SPHERE-MAZE

A Randomized Controlled Trial of a Percutaneous Maze-like Catheter Ablation Strategy for Advanced Persistent Atrial Fibrillation

Protocol Version:	13.1
Date:	17 Nov 2026
Study Type:	Investigator-Initiated Research;
Funding	Funded in part by an unrestricted grant from Medtronic, Inc.
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ClinicalTrials.gov:	To be registered prior to enrollment

Protocol Version History

Version	Date	Description of Changes
1.0	Jan 2025	Original protocol draft
2.0	Jun 2025	Revised eligibility criteria; updated follow-up schedule
3.0	Jan 2026	Revised statistical section; added ILR arrhythmia burden methodology; updated safety definitions
4.0	May 2026	Major revision: Background & Rationale; ethical/monitoring/AE framework; Schedule of Assessments; procedural flowcharts; data management
5.0-8.0	May 2026	internal working drafts
9.0	May 2026	Primary endpoint revised to ordinal AF burden; statistical and procedural workflows updated
10.0	May 2026	Fixed N=100; power calculation, stratification and analysis rules revised; Trial Steering Committee and data-sharing statement added
11.0	May 2026	Echocardiography Acquisition Protocol added (Appendix E); LA diameter eligibility 40–60 mm; block-confirmation rules clarified
11.1	May 2026	Added an option for virtual visits at 1,2, 3, and 9 months
12.0	Jun 2026	Standard PWI in both arms; safety event list and consent updated; DSMB Charter incorporated (Appendix G)
12.2	Jun 2026	Helsinki-approved version (29 Jun 2026). Safety event list and conduction-injury window refined; POD 1 and discharge assessments added
12.3	Oct 2026	LAA thrombus-exclusion window extended to 8 weeks (CT preferred, TEE alternative); virtual-visit rules; PVI energy at operator discretion; CRFs separated from the protocol
12.4	07 Oct 2026	Internal working draft: CRF reconciliation; Schedule of Assessments split
12.5	09 Oct 2026	Internal working draft: monitoring rule, core-laboratory forms, ILR programming
12.6	13 Oct 2026	Internal working draft: adverse-event log and reporting periods
12.7	28 Oct 2026	DSMB Charter v1.7; randomization stratified by site only; mITT as the primary analysis population
12.8	31 Oct 2026	AF/AFL/AT burden and clinical-failure outcomes revised; monitoring completeness and analysis populations updated
13.0	13 Nov 2026	• Three-category primary outcome (AF/AFL/AT burden <0.1%; 0.1% to 1%; >1% or failure) over days 61–365; failure limited to

		repeat ablation or Class I/III antiarrhythmic drug initiation, re-initiation or escalation after blanking. • Death handled while alive; asymmetric monitoring rule for outcome classification. • Proportional-odds primary analysis; sample size justified on base-case distributions (Appendix B replaced); references for planning assumptions added [17–21]. • Binary failure composite added as key secondary outcome; drug-free failure sensitivity analysis added. • Repeat-ablation and antiarrhythmic drug trigger criteria revised (§10.5); PVI-energy subgroup removed. • Primary safety endpoint (descriptive composite of the Table 1 SAEs) replaces the safety benchmark. • Section 19 replaced by the SAE/AE definitions and reporting section: SAE Table 1 and AE Table 2 with event-specific time windows; AESI category removed; §15.2 and the pause triggers aligned. • POD 1 laboratory panel revised; coronary angiography and nitroglycerin provisions added. • DSMB reviews after the first 30 and 70 randomized patients; randomization-sequence firewall. • DSMB Charter v1.10 incorporated as Appendix G, with §6.3 and Appendix 5 (Safety Event Definitions) identical to Section 19. • Appendix D settings finalized; embedded CRFs (Appendix I) removed. • Phrenic nerve assessment protocol revised: sinus node and phrenic nerve localized before SVC isolation and the SVC–IVC line; SVC isolation ≥2 cm above the sinus node; line ≥2 cm posterior to the phrenic nerve, with phrenic capture rechecked after the line; imaging at operator discretion (§8.2, §8.5, §19.3)
13.1	17 Nov 2026	• Participants not blinded to treatment allocation (§4, §7.3, §15.4). The lateral mitral isthmus line remains the preferred mitral line; an anterior mitral line is permitted as an alternative in patients with significant anterior LA scar, in whom a lateral line followed by additional anterior ablation could result in LAA electrical isolation. One mitral line per patient; anterior-line block confirmed by differential pacing and/or activation mapping (Synopsis, §8.2, §8.4, §9.3, §13.4). Intracardiac echocardiography reintroduced as an alternative to pre-procedural CT or TEE for LAA thrombus exclusion, performed at the start of the index procedure before transseptal puncture; not part of the screening requirement before randomization (§9.1, §9.2, §12, Appendix A). AFEQT open-label limitation stated (§13.6). DSMB Charter v1.11: blinding statement aligned with §7.3 (Appendix G, Charter §14). • Statistical revisions (V. Novack): primary proportional-odds analysis without covariate adjustment (Synopsis, §7.1, §13.5); hurdle-model sensitivity analysis removed (§13.5); simulation-based power estimate removed from the SAP commitments (§13.3); statistician added to the title page.

Table of Contents

Protocol Version History 2
Table of Contents 5
1. Synopsis 9
2. List of Abbreviations 11
3. Background and Rationale 13
3.1 Burden of Atrial Fibrillation and Limitations of Current Therapy 13
3.2 The Cox-Maze Procedure as a Conceptual Framework 13
3.3 Percutaneous Maze-like Catheter Ablation 13
3.4 The Affera/Sphere-9 Platform 14
3.5 Benefit–Risk Assessment and Clinical Equipoise 14
4. Study Design 16
5. Study Objectives and Endpoints 17
5.1 Primary Objective 17
5.2 Secondary Objectives 17
5.3 Primary Endpoint 17
5.4 Secondary Endpoints 17
5.5 Safety Outcomes 18
6. Study Population 19
6.1 Inclusion Criteria 19
6.2 Exclusion Criteria 19
7. Randomization 20
7.1 Method 20
7.2 Procedure at the Time of Randomization 20
7.3 Blinding 20
7.4 Randomization Errors 21
8. Study Arms and Ablation Strategies 21
8.1 Control Arm: PVI + Posterior Wall Isolation (PWI) 21
8.2 Investigational Arm: Maze-like Biatrial Ablation 21
8.3 Programmed Stimulation and Isoproterenol Provocation (Both Arms) 23
8.4 Energy Delivery 23
8.5 Sinus Node and Phrenic Nerve Localization 23
9. Procedural Workflow 24
9.1 Pre-procedural Management 24
9.2 Procedural Setup 25
9.3 Mapping and Ablation 25
9.4 ILR Implantation 25
10. Post-operative Management, Blanking Period, and Repeat Procedures 26

10.1 Blanking Period 26
10.2 Antiarrhythmic Drug Management 26
10.3 Cardioversion 26
10.4 Redo Ablation and Treatment Failure 26
10.5 Criteria for Antiarrhythmic Drug Therapy and Repeat Ablation 27
11. Rhythm Monitoring, Core Laboratory, and Arrhythmia Burden Assessment 27
11.1 ILR Monitoring 27
11.2 Rhythm Core Laboratory (Shamir Medical Center) 27
11.3 Echocardiography Core Laboratory (Shamir Medical Center) 28
12. Follow-up Schedule 29
13. Statistical Considerations 30
13.1 Study Design and Hypothesis 30
13.2 Primary Endpoint Definition 30
13.3 Sample Size and Power 31
13.4 Randomization and Analysis Populations 31
13.5 Primary Endpoint Analysis 32
13.6 Secondary Endpoint Analyses 32
13.7 Handling of Missing Data 33
13.8 DSMB Safety Review 34
14. Atrial Mechanical Function by Strain Echocardiography 35
15. Data Safety Monitoring Board and Trial Steering Committee 35
15.1 DSMB Composition and Independence 35
15.2 Safety Monitoring 35
15.3 Safety Stopping Rule 36
15.4 Communication and Confidentiality 36
15.5 Trial Steering Committee 36
16. Ethical Considerations 36
16.1 Institutional Review Board / Ethics Committee Approval 36
16.2 Informed Consent 37
16.3 Study Registration and Data Sharing 37
16.4 Data Protection and Confidentiality 37
17. Study Monitoring 37
17.1 Oversight and Monitoring Plan 37
17.2 Site Initiation 38
17.3 Audit 38
18. Protocol Deviations 38
18.1 Minor Protocol Deviations 38
18.2 Major Protocol Deviations 38
18.3 Emergency Protocol Deviations 39

18.4 Consequences of Persistent Non-compliance 39
19. Adverse Event Reporting 39
19.1 Overview 39
19.2 Definitions 39
19.3 Safety assessments 41
19.4 Recording and reporting 41
19.5 Safety Pause Rule 41
20. Data Management 41
20.1 Case Report Forms and Electronic Data Capture 41
20.2 Subject Identification and Pseudonymization 42
20.3 Data Quality and Query Resolution 42
20.4 Data Security 42
20.5 Data Retention 42
20.6 Publication Policy 42
21. Expected Outcomes and Study Timeline 43
21.1 Expected Outcomes 43
21.2 Study Timeline 43
Appendix A: Schedule of Assessments 44
Appendix B: Pre-specified Outcome Distributions and Power 46
B.1 Pre-specified outcome distributions 46
B.2 Statistical power 46
Appendix C: References 47
Appendix D: ILR Programming and Configuration Specifications 48
Appendix E: Echocardiography Acquisition Protocol 50
E.1 General Information 50
E.2 General Requirements for All Examinations 50
E.3 Baseline Echocardiography Before Ablation 50
E.4 Local Site Acquisition Requirements for Core Lab LA Strain Analysis 51
E.5 Standardized CRF Parameter List (Examinations 1 and 2) 51
E.6 Core Laboratory LA Strain Analysis 53
E.7 Appendix E References 53
Appendix F: Informed Consent Form and Patient Information Sheet 54
Appendix G: Data Safety Monitoring Board Charter 55
Appendix H: Statistical Analysis Plan 72
Appendix I: Clinical Research Forms (CRF) 73

1. Synopsis

Full Title	A Randomized Controlled Trial of a Percutaneous Maze-like Catheter Ablation Strategy for Advanced Persistent Atrial Fibrillation
Short Title / Acronym	SPHERE-MAZE
Study Design	Prospective, multicenter, randomized, controlled, superiority trial
Sponsor	Investigator-initiated. Funded in part by an unrestricted research grant from Medtronic, Inc. The investigator (E. Anter, Shamir Medical Center) holds sponsor responsibilities under applicable national regulations.
Lead Institution / Coordinating Centre	Shamir Medical Center, Israel
Population	Patients aged 18–80 years with advanced persistent AF (AdPerAF): AF diagnosed >1 year, ≥1 AF episode 1–36 months in duration, CHA2DS2-VA ≥2, LA antero-posterior diameter 40–60 mm, undergoing first-time catheter ablation
Sample Size	100 patients (50 per arm) at 3–5 experienced Affera centers (international sites eligible)
Randomization	1:1, permuted-block randomization stratified by participating site only, administered via REDCap. Non-sequential 10-digit random study identifiers used for all blinded core-lab transfers.
Control Arm (n=50)	PVI (WACA) + Posterior Wall Isolation (PWI) using the Affera/Sphere-9 system
Investigational Arm (n=50)	Maze-like biatrial ablation: PVI + PWI + mitral isthmus line + SVC isolation + CTI line + anterolateral SVC–IVC line
Technology Platform	Affera mapping and ablation system with the Sphere-9 catheter (PFA and/or RFA) (Medtronic, Inc., Minneapolis, MN)
Rhythm Monitoring	Continuous ILR (Medtronic LINQ II™) implanted at index procedure; remote monitoring via CareLink™
Follow-up Duration	12 months (with a 60-day blanking period)
Primary Endpoint	The primary outcome is a three-category composite of AF/AFL/AT burden during days 61–365 and clinical treatment failure: category 0, burden <0.1% and no failure event; category 1, burden 0.1% to 1% and no failure event; category 2, burden >1% or any failure event (repeat ablation, or Class I or Class III antiarrhythmic drug initiation, re-initiation or escalation, after the 60-day blanking period; §5.3). Lower categories indicate better outcomes.
Key Secondary Endpoints	Ordinal AF-only burden; binary failure composite (category 2 versus categories 0 and 1); time to first AF/AFL/AT recurrence ≥6 minutes after blanking, with ≥30 seconds additionally reported; clinical treatment failure components; and AFEQT.

	Secondary analyses remain supportive without hierarchical testing or formal multiplicity adjustment.
Safety Endpoint	Primary safety endpoint: proportion of patients with at least one prespecified serious adverse event (Table 1, §19.2), each within its event-specific time window, reported by arm with 95% confidence intervals. Descriptive; no hypothesis testing.
Statistical Design	Superiority; proportional-odds ordinal logistic regression with treatment arm, without covariate adjustment, in the modified intention-to-treat (mITT) population. Two-sided α=0.05. Fixed N=100.
Statistical Power	Under the pre-specified base-case outcome distributions (Appendix B; common odds ratio 3.0), 45 evaluable patients per arm provide 80% power (two-sided α=0.05, Whitehead approximation); N=100 (50 per arm) allows for 10% attrition, and 50 evaluable patients per arm provide 84.5% power.
Core Laboratories	Rhythm and Echocardiography Core Laboratories at Shamir Medical Center, blinded to treatment allocation and organizationally firewalled from enrolling Shamir investigators.
Trial Oversight	Independent Data Safety Monitoring Board (two scheduled safety reviews, after the first 30 and the first 70 randomized patients complete ≥30 days of follow-up; ad hoc reviews as required) and Trial Steering Committee (PI plus two external members).
Estimated Timeline	Site initiation: 6 months · Enrollment: 18 months · Follow-up: 12 months · Analysis: 3 months

2. List of Abbreviations

AAD	Antiarrhythmic Drug	**ACT**	Activated Clotting Time
AdPerAF	Advanced Persistent Atrial Fibrillation	**AE**	Adverse Event
		AF	Atrial Fibrillation
AFEQT	AF Effect on Quality-of-Life Questionnaire	**AFL**	Atrial Flutter
ANCOVA	Analysis of Covariance	**AP**	Antero-Posterior
AT	Atrial Tachycardia	**AV**	Atrioventricular
BSA	Body Surface Area	**CHA_2DS_2-VA**	Composite Stroke-Risk Score
CRF	Case Report Form	**CRO**	Contract Research Organization
CS	Coronary Sinus	**CT**	Computed Tomography
CTI	Cavotricuspid Isthmus	**CVA**	Cerebrovascular Accident
DCCV	Direct-Current Cardioversion	**DSMB**	Data Safety Monitoring Board
EC	Ethics Committee	**ECG**	Electrocardiogram
eCRF	Electronic Case Report Form	**fps**	Frames Per Second
GCP	Good Clinical Practice	**ICE**	Intracardiac Echocardiography
ICF	Informed Consent Form	**ICH-GCP**	ICH Good Clinical Practice
ILR	Implantable Loop Recorder	**IRB**	Institutional Review Board
ITT	Intention-to-Treat	**IVC**	Inferior Vena Cava
LA	Left Atrium / Left Atrial	**LAA**	Left Atrial Appendage
LAVI	LA Volume Index	**LV**	Left Ventricle / Left Ventricular
LVEDD	LV End-Diastolic Diameter	**LVEDV**	LV End-Diastolic Volume
LVEF	LV Ejection Fraction	**LVMi**	LV Mass Index
MAR	Missing At Random	**MI (line)**	Mitral Isthmus (line)
MMRM	Mixed Model for Repeated Measures	**OAC**	Oral Anticoagulation
OR	Odds Ratio	**PFA**	Pulsed-Field Ablation
PP	Per-Protocol	**PV**	Pulmonary Vein
PVI	Pulmonary Vein Isolation	**PWI**	Posterior Wall Isolation
RA	Right Atrium / Right Atrial	**RFA**	Radiofrequency Ablation

RVSP	Right Ventricular Systolic Pressure	**RWT**	Relative Wall Thickness
SAE	Serious Adverse Event	**SAP**	Statistical Analysis Plan
SMC	Shamir Medical Center	**sPAP**	Systolic Pulmonary Artery Pressure
SR	Sinus Rhythm	**TAPSE**	Tricuspid Annular Plane Systolic Excursion
SVC	Superior Vena Cava	**TEE**	Transesophageal Echocardiography
TCL	Tachycardia Cycle Length	**TSC**	Trial Steering Committee
TIA	Transient Ischemic Attack	**VOM**	Vein of Marshall
TTE	Transthoracic Echocardiography		
WACA	Wide-Area Circumferential Ablation		

3. Background and Rationale

3.1 Burden of Atrial Fibrillation and Limitations of Current Therapy

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting more than 50 million individuals worldwide [1]. It is associated with a five-fold increase in stroke risk, a three-fold increase in heart failure, and a two-fold increase in all-cause mortality [2–4]. Persistent AF, defined as AF lasting longer than seven days or requiring cardioversion, accounts for a disproportionate share of AF-related morbidity, hospitalizations, and healthcare cost.

