STELLAR

Safety and Effectiveness Evaluation of the Multi-Electrode Radiofrequency Balloon Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation (STELLAR)

Protocol Number:	BWI_2017_04
IDE Number:	G180139
Sponsor:	Biosense Webster, Inc., a division of Johnson & Johnson with registered office at 33 Technology Drive, Irvine, CA 92618
Funded by:	Biosense Webster, Inc., a division of Johnson & Johnson
Version:	11.0
Date:	15 Nov 2022

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List of Acronyms and Abbreviations

Acronym/ Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Asymptomatic Cerebral Embolic
ACL	Advanced Catheter Location
ACT	Activated Clotting Time
AE	Adverse Event
AEF	Atrioesophageal Fistula
AF	Atrial Fibrillation
AFEQT™	Atrial Fibrillation Effect on Quality-of-Life
AFL	Atrial Flutter
APHRS	Asia Pacific Heart Rhythm Society
AT	Atrial Tachycardia
AV	Atrioventricular
CB-2	Second-Generation Cryoballoon
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
CPK	Creatine Phosphokinase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CS	Coronary Sinus
CT	Computed Tomography
CTI	Cavo-Tricuspid Isthmus
CVA	Cerebrovascular Accident or Stroke
DC	Direct Current
DMC	Data Monitoring Committee
EC	Ethics Committee
ECAS	European Cardiac Arrhythmia Society
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHRA	European Heart Rhythm Association
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
ESC	European Society of Cardiology
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
F	French
FU	Follow-Up
GCP	Good Clinical Practices
HB	Hot Balloon
HRS	Heart Rhythm Society
ICD	Implantable Cardioverter Defibrillator
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICL	Independent Current Location
IFU	Instruction for Use

Acronym/ Abbreviation	Expanded Term
IRB	Institutional Review Board
LA	Left Atrium
LB	Laser Balloon
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MDR	Medical Device Regulation
MEDDEV	Medical Device Directive Guidance
MI	Myocardial Infarction
mITT	Modified Intention to Treat
MMSE	Mini-Mental State Examination
MoH	Ministry of Health
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NAE	Neurological Assessment Evaluable
NIHSS	National Institutes of Health Stroke Scale
NMPA	National Medical Products Administration
NYHA	New York Heart Association
OUS	Outside the United States
PAE	Primary Adverse Event
PAF	Paroxysmal Atrial Fibrillation
PI	Principal Investigator
PN	Phrenic Nerve
PNP	Phrenic Nerve Palsy
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QoL	Quality of Life
RA	Right Atrium
RF	Radiofrequency
RSPV	Right Superior Pulmonary Vein
RV	Right Ventricle
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SOLAECE	Latin American Society of Electrophysiology and Cardiac Stimulation
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
TTM	Transtelephonic Monitoring
UADE	Unanticipated Adverse Device Effect
US	United States
USADE	Unanticipated Serious Adverse Device Effect

Key Roles and Responsible Parties

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CRO(S) AND CORE LAB(S):
The sponsor maintains a list of CRO(s) and Core Lab(s) and their contact information.

INVESTIGATORS:
The sponsor maintains a list of study Investigators and their contact information.

Protocol Agreement and Statement of Compliance Form

Study Title: Safety and Effectiveness Evaluation of the Multi-Electrode Radiofrequency Balloon Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation (STELLAR)

Study Number: BWI_2017_04

I, the undersigned, have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand that I am accepting responsibility to personally supervise this study, and to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country and state regulations, the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined herein and will attempt to complete the study within the time period designated by the Sponsor.

I will provide for training in the protocol and all pertinent instructions to all individuals who will assist in the conduct of this study. I will discuss their responsibilities with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation until it is closed. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms my agreement to accept the above responsibilities. I will accept respective revisions or amendments to this protocol as provided by the Sponsor.

Principal Investigator Name (PRINT)	Signature	Date

Site Name

Site Address

Protocol Summary

Study Name: STELLAR

Study Title: Safety and Effectiveness Evaluation of the Multi-Electrode Radiofrequency Balloon Catheter for the Treatment of Symptomatic Paroxysmal Atrial Fibrillation.

Study Number: BWI_2017_04

Study Description: This clinical study is a prospective, multicenter, single-arm clinical evaluation of the Multi-Electrode Radiofrequency (RF) Balloon catheter (HELIOSTAR™). The purpose of this study is to evaluate the overall safety and effectiveness of the HELIOSTAR™ catheter, in conjunction with the Multi-Electrode Circular Diagnostic catheter (LassoStar™) and Multi-Channel RF Generator, for the treatment of drug refractory Paroxysmal Atrial Fibrillation (PAF). Embedded within the Main Study will be a Neurological Assessment Evaluable (NAE) subset and a Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image (CT/MRA) subset with consecutive enrollment and a prospective design. The same subject can participate in both the NAE and cardiac CT/MRA subsets.

The study will enroll subjects with drug refractory, symptomatic PAF who are candidates for catheter ablation. The first 1-3 subjects for each ablating physician will be considered roll-in subjects to verify consistent workflow for study device components and to minimize any learning curve effects. The roll-in subjects will not be included in the NAE subset, cardiac CT/MRA subset, or in the primary endpoint analyses. The roll-in phase will include a maximum of 240 subjects and the main study phase will include a maximum of 400 evaluable subjects. Subjects will be evaluated prior to the procedure, prior to discharge, and post procedure at 7 days (7-14 days), 1 month (23-37 days), 3 months (76-104 days), 6 months (150-210 days), and 12 months (315-405 days) unless otherwise specified in the protocol.

Objective:

Primary Objective:

To demonstrate the safety and 12-month effectiveness of the HELIOSTAR™ catheter for the treatment of drug refractory PAF. Specifically:

- To demonstrate the safety based on the incidence of early-onset (within 7 days of ablation procedure) primary adverse events.
- To demonstrate the 12-month effectiveness based on the proportion of subjects with freedom from documented asymptomatic and symptomatic Atrial Fibrillation (AF), Atrial Tachycardia (AT), or Atrial Flutter (AFL, of unknown origin[+]) episodes based on electrocardiographic data through the effectiveness evaluation period (day 91-365 post index procedure).

[+]AFL of unknown origin is defined as all AFL except those cavo-tricuspid isthmus (CTI) dependent AFL as confirmed by accepted EP maneuvers (e.g. entrainment or activation mapping) in an EP study

Secondary Objectives:

- To determine the acute procedural success, defined as confirmation of entrance block in clinically relevant pulmonary veins (all pulmonary veins except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge, of the HELIOSTAR™ catheter (with or without the use of a focal catheter).
- To demonstrate the 12-month effectiveness based on freedom from documented symptomatic AF/AT/AFL (of unknown origin) episodes based on electrocardiographic data through the effectiveness evaluation period.
- To evaluate treatment success for subjects treated with the HELIOSTAR™ catheter including subjects who were taking antiarrhythmic drug (AAD) medication past the blanking period.
- To determine the single procedure treatment success rate for subjects treated with the HELIOSTAR™ catheter.
- To assess subject quality of life at 12 months compared to baseline, via the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) Questionnaire, for subjects treated with the HELIOSTAR™ catheter.

Endpoint: **Primary Endpoints:**

- **Safety**
  Incidence of early onset Primary Adverse Events (PAEs) (within 7 days of an ablation procedure which uses the HELIOSTAR™ catheter). PAEs include the following adverse events (AEs) and are defined in section 9.2.3 of the protocol:
  - Device or procedure related death*
  - Atrio-Esophageal Fistula*
  - Myocardial Infarction
  - Cardiac Tamponade/Perforation*
  - Thromboembolism
  - Stroke/ Cerebrovascular Accident (CVA)
  - Transient Ischemic Attach (TIA)
  - Phrenic Nerve Paralysis (permanent)
  - Pulmonary Vein Stenosis*
  - Pericarditis
  - Pulmonary Edema
  - Major Vascular Access Complication/Bleeding
  - Hospitalization (initial or prolonged)**

    * Events are considered and analyzed as primary AEs **even if they occur greater than one week (7 days) post-procedure**.

    ** Excludes hospitalization solely due to arrhythmia recurrence or non-medically urgent cardioversion.

- **Effectiveness**
  Freedom from documented asymptomatic and symptomatic Atrial Fibrillation, Atrial Tachycardia, or Atrial Flutter of unknown origin+ episodes based on electrocardiographic data (≥30 seconds on arrhythmia

monitoring device) through the effectiveness evaluation period (91-365 days post index procedure). Additionally, if a subject meets any one of the following criteria, then the subject will be considered an effectiveness failure:

- Failure to achieve acute procedural success. Acute procedural success is defined as confirmation of entrance block in clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge (with or without the use of a focal catheter).
- Greater than 2 repeat ablations for AF/AT/AFL (of unknown origin[+]) in the blanking period (≤ 90 days post index procedure) or a repeat ablation or surgical treatment for AF/AT/AFL (of unknown origin[+]) during the effectiveness evaluation period.
- Direct current (DC) cardioversion for AF/AT/AFL (of unknown origin[+]) during the effectiveness evaluation period.
- Continuous AF/AT/AFL (except CTI dependent) on a standard 12-lead ECG during the effectiveness evaluation period.
- A Class I and/or Class III AAD is prescribed/taken for atrial arrhythmia other than CTI dependent AFL at any time beyond the 3-month follow-up visit window (i.e., at any time beyond day 105 to 365 post index procedure).
- Oral Amiodarone is prescribed post index ablation procedure.
- Failure to use the HELIOSTAR™ catheter for isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) in the index procedure or repeat procedures during the blanking period.

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by accepted EP maneuvers (e.g. entrainment or activation mapping) in an EP study.

Secondary Endpoints:

- Acute procedural success defined as confirmation of entrance block in clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge (with or without the use of a focal catheter).
- Alternative 12 Month Success: Defined as acute procedural success and freedom from documented symptomatic AF/AT/AFL (of unknown origin) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) through the effectiveness evaluation period. Greater than 2 repeat ablations for AF/AT/AFL (of unknown origin) in the blanking period, a repeat ablation or surgical treatment for AF during the effectiveness evaluation period, DC Cardioversion during the effectiveness evaluation period, Continuous AF/AT/AFL (except CTI dependent) on a standard 12-lead ECG during the effectiveness evaluation period, class I and/or III AAD usage at any time beyond the 3-month follow-up visit window (i.e., at any time from day 105 to 365 post index procedure), oral Amiodarone usage after the index procedure, or failure to use the HELIOSTAR™ catheter for isolation of clinically relevant

PVs (all PVs except those that are silent and/or cannot be cannulated) in the index procedure or repeat procedures during the blanking period constitutes treatment failure.

