capture the array.
5. Carefully withdraw the catheter through the transseptal sheath up to the hemostasis valve.
6. Insert the capture device into the hemostasis valve until the capture device is seated against the inner surface of the sheath hub.
7. Pull the catheter array into the capture device, and then remove the capture device from the hemostasis valve of the sheath.

8 Specifications

Overall length	135 cm ± 5 cm (53.15 in ±1.97 in)
Effective length	105 cm ±5 cm (41.34 in ±1.97 in)
Array configuration	4 arm array
Curve	Standard (19 mm)
Mapping/ablation electrodes	
Number of electrodes	8
Width	2 mm (0.08 in)
Electrode spacing	Asymmetric, 2 mm (0.08 in)
Measured temperature accuracy	± 2 °C (± 3.6 °F)
Single use circuitry	Circuitry allows the RF ablation generator to assess "single use"
Shaft and electrode array OD	3 mm (9 French; 0.118 in) OD Withdrawal through a 3.17 mm (9.5 French; 0.12 in) sheath (minimum)

9 Medtronic limited warranty

For complete warranty information, see the accompanying limited warranty document.

10 Service

Medtronic employs highly trained representatives and engineers located throughout the world to serve you and, upon request, to provide training to qualified hospital personnel in the use of Medtronic products. Medtronic also maintains a professional staff to provide technical consultation to product users. For more information, contact your local Medtronic representative, or call or write Medtronic at the appropriate telephone number or address listed on the back cover.

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Proposed PAS Summary

Medtronic

Alleviating Pain · Restoring Health · Extending Life

Tailored Treatment of Persistent Atrial Fibrillation Post-Approval Study (TTOP-AF PAS)

CLINICAL INVESTIGATION PLAN SUMMARY

06 SEP 2011

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1 Tailored Treatment of Persistent Atrial Fibrillation Post-Approval Study (TTOP-AF PAS)

1.1 Introduction

Medtronic is proposing a prospective, multicenter, non-randomized, Post-Approval Study (PAS) to provide long-term safety and effectiveness of the GENius® Multi-Channel Radio Frequency Ablation Generator, Pulmonary Vein Ablation Catheter® (PVAC®), the Multi-Array Septal Catheter® (MASC®), and the Multi-Array Ablation Catheter® (MAAC®) Catheter System, which will be referred to as the Medtronic Catheter Ablation System (CAS).

1.2 Study Design

Safety and effectiveness will be evaluated against pre-specified performance criteria as determined by the sponsor and FDA. The safety criteria set in this study has been choosen based on previous randomized, controlled radio frequency ablation catheter trials and the effectiveness criteria has been set based on results from the Tailored Treatment of Persistent Atrial Fibrillation (TTOP-AF) pivotal trial and supporting literature.

The minimum enrollment of 263 is estimated to be required in order to achieve the desired sample size for the primary objective analyses. Subjects will be followed for 5 years from the date of the initial study ablation. It is expected to take 12-24 months to enroll 263 subjects.

1.3 Primary Effectiveness Objective

Demonstrate effectiveness (through 12 months) of the Medtronic CAS by assessing the rate of subjects demonstrating chronic treatment success.

Chronic treatment success is defined as:

- 90% reduction in Atrial Fibrillation (AF) burden with AF burden being defined as cumulative time in AF with minimum 30 seconds of AF based on 48 hour holter monitoring outside the 180-day blanking period
  OR
- No interventions for AF (except for repeat ablation using Medtronic CAS or cardioversion within the 180-day blanking period after the index ablation procedure)

Intervention for AF is defined as: an invasive procedure intended for the definitive treatment of AF, including any ablation of the PVs or atrial triggers (other than protocol-specified ablation), interruption of AV nodal function, procedures to alter left atrial conduction or function such as the Maze procedure, the implantation of an atrial pacemaker or atrial defibrillator (whether approved by relevant regulatory authorities or not for such indications), or electrical or pharmacologic cardioversion

of AF, excluding procedures solely directed at the treatment of atrial flutter or atrial tachycardias.

1.4 Primary Safety Objective

Demonstrate safety (through 12 months) of the Medtronic CAS by assessing the rate of subjects experiencing a procedure or device related serious adverse event as defined in **Table 1** below.

Serious adverse events are defined as follows:
a) led to a death, or
b) led to a serious deterioration in the health of the subject that

- Resulted in a life-threatening illness or injury, or
- Resulted in permanent impairment of a body structure or a body function, or
- Required in-patient hospitalization or prolongation of existing hospitalization, or
- Resulted in medical or surgical intervention to prevent, permanent impairment to body structure or a body function, or

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

Table 1: Device or Procedure Serious Adverse Event.

Device and Procedure Serious Adverse Events	With onset between Day 0 and:
Access site complications requiring: Transfusion of 3 or more units or Surgical intervention or Permanent loss or functional impairment	Day 7
Myocardial infarction	Day 7
Pulmonary vein stenosis	Through 12-months
Pulmonary edema	Day 7
Atrio-esophogeal fistula	Through 12-months
Cardiac tamponade	Day 7
Arrhythmias	Day 7
Phrenic nerve palsy	Day 7
Death	Day 7
Hospitalization (prolonged)	Day 7
Stroke	Day 7
Transient ischemic attack (TIA)	Day 7
Cerebrovascular accident (CVA)	Day 7
Thromboembolism	Day 7
Atrial perforation	Day 7
Pulmonary edema	Day 7
Heart block	Day 7
Pneumothorax	Day 7
Pericardial effusion	Day 7
Heart block	Day 7
Pericarditis	Day 7

1.5 Secondary Objectives

The following are a list of secondary objectives, which are intended to provide additional information on the performance of MCAS. There will be no established performance requirements related to these secondary objectives required. The secondary objectives are as follows:

Safety Objective:

- Evaluate the proportion of subjects free from Major Atrial Fibrillation Events (MAFEs) at 1, 2, 3, 4 and 5 years, where MAFE is defined as a serious adverse event (SAE), which has not been categorized as a procedure or device related, as set out in **Table 2**:

Table 2: Major Atrial Fibrillation Events.

Major Atrial Fibrillation Events (MAFEs):
Cardiovascular deaths
Hospitalizations for (primary reason): AF recurrence or ablation Atrial flutter ablation (excluding Type I) Systemic embolization (not stroke) Congestive heart failure Hemorrhagic event (not stroke) Antiarrhythmic drug: initiation, adjustment or complication
Myocardial infarction (MI)
Stroke

Effectiveness Objective:

- Evaluate the proportion of subjects demonstrating chronic treatment success at 2, 3, 4 and 5 years

1.6 Data Collection Overview

Subjects enrolled and treated with the study ablation system will be required to attend regular follow-ups to monitor their condition. Follow-ups are expected to occur at baseline, study ablation procedure, discharge, 3, 6 and 12 months and annually thereafter until subects complete 5 years of follow-up from their index procedure. Data collection will consist of, but will not be limited to:

- History and physican exam
- Review of arrhythmic symptoms
- Anticoaguation use
- Review of antiarrythmic drug use
- 12-lead ECG
- Neurologic exam
- 48-hour Holter monitoring (12 months, 2, 3, 4 and 5 years)

- Quality of life survey

1.7 Procedure Details of Interest

1.7.1 *Monitoring for recurrent atrial fibrillation*

48-hour Holter monitoring will be required at all follow-ups outside the 180-day blanking period. Subjects that demonstrate symptoms of atrial fibrillation between scheduled follow ups with no documented evidence on ECG or 48-hour Holter monitor will be required to wear an event recorder to capture symptomatic atrial fibrillation

1.7.2 *Monitoring for Pulmonary Vein Stenosis*

Subjects will undergo pulmonary vein imaging prior to the procedure. Ablated subjects will be assessed at the protocol defined 6-month follow-up for symptoms that are suggestive of pulmonary vein stenosis. Subjects that demonstrate symptoms suggestive of pulmonary vein stenosis will undergo pulmonary vein imaging to determine pulmonary vein stenosis. Pulmonary vein stenosis will be defined as $\geq$ 70% reduction in diameter.

2 STATISTICAL METHODS AND DATA ANALYSIS

2.1 Sample Size Justification

2.1.1 Primary Effectiveness Endpoint

The sample size is calculated for a one-sample, one-sided exact test of binomial proportions under the following assumptions:

- Power = 80%
- Significance level = 0.025 (one-sided)
- Attrition of 20% at one year
- Assumed underlying effectiveness rate = 50%
- Performance goal = 40%

If the underlying effectiveness rate is assumed 50% at 12 months, a total of 263 evaluable subjects will be required to be enrolled to provide 80% power to meet this effectiveness objective.

2.1.2 Primary Safety Endpoint

The sample size is calculated for a one-sample, one-sided exact test of binomial proportions under the following assumptions:

- Power = 80%
- Significance level = 0.025 (one-sided)
- Attrition of 20%
- Assumed underlying primary safety event rate = 10%
- Performance goal = 16.0%

If the underlying safety event rate is assumed 10%, a total of 239 subjects would need to be enrolled to ensure a minimum of 209 evaluable subjects.

2.1.3 Overall Sample Size

In order to adequately power for both the primary effectiveness and safety hypotheses, we require a sample size of 211 evaluable subjects to complete 12 months of follow-up. We estimate that the attrition rate will be approximately 20%. Therefore, to achieve 211 evaluable subjects to be followed for 12 months and to account for attrition, the final sample size required is 264 subjects with procedure attempts.

Appendix 1: Cerebral Microembolism

Cerebral Micro-embolism: A Review

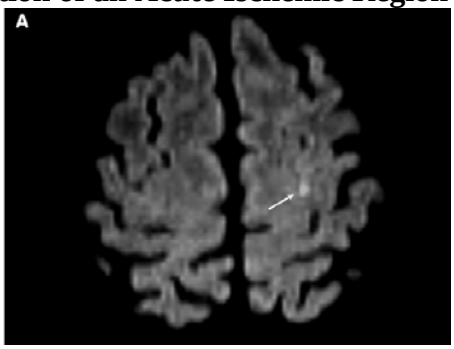
Author - David E. Haines, M.D.; William Beaumont Hospital, Royal Oak, Michigan

Cerebral embolism occurs when a small embolus blocks a blood vessel in the brain. This can result in acute ischemic injury to the part of the brain perfused by that vessel. With time, this acute injury can resolve itself or result in a chronic infarct. Emboli have been known to be caused by a blood clot (thromboembolism), gaseous bubbles, fat or other types of solid particles such as calcium or other tissue fragments[1]. If the patients do not have any clinical symptoms, the emboli are silent. Emboli with very small dimension are referred to as "micro-emboli", and are often silent. In this paper, the methods of detecting the emboli, their observation following invasive medical procedures including AF ablation and the clinical consequences of these emboli will be discussed.

Detection of Emboli

There are two common methods that have been employed to detect cerebral embolization: by neuro-imaging with MRI or CT; and transcranial doppler imaging. MRI helps one assess the anatomical impact of the emboli, whereas transcranial doppler detects the emboli as they traverse through the cerebral artery. An MRI provides exquisite anatomical detail, differentiates hemorrhage from infarct, and using the special technique of diffusion weighted MRI (DW-MRI), it can detect acute cerebral ischemia with high sensitivity. DW-MRI can detect acute ischemic injury as early as 30 minutes and up to 2 weeks after its onset (2). The acute ischemic region presents as a hyperintense (i.e. bright) region against a darker background of normal tissue (**Figure 1**).

Figure 1: Detection of an Acute Ischemic Region with DW-MRI.



Ischemia causes a disruption in the potassium/sodium exchange pump of the cell membrane and compromises the water diffusion characteristic which is detected by the DW-MRI. In comparison, the T2 Flair MRI image is more sensitive to detection of large chronic brain infarcts[2].

The trans-cranial Doppler (TCD) utilizes non-invasive ultrasound imaging of the cerebral arteries. The emboli cause an increase in the amount of reflected ultrasound compared to that

caused by the red blood cells. However the technique cannot determine the size of the emboli or accurately differentiate the composition of the emboli (i.e. gaseous versus solid particles)[3]. The commercially available TCD systems count the number of micrembolic signals (MES) or high-intensity transient signal (HITS). The number of MES has been shown to correlate with the occurrence of clinical ischemic events[4].

Detection of emboli in invasive medical procedures

Cardiovascular and cerebrovascular procedures are associated with a low incidence of overt neurological complications. In many publications with these procedures, DW-MRI imaging has been used to evaluate the acute ischemic injury after the procedure or TCD has been used to measure the total embolic load during the procedure.

Invasive procedures such as cardiac bypass surgery, cardiac valve replacement, transcatheter aortic valve replacement, carotid artery stenting and carotid thromboedarectomy have been associated with acute DW-MRI lesions[2,5]. In many of these studies, the patients did not manifest any neurological symptoms and incidence rate of acute DW-MRI lesions varied from 4% to 47%. DW-MRI lesion rates as high as 47% were reported following cardiac valve replacement[2]. In other studies with the same procedures, neurological symptoms were observed in 3-8% of patients and the incidence of DW-MRI lesions was 14%-68%[2,5]. Even routine diagnostic procedures like coronary and cerebral angiography have been associated with DW-MRI lesions in upto 15% of patients without neurological symptoms[2].