Catheter ablation targeting pulmonary vein isolation (PVI) is standard of care for symptomatic AF refractory to medical therapy. In paroxysmal AF, PVI achieves freedom from arrhythmia in 70–80% of patients at one year [5,6]. In persistent AF, particularly with prolonged AF duration, significant left atrial enlargement, and cardiovascular comorbidities, PVI alone yields freedom from AF in only 40–60% of patients at one year [5,7]. Outcomes worsen with longer AF duration and greater atrial structural disease.

The subgroup with advanced persistent AF (AdPerAF), defined in this protocol as AF diagnosed >1 year prior to enrollment, ≥1 AF episode(s) 1–36 months in duration, CHA2DS2-VA ≥2, and moderate left atrial (LA) enlargement (LA antero-posterior diameter 40–60 mm), represents a particularly challenging population in whom the role of extended substrate ablation beyond PVI remains contested. Empiric linear ablation, PWI, and complex fractionated atrial electrogram ablation have yielded inconsistent results, and no prospective randomized trial has established a superior strategy.

3.2 The Cox-Maze Procedure as a Conceptual Framework

The Cox-Maze procedure, first described in the late 1980s and subsequently refined, remains the most effective treatment for AF [8]. It creates a series of surgical incisions and cryoablation lesions that compartmentalize the atria into electrically isolated segments, preventing the macro-reentrant circuits that sustain AF while preserving sinoatrial node activity. Long-term data demonstrate freedom from AF in 85–95% of patients at five and ten years [9], including patients with long-standing persistent AF. Historical Cox-Maze rhythm monitoring relied on periodic ECGs and symptom reporting, so reported efficacy may overestimate continuous arrhythmia-free survival, but the procedural concept and electrophysiological rationale remain compelling.

Subgroup analyses from surgical series suggest that right-atrial lesion sets, including the CTI line and intercaval right-atrial lesions, are independent predictors of long-term freedom from AF, particularly in advanced atrial disease. This observation supports incorporating right-atrial lesion sets into a comprehensive percutaneous Maze-like strategy and provides the rationale for the biatrial approach in the SPHERE-MAZE investigational arm.

3.3 Percutaneous Maze-like Catheter Ablation

Until recently the principal barrier to replicating a Maze-like lesion set percutaneously has been the small footprint of conventional focal catheters. Point-by-point delivery requires many individual applications per linear lesion, prolonging procedure time and predisposing to gaps that promote reconnection and proarrhythmic macro-reentry. Two technological advances have changed this. First, the Sphere-9 catheter’s large spherical multielectrode footprint enables large-area, contiguous lesions with

substantially fewer individual energy applications. Second, pulsed-field ablation (PFA) removes a critical anatomical constraint [10,11]: PFA's selectivity for cardiac myocytes, sparing the esophagus , phrenic nerves, and surrounding structures, allows safe ablation across the posterior wall and the anteroseptal right atrium, both of which are core components of the surgical Maze but have historically been approached cautiously with thermal energy. Together these advances make a protocolized percutaneous Maze-like strategy feasible within a clinically acceptable procedure duration.

Non-randomized investigations and observational datasets have demonstrated the technical feasibility of biatrial catheter strategies incorporating left- and right-atrial lesion sets. Prospective randomized evidence comparing a standardized Maze-like catheter approach with contemporary standard-of-care PVI+PWI in AdPerAF is lacking.

3.4 The Affera/Sphere-9 Platform

The Affera mapping and ablation system with the Sphere-9 catheter (Medtronic, Inc., Minneapolis, MN) is an integrated next-generation platform that enables simultaneous high-density electroanatomical mapping and delivery of both PFA and radiofrequency ablation through a single multielectrode catheter [13]. The catheter's spherical multielectrode design supports both focal and linear lesion sets, including the posterior wall, mitral isthmus, and intercaval right-atrial lines required for a Maze-like approach. Integrated mapping enables real-time assessment of lesion formation and activation-based confirmation of conduction block. All participating centers have established experience with the Affera system, ensuring standardized procedural execution across sites.

3.5 Benefit–Risk Assessment and Clinical Equipoise

Study population and procedural context. All participants in SPHERE-MAZE are patients with AdPerAF who have a clinical indication for catheter ablation. The index ablation in both arms is performed within standard of care for this indication. The investigational arm introduces a more comprehensive biatrial lesion set relative to PVI+PWI, consistent with strategies already employed at experienced AF centers for advanced persistent AF.

Potential risks. The incremental risk associated with the investigational arm relates to the additional lesion sets in the left and right atria, specifically the mitral isthmus line, CTI line, SVC isolation, and anterolateral SVC–IVC line. Specific risks include prolonged procedure time with attendant anesthetic exposure; proarrhythmic substrate if linear lesions are incomplete; injury to the sinus node necessitating implantation of a permanent pacemaker; electrical isolation of the left atrial appendage, which may require implantation of a left atrial appendage occlusion device; theoretical impairment of atrial mechanical function from more extensive ablation; coronary vasospasm from energy delivery near coronary structures; SVC stenosis; and vagal injury near the SVC–IVC line.

Empirical biatrial lesion sets are already applied in real-world practice for this phenotype, including at Shamir Medical Center, where the observational dataset underpinning the investigational arm was generated. These risks therefore exist in current practice outside any study context. SPHERE-MAZE's contribution is to evaluate the lesion set within a protocolized strategy and rigorous RCT design, providing the first prospective evidence base. All risks will be monitored and reported to the DSMB; specific safety definitions appear in Section 19.

Potential benefits. The primary potential benefit of the investigational arm is a meaningful reduction in AF burden over 12 months of follow-up relative to PVI+PWI. The hypothesis is informed by the mechanistic rationale of the surgical Cox-Maze procedure, by clinical experience with biatrial ablation in AdPerAF at the participating centers, and by published persistent-AF ablation data. Additional potential benefits include reduction of symptomatic recurrences, improved quality of life, and reduced utilization of AADs and repeat ablation procedures. For a population in whom PVI+PWI achieves arrhythmia-free survival in only 40–60% of patients, even modest absolute improvements are clinically meaningful. All participants receive a structured, protocol-mandated follow-up program with continuous ILR monitoring (Medtronic LINQ II™) at no cost, a level of cardiac surveillance beyond routine post-ablation care.

Clinical equipoise. Genuine clinical equipoise exists between PVI+PWI and biatrial Maze-like ablation for AdPerAF: both strategies are practiced internationally by experienced operators, neither has been shown to be superior in a prospective randomized trial, and contemporary guidelines do not endorse one approach over the other in this phenotype. Randomization is therefore ethically appropriate.

Overall benefit–risk conclusion. The investigational arm is conducted entirely within a clinically indicated catheter ablation using approved, commercially available technologies. The incremental procedural risk is proportionate to the potential benefit of substantially improved arrhythmia control in a population with high unmet need. Continuous ILR monitoring, structured follow-up, and independent DSMB and TSC oversight provide robust safeguards.

4. Study Design

SPHERE-MAZE is a prospective, multicenter, randomized, controlled, superiority trial comparing a Maze-like biatrial catheter ablation strategy with standard PVI + posterior wall isolation (PWI) in patients with AdPerAF undergoing first catheter ablation.

Study Type	Prospective, multicenter, randomized, controlled superiority trial
Population	100 patients with AdPerAF undergoing first-time catheter ablation
Randomization	1:1, permuted-block, stratified by site
Blinding	Operators and participants unblinded; Core Laboratory personnel and the primary statistical analyst blinded to treatment allocation; data labels use non-sequential 10-digit study IDs
Follow-up	12 months with 60-day blanking period
Sites	AF ablation centers experienced with the Affera system
Core Laboratories	Rhythm and Echocardiography Core Laboratories at Shamir Medical Center, organizationally firewalled from Shamir enrolling investigators
Trial Oversight	Independent DSMB and Trial Steering Committee
Funding	Partially by unrestricted research grant from Medtronic, Inc.
Registry	ClinicalTrials.gov, registered prior to first patient enrollment

5. Study Objectives and Endpoints

5.1 Primary Objective

To compare the effectiveness of a Maze-like biatrial catheter ablation strategy with standard PVI+PWI in patients with AdPerAF undergoing first-time catheter ablation, using a composite ordinal endpoint of total atrial tachyarrhythmia (AF/AFL/AT) burden and clinical treatment failure during days 61–365 after ablation, as measured by continuous ILR monitoring.

5.2 Secondary Objectives

To evaluate AF-only burden, treatment success as defined by the AFA-ARC consensus, time to first atrial tachyarrhythmia recurrence, the individual components of treatment failure, and AF-related quality of life. To characterize the safety profile of both ablation strategies and to compare procedural metrics, acute procedural success per lesion set, and atrial mechanical function.

5.3 Primary Endpoint

The primary endpoint is a composite ordinal outcome combining total atrial tachyarrhythmia burden (AF, atrial flutter, and AT) during the follow-up period from day 61 to day 365 after the index ablation, measured by continuous ILR and reviewed by the blinded Rhythm Core Laboratory, with clinical treatment failure. Each patient is assigned to one of three ordered categories, with lower categories indicating greater treatment success: Category 0 (success), AF/AFL/AT burden <0.1% and no failure event; Category 1 (low residual burden), AF/AFL/AT burden 0.1% to 1% and no failure event; Category 2 (failure), AF/AFL/AT burden >1% or any failure event.

A failure event is either of the following: (a) initiation, including re-initiation, or escalation of Class I or Class III antiarrhythmic drug therapy after the 60-day blanking period, (continuation of a previously prescribed drug without escalation does not constitute failure); or (b) repeat ablation for any atrial tachyarrhythmia after the 60-day blanking period. Electrical cardioversion, an AF/AFL/AT episode of any duration without one of these events, and repeat ablation during the blanking period are not failure events. A patient with a failure event is assigned to Category 2 regardless of measured AF/AFL/AT burden.

The 0.1% success threshold follows the Atrial Fibrillation Ablation Academic Research Consortium (AFA-ARC) recommendation for continuous monitoring, and the incorporation of clinical failure follows its recommendation for a composite effectiveness endpoint [16]. Treatment arms will be compared using a proportional-odds ordinal logistic regression model (Section 13).

5.4 Secondary Endpoints

Prespecified secondary endpoint :

1. Ordinal AF-only burden during days 61–365, reported as a secondary outcome. The corresponding category and failure-rule specification remain to be specified.
2. Time to first recurrence of any AF/AFL/AT lasting ≥6 minutes after the 60-day blanking period; ≥30 seconds will additionally be reported.
3. Binary failure composite: proportion of patients in category 2 of the primary outcome (AF/AFL/AT burden >1% or any failure event) versus categories 0 and 1.

4. Treatment failure as defined in §5.3: Class I/III AAD initiation/re-initiation or escalation after blanking, or repeat ablation after blanking.
5. Atrial mechanical function by atrial strain echocardiography at 6–9 months.
6. AF-related quality of life by AFEQT, comparing change from baseline at 12 months.

These secondary endpoints are intended to characterize the consistency, clinical relevance, and safety profile of the primary treatment effect. They will be analyzed without hierarchical testing or formal multiplicity adjustment; therefore, findings will be interpreted as supportive and hypothesis-generating.

Supportive / descriptive secondary endpoints:

- AF/AFL/AT burden, AF-only burden and organized AT/AFL burden as continuous variables during days 61–365, with 100% burden assigned from the date of any clinical failure onward. These are failure-penalized sensitivity measures, not purely measured arrhythmia burden.
- Proportion of patients with AF/AFL/AT burden <0.1%, <1%, <5%, <10%, and <25% during days 61–365.
- Longest episode of AF/AFL/AT (LEAF) during days 61–365.
- Proportion of patients receiving Class I or Class III antiarrhythmic drug therapy, and amiodarone specifically, at day 60 and at 12 months, by arm.
- Mechanism of recurrent organized AT/AFL, including lesion-set gap–related arrhythmias, as determined at any repeat procedure.
- Acute procedural success, defined as documented conduction block across all ablation lesion sets as per the rules in §8.2.
- Procedural metrics per procedure, summarized by arm: total procedure time, total fluoroscopy time, total number of energy applications, and energy modality used (PFA, RFA, or both).
- Healthcare utilization: arrhythmia-related hospitalizations and emergency-department visits over 12 months (per-patient counts and incidence).

5.5 Safety Outcomes

Primary safety endpoint: the proportion of patients with at least one serious adverse event listed in Table 1 (§19.2), each counted within its specified time window and irrespective of investigator-assessed relatedness (composite of prespecified procedure-related serious adverse events). Secondary safety outcomes: each Table 1 serious adverse event individually, the subset judged related to the ablation procedure, and the adverse events listed in Table 2. Safety outcomes are reported by arm with 95% confidence intervals and the between-arm risk difference. The study is not powered for safety, and no hypothesis testing will be performed.

6. Study Population

6.1 Inclusion Criteria

Patients must meet ALL of the following criteria:

1. Age 18–80 years at the time of consent.

2. Diagnosis of Advanced Persistent AF (AdPerAF), defined as ALL of: (a) AF diagnosed more than 1 year prior to enrollment; (b) ≥1 AF episode lasting at least 1 month and no longer than 36 months, documented by 2 ECGs / Holters at least 1 month apart; (c) CHA2DS2-VA score ≥2; (d) LA antero-posterior diameter ≥40 mm and ≤60 mm by transthoracic echocardiography (TTE) within 6 months prior to enrollment, measured per Appendix E.

3. Planned first catheter ablation procedure for AF.

4. Ability and willingness to provide written informed consent in accordance with applicable regulatory requirements.

6.2 Exclusion Criteria

Patients meeting ANY of the following criteria will be excluded:

1. Paroxysmal AF (self-terminating episodes lasting <7 days) as the predominant documented rhythm.

2. Persistent AF diagnosis of ≤1 year.

3. CHA2DS2-VA score <2.

4. Long-standing persistent AF with continuous AF duration >3 years.

5. LA antero-posterior diameter >60 mm or <40 mm by TTE.

6. Left ventricular ejection fraction (LVEF) ≤30%.

7. NYHA functional class IV heart failure at time of enrollment. NYHA class I–III is permitted.

8. Severe mitral valve disease (severe mitral regurgitation or any mitral stenosis).

9. Severe pulmonary arterial hypertension (estimated SPAP >60 mmHg).

10. Permanent pacemaker, ICD, or CRT device, including abandoned intracardiac leads.

11. Contraindication to systemic anticoagulation or catheter ablation.

12. Life expectancy <12 months due to non-cardiac illness.

13. Prior left atrial surgical or catheter ablation procedure for any indication.

14. Intracardiac thrombus identified on pre-procedural imaging.

15. Pregnancy

16. Inability or unwillingness to comply with study procedures, informed consent, or follow-up requirements.

7. Randomization

7.1 Method

Randomization will be performed using REDCap (Research Electronic Data Capture), a validated, GCP-compliant electronic platform with full audit trail logging and role-based access control. Randomization will be configured and administered centrally by the coordinating center (Shamir Medical Center) prior to study initiation.

The randomization sequence will use permuted blocks of variable size and will be stratified by participating site only. The randomization sequence is generated before study initiation by the primary statistical analyst, uploaded to REDCap and locked; after upload, the analyst has no access to the allocation list (§7.3).

Each enrolled patient will be assigned a non-sequential, 10-digit random study identifier generated by REDCap. Sequential identifiers (e.g., 001, 002) will not be used for any blinded data transfer. The linkage between local patient identity, site, treatment allocation, and study ID will be maintained only in secure site and coordinating-center logs.

7.2 Procedure at the Time of Randomization

Randomization will occur on the day of the index ablation, after confirmation of eligibility and completion of all baseline assessments, and prior to the patient entering the electrophysiology laboratory. The site investigator or delegate will access REDCap and obtain the assigned treatment arm. Treatment allocation and timestamped confirmation will be recorded in the CRF. Under no circumstances should the randomization module be accessed in advance of a confirmed eligible patient, or the randomization result withheld once generated. Any deviation must be reported as a protocol deviation. The web-based audit trail will capture date, time, and user identity for all randomization events.

7.3 Blinding

Operators and procedural staff will be unblinded to treatment allocation from the moment of assignment, as the assigned ablation strategy determines the procedural workflow and lesion set. Participants are not blinded to treatment allocation. Rhythm outcomes are assessed by continuous ILR monitoring and adjudicated by the blinded Rhythm Core Laboratory, and antiarrhythmic drug therapy and repeat ablation after the blanking period require the documented qualifying criteria in §10.5.
Rhythm Core Laboratory personnel, Echocardiography Core Laboratory personnel, and the primary statistical analyst will remain blinded throughout the study. Aggregate unblinded safety data will be available to the DSMB as specified in Section 15; efficacy data are not provided to the DSMB. DSMB safety reports are prepared by an independent unblinded statistician, who is not the primary statistical analyst, under a documented firewall (DSMB Charter §3, Appendix G). The primary statistical analyst, who generated the randomization sequence (§7.1), receives no treatment-coded outcome data before the primary database lock. The independent unblinded statistician works in a separate data environment and does not share unblinded data or reports with the primary statistical analyst.

Any disclosure of an individual participant’s treatment allocation to blinded personnel will be documented, including the reason, date, and personnel involved.

