Clinical Investigational Plan

Safety and Feasibility of Atrial Deganglionation as an Adjunctive Therapy for Atrial Fibrillation

Protocol No.	CIP-001
Rev	H
Date	31 March 2022
Sponsor:	AtriAN Medical Ltd Unit 204, NUIG Business Innovation Centre, Galway, Ireland
Principal Investigator:	Tamaz Shaburishvili, MD (Tbilisi Heart & Vascular Clinic) 64 Ljubljana Street, Tbilisi, Georgia. Tel +995 32 218 15 55 Ivo Skalsky, MD, (Na Homolce Hospital) Roentgenova 37/2, Praha 5, Czech Republic. Tel +420 257 271 111
Study Manager:	Barry O'Brien, AtriAN Medical Ltd Unit 204, NUIG Business Innovation Centre, Galway, Ireland Tel +353 87 2934292

This protocol has been prepared in compliance with current International Standard EN-ISO 14155:2020, Clinical Investigations of medical devices for human subjects - Good Clinical Practices; Annex A (normative) Clinical Investigation Plan (CIP).

This document contains confidential information for use by the Investigators and their designated personnel participating in this clinical investigation. It should be held confidential and maintained in a secure location.

Approval by Sponsor

All persons below agree on the present CIP. The information it contains is consistent with the current risk/benefit evaluation of the study preparation as well as with the moral, ethical and scientific principles governing clinical research as set out in the current versions of the Declaration of Helsinki and of the guidelines on Good Clinical Practice.

Sponsor		
Name	**Date**	**Signature**
Ken Coffey (Chief Executive Officer)	31-Mar-2022	DocuSigned by: Ken Coffey 1E430D04BF6540B...
Barry O'Brien (Chief Technology Officer/Study Manager)	31-Mar-2022	DocuSigned by: Barry O'Brien 6DF54CC4A1D0496...
Prof. Dr. J.R. (Joris) de Groot, (Cardiologist/Electrophysiologist - Medical Advisor)	31-mrt-2022	DocuSigned by: Joris de Groot FD16C32C8027446...

Investigator Signature Page

I have read this Investigational Plan and agree to adhere to the requirements. I also have read and understand fully the Investigator's Brochure, and I am familiar with the investigational devices and their use according to this protocol. I will provide copies of this Investigational Plan and all pertinent information to all site personnel involved in this study ensuring they are adequately trained. I will discuss this material with them and ensure they are fully informed regarding the study products and the conduct of the study.

I agree to conduct the study as outlined in the Investigational Plan, in accordance with the signed clinical study agreement and to the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation", ISO 14155:2020 (Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice), or the applicable local and international regulations, whichever provide the greater protection of the individual.

In addition, I agree to provide all the information requested in the Case Report Forms presented to me by the Sponsor in a manner to assure completeness, legibility and accuracy.

I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, Case Report Forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the Ethics Committee.

In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than the Sponsor, the Ethics Committee, or the Clinical Events Committee. Any such submission will indicate that the material is confidential.

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Table of Contents

Study Synopsis

Study Sponsor:	AtriAN Medical Ltd., Unit 204, NUIG Business Innovation Centre, Galway, Ireland. Contact Person: Barry O'Brien
Title	Safety and Feasibility of Atrial Deganglionation as an Adjunctive Therapy for Atrial Fibrillation
Protocol Number	CIP 001
Regulatory Status	For Clinical Investigation Use Only
Investigational Device(s)	Open Chest Epicardial Deganglionation (OCED) system
Indications for Use	Intended to ablate the autonomic ganglionated plexi (GP) structures on the epicardial surface of the heart to treat cardiac arrhythmia.
Study Design	A prospective, single-arm, multi-centre exploratory study of safety and feasibility in the treatment of patients undergoing cardiothoracic surgery.
Study Objectives	To assess the safety and feasibility of electroporation/Pulsed Electric Field (PEF) as a technology to achieve selective GP ablation. The primary hypothesis is that selective GP ablation (i.e. with minimal myocardial ablation) will lead to an extension in the atrial effective refractory period.
Study Duration	The study duration is expected to be 24 months including study close out. Patients will begin enrolment and undergo screening and surgical procedures
Study Monitoring	Study monitoring will be conducted by AtriAN designee as per the Monitoring Plan.
Subject Assessments	Screening, baseline evaluations & pre-procedural assessments will be used to determine subject eligibility for GP ablation.
Sample Size	Up to 30 subjects will be enrolled in the study.
Investigational Sites	• Tbilisi Heart & Vascular Clinic, Tbilisi, Georgia. • Na Homolce Hospital, Prague, Czech Republic.
Patient Population	Patients undergoing coronary artery bypass grafting (CABG).
Inclusion Criteria	To be eligible for this trial, subjects must meet all the following inclusion criteria: 1. Age is between 18 and 70 years. 2. Scheduled for open-chest cardiothoracic surgery, for coronary artery bypass grafting. 3. Legally competent and willing to sign the informed consent. 4. Life expectancy of at least 2 years.

Exclusion Criteria	To be eligible for this trial, subjects must NOT meet any the following exclusion criteria: 1. Previous cardiac surgery 2. Prior pericardial interventions 3. Prior pulmonary vein isolation (PVI) 4. Previous or existing pericarditis 5. Persistent or long-standing persistent atrial fibrillation 6. Indication for surgical ablation or PVI for atrial fibrillation 7. Indication for concomitant surgical valve repair or replacement 8. Indication for concomitant left atrial appendage (LAA) ligation or excision 9. History of previous radiation therapy on the thorax 10. History of previous thoracotomy. 11. Prior electrical or mechanical isolation of the Left Atrial Appendage (LAA) 12. The presence of LAA occlusion devices, coronary stents, prosthetic heart valves, pacemakers or implantable cardioverter defibrillators (ICDs) 13. Myocardial infarction within the previous 2 months 14. New York Heart Association (NYHA) Class IV heart failure symptoms 15. Left Ventricular Ejection Fraction (LVEF) < 40%, measured by transthoracic echocardiography (TTE) 16. Left atrial diameter > 5.0 cm, measured by transthoracic echocardiography (TTE) 17. The presence of left atrial thrombus when examined by transesophageal echocardiography (TEE) 18. The presence of atrial fibrillation (AF) attributable to non-cardiovascular causes such as thyroid disease, electrolyte imbalance/dehydration or other reversible causes 19. Active infection or sepsis as evidenced by increased white blood cell count, elevated C-reactive protein (CRP) or temperature > 38.5°C 20. Known or documented carotid stenosis > 80% 21. Stroke or transient ischemic attack within the previous 6 months 22. Known or documented epilepsy 23. Pregnancy or child-bearing potential without adequate contraception 24. Circumstances that prevent follow-ups 25. Drug abuse 26. Patients cannot be enrolled in another clinical study
Primary Safety Endpoint	Rate of device related Primary Safety Adverse Events within 30 days of the procedure. Primary Safety Adverse Events include: 1. Atrial perforation or excessive bleeding (excessive bleeding is defined as bleeding which requires any blood transfusion). 2. Pericarditis 3. Pericardial effusion 4. Cardiac tamponade (if either surgical or percutaneous drainage is required). 5. Constrictive pericarditis, requiring re-operation. 6. Newly developed sinus node dysfunction 7. Newly developed first, second or third degree atrioventricular (AV) block 8. Vasovagal reactions during hospital stay 9. Ventricular fibrillation

Primary Feasibility Endpoints	The primary feasibility endpoint includes confirmation of access and delivery of Pulsed Electric Field energy to targeted ablation sites.
Efficacy Endpoints	The clinical effectiveness endpoints are defined as the following: • A primary efficacy end point will be confirmation of an extension in the atrial effective refractory period (AERP) through the Pulsed Electric Field ablation of the GPs. Experimental and clinical data indicates that GP ablation extends AERPs. • A secondary efficacy endpoint will be the incidence of post-operative atrial fibrillation (POAF) up to the point of patient discharge. Ablation of GPs is a potential prophylactic treatment for post-operative atrial fibrillation. Data will be collected to quantify duration (from ICU arrival) to first incidence of POAF, duration of first POAF episode and standard of care method used to treat the POAF. POAF is defined as any AF of 30 seconds or longer duration.
Clinical Study Requirements	Baseline: (* Standard of Care) • Inclusion/Exclusion criteria • Signed Informed Consent • Frequency of reported episodes of atrial fibrillation * • Medical History including NYHA class * • Documentation of Smoking and Substance abuse * • Medication History, review of current and past Medications* • General Physical Exam* • ECG (12 Lead)* • 24Hr Holter recording documentation of AF, frequency and severity of AF and presence of asymptomatic episodes if relevant • TTE for LVEF and LA diameter* • Blood sample for laboratory investigation comprising Hgb, WBC, Platelet, Na, K, Creatinine, NT-proBnP, Troponin, C-reactive protein, TSH, INR * • Short form-36 (SF-36) QOL • TEE to assess for LA thrombus per elective procedure* <u>Procedure & Post-procedure</u> • GP ablation • AERP • Device Performance • Adverse event assessment • Protocol Deviation assessment • Cardiac Telemetry through to discharge (Post-Operative AF Detection) <u>Discharge</u> • Physical exam • ECG (12 Lead) • Medications • Adverse event assessment • Protocol Deviation assessment

	Follow-Up Intervals at 30 Days (±7days), 3M (±30days), 6M (±45days) and 12M (±60days) • Physical exam • Blood tests (6M only) • Short form-36 (SF-36) QOL (12M only) • Medications • ECG (12 Lead) • 24HR Holter (30 Days, 3M, 6M, 12M) • Adverse event assessment • Protocol Deviation assessment
Statistical Analysis	The study is not powered for any formal hypotheses testing or inference. Therefore, the statistical analyses conducted will be descriptive in nature. The primary safety, feasibility and efficacy endpoints will be summarized with descriptive statistics.