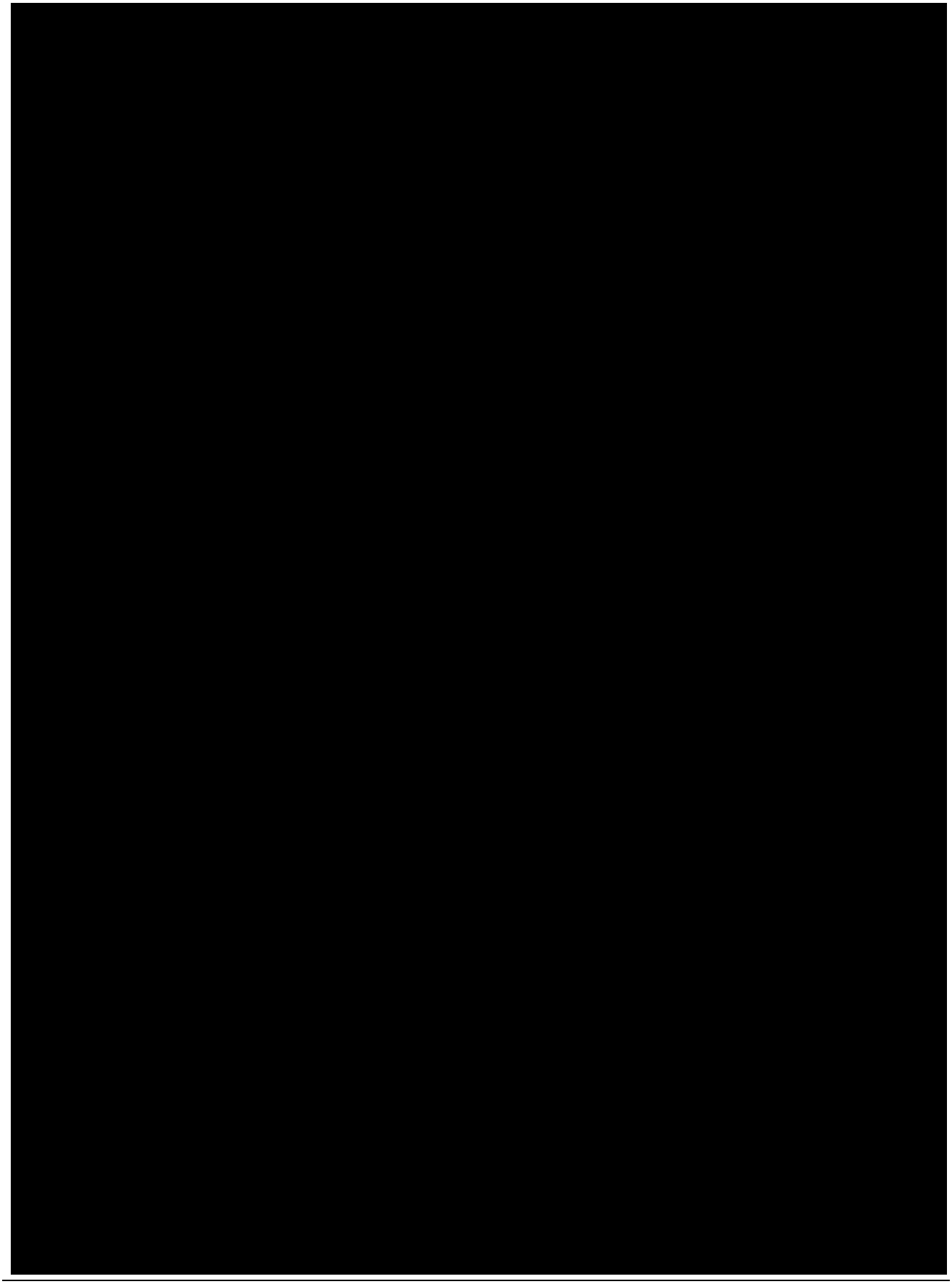
- 12 Month Symptomatic Recurrence Endpoint: Defined as acute procedural success and freedom from documented symptomatic AF/AT/AFL (of unknown origin) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) through the effectiveness evaluation period. Any AAD use throughout the study period will not be considered an effectiveness failure. Greater than 2 repeat ablations for AF/AT/ AFL (of unknown origin) in the blanking period, a repeat ablation or surgical treatment for AF during the effectiveness evaluation period, DC Cardioversion during the effectiveness evaluation period, Continuous AF/AT/ AFL (except CTI dependent) on a standard 12-lead ECG during the effectiveness evaluation period, or failure to use the HELIOSTAR™ catheter for isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) in the index procedure or repeat procedures during the blanking period constitutes treatment failure.
- Quality of life at 12 months compared to baseline as assessed by pre and post ablation AFEQT™ Questionnaire.
- 12 Month Single Procedure Treatment Success: Defined as acute procedural success and freedom from documented symptomatic AF/AT/AFL (of unknown origin) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) through the effectiveness evaluation period. Repeat ablation or surgical treatment for AF at any time, DC Cardioversion during the effectiveness evaluation period, Continuous AF/AT/ AFL (except CTI dependent) on a standard 12-lead ECG during the effectiveness evaluation period, class I and/or III AAD usage at any time beyond the 3-month follow-up visit window (i.e., at any time from day 105 to 365 post index procedure), oral Amiodarone usage after the index procedure, or failure to use the HELIOSTAR™ catheter for isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) in the index procedure constitutes treatment failure.

Population: Patients undergoing catheter ablation for the treatment of drug refractory symptomatic PAF.

Phase: Pivotal

Clinical Sites: Up to 40 clinical sites in the United States (US) and outside the United States (OUS).

[redacted]



[redacted]

Study Duration:	The study duration is anticipated to be approximately 3.5 years; 2.5 years for the enrollment phase and an additional 1 year to complete follow-up.
Subject Study Duration:	Enrolled subjects who undergo the ablation procedure with the investigational device will be followed for 12 months post index procedure.
Study Inclusion criteria:	1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF). a) At least two (2) symptomatic AF episodes within last six (6) months from enrollment. b) At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to, electrocardiogram (ECG), Holter monitor, or telemetry strip. 2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF, contraindication to the AAD, or intolerable side effects to the AAD. 3. Age 18 -75 years. 4. Able and willing to comply with all pre-procedure, post-procedure, and follow-up testing and visit requirements. 5. Signed Patient Informed Consent Form (ICF).
Study Exclusion criteria:	1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g. documented obstructive sleep apnea and acute alcohol toxicity). 2. Previous surgical or catheter ablation for AF. 3. Patients known to require ablation outside the PV ostia and CTI region (e.g. atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson-White). 4. Previously diagnosed with persistent or long-standing persistent AF and/or Continuous AF > 7 days. 5. Any percutaneous coronary intervention within the past 2 months. 6. Valve repair or replacement or presence of a prosthetic valve. 7. Any carotid stenting or endarterectomy within the past 6 months. 8. Coronary artery bypass grafting, cardiac surgery (e.g., ventriculotomy, atriotomy), or valvular cardiac surgical procedure within the past 6 months. 9. Documented left atrium (LA) thrombus within 1 day prior to the index procedure. 10. LA antero posterior diameter > 50 mm. 11. Left Ventricular Ejection Fraction (LVEF) < 40%.

12. Contraindication to anticoagulation (e.g., heparin).
13. History of blood clotting or bleeding abnormalities.
14. Myocardial infarction within the past 2 months.
15. Documented thromboembolic event (including transient ischemic attack) within the past 12 months.
16. Rheumatic Heart Disease.
17. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV.
18. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months.
19. Unstable angina.
20. Acute illness or active systemic infection or sepsis.
21. Diagnosed atrial myxoma or presence of an interatrial baffle or patch.
22. Presence of implanted pacemaker or implantable cardioverter defibrillator (ICD).
23. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
24. Significant congenital anomaly or medical problem that, in the opinion of the investigator, would preclude enrollment in this study.
25. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation.
26. Enrolled in an investigational study evaluating another device, biologic, or drug.
27. Has known pulmonary vein stenosis.
28. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
29. Presence of an inferior vena cava filter.
30. Presence of a condition that precludes vascular access.
31. Life expectancy or other disease processes likely to limit survival to less than 12 months.
32. Presenting contra-indication for the devices (e.g., TTE, Holter, CT, etc.) used in the study, as indicated in the respective instructions for use.

Additional exclusion criteria for NAE subjects:

33. Contraindication to use of contrast agents for magnetic resonance imaging (MRI) such as advanced renal disease, etc. (at PI discretion).
34. Presence of iron-containing metal fragments in the body.
35. Unresolved pre-existing neurological deficit.

Schematic of Study Design

Study Enrollment (N=Up to 400 evaluable + 240 Roll-In)
12 month post-ablation follow-up for all treated subjects

[redacted]

Pre-Ablation: Obtain informed consent and then perform baseline assessments as described in the Section 8 of the Protocol.

Procedure: Perform procedure as described in Section 8 of the Protocol.

Pre-discharge: Perform Pre-discharge assessments as described in Section 8 of the Protocol.

7 Day Follow-up: Call subject 7 days (7-14 days) post procedure to assess adverse events.

1 Month Follow-up: Perform 1 month (23-37 days) post procedure assessments as described in Section 8 of the Protocol.

3 Month Follow-up: Perform 3 month (76-104 days) post procedure assessments as described in Section 8 of the Protocol.

6 Month Follow-up: Perform 6 month (150-210 days) post procedure assessments as described in Section 8 of the Protocol.

12 Month Follow-up: Perform 12 month (315-405 days) post procedure assessments as described in Section 8 of the Protocol.

Roll-in Cohort

Safety Cohort

Effectiveness Cohort

1. Background Information and Scientific Rationale

1.1. Background Information

Atrial Fibrillation is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age to approximately 10% in patients over 80 years of age.[1-3] The primary clinical benefit of AF ablation is improvement in quality of life (QoL) resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3,4] In recognition of this, the elimination of symptomatic atrial arrhythmias was recommended by the 2012 HRS/EHRA/ECAS and 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Consensus Statements on Catheter and Surgical Ablation of Atrial Fibrillation.[3,5] The opinion of the European Society of Cardiology (ESC), as expressed in their 2016 AF Management Guidelines, is that "Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center."[2,6]

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement states that "PVI is now widely accepted as the cornerstone of AF ablation procedures" and that "electrical isolation of the PVs is recommended during all AF ablation procedures."[3] Point-by-point ablation with RF catheters has provided positive results for treating many types of supraventricular arrhythmias,[7,8] including PAF.[7-13] However, the procedure is technically complex and has a long learning curve. Radiofrequency ablation success is highly dependent on operator skill and is associated with a high degree of PV reconnection.[14-16] Additionally, RF ablation carries a major complication rate of roughly 4.5%.[17]

In order to reduce technical complexity and potentially decrease major complications, balloon ablation catheters were developed. Balloon catheters use tissue cooling (cryoballoon), heating (hot balloon) or selective destruction with a laser (laser balloon) to create lesions and isolate PVs.