7.4 Randomization Errors

If a patient is randomized but subsequently found ineligible, the event will be documented and reported to the coordinating center within 5 working days. Such patients will be retained in the ITT population and, if they underwent the index ablation procedure, in the mITT population, and excluded from the PP population. No replacement randomization will be issued; the system continues with the next eligible patient.

8. Study Arms and Ablation Strategies

8.1 Control Arm: PVI + Posterior Wall Isolation (PWI)

Mandatory lesion sets in the control arm:

- PVI by wide-area circumferential ablation (WACA), targeting all four pulmonary veins bilaterally.
- PWI: a roof line connecting the left and right superior pulmonary veins and a floor line connecting the left and right inferior pulmonary veins, electrically isolating the posterior LA wall. Posterior-wall ablation is performed with PFA (see §8.4).

Successful PVI and PWI will be confirmed by pacing demonstration of entrance and exit block in sinus rhythm. A waiting period or isoproterenol/adenosine challenge for assessment of acute PV reconnection is not required: its utility in the setting of PFA is not established, and practice varies across centers.

In the control arm, CTI ablation may be performed if the patient has documented typical atrial flutter at any time prior to the procedure, or if CTI-dependent typical flutter is induced during programmed stimulation or isoproterenol provocation. CTI ablation must use RFA only. CTI ablation under these criteria reflects standard clinical care for documented or induced typical atrial flutter and is not considered a deviation toward the investigational lesion set. No other empiric substrate ablation is permitted in the control arm, including ablation of low-voltage areas, complex fractionated atrial electrograms, or any linear lesion sets not specified above, other than ablation of organized arrhythmias under §8.3.

8.2 Investigational Arm: Maze-like Biatrial Ablation

This strategy integrates left- and right-atrial lesion sets to reproduce the electrophysiological principles of the Cox-Maze procedure using a percutaneous approach. The goal is durable conduction block across defined anatomic corridors to compartmentalize atrial activation and prevent macro-reentry while preserving sinoatrial conduction.

Mandatory LA lesion sets:

- PVI, WACA approach, as in the control arm.
- PWI as in the control arm.
- A lateral mitral isthmus line will be created connecting the mitral annulus to the left pulmonary veins. Bidirectional block across the mitral isthmus line should be confirmed.

  <u>After creation of the lateral mitral isthmus line, these three options may occur</u>:

1. **Bidirectional block achieved after first endocardial pass**
   In this case, no additional CS applications are required, however operators may elect to add 2–3 additional PFA applications from the CS at the corresponding epicardial aspect of the line, using the designated CS PFA energy setting.
2. **Bidirectional block not achieved after first endocardial pass, but achieved after additional endocardial ablation**
   In this case, CS applications are required: 2–3 PFA applications from the CS at the corresponding epicardial aspect of the line, using the designated CS PFA energy setting.
3. **Bidirectional block not achieved despite additional endocardial ablation and CS ablation**
   In this rare case, operators may elect to perform Vein of Marshall (VOM) alcohol ablation as a bailout strategy, provided this is within their clinical expertise and institutional practice. Alternatively, particularly for operators or centers without experience in vein of Marshall alcohol ablation, the procedure may be stopped at this stage. Failure to achieve mitral isthmus block should be documented in the CRF.

Anterior mitral line: the lateral mitral isthmus line is the preferred approach. In patients with significant anterior LA scar, in whom a lateral line followed by additional anterior-wall ablation could result in electrical isolation of the LAA, the operator may instead perform an anterior mitral line. The choice is made before mitral line ablation begins, and the line type and reason are recorded in the Procedural CRF. Only one mitral line is performed per patient. The CS and VOM steps above apply to the lateral line only; failure to achieve block across an anterior mitral line is documented in the CRF. An anterior mitral line performed under these conditions fulfils the investigational lesion set and is not a protocol deviation.

- **Confirmation of mitral line block**: for the lateral mitral isthmus line, bidirectional block should include both of the following: First, pacing from the distal CS, inferior to the ablation line, while mapping the left atrial endocardium with the Sphere-9 catheter. Complete block in this direction should be supported by activation above the line propagating in a medial-to-lateral direction. Second, pacing from the Sphere-9 catheter on the medial side of the line (above the line) should demonstrate block in the opposite direction, evidenced by proximal-to-distal CS activation. Together, these findings establish bidirectional mitral line block. For an anterior mitral line, block is confirmed by differential pacing and/or activation mapping.

Mandatory RA lesion sets:

- SVC isolation, circumferential isolation within the SVC, always above the SVC–RA junction and at least 2 cm above the sinus node (§8.5).
- CTI line performed with RFA only; PFA is not used because of the risk of coronary vasospasm.
- Anterolateral SVC–IVC line, a longitudinal line along the anterolateral aspect of the RA connecting SVC and IVC, traversing the crista terminalis region. This replicates the RA component of the surgical Cox-Maze, which is conventionally placed along the lateral RA across the crista. The line is placed at least 2 cm posterior to the right phrenic nerve (§8.5).
- **Confirmation of SVC isolation**: documenting both entrance and exit block from the SVC.

- **Confirmation of CTI block**: activation mapping and differential pacing from both sides of the line.
- **Confirmation of block across the SVC–IVC anterolateral line** will be performed by positioning the CS catheter on one side of the line and pacing from an electrode adjacent to the line, while mapping activation on both sides of the line with the Sphere-9 catheter. Block will be supported by documentation of delayed activation across the line, with propagation occurring around, rather than directly across, the ablation line.

8.3 Programmed Stimulation and Isoproterenol Provocation (Both Arms)

In both arms, programmed stimulation will be performed at the completion of all pre-specified lesion sets. Isoproterenol infusion is encouraged in both arms to facilitate arrhythmia provocation, titrated to effect (defined as an increase in sinus rate of approximately 20 bpm above baseline). If a sustained, organized AT or AFL with a tachycardia cycle length ≥220 ms is induced during programmed stimulation or occurs spontaneously, it will be mapped and ablated in both arms.

Induced AF will not be targeted with additional empiric ablation in either arm; if AF is the only inducible arrhythmia, the procedure is considered complete once all pre-specified lesion sets and conduction block confirmations are documented.

8.4 Energy Delivery

Energy modality follows these rules:

- PWI in both arms, SVC isolation, and the anterolateral SVC–IVC line - PFA is mandatory.
- CTI line, RFA only; PFA is not used because of the risk of right coronary artery vasospasm.
- PVI - PFA or RFA, at operator discretion during the procedure; the modality used is recorded in the Procedural CRF
- Lateral MI line, endocardial ablation is attempted first (RFA or PFA at operator discretion); if bidirectional block is not achieved, CS ablation with PFA is performed; VOM alcohol ablation is permitted as a bailout; anterior mitral line: endocardial ablation only (RFA or PFA at operator discretion).

Energy delivery parameters will be consistent with approved device labelling and institutional practice.

8.5 Sinus Node and Phrenic Nerve Localization

- **Right atrial mapping:** The right atrial lesion sets are performed after completion of the left atrial lesion sets, with the patient in sinus rhythm. Before SVC isolation and the SVC–IVC line, the right atrium and SVC are mapped in sinus rhythm to localize the sinus node, which is tagged on the electroanatomic map.
- **Phrenic nerve localization:** The course of the right phrenic nerve is mapped by high-output pacing (10 mA/2 ms) from the Sphere-9 catheter, and sites of phrenic nerve capture are tagged on the electroanatomic map. Phrenic nerve capture can be identified during pacing despite neuromuscular blockade.
- **SVC isolation level:** SVC isolation is performed at least 2 cm above the tagged sinus node and always within the SVC, above the RA–SVC junction.

- **SVC–IVC line:** The line is placed at least 2 cm posterior to the tagged course of the right phrenic nerve.
- **Post-ablation check:** After completion of the SVC–IVC line, at the end of the procedure, phrenic nerve pacing is repeated to verify that the nerve can be stimulated as before ablation. Verification of phrenic nerve capture (yes / no) is recorded in the Procedural CRF.
- **Imaging:** Chest X-ray or fluoroscopic sniff test is performed at operator discretion (e.g., for new dyspnea) and is not mandatory in all patients.
- Any patient with documented diaphragmatic paralysis is re-imaged at 3 months; persistence beyond 3 months is an SAE and resolution within 3 months is an AE (§19.2, Tables 1 and 2).

Data collection and safety reporting: Phrenic nerve imaging and findings are recorded in the CRF and reported to the Data and Safety Monitoring Board (DSMB) as specified in §19.

9. Procedural Workflow

9.1 Pre-procedural Management

Preprocedural management of antiarrhythmic drugs (AADs) will be individualized by the treating physician in accordance with patient preference. Class I, Class III, and other AADs may be continued or discontinued before ablation.

Oral anticoagulation will be maintained without interruption through the procedure, consistent with guideline-based practice. For participants receiving a vitamin K antagonist, an INR within the therapeutic range (2.0–3.0) must be confirmed before the procedure.

Left atrial appendage (LAA) thrombus must be excluded in all participants before transseptal puncture. This requirement may be met by preprocedural cardiac computed tomography (CT) or transesophageal echocardiography (TEE), or by intracardiac echocardiography (ICE) at the start of the index procedure.

When preprocedural imaging is used, cardiac CT with a dedicated LAA thrombus assessment is preferred. TEE is an alternative method. Either study may be performed within 8 weeks before the index ablation, provided therapeutic oral anticoagulation is maintained without interruption from the date of imaging through the procedure. If anticoagulation is interrupted or becomes subtherapeutic after imaging, including an INR below 2.0 in participants receiving a vitamin K antagonist, CT or TEE must be repeated before the procedure.

When ICE is used as the primary method of thrombus exclusion, the assessment will be performed after randomization, at the start of the index procedure and before transseptal puncture. ICE is sufficient when the entire LAA is adequately visualized from one or more of the following catheter positions and thrombus can be confidently excluded: the pulmonary artery, the coronary sinus, or the right ventricular outflow tract (RVOT). If visualization is inadequate or the findings are equivocal, transseptal puncture may proceed only after thrombus has been excluded by TEE.

If thrombus is identified, study ablation will be deferred as specified below and any existing randomized allocation will be retained. A randomized participant who does not undergo the index ablation will

remain in the intention-to-treat (ITT) population and will be excluded from the modified intention-to-treat (mITT) population (§13.4).

Patients with suspected or confirmed LAA thrombus will not undergo study ablation until the thrombus has been excluded or resolved per standard care. Additional imaging with TEE, ICE, or CT may be performed at the operator's discretion to clarify equivocal preprocedural findings or to reassess suspected or confirmed thrombus.

Standard pre-operative laboratory testing will be performed per institutional protocol.

9.2 Procedural Setup

- All procedures will be performed under general anesthesia with neuromuscular paralysis.
- Intracardiac echocardiography (ICE) is recommended for transseptal guidance and catheter manipulation, and is required for LAA thrombus exclusion before transseptal puncture when pre-procedural CT or TEE has not been performed (§9.1).
- A single transseptal puncture and sheath will be used for left-atrial access. Additional transseptal access is permitted if clinically required.
- Systemic heparinization will be maintained with an ACT target of 300–400 seconds throughout the left-atrial portion of the procedure.

9.3 Mapping and Ablation

- Electroanatomical mapping may be performed during sinus rhythm, atrial pacing, or AF according to operator preference.
- Confirmation of block for each lesion set follows the rules specified in §8 (PVI/PWI/SVC: entrance and exit block by pacing; MI line, CTI line, anterolateral SVC–IVC line: activation mapping and/or differential pacing). Timing of confirmation during the case is at operator discretion; documented block prior to the end of the case is required for each lesion set; if mitral line block cannot be achieved despite the steps in §8.2, the failure is documented in the CRF.
- Restoration of sinus rhythm by ablation is not a procedural endpoint and is actively discouraged, as it may prematurely truncate the lesion set.
- Coronary angiography is not mandatory. Nitroglycerin may be administered at the operator’s discretion; prophylactic use, use for treatment, and any documented coronary vasospasm are recorded separately in the Procedural CRF.

9.4 ILR Implantation

The Medtronic LINQ II™ ILR will be implanted at the conclusion of the index ablation in all patients, prior to departure from the electrophysiology laboratory or before discharge. The ILR will be configured to detect and log atrial tachyarrhythmia episodes according to a standardized detection algorithm. The ILR implantation site and programming parameters will be standardized across all centers per the protocol-specified configuration document (Appendix D).

10. Post-operative Management, Blanking Period, and Repeat Procedures

10.1 Blanking Period

A 60-day blanking period following the index ablation will be applied for rhythm-burden analyses. Atrial arrhythmias during this period will not be counted toward the primary composite outcome, but all arrhythmia episodes, cardioversions, medication changes, and redo procedures will be documented in the CRF.

10.2 Antiarrhythmic Drug Management

AAD therapy may be continued during the blanking period. When clinically appropriate, discontinuation is encouraged by month 2 post-ablation, particularly for amiodarone. Initiation, including re-initiation after prior use, or escalation of Class I or Class III AAD therapy after the blanking period, which requires the criteria in §10.5, will be recorded in the CRF and will constitute a failure event for the primary endpoint (§5.3). Continuation of a previously prescribed antiarrhythmic drug without escalation does not constitute a failure event.

For this protocol, AAD escalation is operationally defined as:

(a) addition of a new Class I or Class III agent;

(b) switching from a Class I to a Class III agent, or vice versa; or

(c) dose increase of an existing Class I or Class III agent above the highest previously tolerated dose attempted before the index ablation.

Oral anticoagulation will be continued for at least 12 months following ablation in all patients, irrespective of rhythm outcome, consistent with ESC and ACC/AHA guidance for AF ablation in patients with CHA_2DS_2-VA ≥2 [5,14].

10.3 Cardioversion

Electrical or pharmacological cardioversion is permitted and encouraged during the study period when clinically appropriate. DCCVs during the blanking period will be documented descriptively. Electrical cardioversion after the blanking period, and atrial tachyarrhythmia episodes of any duration, do not by themselves constitute failure events; the arrhythmia contributes to measured AF/AFL/AT burden (§5.3). Pharmacological cardioversion with a Class I or Class III agent after the blanking period is captured as antiarrhythmic drug initiation (§10.2).

10.4 Redo Ablation and Treatment Failure

Redo ablation for any atrial tachyarrhythmia (AF, AT, or AFL) will be captured throughout follow-up. Redo ablation after the 60-day blanking period constitutes a failure event for the primary endpoint (§5.3); redo ablation during the blanking period is recorded but is not a failure event. The details of any redo procedure (timing, presenting arrhythmia, mapped mechanism, lesion sets performed, acute outcome, complications) will be captured in the CRF.

10.5 Criteria for Antiarrhythmic Drug Therapy and Repeat Ablation

After the 60-day blanking period, repeat ablation requires documented atrial tachyarrhythmia (AF, AFL, or AT) comprising an episode lasting >24 hours; the patient and treating physician make the final decision. Initiation or escalation of Class I or Class III antiarrhythmic drug therapy after the blanking period requires a documented sustained (>6 minutes) AF, AFL, or AT episode. The choice between antiarrhythmic drug therapy and repeat ablation is at the discretion of the treating physician and the patient's preference. Each decision will be recorded in the CRF with reference to the qualifying episode, and the Rhythm Core Laboratory will confirm that the criteria were met. Any antiarrhythmic drug initiation or escalation, or repeat ablation, that does not meet these criteria will still count as a failure event, will be recorded as a protocol deviation, and will be addressed in a pre-specified exclusion sensitivity analysis; whether exclusion applies to patients or events and the exact implementation must be specified by the study statistician before analysis.

11. Rhythm Monitoring, Core Laboratory, and Arrhythmia Burden Assessment

11.1 ILR Monitoring

Continuous rhythm monitoring will be performed using the Medtronic LINQ II™ implantable loop recorder, implanted during the index procedure. AF burden will be quantified as the percentage of total monitored time spent in AF during the evaluation period. Total atrial tachyarrhythmia (AF/AT/AFL) burden will be quantified analogously. Individual episode durations will be recorded as measured by the ILR without artificial capping (per-episode durations are not capped; burden remains bounded at 100% of monitored time by definition).

11.2 Rhythm Core Laboratory (Shamir Medical Center)

Additional Holter, emergency-department monitor, wearable or other rhythm recordings obtained during follow-up are logged with date, recording type, rhythm finding, documented duration and transmission status. Send de-identified tracings to the coordinating center for blinded Rhythm Core Laboratory adjudication. External recordings require interpretable rhythm and documented duration. Qualifying device-only detections are handled under the separate device-only recurrence rule in §11.2.

All rhythm data, including ILR transmissions, 12-lead ECGs, and any ambulatory rhythm recordings obtained during follow-up, will be reviewed and adjudicated centrally by the Rhythm Core Laboratory at Shamir Medical Center, blinded to treatment allocation. To preserve credibility despite the lead-site/coordinating-center/core-lab co-location, the Rhythm Core Laboratory operates under an organizational firewall: core-lab adjudicators do not enroll patients in the trial, do not have access to randomization or treatment-allocation logs, and operate under physically and administratively separate REDCap user roles. All blinded materials are labelled solely with the non-sequential 10-digit study identifier.