Schedule of Assessments (* Standard of Care)

Schedule of Tests:	**Baseline**	**Procedure**	**Post-Procedure to Discharge**	**Discharge**	**30 Days** ±7 days	**3 Mo** ±30 Days	**6 Mo** ±45 Days	**12 Mo** ±60 Days
Subject Eligibility/ Informed Consent	X							
Medical history & Demographics*	X							
NYHA Score*	X							X
Physical Exam*	X			X	X	X	X	X
TTE for LVEF and LA diameter*	X							
Blood tests*	X						X	
SF-36 QOL	X							X
Medication Log* (AAD-ATT)	X			X	X	X	X	X
ECG (12 Lead) *	X			X	X	X	X	X
TEE to exclude thrombus*	X							
24HR Holter *	X				X	X	X	X
Cardiac Telemetry			X					
Adverse Events	X	X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X
Device Performance		X						
AERP		X						

NYHA – New York Heart Association; TTE – transthoracic echocardiography; LVEF – left ventricular ejection fraction; LA – left atrium; SF-36 – Short Form 36; AAD-ATT – antiarrhythmic drugs and antithrombotic therapy; ECG – electrocardiogram; TEE – transesophageal echocardiography; AERP – atrial effective refractory period.

1. Background and Justification of the Proposed Trial Design

Atrial fibrillation (AF) is the most common chronic arrhythmia in man. In the European Union, its prevalence is 1.5-2% in the total population, and this number is expected to increase in the forthcoming decades[1]. AF is associated with a five-fold increased risk of stroke, a doubled risk of mortality and an increased risk of heart failure and cognitive impairment. Whether AF causes these detrimental concomitant diseases or is merely a marker of a bad vascular prognosis is debated. Similarly, prospective evidence that AF ablation improves prognosis is not yet available. However, a recent propensity matched study from Sweden demonstrated that AF ablation was associated with less stroke and a lower mortality rate[2].

In patients with symptomatic paroxysmal AF refractory for antiarrhythmic drugs (AAD), catheter ablation, pulmonary vein isolation in particular, is a successful treatment strategy[3]. A large proportion of AF patients have more advanced forms of AF, which is persistent (not spontaneously terminating or requiring electrical cardioversion), with enlarged left atria or after previously failed catheter ablations. In those patients, isolation of the pulmonary veins may be insufficient to achieve an acceptable procedural success[4]. The HRS/EHRA/ECAS consensus statement suggests that additional ablation may be warranted in those patients[5].

Therefore, a plethora of additional ablation approaches have been attempted over the last decade, among which the ablation of additional left atrial lines[6], the ablation of continuous fractionated atrial electrograms (CFAE)[7], ablation of rotors[8] and modulation of the autonomic nervous system[9,10]. Interestingly, the recent STAR-AF II trial randomized patients with persistent AF to pulmonary vein isolation (PVI) alone, PVI+CFAE ablation or PVI+ additional left atrial lines and found no difference in AF recurrence among these groups[11]. Basically, all these additional ablation strategies rely in some way on extended ablation of the atrial myocardium, which, in itself, may create channels for conduction and iatrogenic AF recurrences. This could (at least in part) explain the limited efficacy of those additional ablation strategies. If, however, additional ablation strategies could be performed without increasing the risk of iatrogenic AF, this could importantly improve the results of invasive therapy for advanced atrial fibrillation.

Role of the autonomic nervous system

The autonomic nervous system has been demonstrated to play an important role in initiation and perpetuation of AF. Injection of cholinergic agents into the ganglionated plexi (GPs), electrical stimulation of nerves, and pacing induced AF induces proarrhythmic autonomic hyperactivity[12 13], leading to shortening of the atrial and PV APD (parasympathetic effect), and increase of intracellular [Ca^{2+}] (sympathetic effect), resulting in triggered firing and induction of AF. Indeed, injection of botulinum toxin into the epicardial fat pads containing the GPs results in reduction of postoperative AF in patients undergoing coronary artery bypass grafting (CABG) surgery[14], but in addition appears to have a beneficial long-term effect on freedom of AF in this population[15]. However, in patients without pre-existent AF the beneficial effects of botulinum injection into the GPs are less clear[16,17]. Though radiofrequency (RF) ablation of GPs in CABG patients without AF has also shown potential for post-operative AF reduction[18]. The development of post-operative AF is associated with a higher risk of atrial fibrillation and stroke in the long term[19].

GP stimulation also directly affects atrial myocardial electrophysiology in a proarrhythmic manner and consistent with a predominantly parasympathetic action[20]. Disconnecting the extrinsic from the intrinsic cardiac innervation results in shortened regional refractory periods in dogs, and an increased burden of atrial fibrillation and atrial tachycardia (AF/AT) starting after 4-5 weeks[21]. Thus, removing the inhibitory effect of the extrinsic on the intrinsic autonomous cardiac innervation causes proarrhythmogenic hyperactivity of the GPs, which provides the rationale for GP ablation. Indeed, Katritsis et al. demonstrated fewer recurrences in paroxysmal AF patients randomized to catheter ablation of 4 major GPs areas and Marshall's ligament in addition to PVI versus either treatment in isolation. An anatomical approach toward GP ablation conferred less AF recurrence than an evoked vagal response based localization[22]. These were catheter ablation studies in patients with only paroxysmal AF, and it cannot be

discerned whether these effects are caused by GP ablation or by more atrial myocardial ablation, resulting in more rigorous and longer lasting PVI. The AFACT trial attempted to overcome these issues by randomizing patients undergoing thoracoscopic ablation of AF between additional epicardial radiofrequency ablation of the 4 major GPs versus no additional GP ablation. The study showed no benefit in absence of AF after one and two years, but significantly more surgical complications, mainly major bleedings[23]. Also, more sinus node dysfunction was noted in the GP group, and more pacemaker implantations. A sub-analysis of recurrences in AFACT showed that atrial tachycardias were more frequently noted in the GP ablation group, at least suggesting that the myocardial substrate was modified by GP ablation to facilitate atrial tachycardias. Therefore, it is very well possible that epicardial radiofrequency GP ablation in AFACT was not tissue selective, and additional myocardial ablation took place, resulting in the adverse effect of more atrial tachycardias.
Hence, radiofrequency ablation appears not selective for the GPs, and inadvertent myocardial ablation seems to occur both with endocardial as with epicardial approaches. An ablation approach selective for nervous system tissue may overcome this and may combine the potential benefits of GP ablation with the absence of iatrogenic atrial tachycardias.

Electroporation to cause selective irreversible cell damage within the GP - with minimum myocardium ablation.

Electroporation refers to the principle that cell membranes become permeable when subjected to high voltage, which results in apoptosis and cell death. Typically, very short episodes (microseconds) of high voltage are applied to the tissue to ablate. This technology has been used successfully in the treatment of various types of cancer[24,25]. One of the attractive features of the technology is the relative tissue selectivity, allowing ablation of the tissue of choice while sparing the surrounding structures, such as for example vessels[26] Particularly larger cells, such as neurons appear vulnerable for electroporation[27,28]. Therefore, in this instance, the electroporation enables irreversible damage to the GP, while sparing the myocardium and other adjacent tissues.
Electroporation - also known as Pulsed Electric Field (PEF) - now has also successfully been applied to isolate the pulmonary veins during catheter ablation for AF, making use of specificity for myocardial tissue when adjusting the characteristics of the electroporation pulse. The early reports on this strategy indicate that the technology is effective on acute and short-term outcomes, and safe as there were no cases of injury of the oesophagus or phrenic nerves[29,30], supporting the premise that this technology (using adjusted pulse characteristics) is tissue specific.

Electroporation [PEF] - Acute animal experiments

Madhavan et al. have described the effects of GP ablation with DC electroporation in 6 dogs, in which the heart was approached via subxiphoid access[31]. The authors demonstrate that with specially designed catheters, electroporation can be applied to abolish the GP response, with only a limited effect on atrial bipolar voltage, indicating no or limited myocardial ablation. In one animal ventricular fibrillation was induced, as a consequence of inadvertent movement of the catheter over the ventricle. Subsequent work utilized ECG gating of the electrical pulses to ensure that energy is delivered only during the ventricular refractory period; this showed that a much higher voltage than that used for GP ablation was required to cause ventricular fibrillation (VF) (3/3 animals had VF with 3000V, 1/4 with 2500V and none with ≤2000V) when the catheter was positioned on the ventricle. This work showed that GP ablation can be accomplished by applying ten 1000V pulses of 100 µs duration. Atrial effective refractory periods (AERP) consequently prolonged after GP ablation, indicating ceasing of vagal AERP shortening, and AF inducibility decreased. Pathological examination after the ablation procedure showed no pericardial lesions or adhesions, no damage to vessels or to the phrenic nerve, and no injuries to the transverse sinus, oblique sinus or left atrial posterior wall. These data support the acute tissue selectivity of DC electroporation for nervous tissue, sparing the myocardium and surrounding tissues.

Electroporation [PEF] - Chronic animal experiments

In another set of experiments, Padmanabhan et al. used a scoring system from grade 0 to III (from no damage, modified damage, >50% damage and >90% damage) for myocardial damage following GP electroporation[32]. They demonstrated in 6 dogs that after approximately 4 months, there was no myocardial damage following GP ablation in 15/21 ablated GP sites, with only minimal myocardial damage at 5/21 sites and myocardial damage greater than grade I at 1/21 site. All GP lesions were grade III or higher, with documentation of spill over ganglionic lesions at distant, non-ablated GPs. There were no signs of esophageal damage. These data demonstrate that also in the intermediate term, there is no evidence of concomitant damage, supporting the selectivity of the DC electroporation for ablation of nervous tissue with minimal ablation of the surrounding myocardium.