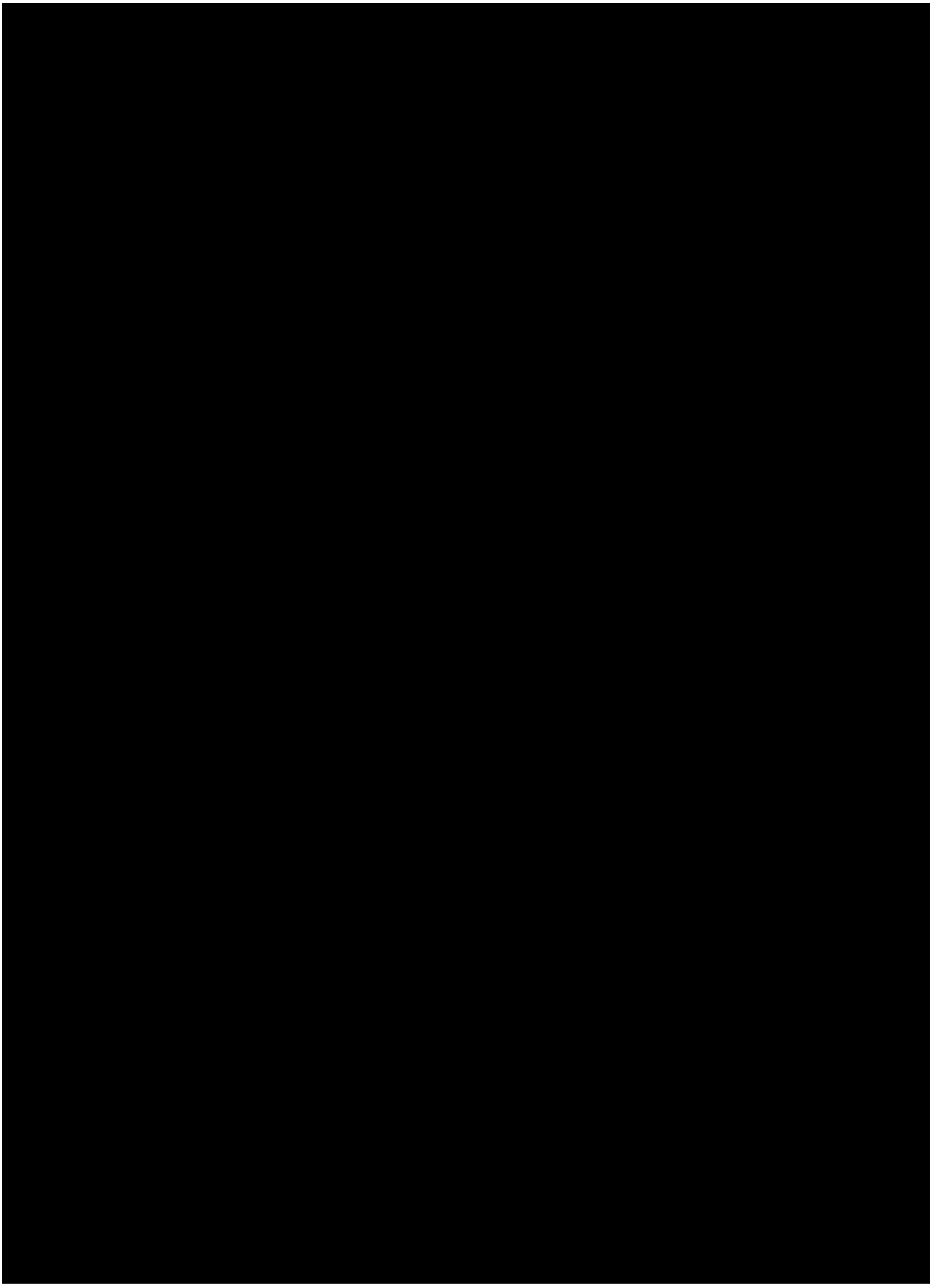
The second-generation cryoballoon (CB-2), so-called because of design improvements over the original first-generation cryoballoon, uses injected refrigerant to ablate tissue that comes in contact with the distal hemisphere of the balloon (cooling zone). While the CB-2 often allows single-shot pulmonary vein isolation (PVI),[18-20] there is still some operator skill involved and various investigators have developed a pull-back technique (incomplete occlusion at the beginning of freezing) to minimize phrenic nerve (PN) injury.[20-23] In addition, PN pacing is required throughout the procedure on the right side so freezing can be immediately aborted if PN palsy (PNP) is observed.[21,22,24-26] Because of this, there is a greater rate of reconduction in the right superior pulmonary vein (RSPV).[27] Investigators who use the CB-2 differ in their recommendation of a "bonus freeze",[27-30] optimal dosing of cryoenergy (240 sec[18,24] vs. 180 sec[20,31] or even less,[26,28]), minimum temperature[32], the need for an endoluminal esophageal temperature cutoff[26,33,34], and whether both sizes (23 mm and 28 mm[35]) should be used versus using the larger balloon exclusively.[19,25,30,34,36] Further disadvantages of this technique are that it is not appropriate for focal touch-ups or repeat ablation of conduction gaps,[27,29] and that the larger balloon, which most investigators seem to prefer[35], may not fit an especially narrow PV ostium.

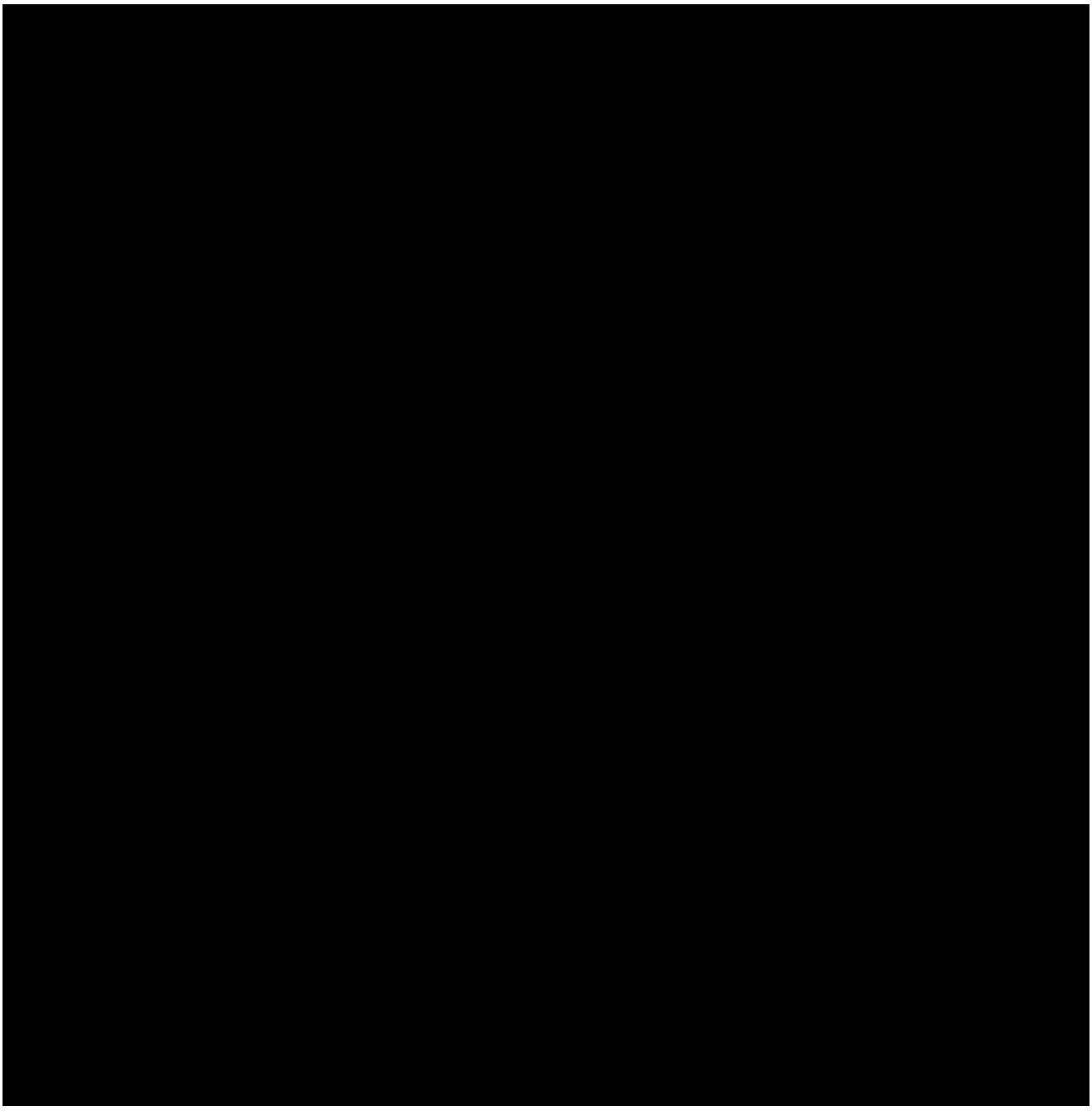
The hot balloon (HB) is a compliant balloon that uses a heated saline/contrast mixture to heat the surrounding tissue and generate thermal lesions. Advantages of the HB system over conventional RF ablation are the possibility of single-shot PVI[37] and reduced risk of

perforation/mechanical injury to endocardium.[38] A disadvantage to this system is that it still requires a fair amount of operator skill and finesse,[39,40] and the balloon position should be checked often by fluoroscopy and repositioned if indentation is noted.[40,41] The need for esophageal temperature monitoring and, when applicable, cooling[41] also increases procedural complexity. The need for PN pacing and/or fluoroscopic monitoring of the diaphragm is still paramount with this system in order to prevent PNP.[40,41] Because central balloon temperature, RF time, and the diameter to which the balloon is inflated are all dependent upon the thickness of the target ablation tissue (each PV, e.g.),[40,41] extensive pre-procedure imaging (intracardiac echocardiography [12] or 3-D Computed Tomography) is required.[40,41] Like the CB-2, HB is not useful for focal touchups or repeat ablation of gaps/ sites of reconduction. To ablate such areas, a conventional irrigated tip RF catheter is still needed.[40]

The laser balloon (LB) is a compliant balloon that can be inflated to a broad range of diameters and contains a central catheter shaft with a fiberoptic endoscope and a second fiber for laser energy delivery. Applications of laser energy last 20-30 seconds and cover a 30° arc with the aim of overlapping lesions by 30-50% to achieve transmurality.[42,43] Esophageal temperature monitoring and PN pacing are still necessary. Ablation in or near the blood source requires decreased energy output;[44] however, the threat of thermocoagulation exists.[45] A common finding with LB ablation is that long procedure times are required for conventional RF ablation.[42,44,46-53] It takes anywhere from 25-50 lesions to successfully isolate one PV.[46-49,54] Higher energy output is associated with decreased procedure time, but at the expense of greater risk of steam pop and balloon damage due to overheating.[46] A disadvantage inherent to this system is that the catheter shaft itself obscures about one fifth of the circumference of the PV ostium, so rotation of the catheter is required to complete ablation of the PV.[42,49] The same problem of obscuring the view occurs with a spiral mapping catheter, so it must be inserted after the balloon is deflated; therefore electrical mapping and ablation cannot be performed simultaneously.[42,53] Furthermore, the endoscopic images are 2-dimensional and therefore do not show the level of the ablation line in relationship to the PV ostium.[42] The possibility of misalignment increases each time the LB is repositioned.[53] Finally, since the LB is not designed as an over-the-wire device, there may be an increased risk of pericardial tamponade.[48,52]

A common advantage to all of these balloon ablation systems is good contact with the target tissue regardless of individual anatomy. A disadvantage is the difficulty of avoiding healthy or already-ablated tissue.





1.5. Potential Risk

1.5.1. Known Potential Risks

Pericarditis: With any balloon-based ablation, pericarditis can occur due to mechanical or thermal irritation of the myocardium.[49] This tends to be underreported[47] as it is usually transient and resolves without intervention.

Phrenic nerve palsy: While the reported incidence of PNP following HB ablation (< 4%)[39-41,55] or LB ablation (≤ 6%)[42-50,52,53,56] is low, the incidence of PNP with CB-2 ablation was reported to range from < 1%[18,27-30,34-36] to 27%,[19-23,25,28,32,56-58] even with continuous phrenic nerve pacing during right-sided ablation and abortion of freezing upon loss of capture. In most cases, PNP with CB-2 is a transient complication,[24] recovering before the end of the procedure,[22,25,32,36] or, if not, by the time of discharge.[19,21,26,28,35,58] However, in

a few cases it has been observed to persist for 10[19,29,30] to 20[20,23] months, suggesting that the injury is permanent.