ILR data submission: At each follow-up visit, the site will perform a full ILR interrogation and transmit the complete episode log and stored electrograms to the Rhythm Core Laboratory via the Medtronic CareLink™ remote monitoring platform. Each transmission will be time-stamped and tracked in the study log. Sites without direct CareLink™ access will export ILR data electronically and transmit de-identified data to the coordinating center by secure file transfer within 48 hours of each follow-up visit.

AF/AFL/AT burden is the percentage of usable monitored time classified as AF/AFL/AT during days 61–365. The blinded Rhythm Core Laboratory corrects classifications when interpretable evidence is available; otherwise the device classification is retained provisionally and flagged as unverified. This is core-lab-reviewed burden incorporating unverified device classifications, not fully adjudicated burden. Confirmed and unadjudicable contributions are stored separately. Missing ECG storage does not by itself establish loss of monitored time or sinus rhythm. A single blinded rhythm reader reviews the available records. Second review is required when the burden estimate lies within the margin around 0.1% or 1% defined in the Rhythm Core Laboratory SOP, and otherwise occurs on request; record the referral reason, second reader and resolution. Use the Rhythm Core Laboratory Summary, Episode Adjudication Log and Daily Monitoring Log. Do not expose treatment allocation or lesion-set details to core-lab staff. First AF/AT/AFL recurrence after blanking includes qualifying device-only detections with documented rhythm classification, onset and duration of at least 6 minutes (with ≥30 seconds additionally reported). Record confirmed versus device-only status and the source identifier. A generic alert without documented qualifying duration and rhythm is insufficient. Repeat time-to-recurrence analysis using ECG-confirmed events only, retaining each participant in the risk set until their first confirmed event or censoring. Automatic detection does not assure capture of every 30-second episode.

ECG submission: 12-lead ECGs obtained at baseline, on Day 0 before the procedure, at POD 1, and at all follow-up visits (including ECGs obtained at a community clinic for virtual visits) will be transmitted to the Rhythm Core Laboratory as de-identified digital files (PDF or XML) within 7 days of each visit and reviewed for rhythm, PR interval, QRS duration, and relevant findings.

11.3 Echocardiography Core Laboratory (Shamir Medical Center)

Follow-up LA strain documentation includes reservoir (LASr), conduit (LAScd) and contraction (LASct) components in apical 4- and 2-chamber views and their two-view averages. Reservoir remains the prespecified strain outcome; conduit and contraction are exploratory. Record raw signed outputs, software sign convention and standardized positive magnitudes, using R-R gating. Record acquisition rhythm/heart rate, model, software version, frame rate, cycle identifiers and selection, tracking quality, excluded segments/reasons, analyzability by component/view, repeat requests, reader and dates. Average accepted beats within each view, then average the two valid views equally; do not substitute a single view for a two-view value. Retain single-view results descriptively. Aim to analyze the acquired three consecutive sinus beats; document any shortfall. Non-sinus-rhythm studies are not analyzed under the prespecified strain substudy. No baseline strain is added.

Two echocardiographic examinations are obtained for each patient:

- Baseline TTE before ablation is accepted in any rhythm. Rhythm and heart rate at TTE are mandatory CRF fields. This examination supports eligibility verification (LA antero-posterior diameter, LVEF averaged over ≥5 cycles, valvular function, estimated systolic pulmonary artery pressure) and must be performed and interpreted at the enrolling center on a GE Vivid system under Appendix E acquisition standards within 6 months before enrollment (§6.1). It is reported into the Pre-procedural CRF in accordance with Appendix E: the eligibility-critical parameters (LA antero-posterior diameter, LVEF, mitral regurgitation and stenosis grade, and estimated systolic pulmonary artery pressure) are mandatory and are verified by the site investigator against the echo report, and the remaining Appendix E.5 parameters are documented under the enrolling-center acquisition standards. Baseline atrial strain is not performed because patients are expected to be predominantly in AF, rendering atrial strain measurements unreliable.

- Follow-up TTE at approximately 6 months post-ablation (acceptable window 6–9 months), performed during stable sinus rhythm. The full study is reported into the CRF by the participating center, and raw-data DICOM images are transferred to the Echocardiography Core Laboratory at Shamir Medical Center for offline LA strain analysis by Dr. Marina Leitman.

Both examinations are reported using the CRF parameter list specified in Appendix E (Echocardiography Acquisition Protocol). The follow-up examination follows the Appendix E acquisition standards and must be acquired on GE Vivid systems (Vivid E95 preferred; Vivid S70 optional) and exported with raw data via USB. Studies deemed inadequate for strain analysis by the Core Laboratory will trigger a request for repeat acquisition within the protocol visit window. The Echocardiography Core Laboratory operates under the same organizational firewall as the Rhythm Core Laboratory (see §11.2).

12. Follow-up Schedule

Baseline NT-proBNP or BNP is mandatory; a missing value is a protocol deviation. Other baseline laboratory requirements remain unchanged; serum creatinine obtained within 3 months before the index procedure is required as the reference value for POD 1.

All patients will be followed for 12 months from the date of the index ablation. Protocol-mandated follow-up visits are summarized in Appendix A. The acceptable visit window is ±14 days for all protocol-mandated visits. Virtual visits (telemedicine) are permitted for some visits as detailed in Appendix A (Schedule of Assessments); in-person attendance is not required provided that ILR data can be transmitted remotely via CareLink™ and a structured clinical assessment can be completed. When a protocol-mandated 12-lead ECG falls at a virtual visit, it is obtained at a community clinic (e.g., Kupat Holim) within the visit window and transmitted to the Rhythm Core Laboratory (§11.2).

Key assessments at each visit:

- Baseline (prior to ablation): informed consent, medical history and baseline clinical characteristics, 12-lead ECG, standard transthoracic echocardiography (eligibility; enrolling center, within 6 months), pre-procedural LAA thrombus exclusion by cardiac CT (preferred) or TEE within 8 weeks, unless excluded by ICE at the index procedure (§9.1), AFEQT questionnaire, medication review, laboratory tests.
- Day 0 (Index Procedure): presenting rhythm and pre-procedural 12-lead ECG on admission, randomization, ICE exclusion of LAA thrombus before transseptal puncture when pre-procedural CT or TEE has not been performed (§9.1), ablation procedure, ILR implantation.
- POD 1: physical examination focused on the vascular access site, 12-lead ECG and overnight telemetry review, blood drawn 12–24 hours after the procedure for serum creatinine and NT-proBNP or BNP, predischarge medications review and AE assessment.
- 1 Month: clinic or telehealth visit; 12-lead ECG, ILR review and remote transmission, medication review, AE assessment.
- 2 Months: 12-lead ECG, ILR review, medication review; AAD discontinuation encouraged; AE assessment.
- 3 Months: 12-lead ECG, ILR review, medication review, AFEQT questionnaire, AE assessment.

- 6 Months: 12-lead ECG, ILR review, medication review, AE assessment. Atrial strain echocardiography acquired at 6–9 months (per §11.3).
- 9 Months: ILR review (remote transmission acceptable), medication review, AE assessment.
- 12 Months: 12-lead ECG, ILR review, medication review, AFEQT questionnaire, AE assessment, study completion.

Given the longevity of the Medtronic LINQ II™ ILR, participating sites may elect to continue remote ILR monitoring and clinical follow-up beyond 12 months. Any such extended follow-up is conducted outside the primary endpoint window and used for exploratory longer-term outcome analyses only.

13. Statistical Considerations

13.1 Study Design and Hypothesis

SPHERE-MAZE is a prospective, multicenter, randomized, controlled superiority trial. Patients are randomized 1:1 to Maze-like biatrial catheter ablation or standard PVI+PWI. The primary hypothesis is that the Maze-like biatrial strategy will produce a more favorable distribution of the composite ordinal outcome (AF/AFL/AT burden and clinical treatment failure) during days 61–365 after ablation compared with PVI+PWI.

The primary endpoint is based on total atrial tachyarrhythmia (AF/AFL/AT) burden because any recurrent atrial tachyarrhythmia, including organized AT or AFL, is clinically relevant to the patient, consistent with the AFA-ARC definition of ablation effectiveness [16]; AF-only burden is a key secondary outcome. Because the investigational strategy involves substantially more extensive ablation and procedural risk, the endpoint is designed so that a positive result reflects a clinically meaningful difference: the success category uses the stringent AFA-ARC threshold of <0.1% burden, and clinical failure (antiarrhythmic drug initiation or escalation, or repeat ablation, after blanking) is incorporated so that interventions that alter measured burden do not bias the comparison. The ordinal design uses more information from continuous ILR monitoring than a single binary responder endpoint.

All statistical tests will be two-sided with a nominal significance level of $\alpha = 0.05$ unless otherwise specified in the final Statistical Analysis Plan (SAP).

13.2 Primary Endpoint Definition

The primary outcome is the three-category ordinal composite defined in §5.3, which combines atrial tachyarrhythmia burden (atrial fibrillation, atrial flutter and atrial tachycardia; AF/AFL/AT) with clinical treatment failure during days 61–365 after the index ablation. Lower categories indicate better outcomes. A patient with a clinical failure event as defined in §5.3 is assigned to Category 2 in every analysis, regardless of measured burden.

Let M be non-overlapping usable monitored seconds, C confirmed AF/AFL/AT seconds, D unadjudicable seconds classified by the device as AF/AFL/AT, and U all unadjudicable candidate atrial-arrhythmia seconds, including D. Burden = $100 \times (C + D)/M$; lower bound = $100 \times C/M$; upper bound = $100 \times (C + U)/M$. Apply the three-category cut-points of §5.3, with known clinical failures assigned category 2 in every analysis. Review overlapping intervals once; do not add duplicate transmissions. Report D/M and U/M. Bounds address uncertainty among captured episodes, not undetected arrhythmia or missing

monitoring. If U cannot be recovered, report bounds as unavailable. The combined-rhythm implementation and failure-penalized continuous derivation require SAP specification.

The primary outcome is a three-category composite of AF/AFL/AT burden during days 61–365 and clinical treatment failure: category 0, burden <0.1% and no failure event; category 1, burden 0.1% to 1% and no failure event; category 2, burden >1% or any failure event under §5.3. Lower categories indicate better outcomes. Burden uses usable monitored time. The blinded Rhythm Core Laboratory corrects classifications when interpretable evidence is available; otherwise device classifications are provisionally retained and flagged. Confirmed and unverified contributions are stored separately. Missing ECG storage does not establish missing monitoring or sinus rhythm.

13.3 Sample Size and Power

The planned sample size is 100 patients (50 per arm). Sample size is constrained by the investigator-initiated funding framework and by feasibility of enrolling a highly selected AdPerAF population across 3–5 experienced Affera centers.

Pre-specified outcome distributions. Power is anchored to investigator-specified distributions of the three primary-outcome categories (category 0 / 1 / 2): control arm 25% / 25% / 50%; investigational arm (base case) 50% / 25% / 25% [17–21]. Under the proportional-odds model, the base case corresponds to a common odds ratio of 3.0 (Appendix B).

Power: Using the Whitehead (1993) normal approximation for the proportional-odds model with two-sided $\alpha = 0.05$, 45 evaluable patients per arm provide 80% power to detect the base-case effect, and 50 evaluable patients per arm provide 84.5% power. Enrollment of 100 patients (50 per arm) allows for 10% attrition. Therefore, the study is powered to detect a large but clinically plausible shift in the distribution of the composite outcome and should be interpreted as an investigator-initiated superiority trial designed to identify a meaningful treatment signal in a highly selected AdPerAF population.

Final SAP. The final SAP, finalised and registered prior to enrollment of the first patient, will pre-specify the operating characteristics of the primary analysis under additional plausible distributional shapes.

13.4 Randomization and Analysis Populations

- Modified Intention-to-Treat (mITT): all randomized patients who underwent the index ablation procedure, analyzed according to the randomized assignment irrespective of treatment received or follow-up completion. Primary analysis population.
- Intention-to-Treat (ITT): all randomized patients, irrespective of treatment received or follow-up completion. Sensitivity analysis population.
- Per-Protocol (PP): randomized patients who received the complete assigned lesion set (in the investigational arm, either a lateral or, under §8.2, an anterior mitral line) without major protocol deviation and meet the following monitoring rule. At least 80% of evaluation-window days must have evaluable ILR monitoring, and at least 75% of monitored days must have at least 6 usable monitoring hours. Apply this two-stage rule to primary burden evaluability and per-protocol eligibility. The definitions of evaluable and monitored day require final SAP specification. mITT retains all randomized patients who underwent index ablation, as randomized; ITT retains all randomized patients.

- Safety: all patients who underwent the ablation procedure and had at least one post-procedure assessment.

13.5 Primary Endpoint Analysis

The primary analysis compares the distribution of composite ordinal AF/AFL/AT burden and clinical-failure categories between treatment arms in the mITT population using a proportional-odds ordinal logistic regression model. The treatment effect is reported as a common odds ratio with 95% confidence interval and two-sided p-value; an OR > 1 favors the investigational arm (greater odds of being in a lower outcome category). Categories are coded 0–2 with lower values indicating better outcomes.

The proportional odds assumption will be assessed graphically and by the Brant test. If materially violated, the pre-specified sensitivity analysis is a non-parametric Wilcoxon–Mann–Whitney test on the ordered categories, with a stratified van Elteren version (by site) as an additional sensitivity. Per-protocol and ITT sensitivity analyses will repeat the primary ordinal analysis in the PP and ITT populations. A baseline-adjusted analysis additionally including LA diameter, AF episode duration, and age as continuous covariates, and rhythm at baseline TTE (AF / sinus rhythm / other) as a categorical adjustment covariate is pre-specified as a covariate-adjusted sensitivity, to improve precision and address residual imbalance. In all analyses of continuous burden, patients with a failure event are assigned 100% burden from the date of the event onward. A further sensitivity analysis applies the stricter AFA-ARC rule, under which any Class I or Class III antiarrhythmic drug use after the blanking period, including continuation, constitutes a failure event. A further pre-specified sensitivity analysis defines failure without the antiarrhythmic drug component (repeat ablation only); patients whose only failure event is antiarrhythmic drug initiation or escalation are classified by their measured burden.

13.6 Secondary Endpoint Analyses

Baseline reporting uses a focused main Table 1 plus a comprehensive supplementary baseline table. The main table includes age, sex, BMI, site, CHA_2DS_2-VA category, AF duration/episode duration, EHRA, NYHA, prior amiodarone, failed AAD count, LA diameter, LAVI, LVEF and rhythm at baseline TTE. All remaining collected baseline clinical, medication, laboratory and echo variables are listed in the supplement, with available denominators and missing counts. No between-arm baseline significance tests.

Secondary endpoints will be analyzed as prespecified supportive outcomes. No formal hierarchical testing procedure will be applied, and no adjustment for multiplicity will be made across secondary endpoints. Nominal two-sided p-values and 95% confidence intervals will be reported where appropriate. These analyses are intended to assess the consistency, clinical relevance, and safety profile of the treatment effect observed for the primary endpoint and will be interpreted as supportive and hypothesis-generating.

Methods. Ordinal AF-only burden will be analyzed using the same proportional-odds model as the primary endpoint. The binary failure composite (category 2 versus categories 0 and 1) will be compared using a site-stratified Cochran–Mantel–Haenszel test, with the risk difference and 95% confidence interval. Time to first recurrence will be analyzed by Kaplan–Meier analysis with a site-stratified log-rank test and a Cox proportional-hazards model adjusted for site. The treatment-failure composite will be

summarized as the proportion of patients experiencing any component and compared using a stratified Cochran–Mantel–Haenszel test; each component will also be reported separately. AFEQT change will be analyzed by ANCOVA on the 12-month score, with baseline AFEQT as a covariate; MMRM across 3- and 12-month visits will be performed as a supportive analysis. Because participants are not blinded to treatment allocation, AFEQT is a patient-reported outcome in an open-label design and will be interpreted with this limitation.

Supportive / descriptive analyses (not in hierarchy). AF/AFL/AT and AF-only burden as continuous variables, assigning 100% from clinical failure onward under §13.5: Wilcoxon rank-sum with Hodges–Lehmann estimator and 95% confidence interval (sensitivity to the ordinatization of the primary endpoint). Proportion of patients below each selected AF/AFL/AT burden threshold: descriptive only, compared with chi-squared or Fisher exact tests. Acute procedural success per lesion set: per-lesion success proportions summarized by arm; no between-arm composite test. Procedural metrics per procedure: parametric or non-parametric tests as appropriate. DCCVs and AAD escalation after the blanking period: per-patient incidence (≥1 event) as primary summary, with event counts modelled by negative binomial regression as sensitivity. Healthcare utilization: arrhythmia-related hospitalizations and ED visits summarized as per-patient counts and incidence. Safety endpoints: proportions with 95% confidence intervals. Atrial strain parameters at 6–9 months: between-arm comparison by t-test or Wilcoxon as appropriate. Primary safety endpoint (§5.5): proportion of patients with any Table 1 SAE, with each Table 1 SAE and each Table 2 AE also reported separately, by arm with 95% confidence intervals; no hypothesis test is performed and no claim of comparable safety is based on these outcomes; the scheduled DSMB safety reviews (§13.8, §15.2) and the safety stopping rule (§19.5) constitute the primary prospective safety safeguards.