The DW-MRI scans are very sensitive for detection of ischemic lesions, and in turn, frequently identify lesions in asymptomatic patients. The clinically silent nature of many DW-MRI lesions may be due to their small size, early resolution of ischemia with regression of the lesions chronically and the location of the lesions[1]. The small size of the “silent” DW-MRI lesions may lead to very subtle neurological defects that are only discernable with sensitive neuro-cognitive tests. This has been extensively investigated following Coronary Artery Bypass surgery. A literature review of 22 publications over the last 30 years with cardiac surgery in which long term neuropsychological testing was done[6] showed the following: seven studies used postoperative DW-MRI; 15 studies used intra-operative TCD to measure the embolic load; in 15 studies no association could be found between the emboli and risk of post-operative cognitive decline; and in 7 studies, an association was observed. A definite link between the emboli and cognitive decline could not be established. This conclusion was also reached in a more recent large study of 356 patients, in which no correlation between the emboli and post operative cognitive decline was observed at 3 months after surgery[7]. Even following Transcatheter Aortic Valve implantation with high rates of acute DW-MRI lesions, there was no difference in the neurologic assessment questionnaire and the global cognitive function test between baseline and following the procedure as well as between patients with and with acute DW-MRI lesions[6].

Generation of emboli during catheter ablation procedures

A variety of mechanisms for systemic embolism have been proposed. Typically they are caused by solid or gaseous emboli. Coagulum and char can form when the peak temperature at the electrode-tissue interface exceeds 100°C[8]. This problem is exacerbated by the use of high

power density, high temperatures, and long electrodes. The heating around the electrode is non-uniform due to the edge effect[9]. Use of external irrigation has been proposed as a method to reduce the accumulation of electrode surface coagulum. Another possible mechanism of embolus generation is the production of microbubbles. Microemboli have been documented during AF ablation procedures using intracardiac echo[10] and TCD[11]. In the latter study, the occurrence of MES correlated with the observation of intracardiac microbubbles by intracardiac echo. Although no DW-MRI scans were done in this study, patients with procedure-related clinical neurological events had significantly higher numbers of MES. Air emboli have been observed to cause acute DW-MRI lesions[12,13] which can regress chronically[13]. Studies indicate that gaseous emboli are also less likely to cause neurological events or cognitive effects than solid emboli[7].

DW-MRI imaging following AF ablation

There have been several studies with AF ablation since 2006 in which DW-MRI imaging was done before and within 24-48 hours after the procedure. More than 850 patients with paroxysmal, persistent and longstanding persistent AF have undergone DW-MRI imaging using various technologies[14-24]. In all studies the incidence of lesions observed on the DW-MRI varied from 4 to 45% (**Table 1**). Most acute lesions were silent, with only 3 reported patients (0.4%) that developed neurological symptoms. About 70% of the AF ablation patients with DW-MRI imaging underwent ablation with irrigated RF ablation catheters. In this group, the incidence of acute DW-MRI lesions varied between 6.8 and 38.3%. The reason for the wide variation is not known. In two studies in which the phased RF technology was compared with irrigated RF, the incidence rate with phased RF was 37.5% and 38.9% and statistically higher than with irrigated RF and balloon cryoablation (**Table 1**). In only one study has neuropsychological testing been conducted[21]. Five neurocognitive domains were evaluated before and at 3 months following ablation. The ablation group showed worse outcome in one of the five domains (verbal memory). The decline was not associated with the presence of acute DW-MRI lesions. The predictors of DW-MRI lesions have been cardioversion during the procedure, ACT levels, ablation technology employed, presence of coronary artery disease, left ventricular volume, and septal thickness.

Table 1: Incidence of Acute DW-MRI Lesions with Various AF Ablation Technologies.

Author	Cryoballon	Phased RF	Irrigated RF	8 mm (Non-Irrigated)
Lickfett[17]			1/10 (10.0%)	
Schrinkel[20]			6/53 (11.3%)	
Neumann[18]	4/45 (8.9%)		3/44 (6.8%)	
Gaita[19]			33/231 (14.3%)	
Gaita[14]	2/36 (5.6%)	14/36 (38.9%)	3/36 (8.3%)	
Herrera[15]	1/23 (4.3%)	9/24 (37.5%)	2/27 (7.4%)	
Mizukami[22]			18/47 (38.3%)	
Deneke[16]		30/72 (41.7%)	3/14 (21.4%)	
Hioki[24]			13/51 (25.5%)	
Aso[23]			17/71 (23.9%)	14/31 (45.2%)
Range	**4.3%-8.9%**	**37.5%-41.7%**	**6.8%-38.3%**	**45.2%**

The mean diameter of a DW-MRI lesion following AF ablation with Phased RF technology is about 0.5 cms (.06 cc in volume) with a range between 0.2 cm (.004 cc) and 1.5 cm (1.0cc)[14-16]. The acute DW-MRI lesion volumes observed with other technologies are in the same range[14-21]. This contrasts significantly with the mean/median volume of the lesions observed following ischemic stroke which ranges between 13-45 cc[25-28]. Therefore, the mean lesion volume following AF ablation is a few hundred times smaller than observed with clinical strokes. Since smaller lesion volumes have been shown to give rise to less severity of symptoms[29]; this may explain their silent nature. Another important observation has been the regression of acute DW-MRI lesions on subsequent long-term MRI imaging[16]. In this recent study, patients with acute lesions following AF ablation had chronic T2 MRI scans at a median of 3 months post AF ablation. 94% of the lesions regressed and all of these were <10 mm in diameter. Only 3 lesions (one in each of 3 patients) that were > 10 mm diameter persisted without causing any neurological symptoms. These lesions were observed in patients who underwent AF ablation with Phased RF or Irrigated RF. Therefore the small acute lesions tend to resolve and not cause a chronic infarct. There have also been other clinical reports of regression of DW-MRI lesions on subsequent T2 imaging[28].

It has been hypothesized that emboli causing the acute lesions could be due to thrombi, tissue coagulum or gas bubbles caused by the ablation process or air introduced during catheter and sheath introduction as well as withdrawal[30]. The exact composition of the emboli causing DW-MRI lesions is still under investigation[31].

Summary

Cerebral emboli can be caused by solid particles or gaseous bubbles. Acute ischemic lesions with DW-MRI have been observed following most invasive cardiac procedures and even diagnostic procedures such as coronary angiography. In many such reports the emboli are clinically silent and no correlation has been observed between these emboli and impact on neurocognitive function. More recently, acute DW-MRI lesions have been reported with AF ablation. In almost all these patients there are no clinical symptoms. This may be due to their small size, lesion regression and location of the lesions. The average lesion volumes following AF ablation are few hundred times smaller than observed following stroke. Also, most of these small lesions regress with time and only the few larger lesions persist.

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Appendix 2: Technical Bulletin

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Medtronic

Current Density and Creation of Radiofrequency Ablation Lesions

Relationship between Electrode Size and Power Efficiency

Technical Bulletin No.1

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice[1]. The rate of AF occurrence increases with age, from less than one percent of the population under age 60 to more than eight percent of the population age 80 and older. Recently, catheter ablation has been accepted as a main-stream therapy for patients with AF[2]. Typical AF ablation approaches utilize radiofrequency (RF) energy delivered in a unipolar manner via the tip electrode of a transvenous catheter. The most common ablation strategies require the operator in a point-by-point process to create long contiguous lesions in the thin-walled left atrium, where undesirable side effects of surplus power delivery can lead to serious complications[3]. Since the majority of power delivered from conventional RF systems is lost to circulatory cooling, AF ablation techniques could benefit from technical improvements that minimize or eliminate the root causes of inefficient power delivery.

An innovative RF ablation system has recently been introduced that is designed to overcome many of the challenges reported using unipolar RF and tipped catheters to create left atrial lesions[4]. This system delivers user-defined combinations of unipolar and bipolar energy via relatively small cylindrical electrodes arranged in an array configuration [Figure 1]. This implementation allows the operator to create long, contiguous lesions with a single RF application, unlike typical hemispherical 4mm & 8mm ablation catheters that must be manipulated in a 'point-to-point' or 'dragging' manner to achieve similar lesion profiles. Early research with RF ablation proved that lesions greater than 7mm in depth could be created using a hemispherical 6F/2mm electrode and peak power of 10W[5]. In order to estimate the appropriate RF power settings for ablation with these smaller cylindrical electrodes, it was necessary to determine the equivalent current density used when creating lesions with conventional electrodes [Figure 2].

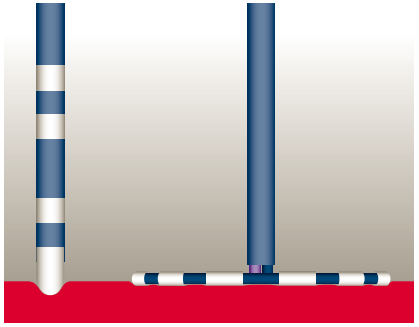

Figure 1: Comparison of 7F 4mm hemispherical omni-directional electrode with Medtronic Ablation Frontiers PVAC® Pulmonary Vein Ablation Catheter® 3mm decapolar array.

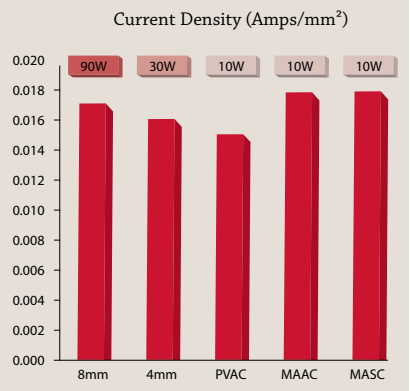

Figure 2: Equivalent current density can be maintained across various electrode sizes by titrating power. A smaller electrode requires less power to achieve equivalent current density.

TECHNICAL INSIGHT

Irreversible thermal injury to cardiomyocytes has been shown to occur at temperatures above 50°C, yet soft thrombus can form at just 80°C and the potential for "steam pops" occurs above 100°C[6]. Thus a desirable RF lesion will be created within the temperature limits of 50 → 80°C. The biophysical mechanism of lesion formation is based on resistive and conductive heating, thus a comparison model can be created by assessing the current density delivered to the tissue.

As current flows through tissue, power is dissipated and thus heat generated via resistive heating. Joule's Law defines the quantity of power (*P*) delivered through a resistive medium as the product of the resistance or impedance (*R*) and the square of current flow (*i*), Equation 1 [Figure 3].

Rearranging the equation [Figure 3] to calculate total current delivered gives Equation 2 [Figure 3]. For a given electrode configuration, the average current density [i_d] per unit area will be equal to the total current divided by the electrode surface area, Equation 3 [Figure 3].

As electrode size decreases, the size of the tissue "corridor" through which current may flow will get smaller, thus increasing the impedance. With all other factors constant, a smaller electrode will experience greater impedance and larger electrode less impedance.

Equation 1 $$P = i^2 * R$$

Equation 2 $$i\,[A] = \sqrt{\frac{P\,[W]}{R\,[\Omega]}}$$

Equation 3 $$i_d\left[\frac{A}{mm^2}\right] = \frac{\sqrt{\frac{P\,[W]}{R\,[\Omega]}}}{SA_{electrode}[mm^2]}$$

Figure 3: Joule's Law shows that power delivered through a resistive medium is equal to the square of current times the impedance. Rearranging and dividing by surface area gives the formula for Current Density based on the electrode size.

Table 1 shows the resultant calculations for Current Density using a matrix of typical electrode sizes at various powers, as well as for the 2mm & 3mm electrodes found on the Medtronic Ablation Frontiers Multi-Array Ablation Catheter® (MAAC®), Multi-Array Septal Catheter® (MASC®) and Pulmonary Vein Ablation Catheter® (PVAC®). Note that this table represents average current densities assuming a homogeneous tissue medium with fixed impedance per unit volume [Figure 4].

These calculations demonstrate that equivalent current densities used in conventional large electrode delivery, can be achieved by delivering approximately 10W to a 2mm or 3mm cylindrical electrode.

	Catheter size (F)	Electrode Length (mm)	Electrode Surface Area (mm²)	Impedance (Ω)	Current Density (A/mm²)	Power 10	20	30	40	50	60	70	80	90
	MAAC & MASC	2	9	355		**0.018**	0.026	0.032	0.037	0.041	0.045	0.049	0.052	0.055
	PVAC	3	14	225		**0.015**	0.022	0.027	0.031	0.035	0.038	0.041	0.044	0.046
	7	4	32	100		0.010	0.014	**0.017**	0.020	0.022	0.024	0.026	0.028	0.029
	8	8	63	60		0.006	0.009	0.011	0.013	0.014	0.016	**0.017**	0.018	0.019

Table 1: Comparison of current density between common electrode sizes and typical RF generator power settings. As electrode size increases, larger amounts of power must be delivered to maintain equivalent current density.

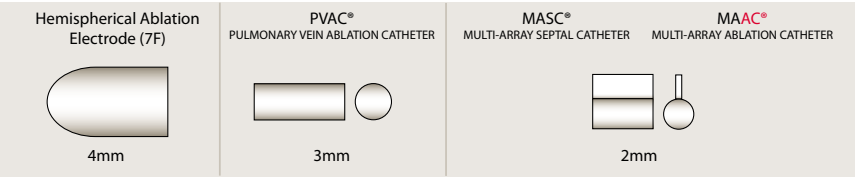

Figure 4: Relative size comparison for radiofrequency electrodes described in Table 1.

CLINICAL IMPLICATIONS

While small electrodes are able to provide equivalent current density and thus equivalent heating to larger electrodes, several other aspects of small electrode deployment may also help to alleviate the root causes of inefficient power delivery.

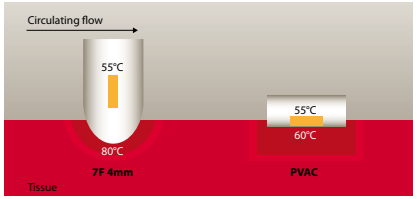

Figure 5: The geometry of the PVAC electrode array allows for thermal measurement predictably at the tissue interface (yellow area represents location of the thermocouple). Also, the relative electrode surface in contact with the tissue is higher with a small electrode in the unidirectional configuration.