Injury to the PN may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of PNP varies from 0% to 0.48% when RF energy is used for point-by-point ablation.[59,60]

Atrioesophageal fistula (AEF): AEF is a rare but catastrophic complication of AF ablation that can occur due to the anatomical proximity of the esophagus to the posterior wall of the LA and that is associated with a high mortality rate.[61] AEF has not been observed in clinical experience with the HB or LB. Only one patient (1.8% of 55 patients) presented with AEF in one prospective observational study with the CB-2[25] and this was the only case found in 18 series of consecutive procedures totaling over 2000 patients.[18-23,25,26,28-30,32,34-36,56-58]

While AEF is uncommon with balloon-based ablation systems, damage to the esophagus is fairly common. One study found that superficial thermal lesions developed in 2% of patients and thermal ulcerations in 10% of patients following CB-2 ablation.[34] Another study showed an incidence of esophageal lesions of 3.19% with CB-2.[26] Esophageal lesions were reported in 1-10% of patients following ablation with the HB.[40,41,55] Cooling saline is sometimes infused into the esophagus during HB ablation,[40,41,55] but this carries with it the further risk of aspiration.[41] Esophageal injury is most often found after LB ablation, with mild thermal lesions found in 7%[42] to 8%[51] of patients and more severe ulcerations found in 5% to 15%.[42,51,56] The severity of esophageal lesions was greater with LB compared to RF catheter ablation in a head-to-head study.[51] Moreover, esophageal temperatures in excess of 38.5°-39°C necessitating cessation of energy delivery and/or repositioning of the balloon occur more than half of the time with LB ablation.[42,43,46] The clinical significance of esophageal lesions, if any, is not known.[20,33,34]

Many electrophysiologists attempt to mitigate esophageal damage by monitoring endoluminal temperature during the ablation procedure. A cutoff temperature of 3°C has 100% sensitivity and 100% specificity for predicting esophageal thermal lesions following CB-2 ablation.[29] However, esophageal temperature during LB ablation has poor specificity for esophageal injury, with no significant correlation between maximal esophageal temperature and incidence and severity of esophageal thermal lesions.[51]

Pulmonary vein stenosis: PV stenosis has not been reported following CB-2 ablation. In clinical experience with HB ablation, PV stenosis was reported in < 2-5% of patients,[39-41,62] and was usually asymptomatic.[41] Similarly, with LB ablation, PV stenosis is rarely reported. In one study, mild stenosis (up to 25% narrowing of the PVs) was found in 44% of patients and moderate stenosis (26-50% narrowing) in 6%; there were no cases of severe stenosis (> 50% narrowing).[48] The risk of pulmonary adverse events (e.g., PV stenosis, thrombus and hypertension) associated with an RF ablation procedure targeting the pulmonary veins is considered small (< 4%).[11,12,63-66]

Thrombus formation: A thrombus may form on the ablation electrode during the application of RF current that could become dislodged and embolize to produce stroke, myocardial infarction, or other ischemic injury. The risk of thrombus is minimal with CB-2, but microthrombi were found in preclinical studies following HB ablation.[37] In the clinical setting with HB, 5 patients of 238 (2.1%) developed a cerebral infarction. However, in each case, this was attributed to arrhythmia recurrence and insufficient anticoagulation.[40]

With LB, data suggest that more energy applications and higher energy output facilitate thermocoagulation.[45,54] Thrombus formation following ablation may also occur on the endocardium may produce arterial or pulmonary embolus.

Pericardial effusion/ cardiac tamponade: Cardiac perforation may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Pericardial effusion was reported in 0.6% - 7.3% of patients ablated with CB-2,[22,35,36,57] and cardiac tamponade in 0.2% - 3%.[18,20,23,32] Pericardial effusion may occur at a rate of 15% in patients treated with the HB.[38] With the LB, LA perforation has occurred from mechanical trauma due to a whipping motion of the sheath toward the LA roof after balloon retraction.[42,52] Aside from these reports, the incidence of pericardial effusion has been < 2%[48,49] and cardiac tamponade ≤5%[47-49,52] with the LB. Significant hemodynamic compromise can result in neurologic injury or death. This risk is greatest in a thin-walled chamber (ie, right atrium, LA, or right ventricle). However, the risk of perforation due to steam pop is reduced when the minimum amount of energy output required to achieve transmurality is used.[46]

Cerebral ischemic lesions: The incidence of TIA is < 3% following CB-2 ablation;[20,28,36] however, in most studies imaging for silent ischemic brain lesions was not performed. In one study in which post procedural imaging was obtained, 13.6% of LB-treated patients were observed to have new embolic brain lesions, and another 2.3% had diplopia secondary to an ischemic lesion.[45] There were similar findings of diplopia due to a suspected ischemic event (1.4%) in another LB study.[47] The incidence of asymptomatic cerebral lesions seen on MRI 1-2 days post-procedure in a randomized controlled study was 24% for LB, which was not significantly different from RF catheter ablation or first-generation CB.[54]

According to the 2017 HRS guidelines, the incidence of ACE lesions can vary from 2%-15% as a complication to AF ablation.[3] It is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms and is therefore 'silent'. Emboli can result from a thrombus, gas, air, tissue or fat. Source of micro-emboli include thrombi, which can develop on sheaths, materials, air introduction through sheath or during catheter exchange.

Coronary artery occlusion: RF current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Research suggests that the risk of coronary occlusion is less than 0.5%.[67,68] Because coronary arterial occlusion could produce myocardial infarction, angina or death, the physician will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

Heart block: The application of RF current close to the atrioventricular (AV) node or HIS bundle could damage or destroy the normal AV conduction system, producing complete heart block and requiring implantation of a permanent pacemaker.

Cardiac perforation: Cardiac perforation may result from catheter manipulation or application of RF current (risk is < 1%).[67,68] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. However, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher above 35-40 watts.

Cardiac valve injury: Injury to a cardiac valve may result from catheter manipulation or the application of RF current (risk < 1%).[67,68] This may produce valvular insufficiency and possibly require surgical valve replacement.

Vascular access / bleeding complication: Vascular access complication, femoral arteriovenous fistula, hematoma, and pseudoaneurysm are commonly reported following CB-2 (typically < 4%),[18-22,25,28,32,35,36,56-58] or LB ablation (< 6%).[47,50,69,70] Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk < 1%).[67,68] These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ.

Hemorrhage could occur as a result of anticoagulation (risk < 0.5%), which may require transfusion.[67,68]

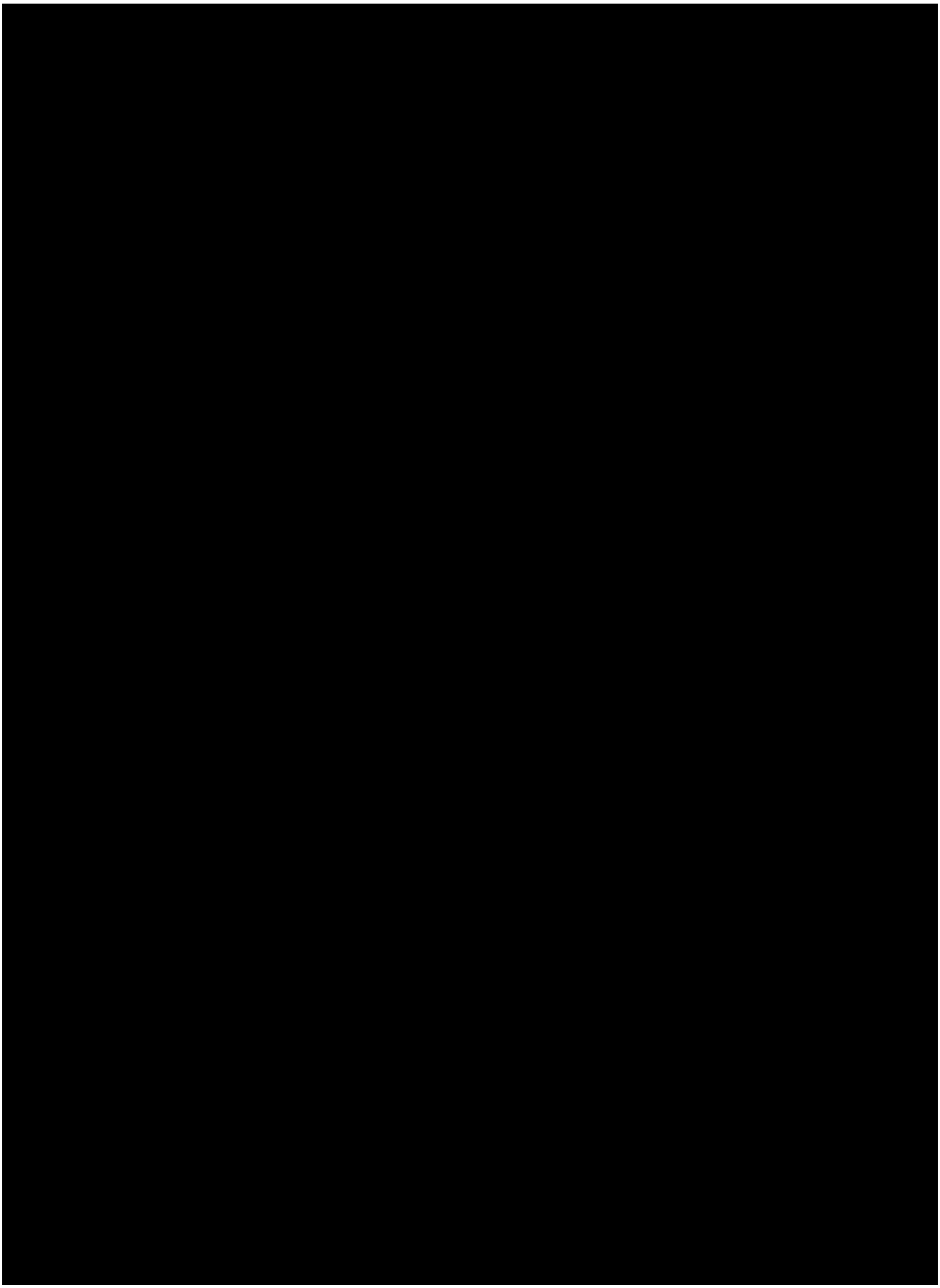
Radiation exposure: Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).[71-73]

