Clinical Investigational Plan Synopsis

Title:	Substrate-Targeted Catheter Ablation to Treat Persistent Atrial Fibrillation
Acronym:	AF Substrate Mapping and Guided Ablation
Purpose:	Evaluate the feasibility of substrate-targeted catheter ablation to treat Persistent AF
Objectives:	Primary Objective • **Assess acute and long-term outcome of patient-tailored substrate-targeted ablation (Substrate) plus modified circumferential pulmonary vein ablation (*Substrate+mCPVA*) versus modified circumferential pulmonary vein ablation alone (*mCPVA*)**
	Secondary Objective • **Map and characterize electrophysiological substrates during AF, including regular and fast activities, complex fractionated electrograms, wave front propagation directions, and fibrosis**
Endpoints:	Primary Endpoint Twelve-month clinical success rate defined as • **Freedom from symptomatic AF off antiarrhythmic drug therapy assessed from the end of the 3 months blanking period to 12 months following the ablation procedure, documented by implantable loop recorder (ILR) monitoring or trans-telephonic (TT) ECG monitoring.**

	Secondary Endpoint
	- Collect maps that identify substrates that could serve as mechanisms of AF maintenance, such as:
	  o Areas with fast but regular activities
	  o Areas with consistent wave front propagation pattern
	  o Areas with low P-P voltage
	  o Areas with complex fractionated electrograms
	- Acute AF termination or significant AF cycle length slowing during RF application in ablation procedure
	- Inducibility of AF by programmed stimuli at the end of the ablation procedure before and after administration of Isoproterenol
	- Freedom from symptomatic atrial tachycardia and atrial flutter off antiarrhythmic drug therapy assessed from the end of the 3 months blanking period to 12 months following the ablation procedure, documented by ILR monitoring or TT ECG monitoring
	- Freedom from asymptomatic AF, atrial tachycardia, and atrial flutter off antiarrhythmic drug therapy assessed from the end of the 3 months blanking period to 12 months following the ablation procedure, documented by ILR monitoring or TT ECG monitoring
	- Need for a new ablation procedure
	- Need to prescribe antiarrhythmic drugs after the blanking period
	AF burden measured by ILR at follow-up visits

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Design:	Prospective, single center, randomized, single-blind, controlled, 2-arm parallel group trial in Milan, Italy (Pr. Pappone, Targeted Research Center) The total duration of the study is expected to be 24 months with ~12 months of enrollment. Approximately 80 subjects suffering from persistent AF will be randomized in a *1:1* fashion to the following investigation arms: - Modified circumferential pulmonary vein ablation alone (*mCPVA*); - Substrate-targeted ablation guided by AF substrate mapping, followed by completion of modified circumferential pulmonary vein ablation (*Substrate+ mCPVA*) • **Ablate the areas that have fast and regular electrical activities, starting from the fastest cycle length (defined by Mean CL in the range of 120-250 milliseconds, and SD CL in the range of 1-30 milliseconds** • **Ablate the areas that have consistent rotational or focal propagation pattern (defined by conduction velocity vectors)** • **Ablate the areas that comprises the slow conduction zone of possible arrhythmia circuits** • **If AF terminates during RF ablation, stimulation protocol will be used to examine if AF is re-inducible. If AF is re-inducible and physician decides to remap, mapping will be performed again for substrate-targeted ablation. If AF is not re-inducible, *mCPVA* will be completed** Subjects will be followed up at 3, 6, 12 months.
Devices used:	- EnSite™ Velocity™ mapping system (CE marked) - Inquiry™ AFocusII™ diagnostic catheter (CE marked) - EnSite Velocity Research Platform consisting of: o EnSite Velocity Research Display Workstation (CE marked) o EnSite Velocity Research Switch (OEM CE marked) o EnSite Velocity Research software (not CE marked) - Any commercially available Radiofrequency (RF) ablation system - Any commercially available irrigated tip RF ablation catheter (minimum 4 electrodes) - Any CE-marked EP diagnostic catheter (minimum 4 electrodes)
Study Population	Patients with persistent AF scheduled to undergo first or second time catheter ablation with approved standard indication by ESC/EHRA Guidelines
Inclusion/Exclusion Criteria	<u>Inclusion Criteria</u> 1. Age between 18 and 85 years 2. Persistent AF 3. Ability to provide informed consent for study participation and be willing and able to comply with study evaluations and follow-up schedule