2. Device Description

AtriAN Medical's treatment involves ablation of ganglionated plexi structures on the epicardial surface of the heart. Using a Pulsed Electric Field (PEF) energy source and specialty catheters, the AtriAN System ablates these structures selectively with no or minimal myocardial injury. The system is known as the Open Chest Epicardial Deganglionation (OCED) system and is intended to ablate the autonomic ganglionated plexi structures on the epicardial surface of the heart. Treatment using this 'OCED' System is delivered as a concomitant procedure during open heart surgery with the intended purpose of eliminating autonomic drivers of atrial fibrillation, including post-operative atrial fibrillation. The system consists of the following components:

2.1 Catheters - Finger & Glove

The Glove catheter is used to ablate the oblique sinus ganglia (inferior right and inferior left ganglia). The Finger catheter is used to ablate the superior left, right superior, Vein of Marshall and transverse sinus ganglia. The Glove and Finger catheters are used separately, and both will be used during the procedure. The main body of the catheter consists of a flexible braided sheath. The distal end of each catheter is steerable via a wire pulling system on the catheter handle. Each electrode has an irrigation hole for infusion of saline to aid with procedure outcomes. On both catheters the back of the electrodes are insulated. Selective GP ablation is performed using monopolar direct current supplied by the PEF Generator.

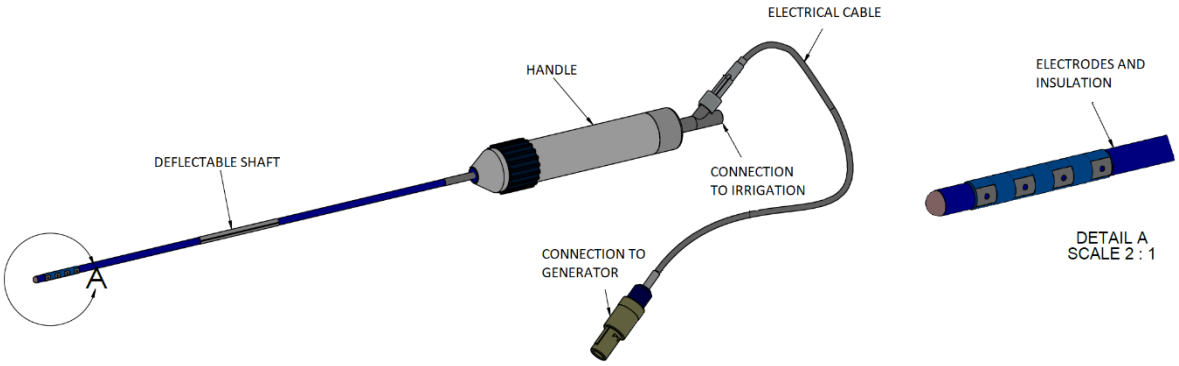

Figure 1: Drawing of the Finger Catheter

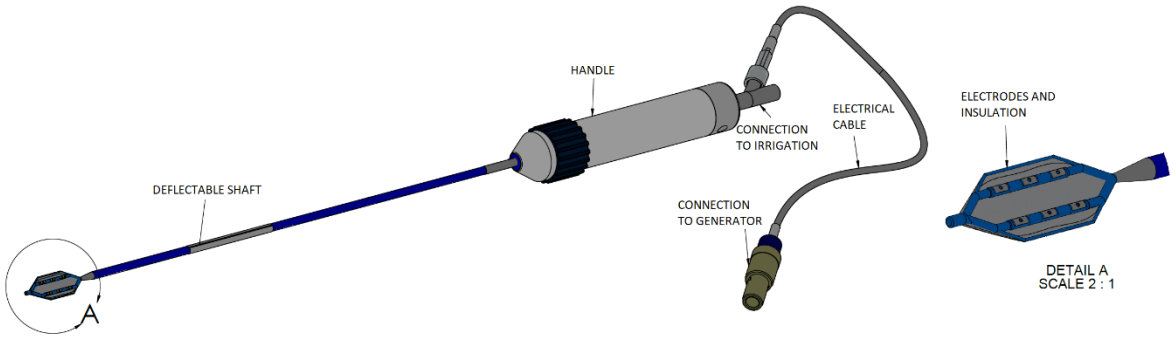

Figure 2: Drawing of the Glove Catheter

2.2 Dispersive Pad

This electrode/pad allows the return of the electrical path from the patient to the generator during the procedure. It has a large surface area and is attached to the patient's body typically in the shoulder or lumbar region. AtriAN will include a commercially available single-use adult dispersive pad as part of the OCED system.

2.3 ECG Synchronization Unit

The purpose of this unit is to trigger the correct timing of the 1000 V DC, 100 µs pulses to the treatment site. This timing is critical and must occur during the ventricular refractory period so as not to induce ventricular fibrillation. AtriAN is using a commercially available synchronization unit; system testing has been performed with this unit integrated with the generator.

2.4 PEF Generator

The PEF generator, with footswitch, provides 1000 V DC, 100 µs pulses to the connected catheter and dispersive pad circuit. The generator includes a user interface for input of treatment parameters which operates on a Linux system. The generator (Model PEFG01) and user interface has been developed specifically by AtriAN for this cardiac treatment.

Figure 3: AtriAN Pulsed Electric Field Generator

3. Intended Use

The Open Chest Epicardial Deganglionation (OCED) system is intended to ablate the autonomic ganglionated plexi structures on the epicardial surface of the heart to treat cardiac arrhythmia.

4. System Training

Training will be provided by AtriAN to site investigation staff on all aspects of the AtriAN system, including selection and input of treatment parameters, connection of system parts, operation of catheters and delivery of ablation pulses. While the targeted anatomical locations are readily identified, training and instruction will be provided in terms of accessing and identifying these in the open-chest setting.

The investigation team will need to be qualified and experienced in both cardiac surgery and cardiac electrophysiology. Specifically, the device will be used during a concomitant median sternotomy and in addition to applying the ablative treatments to the epicardial surface, cardiac pacing and measurements will be required to assess treatment.

5. Risk Benefit Analysis

A comprehensive risk analysis has been performed by AtriAN Medical Ltd in accordance with EN ISO 14971. Use of Failure Modes and Effects Analysis (FMEA) and Hazard Analysis techniques have identified potential device malfunctions and potential user errors along with clinical procedure risks. Mitigation steps to address each of the potential device malfunctions and potential user error risks along with clinical procedure risks have been implemented to reduce the risks as low as possible. These mitigation actions include extensive performance and safety testing, pre-clinical studies, development of Instructions for Use and User Manuals as well as development of user training materials. None of the remaining residual risks are higher than the risks associated with the use of currently available surgical and ablation tools. Section 8.9 of this document presents a list of the anticipated adverse events associated with GP ablation (deganglionation) in the planned concomitant open-chest surgical setting - these represent the risks associated with participation in this trial.

Of the risks directly associated with GP ablation, using the AtriAN system, that of ventricular fibrillation is noted as potentially having the highest severity. However, central to the mitigations here is the use of ECG-gated delivery of pulse energy which ensures that the ablation pulse is delivered during the refractory period of the cardiac cycle. This risk mitigation approach has been demonstrated during AtriAN's pre-clinical (animal) studies. Ventricular arrhythmia was also not observed in clinical studies that utilized voltages and pulse energies higher than AtriAN is using [29, 30]. Ventricular arrhythmia is not an uncommon occurrence during cardiac surgery and is dealt with using standard defibrillation techniques. Therefore, induction of ventricular fibrillation during GP ablation is not expected to harm study subjects.

The anticipated benefit of GP ablation is the reduced likelihood of experiencing post-operative atrial fibrillation in the days after the cardiac surgery [14, 18] - thus reducing the associated risk of stroke and the possibility of extended durations in hospital. The development of post-operative atrial fibrillation is also associated with a higher risk of atrial fibrillation and stroke in the long term (Ref 19) - thus the GP ablation may also reduce the probability of developing these longer-term complications. For patients that may already have paroxysmal atrial fibrillation there is also a potential benefit in that the GP ablation may reduce or eliminate the incidence of this condition [10, 15].

In summary, based on a review of the potential benefits along with the residual risks identified through the completion of risk management activities to date, the overall residual risk is considered appropriate for the clinical benefits. Additionally risk management principles with relating risk control measures are implemented to both the planning and the conduct of clinical investigation, in order to ensure the reliability of the clinical data generated and the safety of subjects.

6. Study Protocol

6.1 Study Objectives

The objective of this first-in-human study is to assess the safety and feasibility of electroporation/PEF as a technology to achieve selective GP ablation.
The primary hypothesis is that selective GP ablation (i.e. with minimal myocardial ablation) will lead to an extension in the atrial effective refractory period.

6.2 Study Design

This is a prospective, single arm, exploratory study of safety and feasibility in the treatment of up to 30 patients undergoing cardiothoracic surgery; as such no control or comparator group is required. The study will be performed at two sites;

- Tbilisi Heart & Vascular Clinic, Tbilisi, Georgia.
- Na Homolce Hospital, Prague, Czech Republic.

The primary feasibility endpoint will be demonstration of ability to access and deliver Pulsed Electric Field energy to all of the targeted ablation sites.
A primary efficacy end point will be to achieve an extension in the atrial effective refractory period (AERP) through the Pulsed Electric Field ablation of the GPs. Experimental and clinical data indicates that GP ablation extends AERPs.

A secondary efficacy endpoint will be the incidence of post-operative atrial fibrillation up to the point of patient discharge. Ablation of GPs is a potential prophylactic treatment for post-operative atrial fibrillation. Data will be collected to quantify duration (from ICU arrival) to first incidence of POAF, duration of first POAF episode and standard of care method used to treat the POAF. POAF is defined as any AF of 30 seconds or longer duration.

This exploratory treatment will be performed on patients undergoing elective open-chest cardiothoracic surgery. Once the heart is exposed, the treatment is performed before the elected procedure; the exploratory treatment and measurements will take 35-40 minutes to complete.

The sponsor will supply the ablation catheters, the pulsed electric field generator, the ECG synchronization unit and the patient dispersive pad. The investigation site will be expected to supply the stimulator and recording system for measurement of AERP, including the necessary temporary epicardial pacing wires. In addition, a conventional irrigation pump and tube set is required on-site for delivery of physiological saline through the ablation catheter during the pulse delivery.