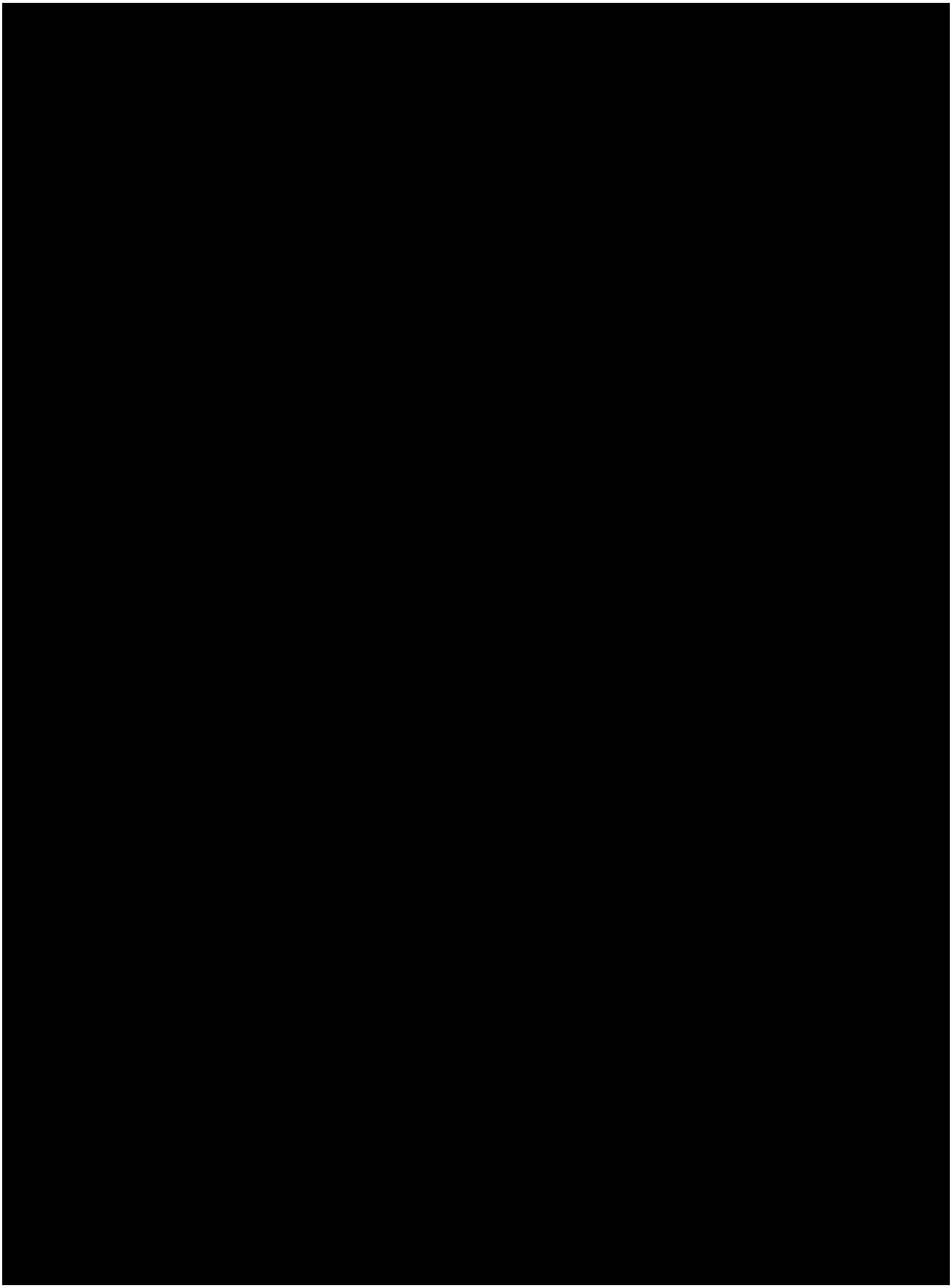
Allergic Reaction: A patient could develop an allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk < 1%).[74-78]

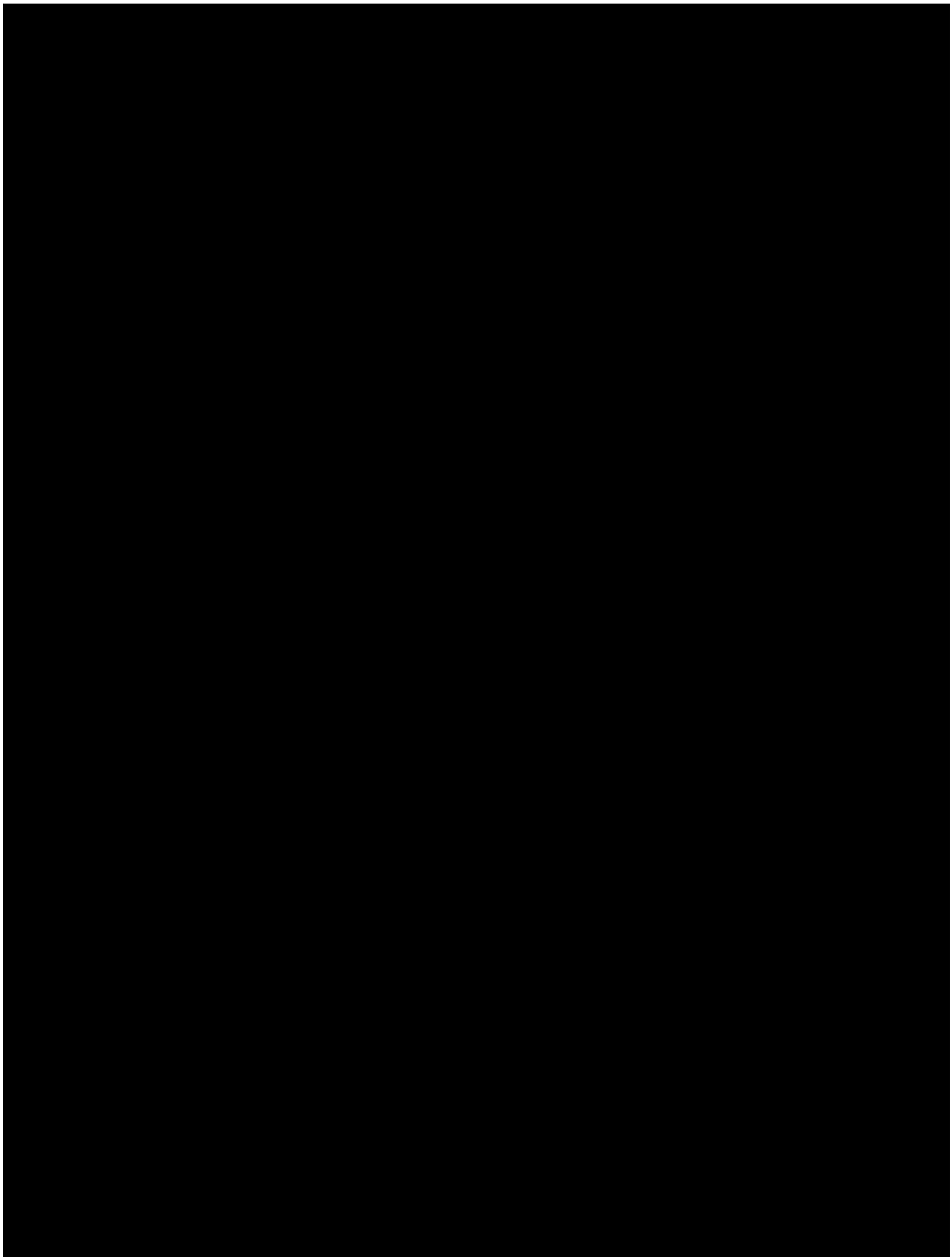
Gastric Hypomotility and Periesophageal Vagal Nerve Injury: Injury to the vagal anterior esophageal plexus can occur when RF energy is applied to the posterior wall of the LA, which can cause acute pyloric spasm and gastric hypomotility. Common symptoms include nausea, vomiting, bloating, and abdominal pain developing within a few hours to a few weeks after the ablation procedure[3].

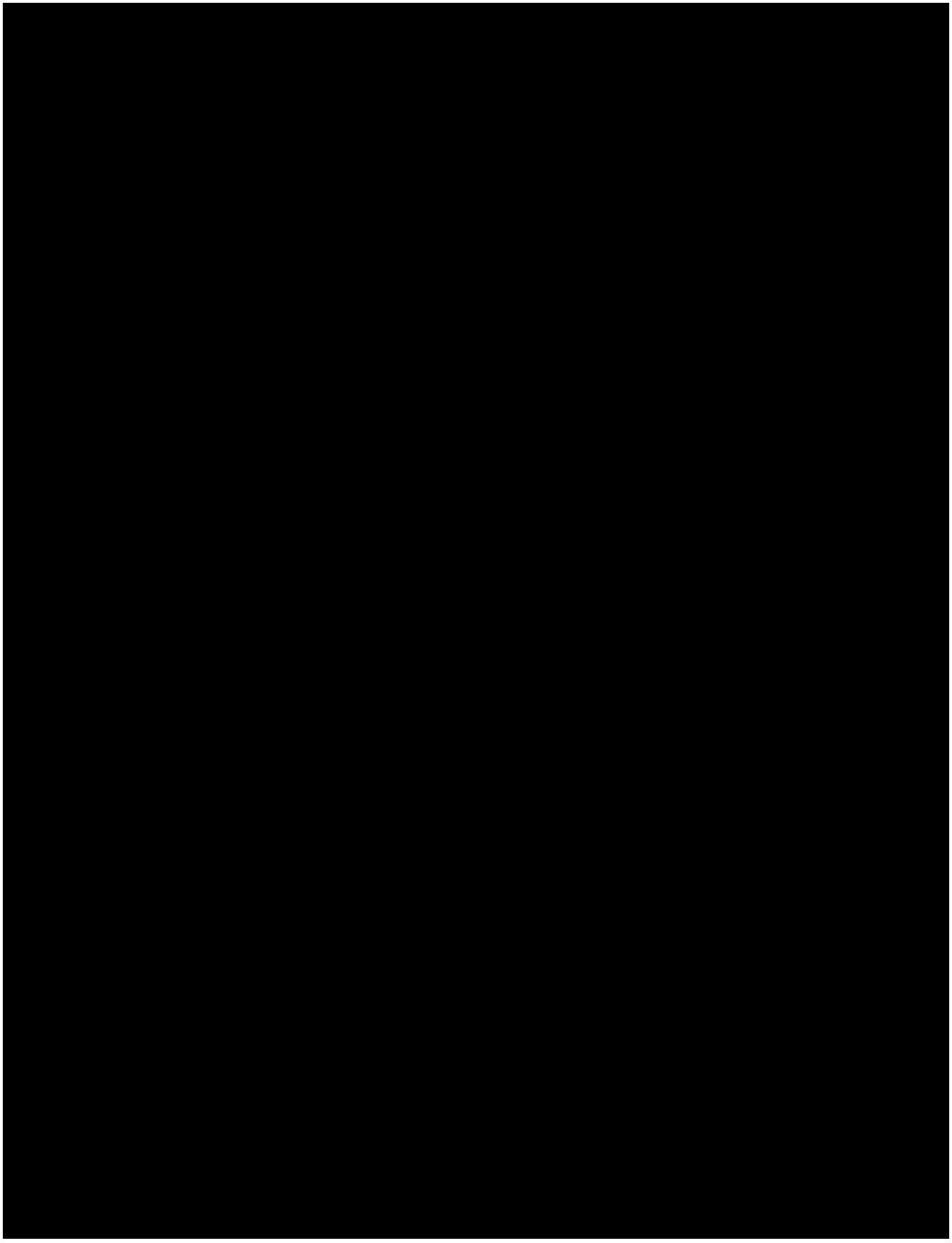
Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk < 0.5%).[67,68] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