Pre-specified subgroup analyses. Treatment effect on the primary endpoint will be reported within pre-specified subgroups defined by LA diameter (<50 mm vs. ≥50 mm), AF episode duration (<6 months vs. ≥6 months), age (<65 vs. ≥65 years), sex, and prior amiodarone use. Subgroup analyses are descriptive (forest plot with within-subgroup point estimates and 95% CIs) and are not adjusted for multiplicity. Analyses using baseline LA antero-posterior diameter, including the <50 vs ≥50 mm subgroup analysis, adjust for rhythm at baseline TTE (AF / sinus rhythm / other).

13.7 Handling of Missing Data

Missing primary data are minimized by ILR follow-up and core-lab review. Day 0 is the local index-procedure date; days 61–365 inclusive span 305 calendar days. At least 80% of evaluation-window days must have evaluable ILR monitoring, and at least 75% of monitored days must have at least 6 usable monitoring hours. Apply this two-stage rule to primary burden evaluability and per-protocol eligibility. The definitions of evaluable and monitored day require final SAP specification. Count actual usable monitoring time, not stored ECG or transmission connectivity. Sum all usable time, including days with less than 6 hours, for the measured-burden denominator. Exclude unrecoverable gaps; never replace them by sinus rhythm. Category 2 is assigned on any observed data when a documented clinical failure occurs or when observed AF/AFL/AT burden exceeds 1%. Categories 0 and 1 require that the monitoring requirement above is met; if it is not met, or burden cannot be reconstructed, and category 2 is not established, the primary category is missing for imputation. Retain partial data and reasons. Continuous failure-penalized analyses follow §13.5.

Primary handling of missingness in the primary endpoint analysis is under the missing-at-random (MAR) assumption using multiple imputation (50 imputations) with treatment arm, the stratification factor (site), baseline LA diameter, AF episode duration, and observed AF/AFL/AT burden in the available portion of the evaluation window as imputation predictors. Sensitivity analyses include: (a) complete-case analysis; (b) worst-category imputation for the investigational arm (tipping-point analysis to identify the missing-data assumption under which the result would no longer favor the investigational arm); and (c) inverse-probability-of-missingness weighting. Device malfunction or explanation prior to completion of the follow-up period is documented as a reason for missing data.

13.8 DSMB Safety Review

Two scheduled unblinded safety reviews by the independent DSMB are performed: after the first 30 randomized patients and after the first 70 randomized patients, have each completed ≥30 days of post-procedural follow-up (DSMB Charter §8, Appendix G). The DSMB examines the incidence, nature, and severity of serious adverse events, procedure-related complications, and protocol deviations and may recommend continuation, protocol amendment, temporary suspension, or early termination on safety grounds. Ad hoc reviews may be convened at any time on safety signals. No adaptive sample-size re-estimation is planned. No efficacy interim analysis or efficacy stopping boundary is pre-specified; early stopping for efficacy is not permitted under this protocol. The DSMB receives safety data only; efficacy data, including AF/AFL/AT burden and the primary outcome, are not provided.

14. Atrial Mechanical Function by Strain Echocardiography

LA mechanical function is assessed by atrial strain echocardiography at approximately 6 months after the index ablation (acceptable window 6–9 months). The follow-up examination is performed in stable sinus rhythm. Baseline atrial strain is not performed because patients are expected to be predominantly in AF at baseline, rendering atrial strain measurements unreliable; atrial strain in this study is therefore used for between-group comparison at follow-up rather than within-patient change.

Each center acquires images under Appendix E and transfers raw DICOM data to the blinded Echocardiography Core Laboratory for GE EchoPAC analysis. Follow-up LA strain documentation includes reservoir (LASr), conduit (LAScd) and contraction (LASct) components in apical 4- and 2-chamber views and their two-view averages. Reservoir remains the prespecified strain outcome; conduit and contraction are exploratory. Record raw signed outputs, software sign convention and standardized positive magnitudes, using R-R gating. Record acquisition rhythm/heart rate, model, software version, frame rate, cycle identifiers and selection, tracking quality, excluded segments/reasons, analyzability by component/view, repeat requests, reader and dates. Average accepted beats within each view, then average the two valid views equally; do not substitute a single view for a two-view value. Retain single-view results descriptively. Aim to analyze the acquired three consecutive sinus beats; document any shortfall. Non-sinus-rhythm studies are not analyzed under the prespecified strain substudy. No baseline strain is added.

15. Data Safety Monitoring Board and Trial Steering Committee

15.1 DSMB Composition and Independence

An independent Data Safety Monitoring Board (DSMB) is established prior to study initiation to provide independent oversight of patient safety throughout the trial. The DSMB comprises physicians and methodological experts with relevant clinical and statistical expertise who are independent of the study investigators, coordinating center, and Medtronic. Members declare any potential conflicts of interest prior to appointment and recuse themselves from any discussion in which a conflict exists. A DSMB Charter (Appendix G) outlining member responsibilities, meeting procedures, data access, and decision framework is agreed by all parties prior to first patient enrollment. As this is an investigator-initiated, non-regulatory scientific study, the DSMB operates in an advisory capacity to the principal investigator rather than to a commercial sponsor; the charter is proportionate in scope to the trial's size and risk.

The DSMB meets at least twice during the study (the two scheduled safety reviews, §13.8). Ad hoc meetings may be convened at any time on safety grounds. At each meeting the DSMB may recommend to the PI: (1) continuation without modification; (2) continuation with enhanced monitoring; (3) protocol modification; (4) temporary suspension for safety review; or (5) early termination on safety grounds (DSMB Charter §15.1).

15.2 Safety Monitoring

The DSMB reviews the incidence, severity, and relatedness of the serious adverse events and adverse events defined in §19.2 (Tables 1 and 2), using the identical definitions in DSMB Charter Appendix 5 (Appendix G).

Repeat ablations, electrical cardioversions and arrhythmia-related hospitalizations are also reviewed as safety-relevant events. Event definitions are those of §19.2 and DSMB Charter §6.3 and Appendix 5 (Appendix G); the closed-session safety report follows the templates in Charter Appendix 4.

15.3 Safety Stopping Rule

Enrollment will be paused and an ad hoc DSMB safety review convened within 14 days if two or more SAEs listed in Table 1 (§19.2) judged related to the ablation procedure are confirmed in the first 20 patients treated in the investigational arm (pause trigger 1; consistent definition with §19.5). This pause applies globally across all participating sites. An ad hoc DSMB safety review is also convened within 14 days if three or more SAEs listed in Table 1 (§19.2) occur among the first 20 patients treated in the investigational arm (review trigger 2); enrollment may continue pending this review unless the DSMB Chair recommends a pause. Trigger 2 is monitored on an ongoing basis by the independent unblinded statistician, who notifies the DSMB Chair without disclosing treatment allocation to blinded study personnel (DSMB Charter §10).

15.4 Communication and Confidentiality

Core Laboratory personnel and the primary statistical analyst remain blinded to treatment allocation until the primary endpoint database lock. Operators and participants are not blinded (§7.3), and investigators have no access to aggregate treatment-coded data. DSMB members have access to unblinded treatment-coded data for safety oversight only; they are bound by confidentiality obligations defined in the DSMB Charter and will not disclose unblinded information outside the DSMB. DSMB recommendations are communicated in writing to the PI within 14 days of each meeting. The PI retains final authority over protocol modifications, consistent with the investigator-initiated nature of this study.

15.5 Trial Steering Committee

A small Trial Steering Committee (TSC) is constituted at study initiation, comprising the principal investigator (chair) and at least two external members (clinical electrophysiologist and methodologist) independent of all participating sites and of Medtronic. The TSC reviews study progress at least twice during enrollment and once during follow-up, advises on operational issues affecting trial integrity, and reviews the SAP prior to database lock. The TSC has no role in unblinded safety review (which is the DSMB's function) but may consider DSMB recommendations and protocol-amendment proposals.

16. Ethical Considerations

The study will be conducted in full accordance with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice (ICH-GCP) guidelines, and applicable national and institutional regulatory requirements.

16.1 Institutional Review Board / Ethics Committee Approval

The study protocol, informed consent form, patient information sheet, and any other patient-facing study materials must be reviewed and approved by the local IRB or Ethics Committee at each participating center prior to initiation of any study-specific procedures. Protocol amendments must be submitted to and approved by the relevant IRBs/ECs before implementation, except in cases of immediate patient safety. Approval letters and correspondence are maintained in the study master file.

16.2 Informed Consent

Written informed consent will be obtained from all patients prior to any study-specific procedures. The discussion includes study objectives, design, risks (with explicit mention of risks specific to the investigational lesion set: atrial mechanical impairment; mitral isthmus injury; sinus node injury associated with SVC ablation, potentially requiring permanent pacemaker implantation; electrical isolation of the left atrial appendage, potentially requiring a left atrial appendage occlusion device; SVC stenosis; CTI-block-related proarrhythmia; vagal injury; coronary vasospasm; and ILR-specific risks: device-pocket complication and MRI compatibility considerations), benefits, alternatives, confidentiality, and the right to withdraw at any time without effect on medical care. The PI or qualified designee conducts the consent discussion. A copy of the signed consent is provided to the patient and retained in the site study file. Patients who decline or withdraw consent receive standard clinical care without penalty or prejudice.

16.3 Study Registration and Data Sharing

The trial will be registered on ClinicalTrials.gov prior to enrollment of the first patient, in compliance with ICMJE requirements. All required registration fields, including study design, eligibility criteria, endpoints, and SAP summary, will be completed prior to registration. The trial registration number will be included in all publications and reports. The investigators commit to making the de-identified individual participant data underlying the published primary results available to qualified investigators on reasonable request, subject to a data-sharing agreement and approval by the Trial Steering Committee, beginning 12 months after publication of the primary results and ending 5 years thereafter.

16.4 Data Protection and Confidentiality

Patient data are collected and processed in accordance with applicable data-protection regulations, including the Israeli Privacy Protection Law and, where applicable, the EU General Data Protection Regulation (GDPR). Each patient is assigned a unique 10-digit study identifier; only this identifier is used in the CRF and for data transfer. Direct patient identifiers are not entered into the central study database. The patient identification log is maintained securely at each site and is not transferred to the coordinating center.

17. Study Monitoring

17.1 Oversight and Monitoring Plan

The coordinating center implements a risk-based monitoring plan appropriate for a multi-center interventional trial. Monitoring activities verify IRB/EC approval and maintenance, signed informed

consent, eligibility verification, completeness and accuracy of primary endpoint data, adverse event identification and reporting, protocol compliance and ablation strategy adherence, ILR implantation and data transmission, and Core Laboratory data receipt and adjudication.

Monitoring is conducted by the study coordinator (Ofir Mitz) at the coordinating center, who serves as central study monitor. Site monitoring may be performed on-site or remotely, using a secure electronic data capture (eDC) system. Central statistical monitoring of data quality, completeness, and consistency is performed throughout enrollment and follow-up. Critical variables, eligibility criteria, informed consent, primary endpoint data, and SAEs, undergo targeted verification for all randomized patients. Non-critical variables are reviewed on a risk-based, sample basis.

17.2 Site Initiation

Each participating site must complete site qualification and a training visit prior to enrollment of the first patient. Site initiation covers protocol training, CRF completion, ILR programming and data transmission, and adverse event reporting procedures. All principal investigators and key study personnel must complete GCP training prior to study initiation.

17.3 Audit

The coordinating center may conduct independent audits of study sites at any time during or after the study. Sites must permit access to all study-related records for monitoring, audit, or regulatory inspection, subject to applicable confidentiality protections.

18. Protocol Deviations

A protocol deviation is any departure from the approved study protocol or applicable regulatory requirements. All deviations must be identified, documented, and assessed for impact on patient safety, data integrity, and study validity.

18.1 Minor Protocol Deviations

Minor deviations are unlikely to affect patient safety or data integrity (e.g., minor visit window violations, missing non-critical CRF fields, minor deviations from ILR programming). Minor deviations are documented in the CRF and communicated to the coordinating center at the next scheduled monitoring contact.

18.2 Major Protocol Deviations

Major deviations may affect patient safety, data integrity, or study validity (e.g., enrolment of an ineligible patient, performance of an ablation strategy not specified by the protocol, omission of a mandatory lesion set in the investigational arm, failure to obtain informed consent prior to study procedures). Major

deviations must be reported to the coordinating center within 5 working days of identification and to the relevant IRB/EC in accordance with national requirements.

18.3 Emergency Protocol Deviations

Deviations necessary to eliminate an immediate hazard to a patient may be implemented without prior approval but must be reported promptly. Patient safety always takes precedence over protocol adherence.

18.4 Consequences of Persistent Non-compliance

Persistent non-compliance at a participating site may result in enhanced monitoring, re-training, or temporary suspension of enrollment, at the discretion of the principal investigator and coordinating center.

19. Adverse Event Reporting

19.1 Overview

SPHERE-MAZE is an investigator-initiated study in which all devices are used within their approved indications; only the lesion set is investigational. Safety assessment therefore focuses on a predefined list of procedure-related events, each with a specific definition and time window. These events constitute the study's safety endpoints and are reported to the Data and Safety Monitoring Board (DSMB).

19.2 Definitions

- **Serious adverse event (SAE).** An event listed in Table 1 that occurs within its specified time window.
- **Adverse event (AE).** An event listed in Table 2 that occurs within its specified time window and does not meet any SAE criterion.
- **Other serious events.** Any other event that is fatal, life-threatening, or results in hospitalization or permanent disability and that the investigator considers possibly related to the procedure will be recorded and reported to the Helsinki committee according to institutional and Ministry of Health requirements.
- **Reclassification.** An event that evolves to meet SAE criteria (e.g., phrenic nerve paralysis persisting >3 months) is reclassified as an SAE. Each event is counted once, at its highest category.
- **Relationship.** For every event the investigator records whether it is related or not related to the ablation procedure.

Table 1. Serious adverse events

#	Event	Definition	Timing window
1	**Death**	Death from any cause.	Within 30 days of the index procedure.

#	Event	Definition	Timing window
2	**Stroke**	New focal neurological deficit of cerebrovascular (ischemic or hemorrhagic) origin with symptoms lasting ≥24 hours, confirmed by a neurologist and/or brain imaging (CT/MRI).	Within 30 days of the index procedure.
3	**Pericardial effusion / tamponade**	Pericardial effusion, with or without tamponade, requiring pericardiocentesis or surgical intervention.	During the procedure or within 30 days.
4	**Coronary vasospasm**	Coronary artery spasm during or after ablation resulting in ≥1 of the following: 1. Hypotension (systolic BP <90 mmHg) 2. Sustained ventricular arrhythmia (VT/VF) 3. Coronary intervention: intracoronary nitroglycerin, balloon angioplasty, or stenting	During the procedure or within 24 hours.
5	**Persistent phrenic nerve paralysis**	New reduced or absent diaphragmatic motion attributed to phrenic nerve injury, documented by chest X-ray or fluoroscopic sniff test, that persists >3 months. *Imaging is performed at operator discretion (e.g., for new dyspnea) and is not mandatory in all patients.* *Any patient with documented paralysis is re-imaged at 3 months; persistence = SAE, resolution = AE (Table 2).*	Onset during the procedure; persistence assessed at 3 months.
6	**Conduction system injury requiring pacemaker**	New sinus node dysfunction (sinus arrest or symptomatic sinus bradycardia) or AV block attributed to the procedure and requiring permanent pacemaker implantation.	Within 30 days of the index procedure.
7	**Hemolysis requiring hemodialysis**	Hemolysis (e.g., hemoglobinuria, elevated LDH or plasma free hemoglobin, low haptoglobin) with acute kidney injury requiring hemodialysis.	Within 7 days of the index procedure.
8	**Heart failure exacerbation**	New or worsening fluid retention requiring treatment and that is the reason for: 1. Prolongation of the hospitalization beyond 48 hours after the ablation procedure, or 2. Readmission for heart failure.	Within 30 days of the index procedure.
9	**Major vascular complication**	Vascular injury (e.g., hematoma, pseudoaneurysm, AV fistula, retroperitoneal bleeding, dissection, occlusion) requiring blood transfusion or vascular intervention (thrombin injection, endovascular or surgical repair).	Within 30 days of the index procedure.
10	**Atrio-esophageal fistula / esophageal perforation**	Communication between the esophagus and the left atrium or pericardium, or esophageal perforation, confirmed by CT, endoscopy, or surgery.	Within 90 days of the index procedure.

Table 2. Adverse events (non-serious)

#	Event	Definition	Timing window
1	**Transient phrenic nerve paralysis**	New reduced or absent diaphragmatic motion attributed to phrenic nerve injury (documented as in SAE 5) that resolves within ≤3 months, confirmed by repeat imaging.	Onset during the procedure.
2	**Coronary vasospasm treated with IV nitroglycerin**	Coronary artery spasm (ST-segment changes and/or angiographic narrowing) requiring IV nitroglycerin for treatment, without any SAE criterion (SAE 4). Nitroglycerin given for prophylaxis does not qualify.	During the index procedure or within 24 hours.
3	**Acute kidney injury**	≥2-fold increase in serum creatinine from baseline. *Serum creatinine is measured within 24 hours after the procedure and compared with a baseline value obtained within 3 months before the procedure. AKI requiring hemodialysis is an SAE (SAE 7).*	Within 7 days of the index procedure.