Unlike conventional tip catheters, which are designed for omni-directional use, these small electrodes are deployed on nitinol frames which only allow for unidirectional tissue contact [Figure 1]. The advantage to this configuration is that it localizes the temperature sensors at the endocardial surface [Figure 5]. By actively measuring temperatures at this junction, a more accurate tissue temperature is achieved because the cooling effect of circulating blood is minimized.

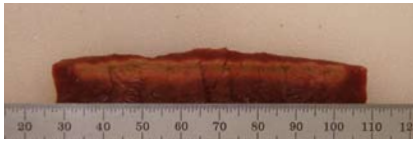

Figure 6: Typical in vitro lesion created by delivering radio-frequency (RF) to bovine myocardium for 60 seconds at target temperature of 60 degrees. The lesion is approximately 6mm deep and 70mm in length.

With greater accuracy between the measured and actual tissue temperature, the power delivery of a temperature driven system becomes more efficient.

The unidirectional configuration together with the pliability of the nitinol frame also allows the multi-electrode array to conform to the variable structures found within the left atrial chamber. This enhances the ratio of electrode-tissue contact that can be achieved when compared to larger electrodes. Since blood has approximately one-half the impedance of tissue, increasing the ratio of electrode surface in contact with the tissue will decrease the amount of current lost to blood flow and provide RF power efficiency improvement.

Successful and safe radiofrequency ablation relies on achieving target temperatures that achieve irreversible thermal injury without the consequences of overheating. Thus effective ablation is achieved by focusing on the primary objective – lesion creation – but can become safer and more efficient when considering all technical aspects of a temperature-driven radiofrequency circuit. The combination of small electrodes that can provide equivalent current density, pliable frames that achieve high electrode-tissue contact area and accurate temperature measurement make it possible to successfully create therapeutic lesions with relatively low power. [Figure 6]

Appendix 3: Technical Bulletin

Medtronic

Electrode Cooling and Creation of Radiofrequency Ablation Lesions

Relationship between Electrode Cooling, Contact, and Power Delivery

Technical Bulletin No. 2

INTRODUCTION

Atrial fibrillation (AF) is considered a disease of aging; however epidemiologic studies such as Framingham and Renfrew/Paisley confirm a large prevalence and incidence, even in middle-aged people.[1,2] For those that remain in AF, many will experience disabling symptoms, poor exercise tolerance, and an increased risk of stroke. While several clinical trials designed to test rate control versus rhythm control strategies consistently demonstrated no mortality benefit or Quality of Life (QOL) improvement; retrospective analysis of the data showed the opposite. When sinus rhythm was restored and maintained, QOL scores improved and the presence of sinus rhythm was associated with a reduction in the risk of death. These findings have led the investigators to conclude that more effective ways of maintaining sinus rhythm with fewer side effects are needed.[3-6]

AF ablation has become an accepted treatment strategy to restore and maintain sinus rhythm. The most common strategy in use today is a point by point approach using unipolar radiofrequency (RF) to electrically isolate the pulmonary veins. In patients with more advanced forms of AF, hybrid strategies have emerged that include pulmonary vein isolation and complex fractionated atrial electrogram (CFAE) or linear ablation in the left atrial body to restore sinus rhythm. For procedures that use RF as the ablative energy, the success or failure to create effective lesions is highly dependent on several factors, including electrode size, delivered RF power, local blood flow, and tissue contact.[7]

The circulatory system of the heart provides a natural coolant for ablation electrodes (Figure 1). In a temperature controlled RF system, when ablation occurs in a high flow region of the left atrium, such as the pulmonary vein antrum, the resultant cooling effect on the electrode will cause an increase in power delivery to achieve and maintain the desired target temperature. Under these conditions lesion depth, width, and volume are increased. Conversely, in areas of low flow or no flow where electrode cooling is minimal, target temperature will be reached with minimal power delivery resulting in small, ineffective lesions.[9] The ability to effectively treat AF may require successful ablation in both high and low blood flow regions thus, different approaches have been implemented to improve electrode cooling in areas of low blood flow. The most common approach relies upon actively cooling the electrode using saline irrigation during ablation. While this method offers the advantage of facilitating increased power delivery to the target tissue, it also effectively disables the temperature feedback loop. This can lead to the risk of overheating the tissue resulting in steam pops, which occur from boiling and gas expansion as the lesion deepens. Steam pops are thought to be the major cause of cardiac perforation during ablation.[10] Recently, an alternative approach has been introduced, which combines modifications to the energy delivery system and the electrode design to enhance passive electrode cooling in a temperature controlled RF system.[11-14]

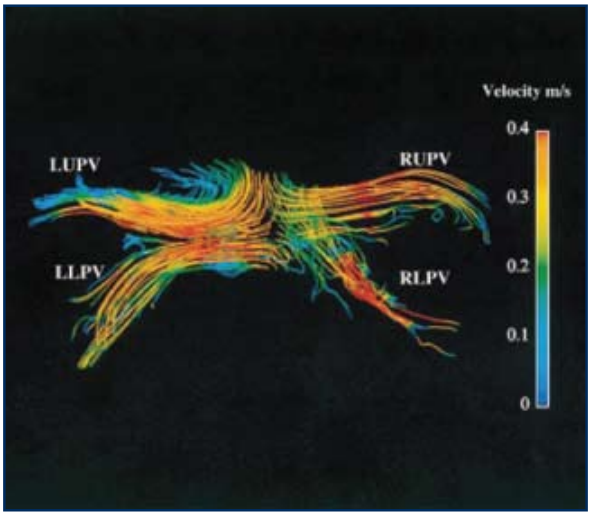

Figure 1: Posterior view of the left atrium showing blood flow patterns in normal sinus rhythm. Flow from the left pulmonary veins are incorporated and recirculated in vortices before draining to the left ventricle. Flow from the right pulmonary veins is constrained between the edge of the vortex and the atrial wall helping to maintain its velocity and direction.[8] Printed with permission from Heart Journal.

TECHNICAL INSIGHT

The biophysical mechanism of lesion formation is based on rapid resistive heating of the tissue in proximity to the ablation electrode. The resistive heating value (current density) will diminish as a function of the cube of the distance from the electrode. However, since the tissue retains heat, slower conductive heating of the surrounding tissue will also occur. Therefore, the temperature of the ablation electrode itself is a function of the opposing effects of heating from the tissue and convective cooling by the blood flowing around the electrode (Figure 2).

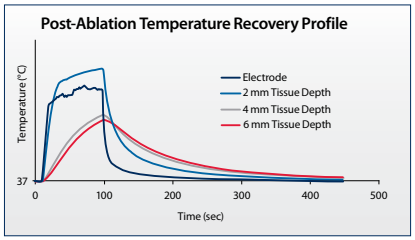

Figure 2: Graph of temperature profile during ablation and recovery period.

During cooling, the mean drop of the underlying tissue's temperature is approximately 3 times slower than the cooling of the electrode.[15] Because lesion size is primarily dependent on the ability to deliver enough power to achieve destructive tissue temperatures, lesion size will vary directly with the magnitude of local cooling.

Duty-Cycled Energy Delivery

Duty-cycled RF delivery is characterized by periods of energy "on" and "off" time. During the "on" time, current travels from the ablation electrode through the tissue to the patient return electrode(s). The passage of current through the tissue causes heating of the tissue. During the "off" time, the electrodes are cooled by blood flow, conducting heat away from the electrode-tissue interface so more power can be delivered during the next "on" time (Figure 3). Since tissue cools significantly slower it will retain the thermal energy of the RF application such that lesion creation is not adversely affected by the momentary cessation of RF delivery. The modulation from "on" to "off" occurs several dozen times per second.

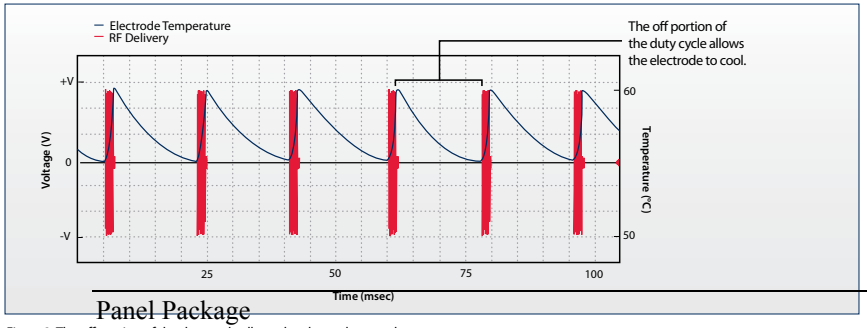

Figure 3: The off portion of the duty cycle allows the electrode to cool.

Electrode Material Composition and Shape

Platinum is commonly used for electrodes because it has a low specific heat, which means that it can easily increase or decrease in temperature when a low amount of heat energy is absorbed or lost, and a high thermal conductivity coefficient, which facilitates a high rate of heat transfer from the tissue during ablation.

Geometry and surface area of an electrode are also important factors in electrode cooling. Increasing the electrode surface area exposed to the blood increases the convective cooling caused by the local blood flow around the electrode. A change to electrode geometry, for example adding a fin, disrupts the local blood flow pattern and creates turbulence to enhance cooling (Figure 4). Finned electrodes can be particularly valuable for enhancing cooling in areas of low blood flow, such as along the interatrial septum and posterior wall. But less necessary for cooling electrodes situated near the PV ostia where the blood flow returning to the left atrium from the pulmonary veins is naturally high.

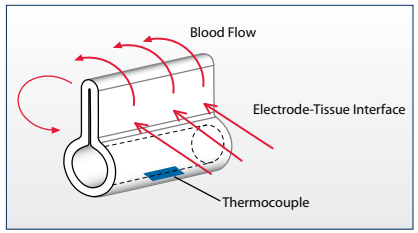

Figure 4: As the blood flows across the electrode the fin disrupts the flow creating turbulence, which can improve the cooling of the electrode.

CLINICAL IMPLICATIONS

Electrode cooling is only one aspect of the equation, but it has the potential to both positively and negatively impact lesion creation. The current accepted standard is to use saline irrigation for cooling in left-sided procedures. The use of saline has been shown to increase power delivery, thus creating lesions of greater depth, width, and volume.[7] The downside to saline use is that it disables the use of temperature as a feedback mechanism, increasing the risk of tissue overheating. Furthermore, the use of saline increases system and procedure complexity and may create stress on the heart and kidneys due to volume overload during prolonged procedures.

An alternative method of electrode cooling has been developed that involves modifications to the energy delivery system and the electrode design to retain the ability of the system to use temperature as a feedback mechanism during ablation. Duty-cycled energy, altered electrode shape, increased surface area, and highly conductive materials all contribute to enhancing the ability of the local blood flow to cool the electrodes. With temperature monitoring intact, a simple display of temperature and power delivery can provide real-time feedback. Achieving target temperature serves as an indicator of contact and the power required to reach target temperature serves as an indicator of the quality of contact and cooling during the ablation.

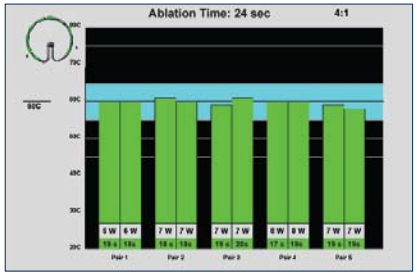

Figure 5: Good contact, good cooling – effective lesion creation

Figure 5 is an example of an ablation where target temperature is being reached with effective power. The green bars suggest that the electrodes are in contact and show that target temperature has been achieved. Each green bar also notates the power being delivered to each electrode. Since the system is power limited, in the 4:1 (bipolar: unipolar) mode the maximum power delivery will be 8W per electrode. In this example between 5 – 7W are being delivered to each electrode indicating that effective cooling is occurring while near close to maximum power is being delivered.

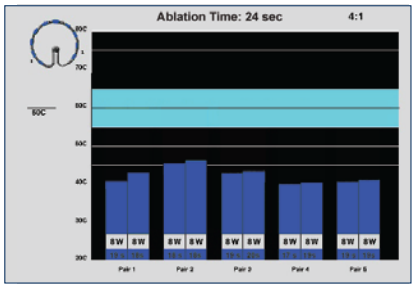

Figure 6: Good cooling, poor contact – ineffective lesion creation

Figure 6 is an example of an ablation where target temperature is not reached when maximum power is delivered. The blue bars indicate that the electrodes have poor or no contact with the tissue and the energy is effectively being delivered into the circulating blood. Because the tissue contact is poor and while electrode temperature is low due to cooling, the system is delivering maximum power (8W) attempting to reach target temperature. Gently manipulating the electrode array to gain better tissue contact should turn the blue bars to green.

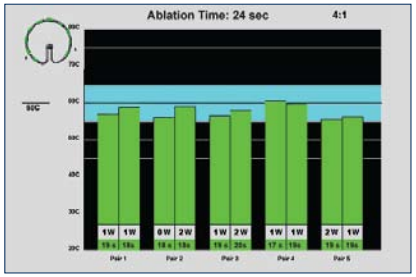

Figure 7: Contact pressure too great , cooling reduced – ineffective lesion creation

Figure 7 is an example of an ablation where target temperature is reached while minimum power is delivered. The green bars indicate that the electrodes are in good contact with the tissue. However, when power delivery is only at 1 – 2W, the user interface is suggestive of limited cooling. This indicates that contact pressure is too high and it is likely that the electrodes are embedded in the tissue where circulating blood is blocked from providing adequate cooling. Gently reducing contact pressure by manipulating the electrode array may expose more of the electrode to the blood, thus potentially improving cooling and providing a subsequent rise in power delivery.