6.3 Study Rationale

This study is intended to evaluate the safety and feasibility of the OCED system to ablate autonomic ganglionated plexi structures on the epicardial surface of the heart. The patient population will be those undergoing coronary artery bypass grafting (CABG).

6.4 Sample size

The study will include up to 30 patients with completed GP ablations. The justification for the number of test subjects is described in the **Statistical Justification** section below.

A subject is considered enrolled once he/she signs the informed consent form. All enrolled subjects will then proceed to complete the screening and any applicable baseline tests. If they do not meet the study criteria they will be withdrawn from the study and will not count towards the treated study population.

If a subject meets all inclusion criteria and none of the exclusion criteria and are deemed eligible for this study, they will be treated with the study device and system. Patients will be followed for approximately 12 months post-procedure.

6.5 Statistical Justification and Analysis of Results

This trial is intended to demonstrate safety and feasibility and is not designed to be a statistically significant study. As a result, no formal statistical hypothesis is planned to derive the appropriate sample size.

For all primary safety and performance endpoints, the 95% 2-sided exact binomial confidence intervals will be presented.

For the secondary end-point of AERP extension, it is anticipated that a 10% extension may be obtained. This will be assessed using Paired t-testing from the pre-treatment and post-treatment AERP values from all patients.

6.6 Site Selection and Training

All operators included in this clinical trial will be trained by the Sponsor in the use of investigational device. Study training will be documented and will include a review of the following:

- the investigational plan,
- ISO 14155, Declaration of Helsinki (2013),
- SAE reporting,
- Good Clinical Practices (GCPs)
- and all study procedures.

Each site will have a site qualification visit to assure the Investigator clearly understands and accepts the obligations incurred in undertaking the study and that the facilities and systems for conducting the study are acceptable. Each site must have equipment for conducting cardiac ablation procedures including equipment for cardiac pacing and recording and should have permission according to local law to perform cardiac ablations.

6.7 Patient Inclusion Criteria

- Age is between 18 and 70 years.
- Scheduled for open-chest cardiothoracic surgery, for coronary artery bypass grafting.
- Legally competent and willing to sign the informed consent.
- Life expectancy of at least 2 years.

6.8 Patient Exclusion Criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Previous cardiac surgery.
- Prior pericardial interventions.
- Prior pulmonary vein isolation (PVI).
- Previous or existing pericarditis.
- Persistent or long-standing persistent atrial fibrillation.
- Indication for surgical ablation or PVI for atrial fibrillation.
- Indication for concomitant surgical valve repair or replacement.
- Indication for concomitant left atrial appendage (LAA) ligation or excision.
- History of previous radiation therapy on the thorax.
- History of previous thoracotomy.
- Prior electrical or mechanical isolation of the Left Atrial Appendage (LAA).
- The presence of LAA occlusion devices, coronary stents, prosthetic heart valves, pacemakers or implantable cardioverter defibrillators (ICDs).
- Myocardial infarction within the previous 2 months.
- NYHA Class IV heart failure symptoms.
- Left ventricular ejection fraction (LVEF) < 40%, measured by transthoracic echocardiography (TTE).
- Left atrial (LA) diameter > 5.0 cm, measured by transthoracic echocardiography (TTE).
- The presence of left atrial thrombus when examined by transoesophageal echocardiography (TEE).
- The presence of AF attributable to non-cardiovascular causes such as thyroid disease, electrolyte imbalance/dehydration or other reversible causes.
- Active infection or sepsis as evidenced by increased white blood cell count, elevated CRP or temperature > 38.5°C.
- Known or documented carotid stenosis > 80%
- Stroke or transient ischemic attack within the previous 6 months.
- Known or documented epilepsy.
- Pregnancy or child-bearing potential without adequate contraception.
- Circumstances that prevent follow-ups.
- Drug abuse.
- Patients cannot be enrolled in another clinical study

The study will involve up to 30 patients with completed GP ablations. Recruitment is anticipated to be completed within 9 months.

Subjects may withdraw from the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Patient recruitment will be terminated prematurely at any time if the risk of serious adverse events exceeds the expected benefit of the trial.

7. Study Endpoints

7.1 Primary Safety Endpoint:

Rate of device related Primary Safety Adverse Events within 30 days of the procedure.

Primary Safety Adverse Events include:

1. Atrial perforation or excessive bleeding (excessive bleeding is defined as bleeding which requires any blood transfusion).
2. Pericarditis
3. Pericardial effusion
4. Cardiac tamponade (if either surgical or percutaneous drainage is required).
5. Constrictive pericarditis, requiring re-operation.
6. Newly developed sinus node dysfunction.
7. Newly developed first, second or third degree atrioventricular (AV) block
8. Vasovagal reactions during hospital stay
9. Ventricular fibrillation

7.2 Primary Feasibility Endpoints:

The primary feasibility endpoint includes confirmation of access and delivery of Pulsed Electric Field energy to targeted ablation sites.

7.3 Efficacy Endpoints:

The clinical effectiveness endpoints are defined as the following:

- A primary efficacy end point will be confirmation of an extension in the atrial effective refractory period (AERP) through the Pulsed Electric Field ablation of the GPs. Experimental and clinical data indicates that GP ablation extends AERPs.
- A secondary efficacy endpoint will be the incidence of post-operative atrial fibrillation up to the point of patient discharge. Ablation of GPs is a potential prophylactic treatment for post-operative atrial fibrillation. Data will be collected to quantify duration (from intensive care unit (ICU) arrival) to first incidence of POAF, duration of first POAF episode and standard of care method used to treat the POAF. POAF is defined as any AF of 30 seconds or longer duration[33].

8. Study Procedure and Data Collection

The following baseline data must be collected prior to the procedure for all subjects meeting the inclusion criteria (*Assumed to be standard of care):

- Baseline:
  - Inclusion/Exclusion criteria
  - Signed Informed Consent
  - Frequency of reported episodes of atrial fibrillation *
  - Medical History including NYHA class *
  - Documentation of Smoking and Substance abuse *
  - Medication History, review of current and past Medications*
  - General Physical Exam*
  - 12 Lead ECG*
  - 24Hr Holter recording documentation of AF, frequency and severity of AF and presence of asymptomatic episodes if relevant
  - TTE for LVEF and LA diameter*
  - Blood sample for laboratory investigation comprising Hgb, WBC, Platelet, Na, K, Creatinine, NT-proBnP, Troponin, C-reactive protein, TSH, INR *
  - Short form-36 (SF-36) QOL
  - TEE to assess for LA thrombus per elective procedure*

The procedures required for screening and baseline may be conducted during more than one visit, provided that all procedures are conducted within 90 days prior to the index procedure.

- ^{123}I-*m*IBG Scintigraphy and SPECT - UMC Amsterdam only

- Study Procedure:

  After opening of the chest (and after cannulation at the discretion of the operator), but before cardiopulmonary bypass and cardioplegia, baseline atrial effective refractory period (AERP) will be determined. The atrial GPs will then be ablated, with AERP measurements performed at intermediate timepoints and after all GP ablations.

  <u>Paralytic Agent</u>

  In addition to standard of care general anaesthesia, a paralytic agent or nerve block needs to be administered to suppress skeletal muscle stimulation. Vecuronium or Rocuronium are the preferred drug options as these have minimal impact on AERP values; however, the baseline AERP reading should be taken with paralytic already administered, just before the first ablation.

  <u>Measurement of AERP</u>

  AERP will be measured at any one, or more, of the following sites: left atrial appendage, left atrium or right atrium, depending on clinician preference. Measurements will be performed using temporary epicardial pacing wires; one wire connected to the measurement site (-ve) and one wire positioned subcutaneously (+ve); the wires are connected to the stimulator unit of an EP system. A standard diagnostic quadripolar EP catheter will be positioned behind the atrium and connected to the EP system for recording atrial activation and sensing of capture. Check that the temperature of the heart is 36˚C -1/+2˚C just before, during or just after AERP measurement.

  AERP will be determined with standard premature pacing protocols. Pace the measurement site (i.e. left atrial appendage, left atrium or right atrium) with a train of 8 S1 cycles at Basic Cycle Length 500 ms, output

in range 10-20 mA, pulse width 2-3 ms, followed by an S2 of 400 ms. Once capture of S2 is confirmed immediately continue with the next pacing train. Progressively shorten S2 by 50 ms per cycle, until loss of capture is observed. Then retry at the last S2 coupling interval that captured and reduce coupling interval of S2 by 10 ms per cycle until loss of capture is observed on 2 consecutive occasions. The longest S2 coupling interval that does not capture is the AERP.

If attempts to measure AERP result in atrial fibrillation or atrial flutter, a cardioversion should be attempted, after which a waiting time of 10 minutes is needed before new attempts to measure AERP are undertaken. If more than one cardioversion is needed, removing that patient from the study analysis should be considered.

Ablation of GPs

The GPs to be ablated in this study are illustrated in Figure 4. The sequence of the ablations will be as follows:

1) Oblique Sinus GP (OSGP)
   These are the retro-atrial GPs located on the posterior left atrium, close to the junction of the pulmonary veins and the left atrium. They are sometimes separately identified as the inferior left GP (ILGP) and inferior right GP (IRGP).
2) Right Superior GP (RSGP)
   This is located on the anterosuperior surface of the right atrium, medial to the superior vena cava/right atrium junction and lateral to the aortic root.
3) Transverse Sinus GP (TSGP)
   This is located at the base of the aorta and pulmonary artery within the transverse sinus.
4) Left Superior GP (LSGP)
   The superior left GP is located at the junction of the left superior pulmonary vein with the posterior left atrium, in the left superolateral area.
5) Ligament of Marshall GP (LMGP)
   This is located between the anterior aspect of the left pulmonary veins and the posterior left atrial appendage.