#	Event	Definition	Timing window
4	**Transient ischemic attack / stroke <24 hours**	Transient focal neurological deficit of presumed cerebrovascular origin resolving within 24 hours, with or without imaging evidence of acute infarction. Deficits lasting ≥24 hours are an SAE (SAE 2).	Within 30 days of the index procedure.

19.3 Safety assessments

- **Renal function:** serum creatinine is obtained at baseline (within 3 months before the procedure) and within 24 hours after the procedure.
- **Phrenic nerve:** right phrenic nerve capture is checked by pacing before and after the SVC–IVC line (§8.5). Chest X-ray or fluoroscopic sniff test is performed at operator discretion (e.g., for new dyspnea) and is not required in all patients. Patients with documented diaphragmatic paralysis are re-imaged at 3 months.
- **Coronary vasospasm:** ECG and hemodynamics are monitored continuously during the procedure. Use of nitroglycerin (prophylactic or therapeutic, route and dose) is recorded.
- **Clinical follow-up:** events are ascertained during the index hospitalization and at the 30-day and subsequent study follow-up visits, and from any intercurrent hospital records.

19.4 Recording and reporting

- **SAEs:** reported to the principal investigator / coordinating center within 24 hours of site awareness using the SAE report form, and forwarded to the DSMB as specified in the DSMB charter.
- **AEs:** recorded in the CRF by the next scheduled follow-up visit.
- **Follow-up:** events are followed until resolution, stabilization, or end of study follow-up.

19.5 Safety Pause Rule

If two or more SAEs listed in Table 1 (§19.2) judged related to the ablation procedure occur within the first 20 patients treated in the investigational arm, enrollment is paused and an ad hoc DSMB safety review is convened within 14 days (pause trigger 1). This pause applies globally across all participating sites. An ad hoc DSMB safety review is also convened within 14 days if three or more SAEs listed in Table 1 (§19.2) occur among the first 20 patients treated in the investigational arm (review trigger 2); enrollment may continue pending this review unless the DSMB Chair recommends a pause. Trigger 2 is monitored on an ongoing basis by the independent unblinded statistician, who notifies the DSMB Chair without disclosing treatment allocation to blinded study personnel (DSMB Charter §10).

20. Data Management

20.1 Case Report Forms and Electronic Data Capture

All clinical and procedural data are collected using standardized case report forms (CRFs) designed and maintained by the coordinating center. CRFs are available in electronic format (eCRF) on the coordinating center's REDCap platform, which includes built-in validation checks, audit trails, and role-based access controls.

Separate CRFs are used for baseline and pre-procedural data through randomization (Pre-procedural CRF), the ablation procedure (Procedural CRF), POD 1 and discharge (POD 1 / Discharge CRF), and each follow-up visit (Follow-up CRF), with an AE/SAE Report Form for each serious adverse event, to be completed by the site PI or qualified designee. Completed CRFs are returned to the study coordinator at the coordinating center within 7 days of the clinical contact. CRFs are maintained as separate, versioned documents and are not reproduced in this protocol (Appendix I).

20.2 Subject Identification and Pseudonymization

Each enrolled patient is assigned a unique, non-sequential, 10-digit study identifier generated by REDCap. Sequential identifiers are not used for blinded data transfer. Only the study ID appears on rhythm data, ECG files, echocardiography files, and other materials sent to blinded Core Laboratories. Direct patient identifiers (name, date of birth, national ID) are not transferred to the coordinating center or Core Laboratories; they are maintained in a secure patient identification log at each site. The site-to-patient linkage log and treatment-allocation log are stored separately with restricted access. Core Laboratory personnel receive only de-identified materials labelled with the random study ID.

20.3 Data Quality and Query Resolution

The coordinating center performs ongoing data quality review, including range checks, logical consistency checks, and cross-field validation. Data queries are issued to site personnel electronically and resolved within 14 days. All query resolutions are documented in the eDC audit trail.

20.4 Data Security

The central database is hosted on a secure, password-protected server with role-based access controls and automatic audit logging. Data are backed up daily. The coordinating center designates a data manager responsible for database maintenance, access control, and data integrity monitoring.

20.5 Data Retention

All study data, including source documents, CRFs, and ILR transmission records, are retained for a minimum of 15 years after study completion, or longer if required by national regulations.

20.6 Publication Policy

The primary results will be submitted for peer-reviewed publication within 12 months of completion of the 12-month follow-up for all patients. Authorship is determined according to ICMJE criteria. The coordinating center coordinates preparation of the primary manuscript. Sites are notified in advance of submission and invited to contribute to the publication.

21. Expected Outcomes and Study Timeline

21.1 Expected Outcomes

The investigational strategy is hypothesized to improve the composite ordinal AF/AFL/AT burden and clinical-failure outcome specified in §5.3. Planning distributions and power are given in §13.3 and Appendix B. Other secondary, safety and mechanical-function outcomes are reported as specified elsewhere in this protocol.

21.2 Study Timeline

Regulatory and Ethics approvals	3–4 months
Site initiation and investigator training	6 months from first approval
Patient enrollment (100 patients, 3–5 sites)	18 months
Patient follow-up (last patient enrolled)	12 months
Core Laboratory data adjudication	Ongoing; final within 3 months of last visit
Database lock and statistical analysis	2–3 months after Core Laboratory completion
Manuscript preparation and submission	Within 12 months of study completion

Appendix A: Schedule of Assessments

Assessment	Baseline	Day 0 pre-procedure	Day 0 intra-procedure	POD1 to discharge	1 mo	2 mo	3 mo	6 mo	9 mo	12 mo
Informed Consent	✓	-	-	-	-	-	-	-	-	-
Medical History & Physical Exam	✓	**✓‡**	-	✓	✓*	✓*	✓	✓	✓*	✓
12-Lead ECG	✓	✓	-	✓	✓	✓	✓	✓	-	✓
LAA thrombus exclusion: cardiac CT (preferred) or TEE, within 8 weeks, unless ICE at Day 0	✓	-	-	-	-	-	-	-	-	-
Medication Review	✓	✓	-	✓	✓*	✓*	✓	✓	✓*	✓
Standard Echocardiography (eligibility; enrolling center, ≤6 months)	✓	-	-	-	-	-	-	-	-	-
Atrial Strain Echo (Core Lab; SR required)	-	-	-	-	-	-	-	✓		-
AFEQT Questionnaire	✓	-	-	-	-	-	✓	-	-	✓
Laboratory Tests	✓	**✓‡**	-	✓	-	-	-	-	-	-
Randomization	-	✓	-	-	-	-	-	-	-	-
Ablation Procedure	-	-	✓	-	-	-	-	-	-	-
LAA thrombus exclusion: ICE before transseptal puncture, if no CT or TEE (after randomization)	-	-	(✓)	-	-	-	-	-	-	-
ILR Implantation (LINQ™)	-	-	**✓§**	**✓§**	-	-	-	-	-	-

ILR Interrogation / Remote Tx	-	-	-	-	✓	✓	✓	✓	✓	✓
AAD Discontinuation Encouraged †	-	-	-	-	-	(✓)	-	-	-	-
Adverse Event Assessment	-	-	✓	✓	✓	✓	✓	✓	✓	✓
Protocol Deviation Review	-	✓	✓	✓	(✓)	(✓)	(✓)	(✓)	(✓)	(✓)

✓ Required. (✓) If clinically indicated or within window. ✓* virtual visits allowed. For virtual visits physical examination is not required; a 12-lead ECG due at a virtual visit is obtained at a community clinic within the visit window and transmitted to the Rhythm Core Laboratory.
‡ Baseline tests need not be repeated on admission if already completed. § ILR implantation occurs once, at procedure completion or before discharge. Day 0 pre-procedure: presenting rhythm and pre-procedural 12-lead ECG on admission (Day 0); POD 1 / discharge assessments per §12 (vascular access-site examination, 12-lead ECG and overnight telemetry review, serum creatinine and NT-proBNP or BNP at 12–24 hours, pre-discharge medication review, and adverse-event assessment).

† AAD discontinuation is encouraged by 2 months post-ablation when clinically appropriate; physician discretion applies.
Visit windows: ±14 days for all protocol-mandated visits. Remote ILR interrogation is acceptable as a substitute for in-person ILR review at any visit. All ILR data are transmitted to the Rhythm Core Laboratory at Shamir Medical Center for central adjudication.

Appendix B: Pre-specified Outcome Distributions and Power

This appendix gives the pre-specified distributions of the three primary-outcome categories used to anchor the power calculation. Categories: 0 = AF/AFL/AT burden <0.1% and no failure event; 1 = burden 0.1% to 1% and no failure event; 2 = burden >1% or any failure event (§5.3). Lower categories are better outcomes. Investigational-arm assumptions are informed by published outcomes of persistent atrial fibrillation ablation with continuous rhythm monitoring [17–21].

B.1 Pre-specified outcome distributions

Category	Control arm	Investigational arm (base case)
0: burden <0.1%, no failure	25%	50%
1: burden 0.1% to 1%, no failure	25%	25%
2: burden >1% or failure	50%	25%

B.2 Statistical power

The base case corresponds to a common odds ratio of 3.0 under the proportional-odds model. Using the Whitehead (1993) normal approximation with two-sided $\alpha = 0.05$, 45 evaluable patients per arm provide 80% power and 50 evaluable patients per arm provide 84.5% power. Enrollment of 100 patients (50 per arm) allows for 10% attrition. Calculation by the study statistician (V. Novack, 11 Nov 2026).

Appendix C: References

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Appendix D: ILR Programming and Configuration Specifications

STUDY PROGRAMMING. Medtronic LINQ II (LNQ22) exclusively. The settings below are the uniform study programming, identical in both arms; document changes, reasons and effective intervals. Device-only classifications are adjudicated by the Rhythm Core Laboratory (§11.2). Technical validation, device-version and export checks, and operating procedures are specified in the Rhythm Core Laboratory SOP, which may be updated without protocol amendment provided these settings are unchanged.

Monitoring profile: AF Ablation; verify each setting after selecting the profile.

AT/AF detection: AT/AF enabled (to capture organized AT/AFL as well as AF); Balanced AF sensitivity; Nominal ectopy rejection; recording threshold All; Detect Very Regular AT Rhythms: On, All Rates. The AT setting increases false positives and review workload; adjudicate rhythm centrally.

R-wave sensing: Start with sensitivity 0.035 mV, Blank after Sense 150 ms and T-wave blanking 150 ms; verify R-wave sensing and absence of P/T-wave oversensing at implantation. Individualize only for documented sensing problems and record the final sensitivity and blanking values.

Safety detection: Study LINQ II settings: tachy ≥150 bpm for 16 beats, rapid-onset requirement Off; brady ≤40 bpm for 12 beats; pause ≥3 seconds; Brady Nighttime ECGs Stored: Up to 3 ECGs. These are study settings, not manufacturer defaults.

Symptom storage: Enable three 10-minute symptom recordings; train participants to mark symptoms. Preserve automatic episode logs, available ECGs and daily burden data; finite device memory cannot guarantee a tracing for every episode.

CareLink schedule: Maintain daily connectivity and automatic daily transmission; check connectivity on working days. Full interrogation and transfer at each scheduled visit within 48 hours. Investigate missing transmissions promptly and record monitoring gaps.

Alert handling: Site clinician and backup review alerts each working day; urgent clinically significant findings are escalated the same day identified. Symptoms requiring urgent care are managed immediately through usual emergency services, without waiting for CareLink. Apply §19 reporting after clinical assessment.

Data limitations: AT/AF detection uses 2-minute analysis periods. This does not ensure detection of every ≥30-second episode or reliable classification of all organized AT/AFL. Use supplementary rhythm recordings under §11.2; retain ≥6-minute recurrence with ≥30 seconds additionally reported under §5.4. Do not infer zero burden during missing monitoring or extrapolate a brief tracing to total AT/AFL burden.

Approval and setup record: Record model, serial number, software/algorithm version, programmed settings, clinic alert recipients, connectivity test and approving investigator/date. Follow the implemented burden and recurrence rules in §13 and the CRF Analysis and Implementation Specification; validate algorithm-filtered export provenance before site use.

Technical source: Medtronic LINQ II LNQ22 Clinician Manual, §§6–8 and Appendix A; manufacturer manual portal https://manuals.medtronic.com. Document the regional manual identifier and verified export tests before site use (Rhythm Core Laboratory SOP).

Appendix E: Echocardiography Acquisition Protocol

Prepared by Prof. Marina Leitman, MD, FESC, FEACVI, Director, Echocardiography Unit & Valvular Heart Diseases Clinic, Shamir Medical Center; Echocardiography Core Laboratory Director.

E.1 General Information

Each patient undergoes two echocardiographic examinations:

- Baseline examination before ablation, accepted in any rhythm; rhythm and heart rate must be recorded.
- Follow-up examination at approximately 6 months after ablation (acceptable window 6–9 months), performed during sinus rhythm.

Participating centers perform and report standard echocardiographic measurements in the CRF. The Core Laboratory performs offline LA strain analysis from transferred raw-data studies.

E.2 General Requirements for All Examinations

All examinations are performed according to current standard echocardiographic recommendations [Lang 2015; Nagueh 2025; Thomas 2025].

The GE Vivid acquisition requirements apply to baseline and follow-up examinations at the enrolling center. Baseline TTE is accepted in any rhythm, with rhythm and heart rate documented. Follow-up strain examination requires stable sinus rhythm.

- Studies must be acquired exclusively on GE Vivid systems: GE Vivid E95 (preferred); GE Vivid S70 (optional).
- All studies must be exported using "Export with Raw Data" via USB device.
- USB media must be labelled with center name and 10-digit study ID.
- A clear ECG signal must be stored with all 2D cine loops and Doppler recordings.

E.3 Baseline Echocardiography Before Ablation

The baseline examination is accepted in any rhythm. Record rhythm and heart rate as mandatory fields; retain the specified measurement standards.

Mandatory screening measurements

LVEF. LVEF must be calculated using the biplane modified Simpson's rule from apical 4-chamber and 2-chamber views. Because of beat-to-beat variability in AF, LVEF should be averaged over at least 5 cardiac cycles. Exclusion criterion: LVEF ≤30%.

Antero-posterior (AP) LA diameter. AP LA diameter must be measured in the parasternal long-axis view at end-systole, when the LA is maximal. Exclusion criteria: AP diameter <40 mm or >60 mm.

The participating center must verify, against the echo report, and document the mandatory screening measurements above and all available parameters related to chamber quantification and valvular anatomy and function in the patient's CRF (see E.5).

E.4 Local Site Acquisition Requirements for Core Lab LA Strain Analysis

- Rhythm status: verify and document that the patient is in stable sinus rhythm at the time of the follow-up echo.
- Required views for LA strain: dedicated apical 4-chamber view and dedicated apical 2-chamber view.
- Avoiding foreshortening: the local operator must deliberately modify the apical views to maximize LA longitudinal and transverse dimensions. The transducer should be moved up 1–2 intercostal spaces if necessary to ensure the LA is not foreshortened and the true LA roof is visualized. Optimize gain settings and focus quality to show the LA endocardial border. Use a narrow sector width focused on LA and mitral annular region. Adequate depth to include the entire LA. Avoid excessive smoothing, noise, reverberation, and shadowing. Avoid dropout of the interatrial septum and LA lateral wall.
- Loop length (sinus rhythm): a minimum of 3 consecutive sequential sinus cardiac cycles must be captured in a single loop for each view without ectopy.
- Frame rate optimization: strictly maintain frame rates between 50–70 fps.
- Breath-hold: operators must instruct the patient to hold their breath at the end of expiration during these acquisitions to eliminate translational respiratory artifacts.

E.5 Standardized CRF Parameter List (Examinations 1 and 2)

To ensure nothing is missed, participating centers must report the same parameters on the CRF for both examinations; for a baseline examination performed at the enrolling center, parameters not available in the report are recorded as not available.

E.5.1 General data

- Study ID
- Centre name
- Date of examination
- Examination type (baseline or 6-month follow-up)
- Patient height and weight
- Body surface area (BSA)
- Heart rhythm during examination and heart rate
- Ultrasound system model
- Image quality: good / acceptable / poor

E.5.2 LV size and geometry

- LV end-diastolic diameter (LVEDD, cm)

- LV end-systolic diameter (LVESD, cm)
- LV end-diastolic volume (LVEDV, mL)
- LV end-systolic volume (LVESV, mL)
- Indexed LV volumes (mL/m²)
- Interventricular septum thickness at end-diastole (IVSd, cm)
- Posterior wall thickness at end-diastole (PWd, cm)

LV mass index (LVMi, g/m²). Calculated using the Devereux formula and indexed to BSA: LVM = 0.8 × 1.04 × [(IVS + PW + LVID)³ − LVID³] + 0.6 g, where IVS is the interventricular septal thickness, PW is the posterior wall thickness, and LVID is the LV internal diameter at end-diastole.

Relative wall thickness (RWT). RWT = (2 × PW) / LVEDD.