In patients with AF, restoration and maintenance of sinus rhythm is associated with QOL and mortality benefits. AF ablation is one therapeutic option that can restore sinus rhythm, but its success is highly dependent on the relationship between contact, electrode cooling, and power delivery. While saline has been frequently used to improve cooling and power delivery, it does so at the expense of temperature monitoring and system complexity. Introducing more effective methods of passive cooling such as duty-cycled energy, altered electrode shapes, increased surface area, and highly conductive materials retains the ability to monitor temperature and with it the ability to provide real-time feedback during the ablation procedure. A simple display of temperature and power delivery can provide the operator with visual indicators of contact quality and cooling effectiveness. This feedback can be used to make adjustments during each ablation, ideally removing the art from ablation and replacing it with more predictable and reliable results.

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Appendix 4: Technical Bulletin

CLINICAL IMPLICATIONS

Successful ablation of atrial fibrillation requires electrical isolation of the pulmonary veins, and even small gaps can reduce efficacy or lead to the creation of post-ablation tachycardias. The ability to deliver RF energy between the electrodes with bipolar energy is beneficial, as it creates a contiguous lesion in the myocardium, rather than a collection of point lesions that is created with a traditional unipolar RF ablation catheter. Similarly, the ability to simultaneously create lesions from multiple electrodes reduces the number of catheter manipulations required and leads to procedure times that are reported to be comparatively short (84-201 minutes).[7]

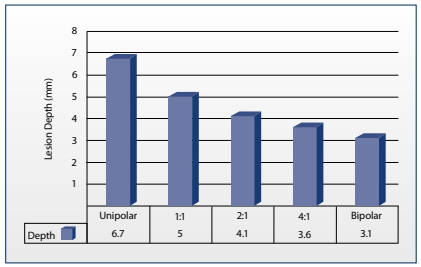

Figure 5. Wijffels, et al. Lesion depth is greater when more unipolar energy is applied.[8]

Unipolar RF energy has been successfully delivered through focal tip catheters to treat cardiac arrhythmias for decades. However, the complexity of the atrial fibrillation ablation procedure using a traditional focal tip ablation catheter necessitates innovation in catheter design and energy delivery methods. Using multi-electrode catheters to deliver phased duty-cycled energy is a major advance in technology that allows for tailored and efficient lesion creation.

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Medtronic

Duty-Cycled, Phased Radiofrequency Ablation

Use of Bipolar and Unipolar Energy Delivery to Control Lesion Depth

Technical Bulletin No. 3

INTRODUCTION

Since the first reported case of percutaneous cardiac catheter ablation, clinicians and scientists have attempted to mitigate the complications that accompany the technique. The genesis of catheter ablation was when Scheinman reported using direct current energy applied through the tip of a pacing catheter electrode to a skin electrode to destroy cardiac tissue.[1] Although the focally arrhythmic myocardium was destroyed, the damage to the atrio-ventricular conduction system rendered the patient pacemaker dependent. Huang eventually described using a radiofrequency (RF) generator to deliver electrical energy at 750 kHz frequency in a unipolar manner through percutaneous catheters.[2] This method resulted in well-delineated coagulation necrosis at the target ablation sites. With little modification to the initial system, unipolar RF energy has been used over the years to successfully treat thousands of focal and reentrant tachycardia patients with acceptable complication rates.

However, the extensive lesion set required and the proximity to sensitive anatomical structures has led to complication rates of 3-6% being reported. Solutions have been sought that more efficiently delivered ablative energy to isolate the pulmonary veins.

Catheter ablation of atrial fibrillation using a number of alternatives to unipolar RF energy has been explored. High-frequency ultrasound, microwave, laser, and cryothermic energy have been delivered percutaneously to isolate pulmonary veins. Each ablative energy source has its advantages and disadvantages, striking a delicate balance between efficient lesion creations and causing damage to adjacent structures. Duty-cycled, phased RF is a method of ablating myocardium by using RF energy in such a way that it mitigates potential damage caused by unipolar ablation systems.

Originally, catheter ablation of atrial fibrillation was directed at the AV node in order to control ventricular response. After Haïssaguerre demonstrated that AF is initiated by focal triggers highly concentrated in the pulmonary veins,[3] ablation techniques targeted these triggers. Difficulty in identifying PV triggers led to the technique of electrically isolating the veins from the left atrium using unipolar RF ablation catheters.[4]

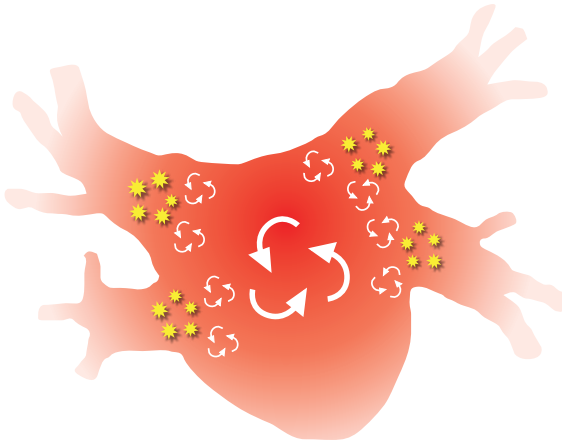

Figure 1. Starbursts represent the location of triggers in the pulmonary veins. The large and small reentrant wavelets represent initiating and sustaining AF in the atrial body.

TECHNICAL INSIGHT

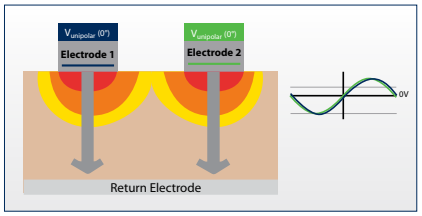

Figure 2a. Schematic demonstrating unipolar energy delivery.
Unipolar circuit/path: potential difference (V_p-0V) = V_p
Bipolar circuit/path: no potential difference (V_p- V_p) = 0

Conventional RF ablation catheters are only capable of delivering RF energy from the ablation electrode to a reference/dispersive electrode. This type of RF energy delivery is called unipolar because there is only one ablation electrode involved in the ablation circuit. On the other hand, bipolar energy delivery is RF energy delivered between a pair of ablation electrodes.

Duty-Cycling

The GENius™ Multi-Channel RF Ablation Generator delivers power in a fashion known as duty-cycling. In addition to enhancing electrode cooling and allowing optimal power delivery, duty-cycling allows each electrode to be controlled separately and independently from its neighbors.

Temperature-controlled systems modulate power output to achieve a defined target temperature. However, in a multi-electrode system, modulating the power output by varying the voltage amplitude of each electrode may create unintended potential differences to neighboring electrodes, leading to power dissipation. By implementing duty cycles and modulating power output to each electrode by varying the length of the 'on' portion of the cycles, power output can vary from electrode to electrode without causing unexpected leakage current.

Phasing

The GENius RF generator is capable of delivering RF power to up to 12 ablation electrodes simultaneously. RF power is delivered in unipolar, bipolar, or combination modes (1:1, 2:1, 4:1 ratio of bipolar to unipolar power). The RF generator's ability to deliver both unipolar and bipolar power concurrently comes from a feature called phasing. The phase of the alternating current that is delivered to each electrode determines the ratio of bipolar to unipolar power.

In the unipolar mode, there is no phase shift between electrodes in a pair; therefore power dissipation occurs only between the ablation electrode and the reference/dispersive electrode (see Figure 2a).

In a combination mode, there is a phase shift between electrodes in a pair causing in a potential difference. As a result, power dissipation occurs between electrodes as well as between each ablation electrode and the reference/dispersive electrode (see Figure 2b).

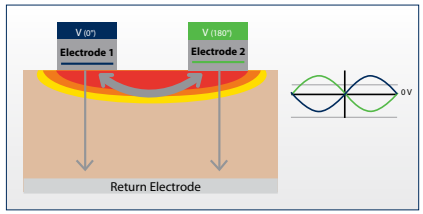

Figure 2b. Schematic demonstrating simultaneous unipolar and bipolar energy delivery.
Unipolar circuit/path: potential difference (V_p-0V) = V_p
Bipolar circuit/path: potential difference (V_p-(-V_p)) = 2V_p

The independent control of power delivery to each electrode results in the ability to respond to local contact, flow, and tissue heating. Though power delivery will vary at each electrode according to its environment, a uniform temperature distribution is created, which results in a uniform lesion.

A 180° phase shift between the electrodes produces a combination field which generates 4:1 ratio. Using the combination fields together with the unipolar fields produce various ratios of 4:1, 2:1, and 1:1 (Figure 3a, 3b, and 3c).

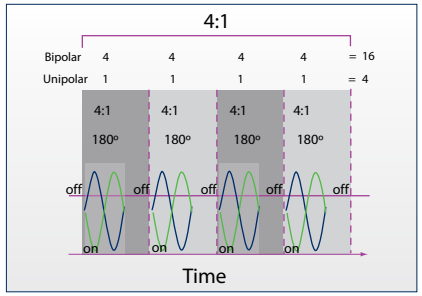

Figure 3a. Chart demonstrating phase shift between electrodes providing unipolar:bipolar ratio of 4:1.

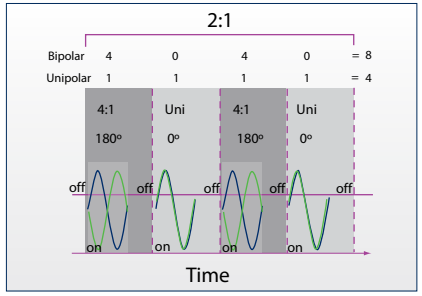

Figure 3b. Chart demonstrating phase shift between the electrodes providing unipolar:bipolar ratio of 2:1.

TECHNICAL INSIGHT

The mixture and direction of power dissipation as determined by energy mode has a strong correlation to lesion depth. A wide range of lesion depths can be generated under identical conditions by varying energy mode; deeper lesions are created with energy modes that contain a higher ratio of unipolar energy. The ability to create shallow lesions with higher ratios of bipolar energy should not be trivialized. By redirecting power from the unipolar path to the bipolar path, lesion contiguity is maintained, along with a notable reduction in depth. Thus, phasing allows a multi-electrode catheter to create range of deep or shallow lesions without sacrificing lesion quality.

The result of duty-cycling and phasing is greater control over energy delivery. Phasing allows for control of the bipolar to unipolar ratio which governs lesion depth and maintains lesion contiguity. Duty-cycling allows for control of power output of each electrode separately to react to local conditions, resulting in uniform lesion creation.

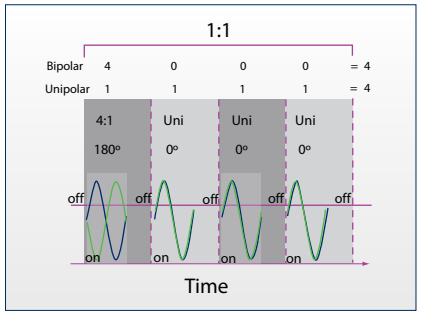

Figure 3c. Chart demonstrating phase shift between the electrodes providing unipolar:bipolar ratio of 1:1.

CLINICAL IMPLICATIONS

The walls of the atrium are composed of one to three or more overlapping layers. The thickest part of the atrium is the anterior wall, which is 3.5-6.5 mm thick in the area of Bachmann's bundle (Figure 4a). The atrial wall behind the aorta is the thinnest, reported to be 1.5-4.8 mm in thickness. Similarly the posterior wall is reported to be very thin (Figure 4b).[5] In thinner anatomies, lesion depth should be reduced to avoid peripheral damage to adjacent structures, such as the esophagus. Current ablation technologies rely on dragging the catheter tip electrode along the atria, reducing power or ablation duration in order to control lesion depth. The challenge in this method is that the catheter design is inherently unstable in the beating heart. Moreover, adjustments to power delivery and/or ablation duration may lead to insufficient lesion formation, which, in turn, may lead to transient electrical propagation, which can result in arrhythmia recurrence and the need for retreatment.

Through phasing and duty-cycling, the GENius RF generator is able to deliver controlled energy delivery to create contiguous, uniform lesions of varying depths (Figure 5). This method is clinically advantageous as it allows for consistent power delivery, regardless of anatomic position of the catheter. By using 4:1 bipolar: unipolar energy in areas of less atrial thickness, it is possible to achieve therapeutic lesions while minimizing the adverse effects of unipolar current density in adjacent structures. Wieczorek, et al.[6] used this system in a series of patients and examined the esophagus with an endoscope to assess damage from the creation of ablation lesions in the left atrium and found normal esophageal mucosa.

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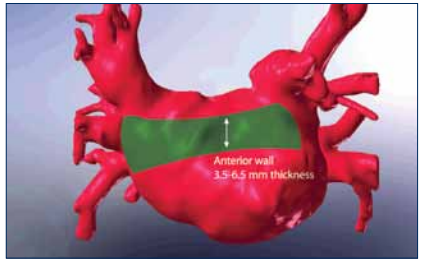

Figure 4a. Anterior projection of left atrium, revealing thickness of anterior wall

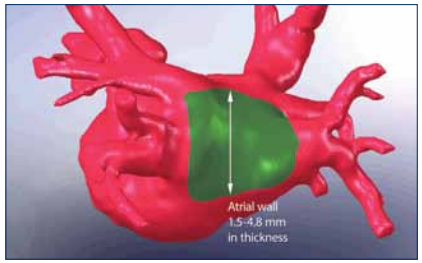

Figure 4b. Posterior projection of left atrium, revealing thickness of atrial wall

Appendix 5: Bibliography

BIBLIOGRAPHY

A comprehensive bibliography for the Medtronic Phased-RF Ablation System (the 'System') is being provided as an Appendix of the Panel Pack. The articles in this bibliography are intended to support PMA approval of the System.

The bibliography is divided into sections by article topic. These sections include:

- Publications referencing the System
- Publications referencing Atrial Fibrillation (AF), including Symptoms, Risk, Population and Other General AF Topics
- Publications referencing Atrial Fibrillation and/or Radiofrequency (RF) Ablation
- Publications referencing Surgical Treatment of Atrial Fibrillation
- Publications referencing Microembolism / MRI.