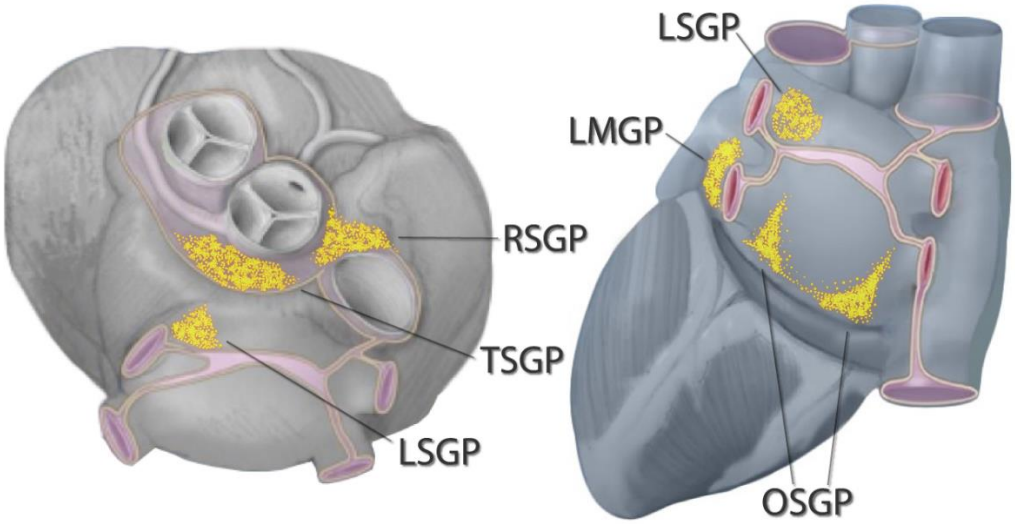

Figure 4: Targeted ablation locations; OSGP, RSGP, TSGP, LSGP and LMGP.

AERP will be determined at baseline (before ablations) and after all ablations are completed. In addition, at the discretion of the operator, intermediate AERP measurements may be made after ablation of the OSGP and after TSGP ablation. The sequence of ablations and measurements is therefore as shown in Figure 5. The OSGP is ablated with the Glove catheter while all other sites are ablated with the Finger catheter. Each ablation sequence consists of 10 sequential ECG-gated pulses; each pulse at 1000 V and of 100 µs duration. Each GP location is ablated with between three and six of these sequences; in some instances a pull-back of a few millimetres or catheter repositioning is allowable between sequences in order to ensure good coverage of the target area. Optionally, the OSGP may be treated using separate approaches from the left and right sides i.e. individually treating the inferior left and inferior right GPs with up to three sequences each, rather than treating them as a single entity. A 0.9% normal saline solution is irrigated through the catheter at a flow rate of 2 ml/min, during ablation only.

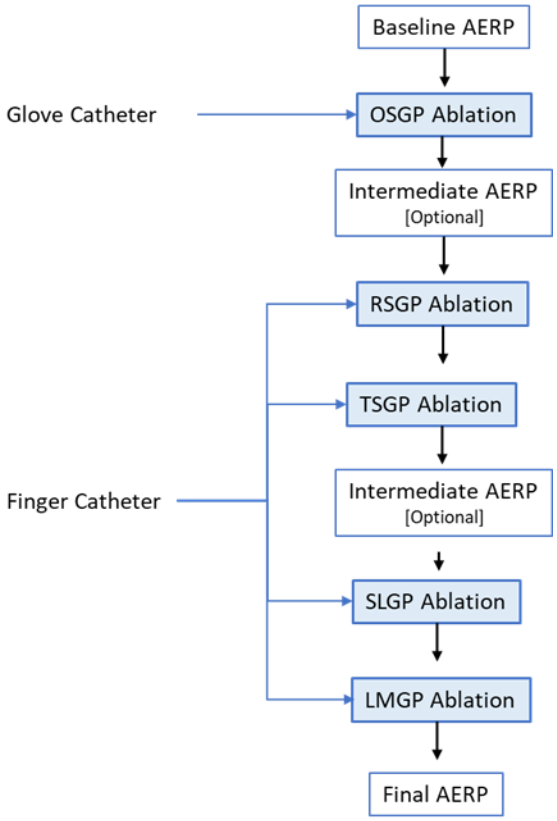

Figure 5: Sequence of ablations and AERP measurements

Document electrical cardioversion or defibrillation during the procedure in the study records. The record should indicate when this was performed i.e. before ablations/measurements, between specific ablations/measurements or after final AERP measurement (during the index procedure).

- Index Cardiac Surgery Procedure
  Upon completion of GP ablations and AERP measurements, the elected cardiothoracic surgery will progress as planned.
- Post-Operative Care and Discharge:
  - Adverse Events and Concomitant AAD-ATT Medication
  - Cardiac telemetry through to discharge.
  - ECG
  - Physical Exam
- Follow-Up at 30 Days:
  - 24 Hr. Holter for Frequency and Duration of atrial arrhythmias
  - Adverse Events and Concomitant AAD-ATT Medication
  - ECG
  - Physical Exam
- 3 months:
  - 24 Hr. Holter for Frequency and Duration of atrial arrhythmias
  - Adverse Events and Concomitant AAD-ATT Medication
  - ECG
  - Physical Exam
- 6 months:
  - 24 Hr. Holter for Frequency and Duration of atrial arrhythmias
  - Adverse Events and Concomitant AAD-ATT Medication
  - ECG
  - Physical Exam
  - Blood sample for laboratory investigation comprising Hgb, WBC, Platelet, Na, K, Creatinine, NT-proBnP, Troponin, C-reactive protein, TSH, INR
- 12 months:
  - 24 Hr. Holter for Frequency and Duration of atrial arrhythmias
  - Short Form-36 (SF-36) QOL
  - Adverse Events and Concomitant AAD-ATT Medication
  - ECG
  - Physical Exam
  - NYHA score

8.1 Informed Consent

Patients will be asked to sign informed consent after an explanation of the risks and potential benefits has been provided. Informed consent must be obtained from each patient prior to conducting any study-related procedures including screening procedures that are not part of the standard of care at the institution. Patients with a planned cardiothoracic surgical procedure will receive written information about the study prior to their scheduled procedure date to give sufficient time to carefully read the patient information letter. During the pre-procedural outpatient clinic visit the investigator or his staff will provide information about the study in case any questions remain. The information is intended to give each participant a thorough understanding of the purpose and the nature of the trial, the cooperation required, anticipated benefits, and potential hazards of the study. The investigator also explains that the subject is completely free to refuse or to withdraw from the study and that if he/she does so then he/she receives standard treatment with the same degree of care. It is the responsibility of the treating physician or his staff to obtain written informed consent (according to local legal requirements and regulations). A consent

form (in the native language) will be made available. The consent form will be signed and dated by both the investigator or his staff and the subject. The subject is obliged to date the informed consent him/herself. The fact that informed consent was obtained is recorded in the Case Report Form (CRF).
Screening failures will not be followed further and will not be counted toward the maximum possible patients who receive treatment.
The Investigator will retain an original of the signed informed consent document in each patient's record, and also provide an original to the patient. The Investigator shall not request the written informed consent of any patient and shall not allow any patient to participate in the investigation, before obtaining Ethics Committee (EC) and or Competent Authority approval.
Prior to starting the study, the Investigator will provide the Sponsor with a copy of the Informed Consent Document approved by the EC with documented evidence that the EC has approved the protocol.

8.2 EDC Data Collection Platform

Study data will be recorded in a limited-access, secure electronic data capture (EDC) system with data entry into electronic case report forms (eCRFs) that capture the data for each enrolled Subject, as required by the clinical study protocol. Data reported on the CRF, which are derived from Source Documents, must be consistent with the Source Documents or the discrepancies must be explained.
Investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the eCRF. eCRFs must be completed by Investigators or their authorized personnel.
An audit trail must be maintained for any changes or corrections to an eCRF.
Paper CRF changes or corrections must be dated, initialled, and explained (if necessary) and must not obscure the original entry. Changes and corrections to eCRFs should be made by the data originator, Investigator or their authorized personnel. If it is necessary for Sponsor personnel to make changes to the eCRF, a justification for the necessity should be documented and any such changes must be endorsed by the Investigator.
By default, users of the EDC system should have view-only permissions, unless the user's specific role requires entering or changing data. A list of all individuals with authorized access the EDC will be maintained. The list of authorized users will reflect the permissions assigned for each user and the dates that access was granted and terminated. Access will be terminated as soon as possible for users that are no longer working on the study (e.g., terminated employees, site closures, Investigator disqualification, etc.) and for users that have demonstrated intentional misuse.
The EDC system will be designed with computer-generated, time-stamped electronic audit trails. Audit trails must apply to the creation, modification or deletion of any data elements and must capture the user that is creating, modifying or deleting data. The reason for modifications and deletion of data should also be captured.
Data will be backed up and archived in a manner that protects against catastrophic loss and ensures the quality and integrity of the data.
Signed electronic records must contain the following information associated with the signing that clearly indicates:

- Printed name of the signer;
- Date and time when the signature is executed; and
- Meaning (such as review, approval, responsibility or authorship) associated with the signature.

An electronic signature must be linked to the respective electronic record to ensure that signatures cannot be excised, copied, or otherwise transferred to falsify and electronic record by ordinary means. Each

electronic signature must be unique to one individual and may not be reused or reassigned to anyone else.

The system facilitating electronic signatures will be designed so that the attempted use of an electronic signature by anyone other than the genuine user requires collaboration by two or more individuals.

8.3 Study Completion

The date of study completion for study subjects who complete all follow-ups is recorded on the STUDY COMPLETION Case Report Form.