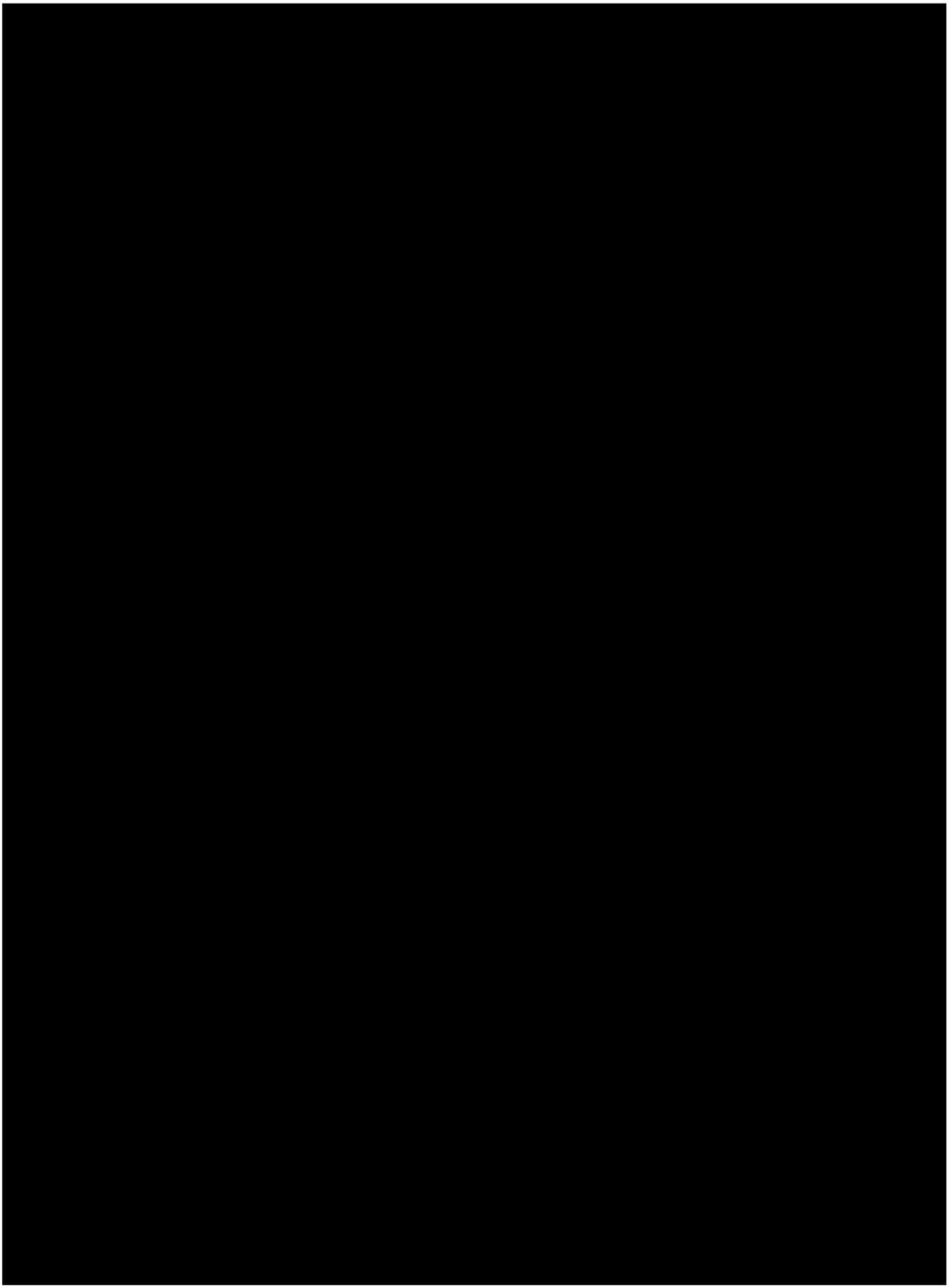
Additional contraindications: Additional contraindications for RF ablation include: hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