Publications referencing the System

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Appendix 6: Learning Curve Analysis

Learning Curve Analysis

Published data demonstrate that increased Medtronic Phased-RF Ablation System experience is associated with reduced procedure time and fluoroscopy time, reduced number of RF applications, increased efficacy, and a shorter learning curve when compared to other AF ablation technology. A summary of the published data from experience operators is presented in **Table 1**.

Table 1. Learning Curve Analysis from Published Data

Ref.	Year	n (pts)	AF Type	Devices Used	Comparison Groups	Clinical Measure	Group 1	Group 2	% Diff
1, 2*	2009	66	Persistent	PVAC, MASC, MAAC	Group 1: 1st 20 pts Group 2: Last 20 pts	Proc Time (min)	151±50	101±15	-33%
						Fluoro Time (min)	40±37	22±8	-45%
						RF applications	48±18	38±6	-21%
3, 4*	2009	210	Paroxsymal	PVAC	Group 1: 1st 50 pts Group 2: Last 50 pts	Proc Time (min)	97±33	82±29	-15%
						Fluoro Time (min)	26±20	25±19	-4%
						RF applications	29±7	23±7	-21%
5*	2009	119	Paroxsymal	PVAC	Group 1: 1st 69 pts Group 2: Last 50 pts	Free from AF (%)	55	80	45%
6	2010	152	Paroxsymal	PVAC	Group 1: 1st 25 pts Group 2: Last 25 pts	Proc Time (min)	112±31	98±18	-13%
						Fluoro Time (min)	23±9	18±7	-22%
						Free from AF (%)	56	68	21%
7*	2011	164	Paroxsymal	PVAC	Group 1: 1st 30 pts Group 2: Last 30 pts	Proc Time (min)	112	97	-13%
						Fluoro Time (min)	22	18	-18%
						Free from AF (%)	53	80	51%
8	2011	109	Paroxsymal and Persistent	PVAC 3D EAM w/ irr RF	Group 1: 3D EAM (n=71, Persistent=28) Group 2: PVAC (n=38, Persistent=8)	Proc Time (min)	252±60	168±41	-33%
						Fluoro Time (min)	75±26	39±14	-48%
						Free from AF (%)	39	68	174%

** = Asterisk indicates abstract/poster data.*

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Appendix 7: 2007 HRS Expert Concensus

Appendix 8: 2006 AF Guidelines

Appendix 9: CSR Excerpt

Clinical Study Report Excerpts

This Appendix contains excerpts from the "Medtronic Cardiac Ablation System: Clinical Study Report in Support of Pre-Market Application" (pages 35-59) submitted to FDA on June 9, 2011. These excerpts are included in the Panel Pack in order to reference this information during Panel activities and provide insight to information contained in the original TTOP-AF clinical protocol. All references in this excerpt refer to the Clinical Study Report (CSR) indicated previously.

Excerpt from the *Medtronic Cardiac Ablation System: Clinical Study Report in Support of Pre-Market Application*:

3.4. Subject Selection

Subjects were identified and screened based on assessment of their routine clinical evaluations that occurred as part of their normal clinical care prior to obtaining written informed consent. The results from the routine clinical evaluation could be used for study purposes for subjects that were subsequently consented and enrolled.

Baseline evaluations performed are summarized in **Table 1** and consisted of the following:

- Documentation of AF on a 12-lead ECG
- Transthoracic echocardiogram (TTE) report within 6 months of the consent date
- Documentation of 48-hour Holter event recording
- SF-36 Quality of Life Survey
- AF Symptom Severity Score

Table 1. Baseline and Follow-Up Procedures

Testing	Baseline	Pre-Discharge	1 Month	3 Month	6 Month
History, Physical Exam, Neurological Evaluation and Medication History	A, M	A	A, M	A, M	A, M
12 lead ECG (within 6 months of screening)	A, M	A	A, M	A, M	A, M
Echocardiogram (TTE) (within 6 months of ablation procedure or screening for medical management arm)	A, M	-	-	-	A, M
Transesophageal Echocardiogram (TEE) (within 72 hours of ablation procedure)	A	-	-	-	-

Testing	Baseline	Pre-Discharge	1 Month	3 Month	6 Month
Symptom Severity Score	A, M	-	A, M	A, M	A, M
PV Stenosis Survey	A	-	A	A	A
SF-36 Quality of Life (QOL) Survey	A, M	-	A, M	A, M	A, M
48-hour Holter	A, M	-	-	-	A, M
CT Scan or MRI	A	-	-	-	A
Adverse Events	N/A	A, M - Collected as Reported			

Key: A=Ablation Management Arm; M=Medical Management Arm; N/A=not applicable, (-) = test not required per protocol

Note: Subjects randomized to the Medical Management arm and crossed over to receive an ablation procedure followed the same data collection and visit schedule as subjects randomized to the Ablation Management arm.

Source: Clinical study files

Subjects that met all inclusion criteria and none of the exclusion criteria upon initial screening were randomized 2:1 to Ablation Management and Medical Management, respectively. The participating study site would enter the inclusion/exclusion criteria for each subject into the NetRegulus electronic data capture system and NetRegulus would then randomly generate the treatment arm assignment for the study subject.

Additional screening was performed related to the exclusion criteria for subjects randomized to Ablation Management. A spiral CT/MRI scan report was required in the prior 3 months of the ablation procedure for measurement and assessment of any irregularities of the pulmonary veins and for comparison to a 6 month follow-up scan. A transesophageal echocardiogram (TEE) was performed within 72 hours of the ablation procedure to rule out the presence of a pre-existing intracardiac thrombus. Subjects underwent a pregnancy test (if appropriate) and were administered a pulmonary vein stenosis survey as well. The presence of a thrombus or a positive pregnancy test was exclusionary for the purposes of the study.

Subjects that failed to meet the inclusion/exclusion criteria were exited from the study prior to study interventions unless prior authorization was obtained and documented from the Sponsor. The inclusion/exclusion criteria for the final protocol (version AG) are defined below.

3.4.1. Inclusion Criteria

- History of symptomatic, continuous AF defined as:
  - Continuous AF lasting greater than 1 year but less than 4 years or nonself-terminating AF, lasting greater than 7 days but no more than 1 year, with at least one failed DC cardioversion. A failed cardioversion was defined as an

unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond 7 days.
  - AF symptoms included the following:
    - Palpitations
    - Fatigue
    - Exertional dyspnea
    - Exercise intolerance (Increased intolerance to routine activities)
- Age between 18 and 70 years
- Failure of at least one Class I or III rhythm control drug
- Willingness, ability and commitment to participate in baseline and follow-up evaluations for the full length of the study.

3.4.2. Exclusion Criteria

- Structural heart disease of clinical significance including:
  - Previous cardiac surgery (excluding coronary artery bypass graft and mitral valve repair)
  - Symptoms of congestive heart failure including, but not limited to, NYHA Class III or IV congestive heart failure and/or documented ejection fraction <40% measured by acceptable cardiac testing
  - Left atrial diameter >55 mm
  - Moderate to severe mitral or aortic valvular heart disease
  - Stable/unstable angina or ongoing myocardial ischemia
  - Myocardial infarction (MI) within 3 months of enrollment
  - Congenital heart disease (not including atrial septal defect or patent foramen ovale without a right to left shunt) where the underlying abnormality increases the risk of an ablative procedure
  - Prior atrial septal defect of patent foramen ovale closure with a device using a percutaneous approach
  - Hypertrophic cardiomyopathy (left ventricular septal wall thickness >1.5 cm)
  - Pulmonary hypertension (mean or systolic pulmonary artery pressure >50 mm Hg on Doppler echo)
- Any prior ablation for AF
- Enrollment in any other ongoing arrhythmia study
- Any ventricular tachyarrhythmia currently being treated where the arrhythmia or the management may interfere with this study
- Active infection or sepsis
- Any history of cerebral vascular disease including stroke or transient ischemic attacks
- Pregnancy or lactation
- Left atrial thrombus at the time of ablation
- Untreatable allergy to contrast media
- Any diagnosis of AF secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiovascular causes
- History of blood clotting (bleeding or thrombotic) abnormalities
- Known sensitivities to heparin or warfarin
- Severe chronic obstructive pulmonary disease (defined as FEV1 <1)

- Severe co-morbidity or poor general physical/mental health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e. other disease processes, mental capacity, substance abuse, shortened life expectancy, etc.)

3.5. Subject Interventions

3.5.1. Ablation Management Procedure and Treatment

General parameters for ablation procedures are outlined in Section 8 of the protocol and are reviewed here. Vascular access, transseptal access, and placement of intracardiac mapping/pacing catheters, as well as the use of fluoroscopy and intra-cardiac echo catheters were all performed according to standard practice. The ablation catheters were passed through the transseptal sheath into the left atrium. Utilization of intracardiac echocardiogram technology and/or an electro-anatomical mapping system could be used to assist in the positioning of study catheters during the procedure according to investigator preference. Placement of a coronary sinus catheter for pacing was a requirement.

Oral anticoagulation could be discontinued and either subcutaneous LMWH or intravenous heparin could be substituted at therapeutic doses until the time of the procedure according to site practice or investigator or site practice. Once transseptal access was obtained, a bolus dose of heparin was introduced either intravenously or delivered through the sheath. No ablations were to occur until the ACT reached 300 seconds. ACT levels were measured at 30 minute intervals (not to exceed 45 minutes) to maintain a level of ≥300 seconds for the duration of the procedure. Pulmonary venograms were made by the injection of contrast material following transseptal access to the left atrium. Adenosine could also be used to enhance the images. Digital subtraction pulmonary venograms could be used in place of procedural venograms.

Esophageal location was monitored by either asking the subject to swallow barium paste to visualize the esophagus or in the event general anesthesia was used, an esophageal temperature probe could be used.

The use of all 3 ablation catheters (PVAC, MASC, and MAAC) were to be used in the listed order for tailoring treatment of each subject's specific source of AF. The pulmonary veins were first mapped and ablated using the PVAC catheter. The PVAC was placed using venogram images to guide placement at the antrum of the targeted pulmonary vein to map electrical potentials. Once optimal positioning of the catheter was obtained, ablation on all 5 bipole channels was performed in a 4:1 (unipolar:bipolar) setting to a target temperature of 60°C for 60 seconds. An additional 4 ablations could be performed with the same settings and duration after rotation of the catheter to identify remaining pulmonary vein potentials.

Both the MASC and MAAC catheters were used to map and ablate CFAEs located on the septum (MASC) and the wall (anterior, posterior, and roof) and along the mitral annular region of the left atrium (MAAC). The MASC catheter was deployed in the left atrium and the sheath

retracted back to the septum toward the right atrium prior to ablation. Ablations occurred for 60 seconds with a target temperature of 60°C using a 1:1 (unipolar:bipolar) modality setting. The MASC catheter was then rotated to identify additional CFAEs and ablation repeated. The MAAC catheter was used to map and ablate along the left atrial wall in a similar fashion. Ablations also occurred at 60°C for 60 seconds. However, a modality of 1:1 or 4:1 was used depending on the location of the ablation. A modality of 4:1 created less lesion depth and was used in regions close to the esophagus. Additional mapping and ablations would occur until the investigator determined that all CFAEs were eliminated.

Right-sided atrial ablations using non-investigational catheters were allowed (e.g. linear ablations) for the study, with the exception of coronary sinus ablations. However within the left atrium, only investigational catheters were used for purposes of ablation. Investigational catheters (PVAC only) were also used for ablations within the superior vena cava.

Electrical cardioversion was used during the procedure to restore sinus rhythm if the subject remained in AF. If the subject converted to sinus rhythm during the ablation procedure, no cardioversion was necessary. Once the subject was in sinus rhythm, the PVAC catheter was again placed to re-map any remaining pulmonary vein potentials. All noted pulmonary vein potentials were ablated using the settings identified above, but with the exception that only channels where potentials were located were selected.

During the course of the procedure, the following information was obtained:

- Total procedure time – Time difference between first venous access and removal of all catheters/sheaths
- Total ablation procedure time – Time difference between first catheter in and last catheter out
- Time of transseptal procedure
- Total fluoroscopy time
- Type and number of catheters used (PVAC, MASC, and/or MAAC)
- RF generator unit used for the procedure (model and serial number)
- Procedure ACTs – Measured every 10 minutes until therapeutic levels reached and then every 30-45 minutes during left atrial access
- Medications administered during the procedure (excluding sedation) including name, route and dosage information
- Pre- and post-ablation pulmonary vein potentials for all accessible pulmonary veins
- Representative pre- and post-ablation electrograms for the MASC and MAAC catheters
- Heart rhythm upon procedure completion

Prior to hospital discharge subjects were monitored with telemetry for recurrence of AF. In addition, subjects underwent a physical examination, neurological assessment, medication review, 12-lead ECG, establishment of systemic anticoagulation and screening for adverse events. Two anticoagulation strategies were allowed during the study. One strategy used

bridging therapy with low molecular weight heparin (LMWH) for subjects that stopped oral anticoagulants before their ablation procedure. LMWH was again resumed following the procedure until an INR of 2.0 was achieved. Oral anticoagulation therapy was additionally resumed after the procedure. The second strategy consisted of the continuation of oral anticoagulation throughout the periprocedure period. If there was an unexplained reduction in blood pressure, the presence of chest pain or shortness of breath, a post-procedure TTE was required along with further evaluation and management.