8.4 Schedule of Events

The tests and measurements to be conducted at baseline, during the treatment procedure, and during follow-up visits are illustrated in the following chart. (*Considered as Standard of Care)

Schedule of Tests:	**Baseline**	**Procedure**	**Post-Procedure to Discharge**	**Discharge**	**30 Days** ±7 days	**3 Mo** ±30 Days	**6 Mo** ±45 Days	**12 Mo** ±60 Days
Subject Eligibility/ Informed Consent	X							
Medical history & Demographics*	X							
NYHA Score*	X							X
Physical Exam*	X			X	X	X	X	X
TTE for LVEF and LA diameter*	X							
Blood tests*	X						X	
SF-36 QOL	X							X
Medication Log (AAD-ATT)*	X			X	X	X	X	X
ECG (12 Lead) *	X			X	X	X	X	X
TEE to exclude thrombus*	X							
24HR Holter *	X				X	X	X	X
Cardiac Telemetry			X					
Adverse Events	X	X	X	X	X	X	X	X
Protocol Deviation	X	X	X	X	X	X	X	X
Device Performance		X						
AERP		X						

NYHA – New York Heart Association; TTE – transthoracic echocardiography; LVEF – left ventricular ejection fraction; LA – left atrium; SF-36 – Short Form 36; AAD-ATT – antiarrhythmic drugs and antithrombotic therapy; ECG – electrocardiogram; TEE – transesophageal echocardiography; AERP – atrial effective refractory period.

8.5 Patient Lost to Follow-Up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects; two of these attempts should include attempting to contact subject via registered mail. The investigator will document the date and type of attempted communication and will complete the STUDY COMPLETION Form when a patient is lost to follow-up.

8.6 Patient Withdrawals and Discontinuation

Subjects have the right to withdraw from the clinical investigation at any time and for any reason without prejudice to their future medical care by the investigation team or investigation site. The investigator will ask for the reason for their withdrawal and will record all information regarding the patient

discontinuation on the STUDY EXIT Case Report Form. An investigator may also withdraw a patient from study participation at any time and shall report the reason for withdrawal to the Sponsor.

A subject may be withdrawn from the clinical investigation for the following reasons:

- Subjects may choose to withdraw from the clinical investigation under the terms of the Declaration of Helsinki and their consent documentation without having to give a reason;
- Any unanticipated adverse reaction which is, in the opinion of the Investigator, related to the treatment and will endanger the well-being of the patient if treatment is continued;
- Development of any intercurrent illness(es), infection or condition(s) that might interfere with the Clinical Investigational Plan;
- Non-compliance with the clinical investigation procedures deemed by the Investigator to be sufficient to cause discontinuation;
- Any problem deemed by the Investigator to be sufficient to cause discontinuation.

Investigator will treat all subjects discontinued from the investigation due to an unanticipated adverse reaction, directly related to the investigation, until the reaction resolves.

Investigator will not replace subjects who have withdrawn from the clinical investigation if they were treated with the investigational device. If possible, Investigator will perform any procedures or assessments planned for the subject at the time of withdrawal.

If the decision to terminate the study is made by the sponsor or the study doctor, the Ethics Committee that approved the study must be notified immediately and will evaluate the reasons for the termination of the study. In urgent cases, the study will be terminated to ensure study participant safety, and the Ethics Committee will be notified as soon as possible.

8.7 Early Termination of Clinical Investigation

Both the Sponsor and Investigator reserve the right to terminate the clinical investigation at any time.

The sponsor may suspend or prematurely terminate either a clinical investigation site or the entire clinical investigation for significant and documented reasons. Such reasons are as follows:

- If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, the sponsor may suspend the clinical investigation while the risk is assessed. The sponsor may terminate the clinical investigation if an unacceptable risk is confirmed.
- Monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

After review of the clinical safety data, the Sponsor and Investigator may agree to terminate the clinical investigation if necessary. If necessary, and after review and consultation with Principal Investigator, Sponsor will make a final determination on whether to terminate the study.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in the clinical study at the investigation sites for which they are responsible.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The Principal Investigator and sponsor will keep each other informed of any communication received from either the EC or the regulatory authority.

If, for any reason, the sponsor suspends or prematurely terminates the investigation at an individual investigation site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the principal investigator or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other principal investigators.

If suspension or premature termination occurs:

- The sponsor remains responsible for providing resources to fulfil the obligations from the protocol and existing agreements for following up the subjects enrolled in the clinical investigation, and
- The Principal Investigator or his/her authorized designee will promptly inform the enrolled subjects at his/her investigation site, if appropriate.

8.8 Adverse Event Reporting

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. All adverse events are to be reported on the ADVERSE EVENT Case Report Form. All adverse events will be documented with the date of occurrence, relatedness to device or procedure, severity, action taken, resolution and any pertinent additional information as identified in MDCG 2020-10/1 and MDR Art. 80(2).
Adverse events associated with users or other persons may be documented separate from adverse events associated with the subject, taking into account the data privacy regulations.

Adverse events are classified based on the definitions as follows (ISO 14155).

Adverse event (AE): any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. **NOTE 1** This definition includes events related to the investigational medical device or the comparator (if applicable). **NOTE 2** This definition includes events related to the procedures involved. **NOTE 3** For users or other persons, this definition is restricted to events related to investigational medical devices.
Adverse device effect (ADE): adverse event related to the use of an investigational medical device. NOTE: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. In addition, this definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) Any adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users, or other persons as defined by one or c) more of the following: 1. life-threatening illness or injury, 2. permanent impairment of a body structure or a body function including chronic diseases, or, 3. in-patient or prolonged hospitalization, or 4. medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, d) foetal distress, foetal death or a congenital physical or mental impairment or birth defect. **Note:** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious health threat: signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons **Note:** This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Serious adverse device effect (SADE): adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated serious adverse device effect (USADE): Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.
Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.
Device Deficiency: Any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.
Device Malfunction: failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.
User Error: user action or lack of user action while using the medical device (3.34) that leads to a different result than that intended by the manufacturer or expected by the user. **Note 1:** Use error includes the inability of the user to complete a task. **Note 2:** Use errors can result from a mismatch between the characteristics of the user, user interface, task or use environment. **Note 3:** Users might be aware or unaware that a use error has occurred. **Note 4:** An unexpected physiological response of the patient is not by itself considered a use error. **Note 5:** A malfunction of a medical device that causes an unexpected result is not considered a use error.

Adverse Event Reporting- Clinical site role:

The Investigator will document all Serious Adverse Events (SAE) and Serious Adverse Device Effects (SADE), including device deficiencies in the study participant's patient file and report it to the Sponsor, within 24-hours of knowledge of event.

In categorising the adverse event and observed device deficiency the principal investigator shall refer to ISO 14155 Annex F- Adverse event categorization. The investigator will document the action taken in relation to the investigational device and to other treatments.

The Investigator will also report to the EC, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect. This information shall be promptly followed by detailed written reports. The Investigator must notify the sponsor once the EC has been notified.

The principal investigator shall supply the sponsor, upon sponsor's request, with any additional information related to the safety reporting of a particular event. Source data are preferentially immediately transferred to the ADVERSE EVENT CRF. When medical reports (lab results, examinations, etc.) associated with adverse events are submitted to the CRO or sponsor, all personal subject

information (name, address, etc.) MUST be removed or redacted. The redacted materials must be identified only with the Site and subject's study numbers.

The investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. The investigator will report all AEs regardless of whether they are anticipated or unanticipated and regardless of classification, seriousness, severity, outcome or causality.

Assessment of Adverse Event Severity:
Where the determination of AE severity rests on medical judgment, the determination of severity must be made with the appropriate involvement of a medically qualified investigator.
The severity of AEs will be graded using the following definitions:

Mild awareness of sign, symptom, or event, but easily tolerated
Moderate: discomfort enough to cause interference with usual activity and may warrant intervention
Severe: incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

Relationship to the Device and related procedure:
The principal Investigator is required to assess whether there is a reasonable possibility that the Study Device or procedure caused or contributed to an AE. The relationship between the use of the device and procedure and the occurrence of each adverse event shall be assessed and categorized and recorded in ADVERSE EVENT CRF.
During this assessment, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Investigation Plan or the Risk Analysis Report shall be consulted. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

Each SAE will be classified according to four different levels of causality as described below per MDCG 2020-10/1:

1. Not related: Relationship to the device, comparator or procedures can be excluded when:
- the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device;
- the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event;
- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device / procedures and the adverse event.

2. Possible: The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an

underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Causal relationship: the serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when:
the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with investigational device use/application or procedures;
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to;
  - the investigational device or procedures have an effect on;
- the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known);
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible);
- other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- harm to the subject is due to error in use;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

The sponsor and the investigators will distinguish between the serious adverse events related to the investigational device and those related to the procedures (any procedure specific to the clinical investigation). An adverse event can be related both to procedure and the investigational device. Complications caused by concomitant treatments not imposed by the clinical investigation plan are considered not related.
Similarly, several routine diagnostic or patient management procedures are applied to patients regardless of the clinical investigation plan. If routine procedures are not imposed by the clinical investigation plan, complications caused by them are also considered not related.

In some particular cases the event may not be adequately assessed because information is insufficient or contradictory and/or the data cannot be verified or supplemented. The sponsor and the Investigators will make the maximum effort to define and categorize the event and avoid these situations.

Where an investigator assessment is not available and/or the sponsor remains uncertain about classifying the serious adverse event, the sponsor should not exclude the relatedness; the event should be classified as “possible” and the reporting should not be delayed.

Adverse Event Reporting - Sponsor role:

The sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation.

The sponsor will review the investigator's assessment of all adverse events and all device deficiencies and determine if an independent review is required by the Clinical Events Committee as described in section 13.9.

The sponsor must report to regulatory authorities, within the required time period as identified in table 1, all serious adverse events and device deficiencies that could have led to a serious adverse device effect, including serious health threat. The sponsor will report this information in a Summary Reporting Form as outlined in MDCG 2020-10/1 and MDR Art. 80(2) or as provided by the regulatory authority.

Table 1: Competent Authorities Reporting timelines

Time period	Reportable events
Immediately, but not later than 2 calendar days after awareness by sponsor of a new reportable event or of new information in relation with an already reported event.	For all reportable events as described in section 5 MDCG 2020-10/1 and MDR Art. 80(2):which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it.
Immediately, but not later than 7 calendar days following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.	Any other reportable events as described in section MDCG 2020-10/1 and MDR Art. 80(2) or a new finding/update to it.

The sponsor shall ensure that the EC and the regulatory authorities are informed of significant new information about the clinical investigation.