E.5.3 LV function

- LVEF by biplane Simpson's method (%)
- Regional wall motion abnormality: yes / no
- Segments involved, if abnormal

E.5.4 LA metrics

- Antero-posterior (AP) LA diameter (mm, from the parasternal long-axis view)
- LA area (cm², measured at end-systole in both apical 4-chamber and 2-chamber views, reported separately for each view)
- LA volume index (LAVI, mL/m², calculated by biplane area-length method, indexed to BSA)

E.5.5 RV size and function

- Basal RV diameter indexed to BSA (cm/m²)
- Tricuspid annulus peak systolic excursion (TAPSE, cm)
- Tricuspid annular S′ velocity (cm/s)
- RV fractional area change (%)

E.5.6 Diastolic function parameters

- Mitral E velocity (cm/s)
- Mitral A velocity (cm/s, if in sinus rhythm)
- E-wave deceleration time (ms)
- Septal e′ velocity (cm/s)
- Lateral e′ velocity (cm/s)
- Average E/e′ ratio
- TR peak velocity (m/s)
- Diastolic function grade, if interpretable

E.5.7 Valvular assessment

For each valve, report stenosis and regurgitation severity as none / mild / moderate / severe. Valves to assess: aortic, mitral, tricuspid, pulmonary.

Report the presence of prosthetic valves or prior valve repair devices: document presence, position, and baseline gradients if applicable.

E.5.8 Additional hemodynamic and structural metrics

- IVC metrics: diameter (cm) and collapsibility (%)
- Estimated systolic pulmonary artery pressure (sPAP, mmHg, if measurable)

E.6 Core Laboratory LA Strain Analysis

The Echocardiography Core Laboratory at Shamir, directed by Dr. Marina Leitman, performs blinded offline analysis using GE EchoPAC. Follow-up LA strain documentation includes reservoir (LASr), conduit (LAScd) and contraction (LASct) components in apical 4- and 2-chamber views and their two-view averages. Reservoir remains the prespecified strain outcome; conduit and contraction are exploratory. Record raw signed outputs, software sign convention and standardized positive magnitudes, using R-R gating. Record acquisition rhythm/heart rate, model, software version, frame rate, cycle identifiers and selection, tracking quality, excluded segments/reasons, analyzability by component/view, repeat requests, reader and dates. Average accepted beats within each view, then average the two valid views equally; do not substitute a single view for a two-view value. Retain single-view results descriptively. Aim to analyze the acquired three consecutive sinus beats; document any shortfall. Non-sinus-rhythm studies are not analyzed under the prespecified strain substudy. No baseline strain is added.

E.7 Appendix E References

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Appendix F: Informed Consent Form and Patient Information Sheet

The Informed Consent Form (ICF) and Patient Information Sheet (PIS) are provided as separate documents. The ICF will explicitly include the incremental risks of the investigational lesion set (atrial mechanical impairment; mitral isthmus injury; sinus node injury associated with SVC ablation, potentially requiring permanent pacemaker implantation; electrical isolation of the left atrial appendage, potentially requiring a left atrial appendage occlusion device; SVC stenosis; CTI-block-related proarrhythmia; vagal injury; coronary vasospasm), ILR-specific risks (device-pocket complication, MRI compatibility considerations), and the patient's right to withdraw at any time without effect on medical care. These materials must be reviewed and approved by the local IRB/EC at each participating site prior to enrollment of the first patient, as specified in §16.1. Site-specific adaptations must be submitted to and approved by the coordinating center prior to use. [ICF and PIS to be appended here as separate documents upon finalization.]

Appendix G: Data Safety Monitoring Board Charter

SPHERE-MAZE

A Randomized Controlled Trial of a Percutaneous Maze-like Catheter Ablation Strategy for Advanced Persistent Atrial Fibrillation

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DATA SAFETY MONITORING BOARD CHARTER

Appendix G to the SPHERE-MAZE Protocol (Version 13.1)

Charter Version 1.11 | 15 Nov 2026 | Confidential – For DSMB Use Only

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Principal Investigator	Elad Anter, MD, Shamir Medical Center, Be'er Ya'akov, Israel
Coordinating Center	Shamir Medical Center, Be'er Ya'akov, Israel
Sponsor Status	Investigator-initiated; funded in part by an unrestricted grant from Medtronic, Inc.
Study Design	Multicenter, randomized, controlled superiority trial; N = 100 (50 per arm)
Protocol Version	13.1
Charter Version	1.11
ClinicalTrials.gov	To be assigned prior to first patient enrollment

1. Purpose

The purpose of this Data Safety Monitoring Board (DSMB) Charter is to define the role, composition, responsibilities, procedures, data access, confidentiality requirements, safety reporting process, and recommendation framework of the DSMB for the SPHERE-MAZE trial.

SPHERE-MAZE is an investigator-initiated, multicenter, randomized controlled trial evaluating a percutaneous Maze-like biatrial catheter ablation strategy compared with standard PVI plus Posterior Wall Isolation in patients with advanced persistent atrial fibrillation, using the Affera/Sphere-9 system (Medtronic, Inc.).

The DSMB is established to provide independent oversight of participant safety and trial conduct. The DSMB operates in an advisory capacity to the Principal Investigator and is independent of the study investigators, participating sites, coordinating center, core laboratories, and funder.

2. Scope of DSMB Oversight

The DSMB reviews accumulating safety data and relevant trial conduct information to ensure that participant safety is appropriately protected throughout the study. The DSMB focuses primarily on:

1. Serious adverse events.
2. Adverse events (Table 2) and the specific serious adverse events (Table 1) defined in Section 6.3 and Appendix 5.
3. Procedure-related complications.
4. Unexpected safety signals.
5. Major protocol deviations with potential patient safety implications.
6. Enrollment and follow-up completeness, when relevant to safety oversight.
7. Any event or pattern of events that may alter the benefit–risk assessment of the study.

The DSMB will not perform a formal interim efficacy analysis. Early stopping for efficacy is not permitted under this protocol.

3. DSMB Composition

The DSMB consists of four independent members with relevant clinical, scientific, and methodological expertise, including:

1. At least one cardiac electrophysiologist or cardiologist with expertise in catheter ablation for atrial fibrillation.
2. At least one physician with clinical trial or patient-safety monitoring experience.
3. A biostatistician, methodologist, or clinical investigator with experience in clinical trial analysis and independent safety monitoring.

One member serves as DSMB Chair, nominated by the members and confirmed by the PI prior to the first meeting. The DSMB Chair coordinates meetings, guides deliberations, communicates DSMB recommendations to the Principal Investigator, and may convene ad hoc reviews.

The DSMB biostatistician, Ido Peles, MD, PhD, is a voting DSMB member and also serves as the independent unblinded statistician. In this role he monitors the triggers in Section 10 and prepares the unblinded safety reports for each review under a separate, restricted data-access role. He is not the

primary trial statistician, who remains blinded throughout the study. Because Dr. Peles and the primary trial statistician work within the same team, a documented firewall is maintained: treatment-coded data, analyses, and DSMB materials will not be shared with the primary trial statistician or any other blinded study personnel.

4. Independence and Conflicts of Interest

DSMB members must be independent of the conduct of the trial. They may not be directly involved in patient enrollment, trial procedures, follow-up, endpoint adjudication, core laboratory review, data management, or primary statistical analysis. Members must also be independent of Medtronic, Inc.

Before appointment, each DSMB member will complete a written Conflict of Interest (COI) disclosure covering financial, academic, institutional, professional, and personal relationships that could be perceived as influencing DSMB judgment (see Appendix 2). COI disclosures are reviewed by the DSMB Chair (and, for the Chair, by another member) and are retained in the study master file.

Members must promptly notify the DSMB Chair of any new potential conflict arising during the trial. A DSMB member with a relevant conflict will be recused from specific discussions or recommendations as appropriate.

Members may receive reasonable remuneration for their time and reimbursement of reasonable expenses. Any such arrangement is disclosed in the COI declaration and is not conditional on any particular recommendation.

5. Confidentiality

All DSMB materials, deliberations, minutes, and recommendations are strictly confidential. DSMB members may have access to unblinded, treatment-coded data for safety oversight. Such information must not be disclosed to investigators, enrolling sites, core laboratory personnel, the primary statistical analyst, study participants, or any external party, including Medtronic, Inc., except as explicitly required for:

1. Patient safety.
2. Ethics committee reporting.
3. Regulatory authority reporting.
4. Implementation of a DSMB recommendation communicated to the PI.

DSMB recommendations communicated to the PI use descriptive language rather than treatment-arm labels unless disclosure of allocation is operationally necessary. DSMB members will not use trial data for any purpose outside their DSMB responsibilities. All DSMB records are retained securely and archived or destroyed per applicable data-protection regulations at the conclusion of the study.

6. Definitions

6.1 Adverse Event

Any untoward medical occurrence in a study participant, whether or not considered related to the study procedure, study device, study intervention, or study participation.

6.2 Serious Adverse Event

Any adverse event that results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; results in a congenital anomaly or birth defect; or is considered medically important by the investigator.

6.3 Safety Event Definitions

The serious adverse events (Table 1) and non-serious adverse events (Table 2) reviewed by the DSMB, with their definitions, time windows and classification rules, are specified in Appendix 5 (Safety Event Definitions). These definitions are identical to those in Protocol §19.2.

7. SAE Reporting and DSMB Notification

Collect each SAE (Table 1) and AE (Table 2) within its event-specific time window (Appendix 5; Protocol §19.2). Later medication changes, cardioversions, redo ablations and healthcare-utilization events remain captured in their designated CRF sections. Use a stable Study ID + sequential AE number. SAE reports are due within 24 hours of site awareness, using the AE/SAE Report Form (Protocol §19.4); AEs are recorded in the CRF by the next scheduled follow-up visit.

The Principal Investigator or designee will provide the DSMB Chair with a written summary of all SAEs promptly after receipt and initial review. The summary will include, when available:

1. Study identifier.
2. Event description.
3. Date of event onset and date of site awareness.
4. Timing relative to the index procedure.
5. Seriousness criteria met.
6. Severity.
7. Event outcome.
8. Investigator-assessed relatedness to the study procedure, investigational strategy, device, or study participation.
9. Whether the event is a Table 1 SAE or a Table 2 AE (Section 6.3 and Appendix 5).
10. Immediate management and corrective actions taken.

All Table 1 SAEs and Table 2 AEs (Appendix 5) are summarized for the DSMB Chair.

Notification of an SAE to the DSMB Chair does not automatically require a full DSMB meeting. The DSMB Chair, in consultation with other DSMB members when appropriate, will determine whether the event can be reviewed at the next scheduled meeting or whether an ad hoc review should be convened immediately.

An ad hoc review should be considered for any SAE that is fatal, life-threatening, related to the investigational lesion set, or suggests a new or unanticipated safety concern.

8. Scheduled DSMB Safety Review

Two scheduled, unblinded safety reviews are conducted: (1) after the first 30 randomized patients (30% of planned enrollment) have each completed at least 30 days of post-procedural follow-up; and (2) after the first 70 randomized patients (70% of planned enrollment) have each completed at least 30 days of post-procedural follow-up. For each review, the data cut-off is the date on which the 30th or 70th

randomized patient, respectively, completes 30 days of post-procedural follow-up; the review database is frozen 2 weeks after the cut-off.

At each scheduled review, the DSMB reviews cumulative safety data, including SAEs (Table 1), AEs (Table 2), procedure-related complications, deaths, hospitalizations, readmissions, and major protocol deviations relevant to patient safety.

The DSMB also applies the pre-specified safety pause and review triggers (Section 10).

The DSMB may additionally review enrollment progress, follow-up completeness, missing safety data, and data-quality issues that could affect safety interpretation.

9. Ad Hoc DSMB Reviews

Additional ad hoc DSMB meetings may be convened at any time if:

1. A safety pause or review trigger (Section 10) is met.
2. A fatal or life-threatening SAE occurs and is considered related to the study procedure or investigational strategy.
3. An unexpected safety signal emerges that may require immediate action.
4. A single event or case raises significant concern regarding the safety of the investigational lesion set.
5. The DSMB Chair, Principal Investigator, coordinating center, ethics committee, regulatory authority, or institutional body requests review on safety grounds.

Ad hoc meetings may be conducted virtually or in person and should be convened as soon as practicable given the urgency of the safety concern. The Principal Investigator may also voluntarily pause enrollment pending DSMB review if a serious safety concern arises, even if the formal Pause trigger 1 threshold has not been met.

10. Safety Pause and Review Triggers

Pause trigger 1 and Review trigger 2 are pre-specified in the protocol (§§ 15.3 and 19.5):

> **Pause trigger 1 (related SAEs):** if two (2) or more SAEs listed in Table 1 (Appendix 5) judged by the investigator as related to the ablation procedure occur among the first 20 patients treated in the investigational arm, enrollment is paused at all participating sites and an ad hoc DSMB safety review is convened within 14 calendar days. The unblinded statistician monitors this trigger on an ongoing basis and notifies the DSMB Chair when it is met, without disclosing treatment allocation to blinded study personnel.
>
> **Review trigger 2 (Table 1 SAEs):** if three (3) or more SAEs listed in Table 1 (Appendix 5) occur among the first 20 patients treated in the investigational arm, an ad hoc DSMB safety review is convened within 14 calendar days. Enrollment may continue pending this review unless the DSMB Chair recommends a pause. The unblinded statistician monitors this trigger on an ongoing basis and notifies the DSMB Chair when it is met, without disclosing treatment allocation to blinded study personnel.

Following an ad hoc review triggered by either trigger, the DSMB may recommend: continuation without modification; continuation with enhanced monitoring; protocol modification; temporary suspension; or early termination on safety grounds.

The DSMB may recommend modification of either trigger at any scheduled or ad hoc review. A modification of either trigger takes effect only through a protocol amendment approved by the ethics committee.

11. Meetings

DSMB meetings may be conducted virtually or in person. A quorum consists of at least three of the four DSMB members, including either the DSMB Chair or a designated acting Chair. Whenever possible, all four DSMB members should participate, particularly for major recommendations regarding protocol modification, suspension, or termination.

The unblinded statistician (the DSMB biostatistician, Section 3) presents the safety data in the closed session. The Principal Investigator or study coordinator may be invited to attend the open session but may not participate in closed-session deliberations.

Decisions are reached by consensus where possible; if consensus is not achieved, recommendations are made by simple majority of the members present, with the DSMB Chair (or acting Chair) holding the casting vote in the event of a tie, and the minutes document dissenting opinions.

In exceptional circumstances, the Chair may seek agreement by written circulation (email), but such decisions must be ratified at the next meeting.

12. Open and Closed Sessions

12.1 Open Session

The Principal Investigator, study coordinator, or other invited study personnel may present general trial progress, enrollment status, follow-up status, data completeness, protocol deviations, and blinded or non-confidential operational information. Non-DSMB personnel leave before the closed session.

12.2 Closed Session

Only DSMB members attend. The unblinded statistician attends as a DSMB member (Section 3). The DSMB reviews unblinded, treatment-coded safety data and any other confidential information required for safety oversight. All recommendations are formulated in this session.

12.3 Reporting Session

The DSMB Chair communicates the recommendation category and key points verbally to the PI immediately following the closed session. Written confirmation is transmitted within 14 calendar days.

13. Data Reviewed by the DSMB

The DSMB may review the following data, overall and by treatment arm where appropriate:

1. Enrollment status and baseline patient characteristics.
2. Procedural completion, assigned treatment received, and procedural metrics relevant to safety.
3. All serious adverse events, with investigator attribution.
4. Serious adverse events (Table 1) and adverse events (Table 2) as defined in Appendix 5, by event type.
5. Protocol deviations with potential patient safety implications.

6. Patient withdrawals, loss to follow-up, and missing safety data.

7. Any event triggering assessment of the safety pause or review triggers.

8. Repeat ablations, electrical cardioversions, and arrhythmia-related hospitalizations, as safety-relevant events.

Templates for the closed-session safety report (dummy tables) are provided in Appendix 4.

14. Data Preparation and Blinding

The unblinded statistician (Section 3) prepares confidential DSMB safety reports from data supplied by the coordinating center, using non-sequential 10-digit study identifiers, consistent with the pseudonymization approach specified in the protocol (§20.2).

For the scheduled and ad hoc safety reviews, the DSMB may receive treatment-coded or unblinded safety summaries as needed for independent oversight. The treatment code and all unblinded data remain confidential to the DSMB and the unblinded statistician.

Core Laboratory personnel, the primary statistical analyst (Victor Novack, MD, PhD), and other blinded study personnel remain blinded to treatment allocation until the primary endpoint database lock. Operators and participants are not blinded (Protocol §7.3), and investigators have no access to aggregate treatment-coded data.

15. DSMB Recommendation Framework

15.1 Recommendation Options

After each scheduled or ad hoc review, the DSMB issues one of the following formal recommendations to the Principal Investigator:

Recommendation	Definition
1 – Continue	The trial may proceed without modification. The safety profile is consistent with expectations.
2 – Continue with enhanced monitoring	The trial may continue but with specific additional safety measures, monitoring, or reporting requirements as specified by the DSMB.
3 – Modify protocol	A specified amendment is required (e.g., eligibility restriction, additional patient information, enhanced follow-up, or procedural safeguard). The nature of the modification is specified.
4 – Suspend	Enrollment is temporarily paused pending further safety evaluation. The DSMB specifies a timeline for follow-up review.
5 – Terminate	The trial is stopped on safety grounds. The DSMB provides written rationale and recommended clinical management for enrolled patients.