Recurrence of AF required additional management. If desired, the investigator could prescribe an AAD that the subject had failed prior to the ablation procedure. Alternatively, a repeat ablation procedure could be performed during the follow-up period of the initial ablation procedure. The protocol stated that the retreatment ablation procedure should occur within 90 days of the index ablation, whenever possible. The ablation retreatment followed the same procedure and follow-up assessments as for the index ablation. However, a TEE did not need to be repeated for subjects undergoing a retreatment ablation if the subject had documented therapeutic anticoagulation since the index procedure. Neither AAD therapy or ablation retreatment constituted a chronic treatment failure during this period provided that the subject was off all AADs prior to the 6 month visit. If a subject required the use of an AAD after their ablation procedure, the AAD needed to be discontinued 5 days prior to starting the 48-hour Holter recording for assessment of treatment success, with the exception of amiodarone. Amiodarone needed to be discontinued 28 days prior to the start of the Holter recording for evaluation of treatment success.

New onset atrial tachyarrhythmias that were exposed during or following the ablation procedure were recorded in the CRF as part of the follow-up management for subjects. The new arrhythmias would be documented for unscheduled as well as scheduled follow-up visits. Some of these arrhythmias were self-limiting while others required additional intervention. DC cardioversion was recommended to restore sinus rhythm prior to scheduling a repeat ablation procedure. If an arrhythmia (AF, atrial flutter, or atrial tachycardia) was documented on a 48-hour Holter recording, a total of 2 ablation procedures had been performed, the chronic efficacy endpoint was not met and the subject was considered a treatment failure.

3.5.2. Medical Management Treatment

Medical Management subjects were placed on an AAD dose that had previously failed or a new drug. Amiodarone was allowed up to a maximum allowable dosage of 200 mg/day. AAD therapy was expected to begin promptly after randomization. Changes to AAD dosage and/or change to another drug or combination of drug were allowed during the 6 month follow-up period when determined clinically necessary by the investigator.

In addition to AAD use, subjects were expected to receive adequate anticoagulation with warfarin during the course of the study to achieve and maintain an INR level >2.0.

DC cardioversions to restore sinus rhythm were also allowed in the Medical Management group. Up to 2 failed DC cardioversions that were separated by a minimum of 30 days constituted a chronic treatment failure during the 6 month follow-up period. A failed cardioversion was defined as a failure to convert to sinus rhythm or to maintain sinus rhythm for >30 days.

3.5.3. Follow-Up Schedule for all Randomized Subjects

The follow-up visit schedule for subjects in both the Medical Management and Ablation Management arms began on the day of treatment. All follow-up visits and acute safety assessments were started from the day of the ablation procedure for Ablation Management subjects. If an Ablation Management subject required a repeat ablation for AF recurrence, the follow-up visit timeline would restart on the date of the retreatment ablation procedure.

All study subjects were required to have follow-up assessments at 1, 3, and 6 months for the purpose of assessing arrhythmia recurrence, use of medications (AADs and anticoagulation), and AE occurrence. Subjects in Ablation Management also had a pre-hospital discharge visit that was not applicable to subjects in Medical Management. Office visits at 1, 3, and 6 months included history, physical examination, neurological assessment, symptom severity score, ECG, SF-36 survey, and documentation for the use of medications and anticoagulation agents, the occurrence of AF interventions, and an AE review. Additionally, Ablation Management subjects had a pulmonary vein stenosis survey obtained at every follow-up visit and a CT/MRI scan performed at the 6 month visit. Forty-eight (48) hour Holter monitoring was performed at the 6 month visit for both Ablation and Medical Management subjects.

Medical Management subjects that demonstrated chronic treatment failure under drug therapy were allowed to crossover and receive an ablation procedure. The crossover of subjects could occur no sooner than 4 months after randomization and only after the subject demonstrated efficacy failure on a 48-hour Holter recording. Crossover subjects followed the same eligibility criteria and pre-procedure testing requirements as those subjects initially randomized to Ablation Management. Crossover subjects began a new follow-up schedule on the day of the ablation procedure and underwent follow-up visits as described for subjects in Ablation Management. Data for safety and efficacy endpoints for crossover subjects was analyzed separately.

Clinical information and procedures performed related to arrhythmia that occurred during unscheduled visits during the 6 month follow-up period were also documented. However, there were no study-required procedures defined for these visits.

3.5.3.1. Follow-Up for Ablation Management

All Ablation Management subjects were expected to have pre-hospital discharge visit and additional follow-up visits at approximately 1, 3, and 6 months post-procedure. The required follow-up testing was calculated based on the date of the index ablation procedure or re-calculated from the date of the retreatment procedure. All safety information from the index ablation was captured in addition to the safety information for the retreatment ablation.

Subjects that had an ablation attempt but who did not ultimately receive an ablation were followed at pre-hospital discharge and for an additional 30 days. If there were on-going procedure and/or device-related AEs, those subjects were followed until the AEs were resolved or until 30 days after the 6 month follow-up visit. If the condition was ongoing 30 days after the 6 month visit the condition was considered on-going.

3.5.3.2. Follow-Up for Medical Management

Medical Management subjects were required to have 3 visits corresponding to their 1, 3, and 6 month follow-up period with all study-related procedures completed before subject participation in the study was considered completed.

Crossover ablations could occur no sooner than 4 months after randomization. Subjects that were initially randomized to Medical Management that crossed over to receive an ablation procedure followed the same follow-up visit schedule for subjects initially randomized to Ablation Management.

3.6. Adverse Events, Serious Adverse Events and Unanticipated Adverse Device Effects

3.6.1. Protocol Definitions of Adverse Events

AEs, SAEs, SADEs and any unanticipated adverse device effects (UADEs) were assessed and reported using protocol definitions, beginning with the date of randomization. AEs were coded according to a pre-specified list of codes defined with input from the Scientific Advisory Board.

The following AE definitions were used by study centers:

- An AE was defined as any untoward medical occurrence for a subject.
- An Adverse Device Effect (ADE) was defined as any untoward and unintended response to a medical device.
- Serious Adverse Events (SAEs) were defined as any adverse event:
  - Resulting in death
  - Which is life-threatening
  - Resulting in a significant incapacity
  - Resulting in a disability that requires hospitalization (initial or prolonged)
  - Resulting in an intervention to prevent permanent impairment/damage
- A Serious Adverse Device Effect (SADE) was defined as an adverse device effect that results in any of the consequences characteristic of a SAE or that might have led to any of these consequences if suitable action had not been taken, if intervention had not been made, or if circumstances had been less opportune through the follow-up phase. SADEs were recorded for both index and retreatment ablation procedures for the 7-day post-procedure follow-up period.

Disability/incapacity was defined as a substantial disruption of a person's ability to conduct normal life functions. A life-threatening adverse event meant that the study subject was at a substantial and immediate risk of dying due to that AE as it occurred.

All AEs (serious and non-serious) were recorded on the Adverse Event CRF. Specific data about the event including onset date, investigator-determined relatedness, description, treatments rendered and resolution were captured by investigative centers and entered into the electronic database. A planned hospital admission or unscheduled medical visit for AF that occurred within the follow-up period (DC cardioversion, in-patient medication change, or ablation) did not constitute an SAE but was reported as an additional intervention to the management of persistent AF. In the event that the subject suffered an untoward or unanticipated complication as a result of the arrhythmia (i.e. thrombotic event, pulmonary edema, etc.) an AE would be reported. AEs were also reported if a condition developed from a new or recurrent arrhythmia that manifested with symptoms other than those that were allowed for the study (Refer to Section 4.3.2.2 Baseline AF Symptoms).

UADEs were also assessed in the study. UADEs were any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the subjects.

The Data and Safety Monitoring Board in accordance with the CEC/DSMB Charter adjudicated all potential SAEs and made the final decision concerning categorization.

3.6.2. Clinical Events Committee / Data and Safety Monitoring Board

The CEC/DSMB had the responsibility to independently review and comment on all data and safety aspects of the trial and make recommendations based on their findings. Refer to **Section 3.9.2.3** regarding the CEC/DSMB's adjudication responsibilities. Their recommendations could also include termination of the trial. All recorded minutes of their actions were kept on file and are available for review as requested. Members of the CEC/DSMB committee charter, meeting dates to develop their charter, review of study progress, adjudicated adverse events, a list of meeting attendees, and the content of the AE meetings is summarized in **Appendix 3**.

3.7. Objectives

3.7.1. Primary Effectiveness Outcome

The primary endpoint for chronic effectiveness was the evaluation of the proportion of ITT subjects with treatment success computed at the 6 month visit.

3.7.1.1. Effectiveness Outcome Measurement

In order to be classified as a chronic success, both the Ablation and Medical Management subjects were required to achieve a 90% or greater reduction in clinically significant AF by the 6 month visit based on a 48-hour Holter recording. Clinically significant AF was defined as a sustained (symptomatic or asymptomatic) AF episode lasting for longer than 10 consecutive minutes in duration.

Subjects in Ablation Management were also required to meet the following endpoints to be classified as Chronic Treatment Successes:

- The subject was off all Class I or III AADs at the 6 month follow-up.
- All procedures (index and retreatment) conducted on a subject during the treatment period were deemed acutely successful. The criteria for defining acute success are described in detail in **Section 5.3.1**.

3.7.1.2. Chronic Efficacy Endpoint Analysis

The statistical analysis of the chronic efficacy endpoint consisted of a between treatment group comparison of the proportion of subjects achieving treatment success and is defined further in Section 4.2.1 of the v1.2 Statistical Analysis Plan (**Appendix 4**).

The primary effectiveness endpoint was tested on a protocol specified ITT basis using a chi-square test of homogeneity at a one-sided α=0.025 (two-sided α=0.05 level of significance). The hypothesis for superiority of the Medtronic Cardiac Ablation System relative to optimal medical management was:

$$H_0 : p_A \leq p_M \quad vs. \quad H_a : p_A > p_M$$

where p_A = the proportion of successfully treated subjects in Ablation Management and p_M = the proportion of successfully treated subjects in Medical Management. The primary efficacy analysis was evaluated at the significance level of 0.0245 (one-sided). Passive missing value imputation was used for both treatment groups in the computation of the test statistic.

The occurrence of a new arrhythmia such as atrial flutter or atrial tachycardia was not considered a treatment failure, but instead was categorized and reported separately (**Section 6.6.4)**.

3.7.2. Primary Safety Outcomes

3.7.2.1. Acute Safety Endpoint

The primary endpoint for acute safety was a success/failure variable calculated for each subject in Ablation Management at the 7 day post-procedure time point. Any subject with at least one AE adjudicated by the CEC/DSMB as both serious and either probably or definitely procedure (SAE) and/or device-related (SADE) occurring within 7 days post-procedure was considered an acute safety failure, regardless of whether the event occurred following the index or retreatment ablation procedure.

3.7.2.2. Acute Safety Endpoint Analysis

The statistical analysis of the acute safety endpoint consisted of a comparison of the proportion of Ablation Management subjects failing to complete the 7-day post-procedure period without an SADE and a historical control SADE rate. An acceptable safety endpoint target value was based on a review of literature (dated between 2001 and 2006) consisting of a meta-analysis evaluating safety associated with left atrial AF ablation and on review of approved ablation procedures for right-sided atrial flutter which is described in more detail in Appendix 5 of the TTOP-AF protocol. Using the information obtained from the literature review, a historical control maximum rate for SADEs was defined at 16%, as this was the highest approved one-sided 95% confidence bound allowed for a right-sided procedure.

The acute safety objective was determined with a protocol-specified ITT analysis using an exact, one-sample binomial test at a one-sided α=0.025 level of significance. The hypothesis was that the proportion of acute safety failures in Ablation Management was statistically significantly lower than the objective performance criterion of 16%:

$$H_o\text{: } p_A \geq 0.16 \text{ vs. } H_a\text{: } p_A < 0.16$$

where p_A = the proportion of acute safety failures in Ablation Management. Passive missing value imputation was used in the computation of the test statistic. Further definition regarding the analysis for acute safety is defined in Section 5.2.1 of the Statistical Analysis Plan (**Appendix 4**).

3.7.2.3. Chronic Safety Endpoint

The primary endpoint for chronic safety was a success/failure variable calculated for each subject at the 6 month time point. Any subject that had at least one AE that met designated seriousness and relatedness criteria for the particular treatment group (defined below) as adjudicated by the CEC/DSMB was considered a chronic safety failure. The AEs in Ablation Management that were acute (≤7 days) were not included in the calculation of the chronic safety primary endpoint.

The definitions of AEs that characterized a subject as a chronic safety failure were as follows:

- Ablation Management – Events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the ablation procedure (SAEs) and/or the device (SADEs) during the 6 month follow-up period (excluding the first 7 days post-procedure).
- Medical Management – Events adjudicated by the CEC/DSMB to be both serious and either probably or definitely related to the AADs, or events related to AF during the 6 month follow-up period.

The occurrence of a new arrhythmia such as atrial flutter or atrial tachycardia was not considered an AE, but instead were categorized and reported in a separate table within **Section 6.6.4** of this report. Hospital admissions to treat these arrhythmias (cardioversion and ablation) did not

constitute an SAE but were reported as an additional intervention to the management of persistent AF.

3.7.2.4. Chronic Safety Endpoint Analysis

The statistical analysis of the chronic safety endpoint consisted of a between treatment group comparison of the proportion of subjects failing to remain free of serious procedure and device-related events during the entire 6 month follow-up period.

The follow-up period was defined as 6 months post-randomization for Medical Management subjects. However, since subjects in Medical Management were allowed to crossover to receive an ablation procedure after 4 months of unsuccessful medical therapy, the 6 month endpoint could be shortened by up to two months for these subjects. The follow-up period for subjects in Ablation Management was defined as the time from randomization until 6 months following the last ablation procedure. However, the 7 day post-procedure window following each ablation procedure was not included in the Chronic Safety Endpoint analysis.

Given the disparity in the length of time at risk, and the expected low rates of SAEs in Medical Management, the chronic safety endpoint was not powered to detect a statistically meaningful result.