In the case of a multicentre clinical investigation, the sponsor will inform all principal investigators in writing of all the serious adverse events at all investigation sites that have been reported to the sponsor.

In the case of a serious adverse device effects the sponsor will determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

8.9 Anticipated Adverse Events

The following adverse events have been identified for the atrial deganglionation and for the open-chest cardiac surgery.

Note: Arrhythmia events are not uncommon during cardiac surgery procedures and will not be identified as adverse events if AE/SAE definitions per section 8.8 are not met.

Study-specific SAEs that may be directly related to atrial deganglionation:	
Note:	**Each event must first meet the SAE definition as described in section 8.8 to be defined as an SAE.**
1.	Emergency during the procedure requiring change in surgical strategy
2.	Atrial perforation or excessive bleeding (excessive bleeding is defined as bleeding which requires any blood transfusion).
3.	Hemothorax or pleural effusion

4.	Pericarditis
5.	Pericardial effusion
6.	Cardiac tamponade (if either surgical or percutaneous drainage is required).
7.	Constrictive pericarditis, requiring re-operation.
8.	Documented atrial or ventricular arrhythmia during hospital stay
9.	Newly developed sinus node dysfunction.
10.	Newly developed first, second or third degree AV block
11.	Persistent chest pain
12.	Phrenic nerve damage
13.	Hypotension
14.	Prolonged Hospitalization
15.	Vasovagal reactions during hospital stay
16.	Perforation of great vessels
17.	Perforation of lung
18.	Perforation of esophagus
19.	Myocardial damage
20.	Burns
21.	Ventricular fibrillation
22.	Coronary sinus damage
23.	Pulmonary vein stenosis
24.	Infection

SAEs related to open-chest CABG surgery:	
Note:	**Each event must first meet the SAE definition as described in section 8.8 to be defined as an SAE.**
1.	Death (within the first 30 days post-operative or > 30 days if procedure related
2.	Cardiac or respiratory arrest/depression during hospital stay
3.	Stroke (resulting in neurological deficit lasting more than 24 hours or lasting 24 hours or less with a brain imaging study showing infarction).
4.	Transient Ischemic Attack (TIA) or a neurological deficit lasting less than 24 hours, and if an imaging study is performed showing no evidence of infarction.
5.	Myocardial infarction (according to ESC Guidelines definition)
6.	Documented atrial or ventricular arrhythmia during hospital stay
7.	Congestive heart failure, including volume overload
8.	Prolonged Hospitalization
9.	Coronary artery dissection, spasm or occlusion
10.	Perforation of the lung
11.	Hemothorax or pleural effusion
12.	Pneumothorax
13.	Persistent pneumothorax (requiring intervention)
14.	Pneumonia
15.	Pulmonary edema
16.	Pulmonary embolism
17.	Pulmonary hypertension
18.	Pericarditis
19.	Pericardial effusion
20.	Cardiac tamponade (if either surgical or percutaneous drainage is required).
21.	Constrictive pericarditis, requiring re-operation.
22.	Thrombosis – deep vein thrombosis or pulmonary embolism
23.	Significant chest wound
24.	Anesthesia or paralytic drug reaction

8.10 Emergency Contact Details for Reporting Adverse Device Effects

Contact Name: Barry O'Brien
Phone +353 87 2934292
Email: barry.obrien@atrianmedical.com

8.11 Device Deficiencies and Malfunctions

All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the medical devices shall be documented and reported to the Sponsor.

The DEVICE DEFICIENCY FORM is specific for reporting all device deficiencies, or malfunctions that occur during the course of the trial, whether or not they were associated with an adverse event. Device Deficiency Forms should be submitted to the Sponsor within 24 hours of the occurrence defining the device deficiency. Where possible, the investigational device should be returned to the study Sponsor for analysis as soon as possible from the time of the failure or malfunction. An investigation of device failures and malfunctions will be conducted by the study sponsor. Any adverse events associated to device deficiencies or malfunctions should be recorded in the Adverse event form. In these cases the

Sponsor should review the risk analysis to determine if appropriate corrective and preventive actions are in place to protect the safety of subjects, users, and other persons.

9. Study Conduct

9.1 Ethics

This study will be conducted in conformity with the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: a guide for manufacturers and notified bodies) and NB-MED 2.7/3 (Clinical investigations: serious adverse event reporting), ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), or the applicable local and international regulations, whichever provide the greater protection of the individual. The clinical investigation plan and other relevant documentation shall be submitted to the appropriate Ethics Committee for review. In countries in which additional requirements apply (e.g., notification to, or approval from the Competent Authority), the study may start only after all regulatory requirements are fulfilled.

9.2 Regulatory Considerations

The study will be reviewed by the relevant Ethics Committees, and by the relevant Competent Authority as well. The study will not start without the written approval of the Ethics Committee and, where needed, the Competent Authority approval and after the completion of any other local regulation requirement.

9.3 Investigator Responsibilities

The role of the Principal Investigator (PI) is to implement the day-to-day conduct of this clinical investigation as well as to ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation in accordance with ISO 14155 for the conduct of clinical investigations of medical devices. The PIs shall be qualified by education, training and experience for the proper conduct of this clinical investigation. The investigative sites will have the required number of eligible subjects, a qualified investigation team, and adequate facilities for the foreseen duration of this study. The PIs will provide the sponsor copies of all communication with the EC, will perform safety reporting to both the sponsor and the EC according to EC requirements and to this clinical investigational plan and will promptly report to the EC any deviations that affect the right, safety, or well-being of the subject, or the scientific integrity of the clinical investigation, as required by local regulations. The PIs shall ensure compliance with the Informed Consent process and with the clinical investigational plan/protocol and will provide adequate medical care to the subjects during and after their participation in the clinical investigation.

9.4 Confidentiality and Data Protection

All subject data is identified with the unique patient identifier number. After obtaining subject's consent, the investigator will permit the study monitor, independent auditor or regulatory agency personnel to review that portion of the subject's medical record that is directly related to the study. This shall include all study relevant documentation including subject medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the subject is in the study, and autopsy reports for any deaths occurring during the study (where available). Health data will be recorded and forwarded to the sponsor of the study, AtriAN Medical Ltd, and to participating Ethics Committees and Competent Authorities, for evaluation as required. Any information that is obtained in connection with this study that can be identified with the subjects will remain confidential. Any data that may be published in scientific journals will not reveal the identity of the study participants.

10. Insurance

In order to cover possible damage to health, in relation to participation in this study, AtriAN Medical has, as required by law, obtained appropriate insurance coverage.

11. Protocol Deviations

The Investigator is not allowed to deviate from the protocol without prior approval by AtriAN Medical and prior review and documented approval from the governing Ethics Committee and/or Competent Authority. Prior approval is not needed for minor deviations in relation to timing of follow-ups provided the investigator notifies the sponsor or monitor once such a deviation occurs.

Under emergency circumstances, deviations from the clinical investigation plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the Ethics Committee.
Reports of any deviation from the clinical investigational plan as per above emergency circumstances will be reported to the Sponsor and to the Ethics Committee as soon as possible after detection, but no later than twenty-four (24) hours from the time of the deviation.
Deviations must be documented on the appropriate PROTOCOL DEVIATION Case Report Form.
Any report of withdrawal of Ethics Committee approval will be submitted to the Sponsor within five (5) working days.

Protocol deviations will be summarized by the designated Clinical Study Monitor and analysed by AtriAN Medical for the impact to the overall integrity of the study. Input from an independent statistician and/or a CEC (clinical events committee) may be obtained to determine if the deviation warrants disqualifying the Investigator. Disqualification is warranted when an investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur, which do not warrant disqualification from a study, AtriAN Medical will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

12. Device Accountability

Access to investigational devices shall be controlled and the investigational devices shall be used only in the clinical investigation and according to the CIP. The sponsor shall keep records to document the physical location of all investigational devices from shipment of investigational devices to the investigation sites until return or disposal.
When the enrolment is complete, the investigator shall return to the study sponsor any unused devices and a copy of the completed device inventory. The investigator's copy of the device reconciliation report must document any unused devices that have been returned to the study sponsor.

The Principal Investigator is responsible to keep records documenting the receipt, use and return or disposal of the investigational devices. For that, a form (Device Accountability Log) will be provided to the site that will record the model, lot number, and date received by the site.
Upon receipt of devices, the Device Accountability Log must be completed and the contents of the packaging inspected for:

- Any evidence of damage that could affect the integrity of the device (generator or catheter)
- Any evidence of damage that could affect the sterility of the device (catheter only)
- Any issues with the packaging should be brought to the attention of the study sponsor as soon as possible.

13. Study Management

13.1 Data Management

The Sponsor will be responsible for the organization and entry of all clinical data collected during the study. Standardized Case Report Forms (CRFs) will be provided by the Sponsor and used to record study subject data. The Principal Investigator is responsible for ensuring accuracy and completeness of all study documents. CRF completion instructions and training is to be provided by the sponsor.

The Investigator will be queried on errors concerning data completeness and consistency. All activities will be performed according to Standard Operating Procedures and applicable regulatory requirements.

13.2 Data Collection

Each patient will automatically be assigned with a unique, sequential patient identifier. CRF worksheets will be completed for each study patient based on the source documents and then entered into the EDC system. Instances of incomplete or inconsistent data will be resolved with the site through issuing a query or other means of communication, as necessary. The site is responsible to respond and/or correct the data for all queries issued in a timely manner. All queries and changes to the data is automatically tracked within the audit trail.

Completed CRF worksheets will be verified by a monitor against the subject's medical records and verified against the EDC system entries before the site can apply electronic signatures.

13.3 Source Documents

Source documents may include a patient's medical record, hospital charts, clinic charts, the Investigator's study files, questionnaires, and the results of diagnostic tests such as laboratory tests, electrocardiograms, CT angiograms, MR angiograms, echocardiograms and the like. The Investigator's copy of the CRFs (worksheets) serves as part of the Investigator's record of a patient's study-related data.