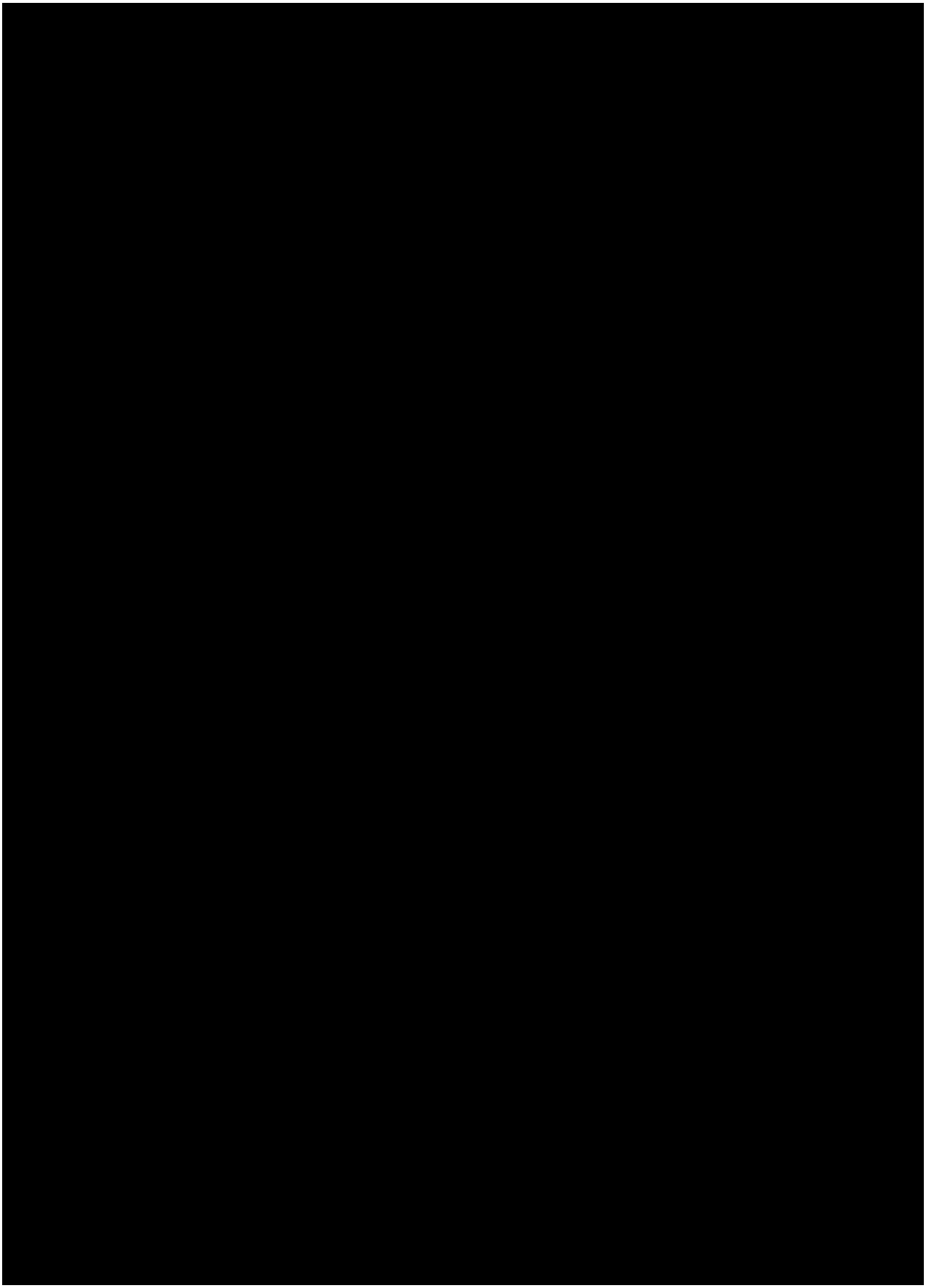


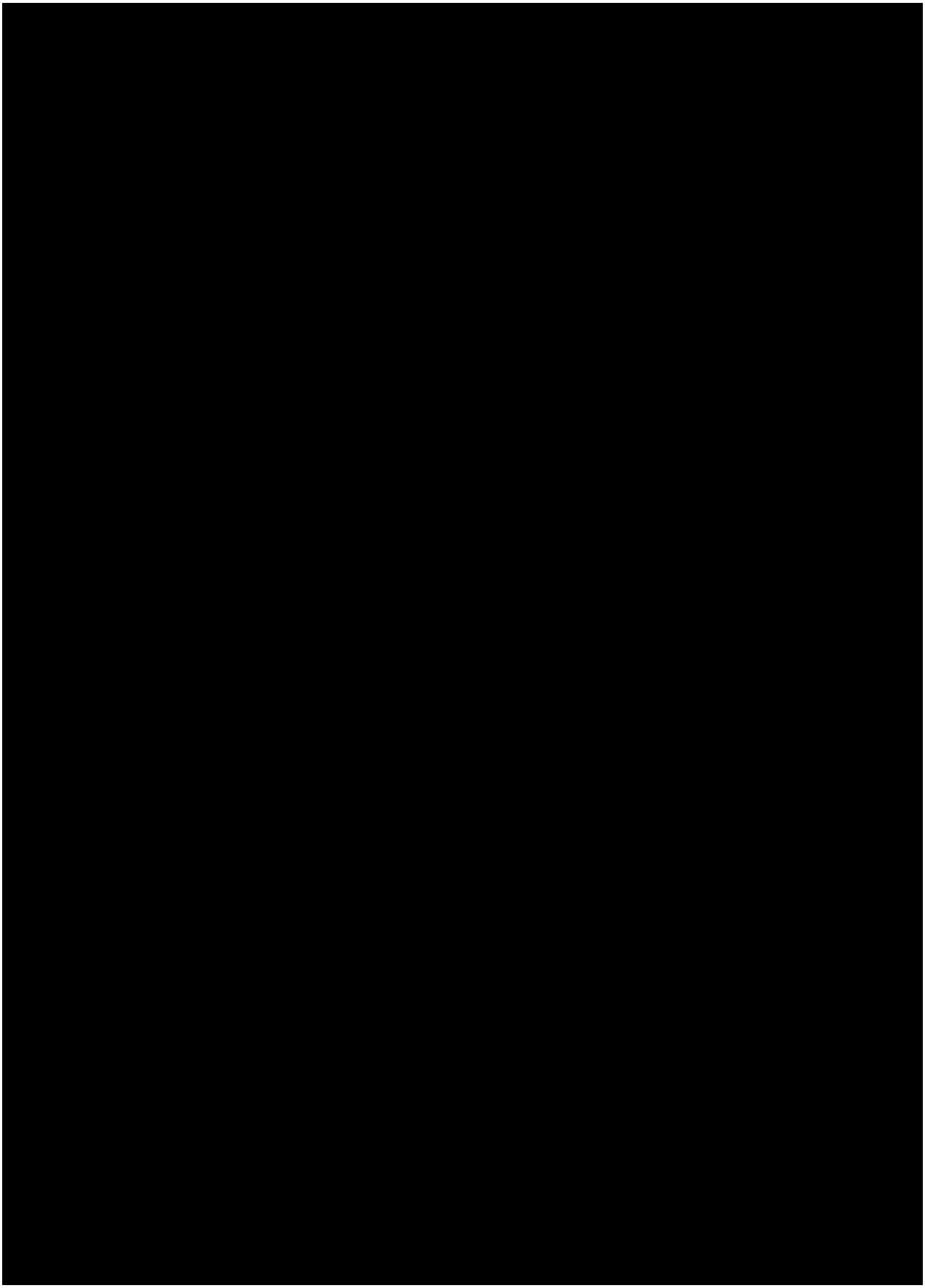


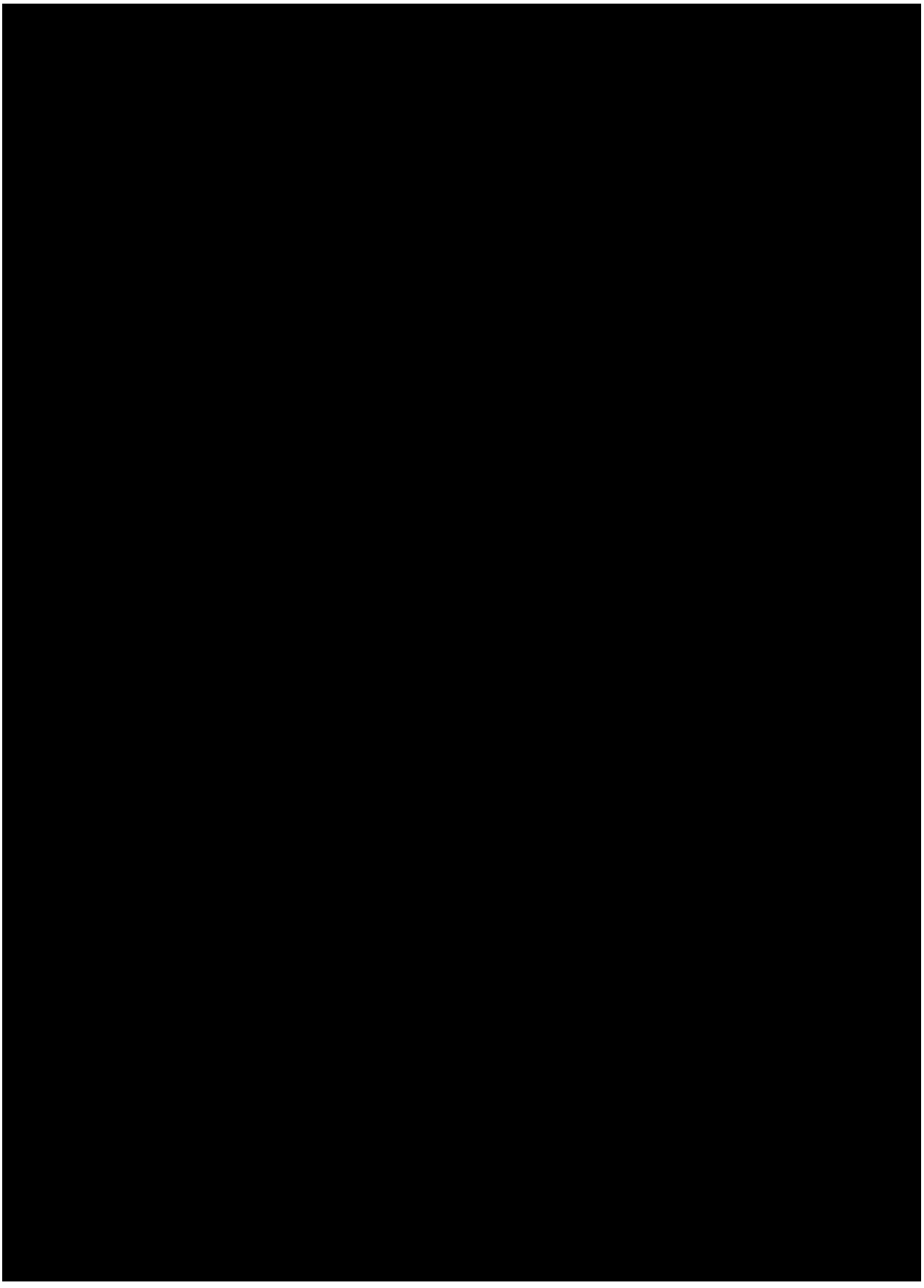












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4. Study Population

4.1. Subject Inclusion Criteria

Candidates for this study MUST meet **ALL** the following criteria:

1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF).
    a. At least two (2) symptomatic AF episodes within last six (6) months from enrollment.
    b. At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to, ECG, Holter monitor, or telemetry strip.
2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF, contraindication to the AAD, or intolerable side effects to the AAD.
3. Age 18 -75 years.
4. Able and willing to comply with all pre-, post- and follow-up testing and visit requirements.
5. Signed Patient Informed Consent Form.

4.2. Study Exclusion Criteria

Candidates will be excluded if **ANY** of the following criteria apply:

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., documented obstructive sleep apnea and acute alcohol toxicity).
2. Previous surgical or catheter ablation for AF.
3. Patients known to require ablation outside the PV ostia and CTI region (e.g. atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia, and Wolff-Parkinson-White).
4. Previously diagnosed with persistent or long-standing persistent AF and/or Continuous AF > 7 days.
5. Any percutaneous coronary intervention within the past 2 months.
6. Valve repair or replacement or presence of a prosthetic valve.
7. Any carotid stenting or endarterectomy within the past 6 months.
8. Coronary artery bypass grafting, cardiac surgery (e.g., ventriculotomy, atriotomy), or valvular cardiac surgical procedure within the past 6 months.
9. Documented left atrium (LA) thrombus within 1 day prior to the index procedure.
10. LA antero posterior diameter > 50 mm.
11. Left Ventricular Ejection Fraction (LVEF) < 40%.
12. Contraindication to anticoagulation (e.g., heparin).
13. History of blood clotting or bleeding abnormalities.
14. Myocardial infarction within the past 2 months.

15. Documented thromboembolic event (including transient ischemic attack) within the past 12 months.
16. Rheumatic Heart Disease.
17. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV.
18. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months.
19. Unstable angina.
20. Acute illness or active systemic infection or sepsis.
21. Diagnosed atrial myxoma or presence of an interatrial baffle or patch.
22. Presence of implanted pacemaker or implantable cardioverter defibrillator (ICD).
23. Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
24. Significant congenital anomaly or medical problem that, in the opinion of the investigator, would preclude enrollment in this study.
25. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation.
26. Enrolled in an investigational study evaluating another device, biologic, or drug.
27. Has known pulmonary vein stenosis.
28. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
29. Presence of an inferior vena cava filter.
30. Presence of a condition that precludes vascular access.
31. Life expectancy or other disease processes likely to limit survival to less than 12 months.
32. Presenting contra-indication for the devices (e.g., TTE, Holter, CT, etc.) used in the study, as indicated in the respective instructions for use.

Additional exclusion criteria for NAE subjects:

33. Contraindication to use of contrast agents for MRI such as advanced renal disease, etc. (at PI discretion).
34. Presence of iron-containing metal fragments in the body.
35. Unresolved pre-existing neurological deficit.

4.3. Strategies for Recruitment and Retention

Historically, women and minorities have been underrepresented in or excluded from many clinical studies[79-81]. Site selection is expected to provide geographical diversity to provide opportunities for the inclusion of women and minorities in the trial. Sites will be instructed to screen all patients who may be eligible for participation in the study without regard to sex or race. Statistical analysis of primary safety and effectiveness endpoints will be carried out to evaluate any differences between gender. Subjects will be encouraged to remain in the study until they have completed the protocol required follow-up period.

4.4. Subject Withdrawal or Termination

4.4.1. Reasons for Withdrawal or Termination

Subjects are free to withdraw from participation in the study at any time upon request without penalty or loss of benefits to which they may otherwise be entitled.

An investigator may terminate a subject's participation in the study if:

- Any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs where continued participation in the study would not be in the best interest of the subject.
- The subject no longer meets eligibility criteria or meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Early termination of the site and/or study by the sponsor.
- Subject withdraws consent.
- Subject is lost to follow up.

Subjects should be encouraged to remain in the study until they have completed the protocol required follow-up period.

4.4.2. Handling of Subject Withdrawals or Termination

If a subject is removed or withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF). If the subject is withdrawn due to an AE or SAE, the Investigator should follow the subject until the AE/SAE has adequately resolved, stabilized, or is explained.

If a subject is unable to complete follow-up or cannot be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator MUST send a certified letter to the subject. If the subject does not respond to the letter within 4 weeks, then the subject will be considered "lost to follow-up" for the study.

Subjects who have signed the ICF but are found to be ineligible PRIOR to insertion of the study catheter will be recorded as screen failures in the eCRF.

4.5. Subject Accountability

- **Pre-Screen Failure:** Patients that are pre-screened, but do NOT sign an ICF. Information on reasons for pre-screen failures will be captured and descriptive analysis will be performed.
- **Enrolled Subjects**: Subjects who sign the study ICF.
    - **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will not be included in the primary endpoint analyses and will only be followed between the time of ICF signature and exclusion from the study for adverse event reporting. Subjects who signed the ICF but are found to be ineligible prior to the procedure will be recorded as screen failures in the eCRFs.
    - **Evaluable Subjects**: All enrolled subjects who have the study catheter inserted.

- **Roll-In Subjects:** Enrolled Subjects who have the study catheter inserted and RF delivered with the study catheter during the Roll-In phase of the ablating investigator. These subjects will not be included in the primary endpoint analyses and will be analyzed separately.
- **Discontinued Subjects**: Evaluable subjects who have the study catheter inserted but do not undergo ablation (i.e., no RF energy is delivered with the study catheter). Discontinued subjects will remain in follow-up for 3 months post catheter insertion. If a SAE is reported for a discontinued subject, the subject will be followed until event resolution (with or without sequelae), stabilization, or until the event is adequately explained.
- **Lost to Follow-up Subjects:** Subjects who are enrolled and evaluable, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject).
- **Withdrawn / Early Termination Subjects:** Subjects who withdraw consent for study participation or are withdrawn/terminated from the study by the investigator prior to completion of all follow-up visits.
- **Completed Subjects:** Enrolled subjects who have not been excluded, discontinued, withdrawn, terminated early, or lost-to-follow-up prior to the final study visit.

5. Responsibilities

5.1. Investigator Responsibilities

Investigators at each participating clinical site will have the following responsibilities:

- Supervising the study at their respective site.
- Assuring compliance by site personnel within the provisions of the protocol.
- Providing the Sponsor with:
  - Signed, dated Investigator Agreement
  - Written institutional review board (IRB) / ethics committee (EC) approval letters and IRB/EC-approved consent forms
  - Signed, dated Financial Disclosure form for each participating investigator
  - Curriculum vitae for each investigator
  - Copy of current medical license for each study investigator, as applicable.
- Maintaining an accurate and current Delegation of Authority log which identifies individuals authorized to perform work for the study.
- Completing the appropriate training on the device and the study protocol prior to enrolling and treating subjects.
- Maintaining accurate and current logs for the study as requested by the study team, including but not limited to:
  - Subject pre-screening log
  - Delegation of authority log
  - Device Accountability log
  - Adverse event log.

- Obtain initial and amendment (if applicable) IRB/EC approval and, if applicable, routine review/approval for the study protocol and informed consent as instructed by the IRB/EC.
- Obtain Patient ICF prior to subject participation.
- Perform medical procedures as described in this protocol.
- Order tests required by the study protocol.
- Follow subjects until the end of the study.
- Accurately complete and sign eCRFs in a timely manner.
- Maintain relevant source documentation and allow Sponsor direct access to perform monitoring or auditing duties.
- Maintain records and provide reports according to prevailing regulatory requirements.
- Share relevant study-related information with delegated study staff.
- Inform the appropriate entities (e.g., Sponsor, CA, IRB/EC) in a timely manner regarding the occurrence of AEs and/or product malfunctions/deficiencies.
- Immediately notify the sponsor of any pending Regulatory Authority audits/inspection at the study site and allow access to study records for authorized regulatory entities.
- Make sufficient effort to maintain contact with treated subjects who fail to comply with the follow-up requirements.
- Maintaining study records for at least 2 years, or as specified per country specific record retention requirements, after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Comply with IRB/EC and Sponsor annual report requirements, including the final report.