The chronic safety objective was tested on a protocol-specified ITT population using the chi-square test of homogeneity conducted at a one-sided α=0.025 level of significance. The hypothesis of non-inferiority of the Medtronic Cardiac Ablation System relative to optimal medical management was:

$$H_0: p_A \geq p_M + 6\% \text{ versus } H_a: p_A < p_M + 6\%$$

where p_A = the proportion of failed subjects in Ablation Management and p_M = the proportion of failed subjects in Medical Management. Passive missing value imputation was used in both groups for the computation of the test statistic. Further definition regarding the analysis for acute safety is defined in Section 5.2.1 of the Statistical Analysis Plan (**Appendix 4**).

3.7.3. Secondary Objectives

The following secondary endpoints are intended to provide additional data on the Medtronic Cardiac Ablation System. For subjects who had a retreatment procedure, data from the most recent ablation procedure is included in these secondary analyses. Acute effectiveness had a pre-specified hypothesis identified in the Statistical Analysis Plan (Section 4.2.2) for subjects randomized to Ablation Management. For all other secondary endpoints no established performance criterion was identified, therefore, descriptive statistics are presented (Section 4.2.2 in the Statistical Analysis Plan) (**Appendix 4**).

3.7.3.1. Acute Effectiveness

Acute efficacy was determined as a treatment success/failure endpoint for each subject in Ablation Management at the time of the ablation procedure. A subject was considered successfully treated if all of the following were true:

- Medtronic ablation catheters were used to achieve procedure success.
- All accessible pulmonary veins were isolated.
- A minimum of 50% reduction of CFAEs and high frequency intracardiac electrogram amplitudes were mapped and ablated with Medtronic ablation catheters.
- Sinus rhythm was achieved upon leaving the electrophysiology lab (± DC cardioversion).

Procedure data were captured on CRFs that included ablation time by catheter, whether or not pulmonary veins were isolated, and if septal/left atrial wall CFAEs were eliminated. Documentation of sinus rhythm after the procedure was acquired by rhythm strips or a12-lead electrocardiogram using the electrophysiology laboratory recording system.

For subjects that received a repeat ablation procedure, both the index and repeat ablation procedure had to be deemed acute successes for the subject to qualify as an acute efficacy success. However in the case of a retreatment procedure, the requirement for a minimum of 50% reduction of CFAEs using Medtronic ablation catheters was not required for the treatment to be deemed an acute success.

3.7.3.1.1. Acute Effectiveness Analysis

The statistical analysis of the acute effectiveness endpoint consisted of a comparison of the proportion of subjects achieving acute treatment success with a target success rate of ≥90%. An exact, one-sample binomial test was conducted at a one-sided α=0.05 level of significance to test the following hypothesis that the percent of successes is equal to or greater than 90%:

$$H_0 : p_A \leq 0.90 \quad vs. \quad H_a : p_A > 0.90$$

where p_A = the proportion of acutely successful subjects in Ablation Management. Further definition regarding the analysis for acute safety is defined in Section 4.2.2 of the Statistical Analysis Plan (**Appendix 4**).

3.7.3.2. Secondary Safety Variables

The secondary safety variables for this study are:

- All adverse events
- Acute safety endpoints evaluated by pooled site
- Chronic safety endpoints evaluated by pooled site

AEs were observed for each subject from enrollment until the termination of the study. The CEC/DSMB adjudicated each AE for device relatedness and classification as serious/non-serious or a nonevent.

3.7.3.2.1. Secondary Safety Analysis

All Adverse Events

Counts and percentages of subjects reporting at least one occurrence were summarized for each AE by treatment group.

Acute Safety Endpoints by Subgroup

After pooling of sites using the site pooling algorithm described in Section 2.5 of the Statistical Analysis Plan, a chi-squared test of homogeneity of acute safety failure proportions across study sites was conducted. The test was conducted at the two-sided α=0.15 level of significance.

Acute safety results were also analyzed by gender.

All subgroup analyses were performed on the ITT population with passive missing value imputation. Further definition regarding the analysis for the subgroup acute safety is defined in Section 5.2.2 of the Statistical Analysis Plan (**Appendix 4**).

Chronic Safety Endpoints by Subgroup

After pooling of sites using the site pooling algorithm described in Section 2.5 of the Statistical Analysis Plan, a Breslow-Day test of homogeneity of the odds ratios across study sites (site by treatment interaction) was conducted. The test was conducted at the two-sided α=0.15 level of significance.

Chronic safety results were also analyzed by gender.

All subgroup analyses were performed on the ITT population with passive missing value imputation. Further definition regarding the analysis for the subgroup acute safety is defined in Section 5.2.2 of the Statistical Analysis Plan (**Appendix 4**).

3.7.3.3. Other Secondary Objectives

The following are a list of other secondary objectives that were evaluated as part of the TTOP-AF study.

3.7.3.3.1. Chronic Efficacy Evaluated by Pooled Site

After pooling sites using the site pooling algorithm described in Section 2.5 of the Statistical Analysis Plan (**Appendix 4**), a Breslow-Day test of homogeneity of the odds ratios across study sites (site by treatment interaction) was conducted on the chronic efficacy endpoint. The test was conducted at the two-sided α =0.15 level of significance.

Chronic efficacy results were also analyzed by gender.

All subgroup analyses were performed on the ITT population with passive missing value imputation. Further definition regarding the analysis for the subgroup acute safety is defined in Section 4.2.2 of the Statistical Analysis Plan (**Appendix 4**).

3.7.3.3.2. Left Atrial Diameter

Left atrial diameter (LAD), as measured by TTE looking at the longitudinal long axis, was captured at baseline and at the 6 month follow-up visit in both Ablation and Medical Management. Echocardiograms were read by the investigational site and LAD was transcribed to CRFs.

3.7.3.3.3. Left Ventricular Ejection Fraction

Left ventricular ejection fraction (LVEF), as measured by TTE, was captured at baseline and 6 months in Ablation and Medical Management. Echocardiograms were read by the investigational site and LVEF was transcribed to CRFs.

3.7.3.3.4. Symptom Severity Score

Subjects were asked to rate the severity of AF-related symptoms (protocol- specified), on a scale from 1 (no symptoms) to 5 (most severe), during each follow-up visit. The symptoms included palpitations, fatigue, shortness of breath, lightheadedness or dizziness, and lack of energy during exertion or exercise. The scores were tabulated at the 1, 3 and 6 month follow-up visits. Scores could range from 5 to 25, indicating a spectrum of subject status from asymptomatic to severely symptomatic.

3.7.3.3.5. Quality of Life

Subjects in both treatment arms completed quality of life questionnaires at each follow-up visit. The SF-36 questionnaire was administered to subjects at baseline, 1 month, 3 and 6 month follow-up visits. Each subject recorded their responses on source worksheets that were provided to them by study staff.

3.7.3.4. Other Secondary Endpoint Analyses

Analyses of LAD, LVEF, AF Symptom Severity Score, and all Quality of Life scores from the SF-36 Health Survey were performed as a repeated measures analysis of variance with the baseline value as a covariate, treatment group as a fixed effect and visit (time) as a repeated measurement. The analyses of these secondary endpoints are defined further in Sections 4.1.2 and 4.2.2 of the Statistical Analysis Plan (**Appendix 4**).

3.8. Statistical Methods

3.8.1. Sample Size

This study was powered for the chronic effectiveness endpoint and for the acute safety endpoint. It was not powered for the chronic safety endpoint as detailed in Appendix 5 of the protocol. In order for the study to be considered a success, both the acute safety and chronic efficacy endpoints needed to be statistically significant. The chronic safety endpoint needed to be clinically acceptable, but not necessarily statistically significant. The sample size calculation methods are detailed below.

3.8.1.1. Chronic Effectiveness Endpoint

For the chronic effectiveness endpoint, with a 2-to-1 treatment group allocation, in order to have an 80% chance of detecting a 20% increase in treatment success in Ablation Management relative to Medical Management if, in fact, that difference exists, would require n=93 subjects in Ablation Management and n=47 subjects in Medical Management. A treatment success rate of 10% for Medical Management was used for this sample size calculation (see Appendix 5 of the protocol). This sample size calculation was based on a two-sided α=0.05 level of significance and assumed the response data was from a binominal distribution.

3.8.1.2. Acute Safety Endpoint

For the acute safety endpoint, the goal was to verify that the proportion of subjects experiencing SADEs immediately after treatment in Ablation Management was lower than historical rates of SADEs. Based on the results of previous studies (see Appendix 5 of the protocol), the maximum rate of subjects observing SADEs was 16%. In order to have an 80% chance of showing that the acute SADE rate in Ablation Management is 8%, a sample size of n=135 subjects was required. This sample size calculation was based on a two-sided α=0.05 level of significance and assumed the response data was from a binominal distribution.

3.8.1.3. Overall Sample Size

In order to ensure adequate power for both the chronic effectiveness and acute safety hypotheses, with a 2-to-1 treatment group allocation, the sample sizes were increased to 140 subjects in the Ablation Management arm and 70 subjects in the Medical Management arm.

3.8.2. Statistical Methods

The majority of the statistical analyses were performed by StatKing Consulting, Inc. (Fairfield, OH). Some statistical analyses were also performed by Medtronic Ablation Frontiers statistical staff as well. Analyses were performed according to the Clinical Protocol (version AG), the Statistical Analysis Plan (version 1.2, dated July 2, 2009), and the following supplemental documents:

- Supplemental Data Analysis document, version 1.1, dated November 13, 2009
- Supplemental Population Analysis document, version 1.1, dated November 30, 2009
- Supplemental Long-Term Follow-Up Data Analysis document, version 1.0, dated March 10, 2010
- Supplemental Population Analysis document, version 1.0, dated November 16, 2009
- Supplemental Data Analysis document, version 1.2, dated March 30, 2011
- Supplemental Population Analysis document, version 1.2, dated April 5, 2011
- Supplemental Data Analysis II document, version 1.0, dated April 15, 2011
- FDA Responses-Long Term Follow-Up Data – Table Specifications Document, version 1.1, dated April 26, 2011

The Statistical Analysis Plan and all supplements are included in **Appendix 4.**

3.8.3. Analysis Populations

The analysis of the primary and secondary efficacy and safety variables, with the exception of SF-36 Quality of Life Measures, were conducted using each of the ITT, Evaluable for Efficacy (EE), and Per Protocol (PP) populations as defined in Section 2.2 of the Statistical Analysis Plan. The primary analysis and the remainder of the safety analyses will be on the ITT population. Each population is defined below:

ITT Population – The ITT population includes all study subjects that have been randomized. All data were analyzed according to the subject's assigned randomization group.

EE Population – The EE population includes all study subjects in the ITT population who complete the study with no major protocol deviations (specified in Section 4.4.5). All data were analyzed according to the subject's assigned randomization group.

PP Population – The PP population includes all study subjects in the ITT population who complete the study with no major protocol deviations (specified in Section 4.4.5). All data were analyzed according to the treatment actually received by the subject during the study.

Section 4.4.5 of this report contains a list of pre-specified major deviations that were used to define the EE and PP populations. After applying the pre-specified criteria, the EE population consisted of the same subjects as the PP population. For this reason, only the ITT and PP population results will be reported in this Clinical Study Report.

For analyses that are not pre-specified, methods are specified within the appropriate section.

3.8.4. Missing Data Conventions

A total of 4 missing value imputation techniques were used for the analysis of the primary endpoints (Section 2.3, Statistical Analysis Plan) (**Appendix 4**). The chronic efficacy, acute safety and chronic safety endpoints were statistically analyzed for each analysis population for each missing value imputation technique specified below.

Passive – All missing success/failure endpoints will be assumed failures for both treatment groups.

Best-case – All missing success/failure endpoints for Ablation Management subjects will be assumed successes and all missing success/failure endpoints for Medical Management subjects will be assumed failures.

Worst-case – All missing success/failure endpoints for Ablation Management subjects will be assumed failures and all missing success/failure endpoints for Medical Management subjects will be assumed successes.

Iterative – All missing success/failure endpoints in each treatment group will first be assumed failures. Then each failure will be changed to a success one at a time, first for one treatment

group and then for the other, in order to determine where the "break-even" point is in terms of detecting significance. See Section 2.3.2 of the Statistical Analysis Plan (**Appendix 4**) for details regarding this procedure.

The primary missing value imputation technique for all primary endpoint analyses is the passive method of imputation. All other missing value imputation methods were used solely for the purpose of sensitivity/robustness analysis.

3.9. Conduct of the Study (Quality Assurance of Data)

3.9.1. Study Responsibilities

3.9.1.1. Study Sponsor

The Sponsor, Medtronic Ablation Frontiers was responsible for the overall conduct of the trial, including ensuring that the clinical trial was conducted in compliance with GCP and all applicable regulatory requirements. Sponsor personnel followed approved Standard Operating Procedures in fulfilling study activities; including site selection, start-up and regulatory document maintenance activities as well as training of clinical site personnel. The Sponsor was responsible for the manufacturing, distributing and accounting for all experimental devices.

3.9.1.2. Investigator Selection, Responsibility, Training and Performance

Medtronic Ablation Frontiers selected qualified Investigators based upon training and experience in left atrial ablation procedures, and shipped devices only to participating Investigators. Each Investigator had a fully executed clinical contract, IRB/MEC approvals, a signed and dated curriculum vitae and a signed statement attesting to the Investigators' agreement to conduct the study in accordance to the investigational plan, applicable Federal regulations and other specific conditions of approval as may have been imposed by the local governing IRB. Financial disclosure information for all Investigators per 21 CFR Part 54 is provided in the PMA.

Study sites were determined to have a sufficient volume of patients available to allow timely enrollment of subjects into this study. The Sponsor monitored the Investigators for evidence of noncompliance with the signed agreements, investigational plan, or conditions included in approvals imposed by an IRB and took necessary steps to ensure such compliance.