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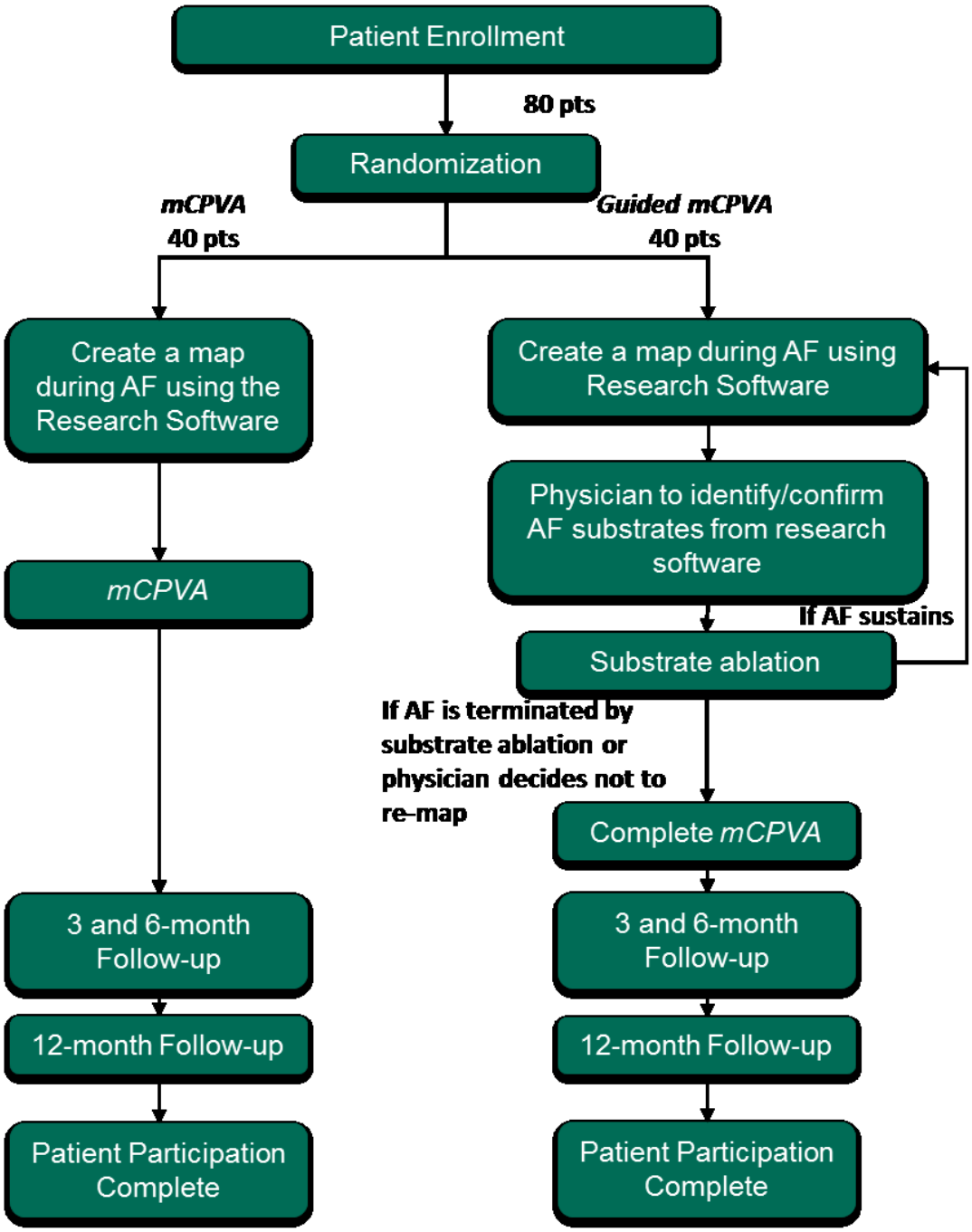
	Exclusion Criteria 1. Two or more previous AF ablations 2. Secondary AF 3. Hyperthyroidism 4. Left ventricular ejection fraction <30% 5. NYHA functional class IV 6. Left atrial area > 35 cm^2 7. Uncorrected severe valvular heart disease 8. Contraindication to anticoagulation 9. Presence of left atrial thrombus 10. Recent (<6 Months) myocardial Infarction or unstable angina or coronary artery by-pass 11. Thoracic surgery for congenital, valvular or aortic disease 12. History of cerebrovascular accidents 13. Pregnancy 14. Significant comorbidities such as cancer, severe renal insufficiency requiring hemodialysis, severe obstructive lung disease, cirrhosis, with a life expectancy less than 2 years
Data Collection	- **Pre-procedure: Data collection per standard clinical practice for patients undergoing AF ablation** - **During-procedure: EnSite Velocity Study Backup DVDs, including 3D geometry of LA, contact maps collected by AFocus II catheter, electrograms, RF lesion locations, marker locations, electrode locations, user annotations, events of acute AF termination or significant CL slowing** Post-procedure: AF recurrence documented by ILR or TT ECG monitoring

1. Study Flow Chart



2. Statistical analysis

In subjects with persistent AF, it is possible to demonstrate a one-year clinical difference among the two therapies with a significance level of 0.5 and a power of 0.80 using a Log-rank test in 38 subjects per group, estimated success of 50% and 80% in the control arm and mapping arm, respectively. The expected difference is based on extensive experience of the operators. Considering 5% drop-out rates, thus a total of 80 subjects will be included and assigned to either treatment group according to a randomization schedule stratified by the previous ablation procedures (none and one previous ablation procedure). Categorical and continuous variables are expressed as absolute and relative frequencies or as mean±SD or median (interquartile range [IQR]) as appropriate. Comparisons of continuous variables were done with a Student t-test or the Mann-Whitney U test as appropriate and binomial variables with chi-square or Fisher test. Long-term outcome was assessed, after a single ablation procedure, by Kaplan-Meier method and compared using the log rank test. A 2-tailed probability value of ≤ 0.05 was deemed significant. Statistical analyses were conducted using SPSS (SPSS v22, USA).