The DSMB may also request additional data, analyses, case narratives, or clarification from the PI before issuing a final recommendation.

15.2 No Efficacy Stopping

The DSMB is not empowered to recommend early termination for efficacy. No efficacy stopping boundary is pre-specified. The DSMB receives safety data only; efficacy data, including AF burden and the primary endpoint, are not provided. Repeat ablations, cardioversions, and arrhythmia-related hospitalizations may be reviewed as safety-relevant events.

16. Communication of DSMB Recommendations

The DSMB Chair communicates the DSMB recommendation verbally to the PI at the conclusion of each meeting and provides written confirmation within 14 calendar days, or sooner when urgent safety concerns exist. For urgent recommendations (Suspension or Termination), verbal communication is followed by written confirmation within 48 hours.

Written recommendations include:

1. Date of DSMB meeting.
2. Members present.
3. General description of data reviewed (without unblinding the PI to treatment-specific rates unless required).
4. Formal recommendation (one of the five categories).
5. Rationale for the recommendation.
6. Requested actions, timelines, or follow-up.

The Principal Investigator retains final responsibility for trial conduct and for implementing DSMB recommendations, consistent with the investigator-initiated nature of this study. Any decision not to follow a DSMB recommendation must be documented in writing with justification and communicated to the DSMB Chair within 14 days of receiving the written recommendation.

17. Reporting to Ethics Committees and Regulatory Authorities

The Principal Investigator or designee is responsible for reporting SAEs, safety pauses, protocol amendments, and DSMB recommendations to applicable ethics committees, institutional review boards, regulatory authorities, and participating sites, as required by local regulations and institutional policies.

If the DSMB recommends protocol modification (Recommendation 3), suspension (4), or termination (5), the Principal Investigator will notify relevant oversight bodies in accordance with applicable requirements. The DSMB Chair may be requested to provide a brief written statement to accompany such notifications.

The DSMB does not communicate directly with Medtronic, Inc. regarding safety findings or recommendations. Medtronic's access to safety information is limited to SAE reports submitted through standard regulatory channels by the coordinating center.

18. Meeting Minutes and Documentation

Confidential minutes are prepared for each DSMB meeting. Open-session minutes may summarize trial progress, general discussion, and DSMB recommendations without including unblinded treatment-specific information. Closed-session minutes document confidential deliberations and unblinded safety findings and are maintained separately from open-session minutes.

Minutes are approved by the DSMB Chair within 14 days of each meeting. Closed-session minutes are retained by the DSMB and are not distributed to blinded investigators, Core Laboratory personnel, or the primary statistical analyst.

All DSMB records are maintained in a secure DSMB file and retained for a minimum of 15 years after study completion, or as required by applicable regulations.

19. Relationship to the Trial Steering Committee

The DSMB is responsible for independent safety oversight. The Trial Steering Committee (TSC) is responsible for broader study oversight, operational guidance, study progress, and trial integrity. The TSC does not attend DSMB meetings and does not have access to unblinded treatment-specific safety data, unless access is required for patient safety or a protocol-level decision following a DSMB recommendation.

DSMB recommendations are communicated to the PI. The TSC may be informed of the recommendation category and any resultant protocol amendments, consistent with the blinding requirements of Section 5.

20. Administrative Provisions

20.1 Charter Approval and Amendments

This Charter is reviewed and approved by all DSMB members and the Principal Investigator before enrollment of the first patient. Amendments may be made if required during the study; any amendment is documented, assigned a new version number, and approved by the DSMB Chair and Principal Investigator before taking effect.

20.2 Liability and Indemnification

DSMB members acting in good faith and within the scope of this Charter are not personally liable for recommendations made in their capacity as DSMB members. The Principal Investigator and coordinating center ensure that appropriate indemnification arrangements are in place at study initiation.

20.3 Dissolution

The DSMB is dissolved after the primary endpoint database lock and completion of all post-trial safety follow-up obligations. Members remain bound by confidentiality obligations in Section 5 after dissolution.

21. Signatures

By signing below, each party confirms having read and agreed to the terms of this DSMB Charter and commits to fulfilling the responsibilities described herein.

Role	Name and Institution	Signature	Date
Principal Investigator	Elad Anter, MD Shamir Medical Center		

Role	Name and Institution	Signature	Date
DSMB Chair	Name: _____ Institution: _____		
DSMB Member	Name: _____ Institution: _____		
DSMB Member	Name: _____ Institution: _____		
DSMB Member (Biostatistician)	Name: _____ Institution: _____		

Appendix 1: DSMB Member Acceptance and Confidentiality Agreement

I, _____, agree to serve as a DSMB member for the SPHERE-MAZE trial. By signing below I confirm that:

1. I have read and understood the SPHERE-MAZE DSMB Charter (Version 1.11).
2. I am independent of the Principal Investigator, all co-investigators, all participating sites, and Medtronic, Inc.
3. I have disclosed all actual or potential conflicts of interest on the attached COI Disclosure Form (Appendix 2).
4. I agree to maintain strict confidentiality of all unblinded data and DSMB deliberations, both during and after my tenure.
5. I will promptly notify the DSMB Chair of any new conflict of interest arising during my tenure.
6. I will not use information from DSMB reviews for any purpose other than fulfilling my DSMB responsibilities.

Name: _____

Institutional Affiliation: _____

Role on DSMB: ☐ Chair ☐ Clinical Member ☐ Biostatistician / Methodologist

Signature: _____ Date: _____

Appendix 2: Conflict of Interest Disclosure Form

SPHERE-MAZE DSMB – Member name: _____

Please answer Yes or No for each item. If Yes, provide details in the right-hand column.

Potential Conflict	Yes / No	Details (if Yes)
Employment by, or consultancy agreement with, Medtronic, Inc. or its subsidiaries in the past 3 years		
Research funding from Medtronic, Inc. in the past 3 years		
Financial relationship with any participating site		
Equity ownership in Medtronic, Inc. or a competing company		
Advisory board membership for Medtronic, Inc. or a direct competitor in the past 3 years		
Close professional relationship with the Principal Investigator or study investigators in the past 3 years (e.g., co-authorship, shared grants, mentorship, or institutional reporting relationship)		
Any other financial, intellectual, or personal interest that could be perceived as a conflict		

I confirm that the above disclosures are complete and accurate to the best of my knowledge.

Signature: _____ Date: _____

Appendix 3: Standard DSMB Meeting Agenda

SPHERE-MAZE DSMB Meeting [Number] – [Date] – [Virtual / In Person]

Open Session (PI / study coordinator present)

1. Welcome, confirmation of quorum, approval of previous meeting minutes.
2. COI declarations reviewed and confirmed by Chair.
3. PI report: enrollment and follow-up status, protocol deviations, operational issues.
4. Blinded summary of adverse events (if applicable).
5. Questions from DSMB to PI. PI and non-DSMB personnel leave.

Closed Session (DSMB members and unblinded statistician only)

6. Presentation of unblinded safety report.
7. Review of SAEs and AEs by treatment arm.
8. Assessment of safety pause and review trigger criteria.
9. Review of protocol deviations with safety implications.
10. DSMB deliberation and formulation of recommendation.
11. Preparation of written recommendation summary.

Reporting (Chair and PI)

12. Chair communicates recommendation category and key points verbally to PI.
13. PI provides initial verbal response.
14. Written recommendation transmitted within 14 days.

Appendix 4: DSMB Safety Report Templates (Dummy Tables)

The tables below are templates for the closed-session safety report prepared by the independent unblinded statistician for each scheduled review (Section 8). Treatment arms are presented as Arm A and Arm B; the treatment code is held by the unblinded statistician and is available to the DSMB on request. For the open session, Tables 1 and 3 are presented pooled across arms only. Categorical data are presented as n (%) and continuous data as mean ± SD or median [IQR]. Cells are blank in the template and are populated at each review. The DSMB may adapt these templates at its first meeting.

Table 1. Enrollment, follow-up, and data completeness

Status	Arm A	Arm B	Total
Randomized			
Underwent index ablation			
Complete assigned lesion set delivered			
Incomplete lesion set or crossover			
Completed 30-day follow-up			
Completed 90-day follow-up			
Withdrawn			
Lost to follow-up			
Missing safety data (patients)			

Table 2. Baseline characteristics

Characteristic	Arm A	Arm B	Total
Age, years			
Female sex			
CHA_2 DS_2 -VA score			
LA antero-posterior diameter, mm			
Duration of longest AF episode, months			
LVEF, %			
History of heart failure			
Prior amiodarone use			

Table 3. Procedural characteristics

Characteristic	Arm A	Arm B	Total
Procedure time, min			
Fluoroscopy time, min			
Energy modality: PFA / RFA / both			

Characteristic	Arm A	Arm B	Total
Acute block across all assigned lesion sets			
Intraprocedural cardioversion			
Index hospitalization length, days			

Table 4. Summary of serious adverse events

Patients (events)	Arm A	Arm B	Total
Patients with ≥1 SAE			
Total number of SAEs			
Patients with ≥1 SAE related to the procedure			
Total number of SAEs related to the procedure			
Deaths (all-cause)			

Table 5. SAEs (Table 1) and AEs (Table 2) per Appendix 5, patients with ≥1 event

Event	Arm A	Arm B	Total
SAE 1. Death			
SAE 2. Stroke			
SAE 3. Pericardial effusion / tamponade			
SAE 4. Coronary vasospasm			
SAE 5. Persistent phrenic nerve paralysis			
SAE 6. Conduction system injury requiring pacemaker			
SAE 7. Hemolysis requiring hemodialysis			
SAE 8. Heart failure exacerbation			
SAE 9. Major vascular complication			
SAE 10. Atrio-esophageal fistula / esophageal perforation			
Any Table 1 SAE (primary safety endpoint)			
AE 1. Transient phrenic nerve paralysis			
AE 2. Coronary vasospasm treated with IV nitroglycerin			
AE 3. Acute kidney injury			
AE 4. Transient ischemic attack / stroke <24 hours			
Any Table 2 AE			

Table 6. Safety pause and review trigger status (Section 10)

Trigger	Events	Threshold	Met (Y/N)
Trigger 1: Table 1 SAEs related to the ablation procedure, first 20 patients treated in the investigational arm		≥2	
Trigger 2: SAEs listed in Table 1, first 20 patients treated in the investigational arm		≥3	

Table 7. Other safety-relevant events and protocol deviations

Patients with ≥1 event	Arm A	Arm B	Total
Arrhythmia-related hospitalization			
Repeat ablation			
Electrical cardioversion			
Protocol deviation with potential safety implications			

Listing 1. SAE and AE line listing (cumulative; new or updated entries since the previous review flagged)

Study ID	Arm	Event	Onset (days post-ablation)	Seriousness criteria	Relatedness	Table 1 / Table 2 event	Outcome

Appendix 5: Safety Event Definitions

Version 1.1 | 13 November 2026 | Appendix to the DSMB charter

1. Purpose

This document defines the safety events reviewed by the DSMB for SPHERE-MAZE, an investigator-initiated study using approved devices with a new ablation lesion set in patients with persistent atrial fibrillation. The definitions are identical to those in the study protocol (Protocol §19.2).

2. Classification rules

- **SAE:** an event listed in Table 1 occurring within its time window.
- **AE:** an event listed in Table 2 occurring within its time window and not meeting any SAE criterion.
- **Counting:** each event is counted once, at its highest category. An AE that evolves to meet SAE criteria (e.g., phrenic nerve paralysis persisting >3 months) is reclassified and re-reported as an SAE.
- **Relationship:** the investigator's assessment (related / not related to the procedure) is provided for each event; the DSMB may request additional source documents.

3. Serious adverse events (Table 1)

#	Event	Definition	Timing window
1	**Death**	Death from any cause.	Within 30 days of the index procedure.
2	**Stroke**	New focal neurological deficit of cerebrovascular (ischemic or hemorrhagic) origin with symptoms lasting ≥24 hours, confirmed by a neurologist and/or brain imaging (CT/MRI).	Within 30 days of the index procedure.
3	**Pericardial effusion / tamponade**	Pericardial effusion, with or without tamponade, requiring pericardiocentesis or surgical intervention.	During the procedure or within 30 days.
4	**Coronary vasospasm**	Coronary artery spasm during or after ablation resulting in ≥1 of the following: 1. Hypotension (systolic BP <90 mmHg) 2. Sustained ventricular arrhythmia (VT/VF) 3. Coronary intervention: intracoronary nitroglycerin, balloon angioplasty, or stenting	During the procedure or within 24 hours.
5	**Persistent phrenic nerve paralysis**	New reduced or absent diaphragmatic motion attributed to phrenic nerve injury, documented by chest X-ray or fluoroscopic sniff test, that persists >3 months. *Imaging is performed at operator discretion (e.g., for new dyspnea) and is not mandatory in all patients.* *Any patient with documented paralysis is re-imaged at 3 months; persistence = SAE, resolution = AE (Table 2).*	Onset during the procedure; persistence assessed at 3 months.
6	**Conduction system injury requiring pacemaker**	New sinus node dysfunction (sinus arrest or symptomatic sinus bradycardia) or AV block attributed to the procedure and requiring permanent pacemaker implantation.	Within 30 days of the index procedure.

#	Event	Definition	Timing window
7	**Hemolysis requiring hemodialysis**	Hemolysis (e.g., hemoglobinuria, elevated LDH or plasma free hemoglobin, low haptoglobin) with acute kidney injury requiring hemodialysis.	Within 7 days of the index procedure.
8	**Heart failure exacerbation**	New or worsening fluid retention requiring treatment and that is the reason for: 1. Prolongation of the hospitalization beyond 48 hours after the ablation procedure, or 2. Readmission for heart failure.	Within 30 days of the index procedure.
9	**Major vascular complication**	Vascular injury (e.g., hematoma, pseudoaneurysm, AV fistula, retroperitoneal bleeding, dissection, occlusion) requiring blood transfusion or vascular intervention (thrombin injection, endovascular or surgical repair).	Within 30 days of the index procedure.
10	**Atrio-esophageal fistula / esophageal perforation**	Communication between the esophagus and the left atrium or pericardium, or esophageal perforation, confirmed by CT, endoscopy, or surgery.	Within 90 days of the index procedure.

4. Adverse events, non-serious (Table 2)

#	Event	Definition	Timing window
1	**Transient phrenic nerve paralysis**	New reduced or absent diaphragmatic motion attributed to phrenic nerve injury (documented as in SAE 5) that resolves within ≤3 months, confirmed by repeat imaging.	Onset during the procedure.
2	**Coronary vasospasm treated with IV nitroglycerin**	Coronary artery spasm (ST-segment changes and/or angiographic narrowing) requiring IV nitroglycerin for treatment, without any SAE criterion (SAE 4). Nitroglycerin given for prophylaxis does not qualify.	During the index procedure or within 24 hours.
3	**Acute kidney injury**	≥2-fold increase in serum creatinine from baseline. *Serum creatinine is measured within 24 hours after the procedure and compared with a baseline value obtained within 3 months before the procedure. AKI requiring hemodialysis is an SAE (SAE 7).*	Within 7 days of the index procedure.
4	**Transient ischemic attack / stroke <24 hours**	Transient focal neurological deficit of presumed cerebrovascular origin resolving within 24 hours, with or without imaging evidence of acute infarction. Deficits lasting ≥24 hours are an SAE (SAE 2).	Within 30 days of the index procedure.

5. Reporting to the DSMB

- **Expedited: each SAE is sent to the DSMB chair within 7 days of site awareness (24 hours for death).**
- **Scheduled reviews: cumulative SAE and AE tables are provided at each scheduled DSMB meeting (after the first 30 and the first 70 randomized patients; Section 8).**
- **Ad hoc review:** any procedure-related death or atrio-esophageal fistula triggers an ad hoc DSMB review.
- **Content of each SAE report:** patient study ID, procedure date, event category (Table 1 number), onset date, brief narrative, treatment, outcome, investigator relationship assessment, and relevant source documents (e.g., imaging, ECG, discharge letter).
- **Cumulative tables:** number and percentage of patients with each SAE and AE, overall and per enrolled patient, with a listing of individual events.

Appendix H: Statistical Analysis Plan

The Statistical Analysis Plan is a separate document, drafted by the study statistician on the basis of Protocol Version 13.1 and finalized and signed before enrollment of the first patient (§13.3). Until then, the CRF Analysis and Implementation Specification v1.1 (13 Oct 2026) defines the monitoring, burden, recurrence and echo derivations.

A full Statistical Analysis Plan (SAP) will be prepared by the independent biostatistician and finalized prior to enrollment of the first patient. The SAP will provide full pre-specified detail for all primary and secondary analyses outlined in §13, including exact model specifications and software; covariate definitions.

Appendix I: Clinical Research Forms (CRF)

The CRFs are maintained as separate, versioned documents and are not reproduced in this protocol. The CRF set comprises the Pre-procedural CRF, Procedural CRF, POD 1 / Discharge CRF, Follow-up CRF, AE/SAE Report Form, Rhythm Core Laboratory Summary, Rhythm Episode Log, Daily Monitoring Log, Echo Core Laboratory Form, Echo Measurements Supplement, and ILR Setup Change Log. The CRFs will be revised to Protocol Version 13.1 after its internal approval.