3.9.1.3. Scientific Soundness

Many strategies for minimizing error and bias in the clinical study were utilized in the TTOP-AF pivotal trial. Subjects were qualified for study participation under inclusion and exclusion criteria and then randomized to treatment groups. Subjects were treated in accordance with study procedures administered consistently across all study sites by appropriately trained and skilled study staff. Study progress and protocol compliance were overseen by Medtronic Ablation Frontiers. Adverse events were formally adjudicated by an independent CEC/DSMB

committee (Section 3.6.2). Regular site monitoring and data quality standards were maintained throughout the study**.**

3.9.2. Independent Review Committees

3.9.2.1. Institutional Review Board / Medical Ethics Committees

The TTOP-AF Clinical Investigational Plan and all informed consent documents required prior IRB/MEC approval. Signed written informed consent was mandatory for all study subjects and was to be obtained prior to enrollment in the TTOP-AF Pivotal Trial in accordance with 21 CFR Part 50 and Good Clinical Practices. Each site provided Medtronic Ablation Frontiers with a copy of their original IRB/MEC approval letter and the IRB/MEC approved consent form. Documentation of continuing IRB annual renewals were provided as appropriate.

3.9.2.2. Scientific Advisory Board

The Scientific Advisory Board was formed to advise the Sponsor during early development of the Medtronic Cardiac Ablation System and assisted in composing the TTOP-AF Clinical Investigation Plan. The Board provided input on study endpoints and assisted in defining the subject population. Refer to **Table 2** for a listing of Scientific Advisory Board Members.

Table 2. Scientific Advisory Board Members

Scientific Advisory Board Member	Affiliated Center
Ken Ellenbogen, MD	Director of Cardiac Electrophysiology Virginia Commonwealth University Medical College of Virginia Hospitals 411 Wishart Court Richmond, VA 23229-7082 Tel: 804.828.7565
Hugh Calkins, MD	Director of Arrhythmia Service Johns Hopkins Hospital 1741 Circle Road Ruxton, MD 21204 Tel: 410.955.7405
Hakan Oral, MD	Professor & Director of Cardiac Electrophysiology University of Michigan Cardiology, B1F245 1500 E. Medical Center Drive Ann Arbor, MI 48109-0022 Tel: 734.936.8354
Fred Morady, MD	Professor of Cardiovascular Disease University of Michigan Cardiology, B1F245 1500 E. Medical Center Drive Ann Arbor, MI 48109-0022 Tel: 734.763.7392

Source: Clinical Study file

3.9.2.3. Clinical Events Committee / Data Safety Monitoring Board

The CEC/DSMB was formed to review and adjudicate all adverse events and oversee the conduct of the TTOP-AF clinical study. The Committee was comprised of independent physicians who were not participating in the clinical study but who had significant experience in the field of ablation management. The CEC/DSMB also included an independent biostatistician who was not a voting member. The biostatistician was responsible for facilitating the meetings and ensuring an accurate and consistent adjudication process. Refer to **Appendix 3** for the group's charter and operating principles that contains standardized definitions to ensure consistent adjudication.

The CEC/DSMB was responsible for adjudicating all AEs, including deaths, by determining the relatedness of each event to the:

- Subject's underlying disease,
- Ablation procedure,
- Investigational components of the ablation system, and
- Antiarrhythmic drug (AAD) therapy.

There were instances observed where an event could be determined as being related to 3 of the 4 groups. For purposes of reporting, if an event was related to more than one group, the event was

included in each group (e.g. an event probably related to an AAD and underlying condition would be noted in both groups).

Relatedness to the groups was assigned as not related, possibly related, probably related or definitely related. To add further clarity to the severity and potential long-term implications of a SAE, the CEC/DSMB classified all serious events into two categories using the following definition:

- Category I – Death or event with permanent impairment or injury
- Category II – Event with no permanent impairment as a result of an intervention or a self-resolving condition

AEs reported by the investigational site and presented to the CEC/DSMB could also be adjudicated by the committee as non-events. A non-event was classified as an occurrence determined to be minor in nature or not a safety event requiring adjudication. Non-events did not contribute to the primary safety endpoints but were recognized and tabulated in the AE section (**Section 7.8**).

In addition to event adjudication, the CEC/DSMB was also responsible for overseeing the conduct of the study. The CEC/DSMB could recommend to the Sponsor to continue the study as designed, continue the study with modifications, or to recommend stopping the study early based on safety reviews. The CEC/DSMB also reviewed primary chronic effectiveness and acute safety endpoint analyses conducted after pre-specified interim analysis criterion were met. Refer to **Appendix 3** for a summary of their interim recommendation.

3.9.3. Core Laboratories

Core laboratories used during the course of the study are detailed in **Appendix 5**.

3.9.3.1. Imaging Core Laboratory

All medical images and off-site radiological assessments were managed by eImage, Inc. (eImage), an independent medical imaging core laboratory. Two board-certified radiologists selected based upon their experience and knowledge in evaluating MRI or CT scans, performed an independent radiology review of the images for pulmonary vein stenosis. Reviewers were not made aware of study institution, site number, subject identification, clinical information, on-site evaluations or treatment. Reviewers were not blinded with regard to the chronology of the scans during the second read session. A blinded Read Monitor from eImage supervised the read session and maintained blinding throughout the course of the review session while assisting the radiologist with image viewing functions. The results of the independent radiological assessments were reported to the Sponsor representative and the designated statistical group.

The Reviewers made their independent determination as to the percentage of narrowing of the pulmonary veins for each subject's baseline and 6 month images. For any subjects demonstrating PV stenosis for any pulmonary vein at any imaging time point, a consensus read

between both radiologists occurred. Upon conclusion of the consensus read, only the agreed upon value representing the pulmonary vein stenosis value was reported in the final read database delivered to the Sponsor.

3.9.3.2. Holter Core Laboratory

CoreLab Partners, Inc. (formerly Medifacts International, Inc.) collected all baseline and 6 month 48-hour Holter recordings for chronic effectiveness endpoint analysis for both Ablation and Medical Management. Holter recordings were read from a compact flashcard that was couriered from the investigational sites. Baseline Holter summary reports were sent from CoreLab Partners to the investigational site and to the Sponsor prior to randomization to determine if study entrance criteria were fulfilled.

Holter recordings were analyzed at CoreLab Partners using two unblinded Holter analysts. Initially, the data was analyzed by using software to determine the overall dominant rhythm and to identify pertinent arrhythmias. One Holter analyst then reviewed the software analysis and manually corrected any events wrongly identified by the software and to remove any artifacts. Three (3) examples of each event were included in the report. The following, if present, were always included:

- Pause – the longest plus two others
- Bradycardia – the longest, the slowest, plus one other
- VT and/or Salvo – the longest and fastest plus one other
- Bigeminy – the longest, plus two others
- Trigeminy – the longest, plus two others
- SVT – the longest, the fastest, plus one other
- Maximum heart rate
- Minimum heart rate
- Dominant rhythm – three examples
- Any other rhythms / AV blocks seen, to include transition examples (e.g. Sinus rhythm to AF or AF to sinus rhythm)

The second Holter analyst performed the following steps to review the quality of an analyzed Holter recording:

- Reviewed the subject demographics entered in the subject information fields for missing or incorrect data.
- Ensured appropriate study set-up was selected for the analysis.
- Reviewed strip list selections for appropriate labeling and capture of abnormalities.
- Performed a full disclosure page by page scan for any missed findings.
- Reviewed all information in the report for accuracy.
- If, as a result of the review, revisions were required, corrections were made and reviewed with the original Holter analyst for quality review.
- Final review of the analyzed Holter was completed and signed off by the cardiologist.

After both Holter analysts reviewed the data and the results signed off by a cardiologist, the recordings were sent to the investigational site and to the Sponsor. The statistical vendor (StatKing) was sent a master transfer of the Holter data in a secured file for endpoint analysis.

3.9.4. Monitoring

Monitoring of investigational centers was performed and included, but was not limited to: verification of inclusion and exclusion criteria; source document verification of protocol required data; review and verification of investigative device disposition log; review of written informed consent forms; review and documentation of AEs as required in each geography; and review and documentation of deviations to the Clinical Investigation Plan.

Three (3) contract monitors were used to review source documentation against the electronic case report form data entered into the NetRM electronic data capture system. A fourth contract monitor reviewed the source documentation against the paper case report forms for The Netherlands site. The monitors also reviewed the site's regulatory documents for completeness and GCP compliance.

One hundred percent (100%) source document verification was performed to ensure CRF accuracy. For each monitoring visit, monitors were required to sign a monitoring log kept at the site and also prepare a written report documenting their activities. Following each visit, monitors prepared a summary letter or email to the site summarizing the visit and any action items identified.

3.9.5. Data and Quality Management

3.9.5.1. Data Transmittal and Record Retention

Data obtained in the United States for this study was completed using electronic CRFs. The Netherlands site completed paper CRF forms. Once the monitor reviewed the data on the paper CRFs to source documents, photocopies of the paper CRFs were made and left at the site. The original CRFs were sent to Medtronic Ablation Frontiers and entered into the electronic database by a data entry person. Once all data had been entered into the electronic data capture system, a second person verified the entry by comparing the hard copy of the CRF to the data entered into the database. Once all entries were verified, the CRFs were filed in locked, filing cabinets as all information could be retrieved electronically, except for the CRFs obtained from The Netherlands. The paper CRFs from The Netherlands were filed in fireproof filing cabinets.

The database used during the TTOP-AF clinical study was developed and maintained by Parametric Technology Corporation (PTC), formerly NetRegulus. NetRM is an internet accessible, password protected electronic data capture system that allowed coordinators to enter data and study investigators to sign off study CRFs. The NetRM System was validated against functional specifications in accordance with 21 CRF Part 11.10(a). After training occurred, each user was provided with a user name and password from the Sponsor. Upon login, the user was

requested to change their password for security purposes. A full back-up of the data was conducted by PTC on a weekly basis, with periodic back-ups conducted on a nightly basis. The Strategic Information Group worked with PTC to provide customization to the NetRM system by automating coding functionality (i.e. protocol deviation codes, World Health Organization drug codes, adverse event coding). Finally, the Strategic Information Group prepared the data by updating any necessary scripts, running/testing the updated scripts, running/testing the java extract program and providing the results, for the statistical group, StatKing Consulting, Inc. for analysis.

3.9.5.2. Data Processing and Quality Control

After entry of CRF data into a central, controlled study database, a second data entry person verified the entries to complete the monitoring process.

Edit checks were performed to identify possible discrepancies, including blank fields, statistical outliers and date and unit inconsistencies. Each suspect data field identified by this process was corrected by reference to the original CRF. Sites received either a query notice from the electronic data capture system or a communication via phone or email for resolution of queries. If the CRF required changes, the database person would reopen the CRF for corrections. All actions were documented in the audit trail. A data clarification request (DCR) form was used for The Netherlands site to resolve queries. Once the DCR form was completed, it was sent back to the site in pdf format via email for them to complete, sign and return. Any changes were updated in the database and verified by a second person as described above. These processes continued repeatedly until all queries were resolved.

3.9.5.3. Managing Study Deviations

Deviations from the protocol that occurred during the course of the study were documented by study monitors during periodic site visits and by study personnel during edit checks. These findings were outlined in the summary monitoring reports and placed into the electronic database. Relevant findings were referred to the Sponsor for review and recommendations; re-training of site personnel and corrective actions were taken whenever necessary. **Section 4.4.5**, Protocol Deviations, provides a summary of the findings and **Appendix 6**, Protocol Deviations, provides a detailed listing of study deviations.

3.9.5.4. Confidentiality and Protection of Study Files

Subject confidentiality was maintained throughout the clinical study. Once informed consent was obtained, subjects enrolled in the study were assigned a unique identifier indicating the site number, the subject number and the subject's initials. All identifiers were listed on the subject screening log kept at each site. Any documents received by the Sponsor to support and/or provide source document verification were redacted and assigned the appropriate subject identifier. All other unique identifiers, for example, Social Security numbers, addresses, etc.

were also redacted as appropriate. All CRFs and study related documents were organized by site and subject and stored in locked filing cabinets.

All information and data sent to Medtronic Ablation Frontiers concerning subjects or their participation in this study was considered confidential. All data used in the analysis and reporting of this evaluation were used in a manner without identifiable reference to any subject enrolled in the study. Hard copies of all study documentation including CRFs were kept in a locked, secure location. Computer access for data entry, management and analysis was password protected and controlled according to responsibility.

3.9.6. Accountability of Investigational Devices

Medtronic Ablation Frontiers supplied each Investigator with an adequate number of investigational devices for completion of the study. Medtronic Ablation Frontiers maintained records for each site of the number of devices shipped, used and returned. Throughout the study, device accountability records were regularly reviewed by the contracted monitors. The Investigator was responsible for ensuring that the device accountability records were complete and up to date at all times. All devices used during the course of the study have been accounted for and documented (**Appendix 7**).

Appendix 10: SAEs

Serious Acute Safety Events for Medical Management Crossovers

Seven (7) Medical Management Crossover subjects experienced 7 acute SAEs that were adjudicated as being definitely-related to the procedure, of which none were probably- or definitely-related to the device. The acute serious adverse events for Medical Management crossover subjects are illustrated in **Table 1**.

Table 1. Acute Serious Adverse Events – Medical Management Crossovers

Description of Events	Number Acute AEs N=43 n
Probably or Definitely Related to the Investigational Devices	
No events	0
Probably or Definitely Related to the Procedure	
Transient ischemic attack	1
Hypotension post-ablation	1
Right groin hematoma	1
Cardiac tamponade	1
Pericardial effusion	1
Chest pain secondary to pericarditis	1
Pseudoaneurysm groin	1
Total	**7**