The Investigator is responsible for ensuring that data are properly recorded in each patient's source data, CRF-worksheets (paper hardcopies) and related documents and ensure timely transfer to the CRF. The Investigator who signs the Protocol Signature Page should sign the CRFs requiring signatures to ensure that the observations and findings are recorded correctly and completely.

Source data from baseline through the 12-month follow-up shall be uploaded/transferred to the database. All CRFs will be reviewed for completeness, accuracy and clarity. Queries for missing or unclear data will be made as necessary and have to be answered within 10 business days

13.4 Record Retention

All study-related correspondence, patient records, consent forms, records of the distribution and use of the investigational products, and copies of CRFs should be maintained on file for 15 years past the completion of the study. AtriAN Medical requires that it be notified in writing if the Investigator intends to leave the hospital so that both parties can be assured a new responsible person is appointed in the hospital.

13.5 Study Summary

The Sponsor is responsible for preparing a final report in accordance with ISO 14155 requirements. The PI will review and sign the document, and AtriAN Medical will supply it to the governing Ethics Committees and to the respective regulatory authorities.

13.6 Amendments to the Protocol

Any modifications to the CIP shall be agreed and signed by the investigator(s). The amendment should be submitted to their respective Ethics Committee that originally approved the investigation, and, where applicable, also to the Competent Authority. A summary explaining the changes, the rationale for changes and other documents will be provided in accordance with applicable requirements, to ECs and regulatory authorities.

13.7 Monitoring

Sponsor personnel or their designees will perform study site monitoring. The site will be visited per the monitoring plan to ensure that the study is conducted in full compliance with all applicable regulations, and with the study protocol.

- Written IRB / Ethics Committee approval for conduct of the study
- Text of the site's approved written study-specific patient consent document
- Signed Investigator's Agreement
- Signed Clinical Trials Agreement (CTA)
- Site Signed Activation Letter

Monitoring will ensure continued protocol compliance, adequate patient enrolment, accurate data reporting, the reporting of adverse events and adequate accounting of study device shipments. Monitoring shall require 100% source data verification (SDV) to validate accuracy of data transcribed to the CRFs.

At the close of the study at an investigational site, the clinical monitor will make a final on-site visit. The purpose of this visit is to collect all outstanding study data documents, ensure that the investigator's files are accurate and complete, review record retention requirements with the investigator, make a final accounting of all study supplies shipped to the investigator, provide for appropriate disposition of any remaining supplies, and ensure that all applicable requirements are met for the study. The observations and actions made at this visit will be documented as a final report for investigator and sponsor acceptance.

13.8 Monitor or Designee Names and Addresses

Site	Monitor
Tbilisi Heart & Vascular Clinic	Clinical Accelerator, 11 Saakadze Descent "LTD Panorama", Floor 3, Office 306, Tbilisi 0160, Georgia.
Na Homolce Hospital, Prague	High Tech Med Consult, 155 00 Prague 5, Frimlova 1322/4e, Czech Republic

13.9 Clinical Events Committee

The Sponsor will coordinate the convening of meetings of the Clinical Events Committee (CEC) in accordance with the Quality Assurance Procedure and the Charter specific to this study. The CEC has the responsibility to review all Adverse Events requiring classification, level of severity, relatedness to device and/or procedure and resolution that are in question and may make recommendations as to procedure based on their findings. Their recommendations may include the termination of the trial. All recorded minutes of their actions will be kept on file and available for review as requested. All sites will be kept informed of any decisions made by this CEC.

14. Ethics Committee Approval

This clinical investigation will not begin until the required approvals are obtained for the appropriate EC or national regulatory authority.

15. Statement of Compliance

The study is conducted in full accordance with the principles in the latest version of the "Declaration of Helsinki" (2013) and with other local laws and regulations.

The study will not commence until written approval has been obtained from the Ethics Committee and regulatory authority where applicable.

No changes are anticipated to be made to the device during the study. Any changes that must be made will be qualified before being implemented to the same functional specifications used for the original product.

16. Publication Policy

All parties shall observe data confidentiality rules during the course of the study. The privacy of each study subject and confidentiality of his/her information shall be preserved in reports and publication of any data. Study subjects shall be identified on study documentation by a unique study identification number. The investigational site may maintain a separate identification log, however all study documentation and/or medical records collected and used for study purposes will remain anonymous so that an individual study subject cannot be identified outside the study.

It is the intention of the sponsor that the results of the study will be published. Upon the prior written consent of Sponsor, Investigator shall have the rights to publish papers related to the Study. Individual investigators cannot publish on the study or a sub-set of the study before the full study results are published. If the sponsor decides not to publish the full study, then investigators may publish their own data. Investigators cannot publish on the system technology without written permission from the sponsor.

If written permission from the Sponsor is provided, the PI may publish and/or present the results of the Study conducted at their site, provided that, prior to any such publication or presentation, the site and/or the PI shall furnish the Sponsor with two (2) hard copies and one electronic copy of any materials intended for publication or presentation at least sixty (60) days prior to the submission of manuscripts.

17. Revision History

Change Control Form Number	Revision	Description of Change	Effective Date
Form-249	A	Initial Release	Refer to CompanionQMS for Date and Time.
Form-259	B	Updates include the following: a) Page 1 Cover Page - identifying Principal Investigator for all sites, b) Page 6 Study Synopsis & page 19 Section 6.8 Patient Exclusion Criteria - remove start date to accommodate Covid19 c) Page 20 Section 6.4 Sample size - to include "up to" 30 patients d) Page 21 Paralytic Agent – updated to include Rocuronium e) Page 24 Ablation of GPs – inclusion to document occurrence of electrical cardioversion or defibrillation f) Page 37 Section 13.9 Clinical Events Committee, update to refine requirements.	Refer to CompanionQMS for Date and Time.
Form-267	C	Updates to: a) Section 8 Study procedure and Data Collection to provide clarification on AERP Measurement, b) Section 13.4 Record Retention - modified retention period from 5 years to 15 years to align General Data Protection Regulation(EU) 2016/679 and Clinical Directive 2001/20/EC requirements	Refer to CompanionQMS for Date and Time.
Form-278	D	Updates for: Removal of removal of Spirometry and Exercise tests from Synopsis for Clinical Study Requirements and Schedule of Tests and from section 8 Study Procedure and Data Collection and section 8.4 Schedule of Events. Inclusion of temperature of the heart for AERP measurement. Typographical error correction for documenting electrical cardioversion or defibrillation during the procedure.	Refer to CompanionQMS for Date and Time.
Form-287	E	Updates for inclusion of 24-hour Holter to the 30 Day Follow-Up, in the following sections: Study Synopsis Ablation of GPs, and Schedule of Events	Refer to CompanionQMS for Date and Time.

Change Control Form Number	Revision	Description of Change	Effective Date
Form-295	F	Complete rewrite of section 8.8 Adverse Event Reporting to align with requirements of ISO 14155:2020 and MDCG 2020-10/1 'Safety reporting in clinical investigations of medical devices under the Regulation". Update Investigators signature Page to provide additional clarity. Updates throughout to align with requirements of ISO 14155:2020, as follows: a) Section 5 Risk Benefit Analysis b) Inclusion of Section 8.10 for Emergency Contact Details for Reporting ADE, c) Modification to Section 8.11 Device Deficiencies and Malfunctions d) Section 15 Statement of Compliance	Refer to CompanionQMS for Date and Time.
Form-308	G	Removed Petr Neuzil, MD as PI for Prague on cover page. Section 8 Study Procedure and Data Collect, updated as follows: a) Measurement of AERP modified to allow measurements to be taken one or more of the following sites, i.e. left atrial appendage, left atrium and right atrium. b) Inclusion of -1/+2˚C tolerance of temperature of heart. c) Update pacing output from 10 mA to range of 10-20 mA. d) Intermediate AERP modified to optional requirement at the discretion of the operator as per modified figure 5.	Refer to CompanionQMS for Date and Time.
Form-349	H	a) Removal of references to, and details of activities at, UMC Amsterdam as patients will not be enrolled there. b) Typographical corrections and minor formatting throughout. c) Cover Page - updated for inclusion of new revision and date d) Section 8 - Updated pulse width from 2ms to include a range of 2-3 ms to accommodate for patient to patient variability (anatomy and adipose tissue effects, etc.) and variability in pacing wire contact area mean higher values may sometimes be needed.	Refer to CompanionQMS for Date and Time.

Change Control Form Number	Revision	Description of Change	Effective Date
		e) Section 8.9 - update to include additional clarification for SAEs related to atrial deganglionation and open-chest CABG surgery.	

18. Bibliography

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Approval Sign-off

By signing this page, the approver acknowledges that they have read and understood the change, and, *where applicable*, agree to adhere with the requirements of the document.

Document Number	CIP-001	**Title**	Clinical Investigation Plan for OCED System	**Revision**	G to H

Description of Change/Approval	Updates identified as follows: a) Removal of references to, and details of activities at, UMC Amsterdam as patients will not be enrolled there. b) Typographical corrections and minor formatting throughout. c) Cover Page - updated for inclusion of new revision and date d) Section 8 - Updated pulse width from 2ms to include a range of 2-3 ms to accommodate for patient to patient variability (anatomy and adipose tissue effects, etc.) and variability in pacing wire contact area means higher values may sometimes be needed. e) Section 8.9 - update to include additional clarification for SAEs related to atrial deganglionation and open-chest CABG surgery.

Name	**Title/Function**	**Signature**	**Date**
Jack Slovick	Regulatory Affairs on behalf of AtriAN Medical	DocuSigned by: Jack Slovick 3990FB77CDA34EF...	31-Mar-2022
Laura Minarsch	Clinical Consultant on behalf of AtriAN Medical	DocuSigned by: Laura Minarsch 58A15A60D463450...	31-Mar-2022
Prof. Dr. J.R. (Joris) de Groot,	Cardiologist/Electrophysiologist - Medical Advisor	DocuSigned by: Joris de Groot FD16C32C8027446...	31-mrt-2022