5.2. Sponsor Responsibilities

The Sponsor (Biosense Webster, Inc.) will be responsible for the following:

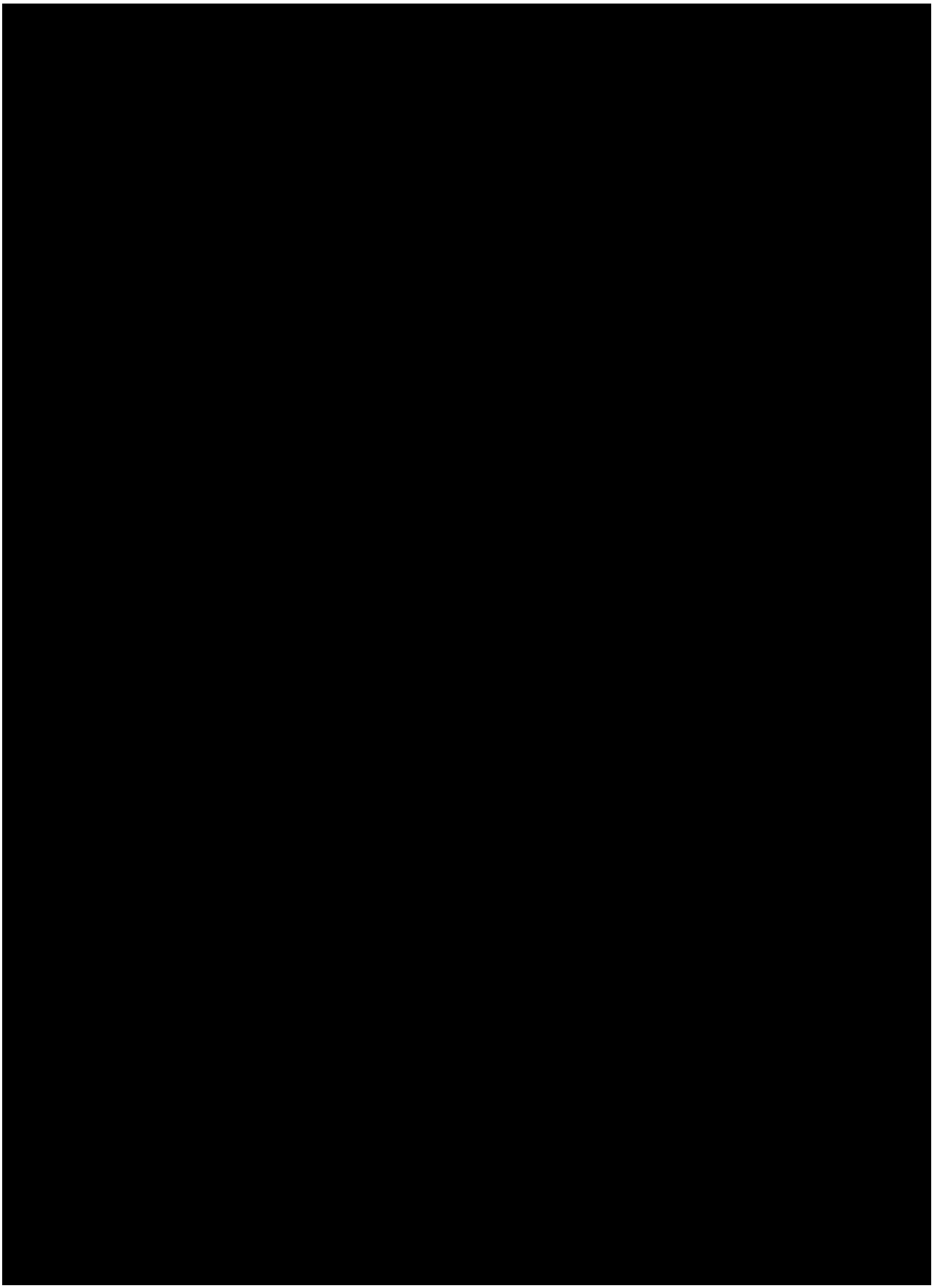
- Conduct pre-study site assessment and approval.
- Create and modify (if applicable) study documents including but not limited to the protocol, case report forms (CRFs), and informed consent.
- Select appropriately qualified and trained individuals, including monitors, to conduct the study.
- Conduct protocol and device training for investigators and research personnel as applicable.
- Establish study-specific committees for study oversight.
- Obtain signed study contracts from investigators/hospitals, contract research organizations (CROs), and other involved parties.
- Ship investigational devices to each site.
- Monitor sites for the duration of the study.
- Maintain study database.
- Inform investigator of his/her responsibilities.
- Submit and obtain approval for study from applicable regulatory agencies.

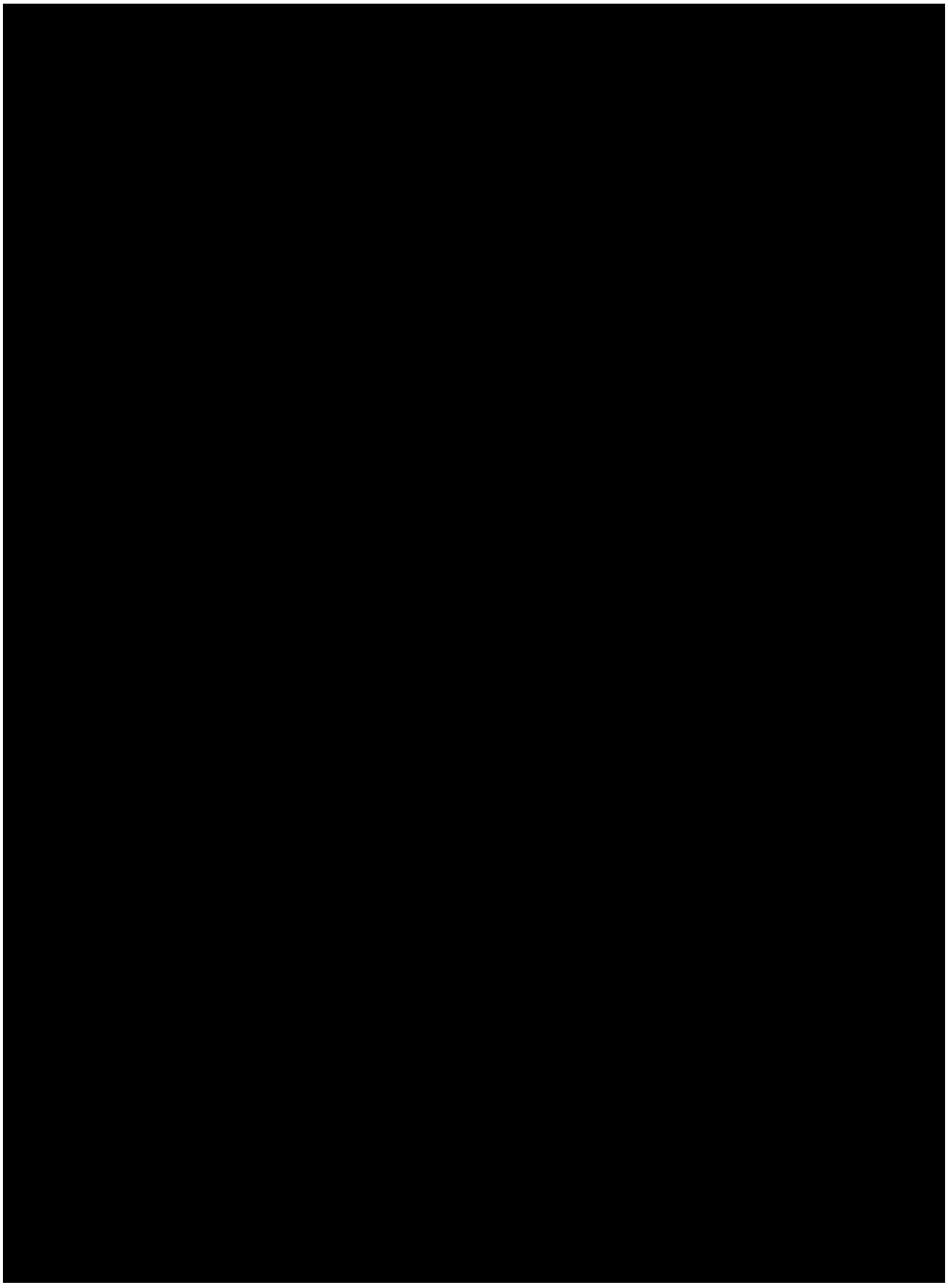
- Prepare reports summarizing the status of the study no less than annually. These reports will be supplied to the Principal Investigator at each site.
- Prepare and submit final clinical study report to applicable regulatory agencies.
- Update Report of Priors, instructions for use (IFU), investigator's brochure (IB), and Risk Analyses, as applicable.
- Prepare and update investigators on safety issues, if needed.
- Report to study investigators and regulatory agencies, as required.
- Have AEs reviewed by the study specific committees and/or study specific reviewers, as required.
- Communicate with the Food and Drug Administration (FDA) / Competent Authority (CA) as needed.
- Submit any amendments to the Clinical Study Protocol/Investigational Plan to the FDA/CA.

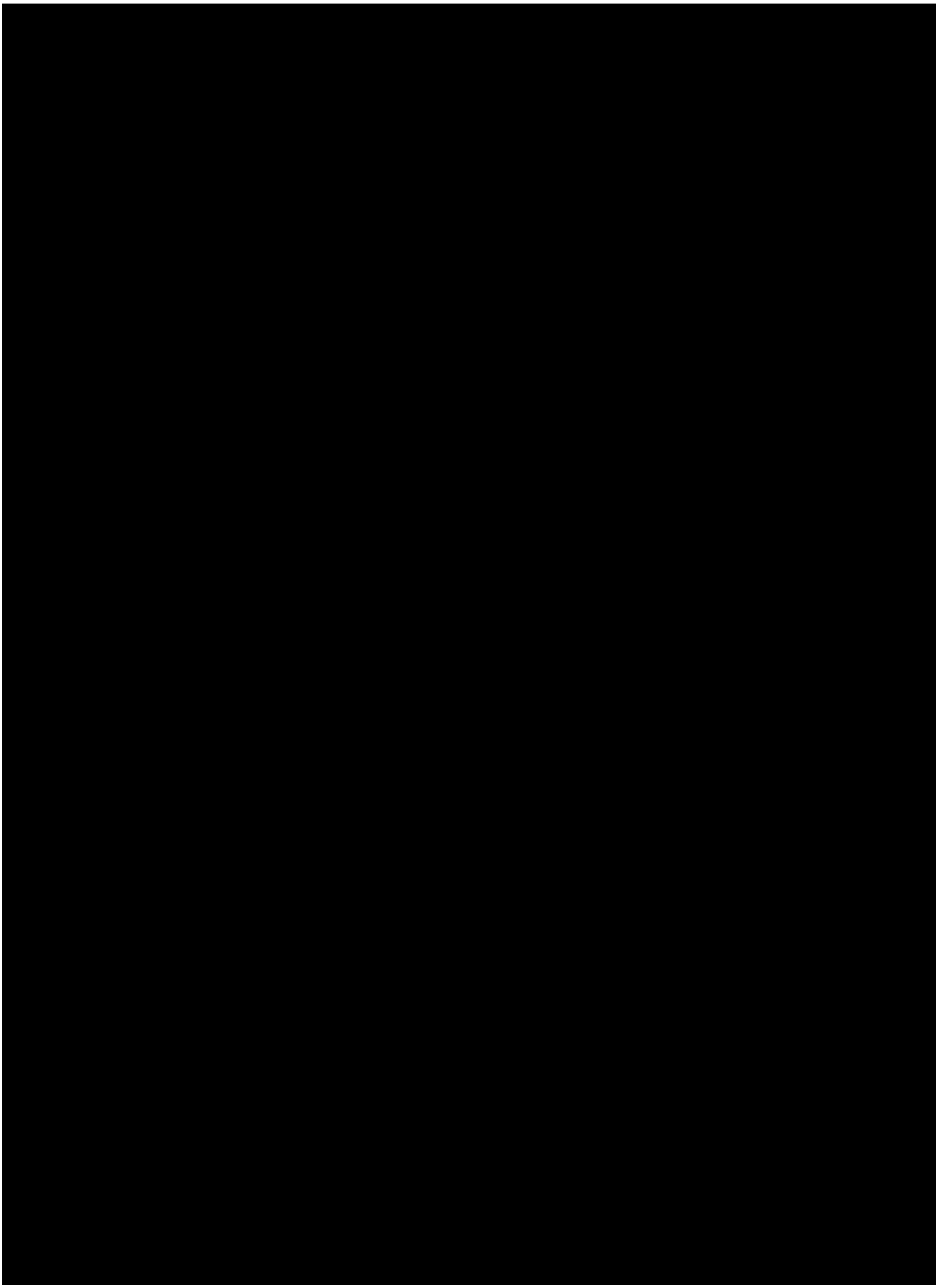
5.3. Training

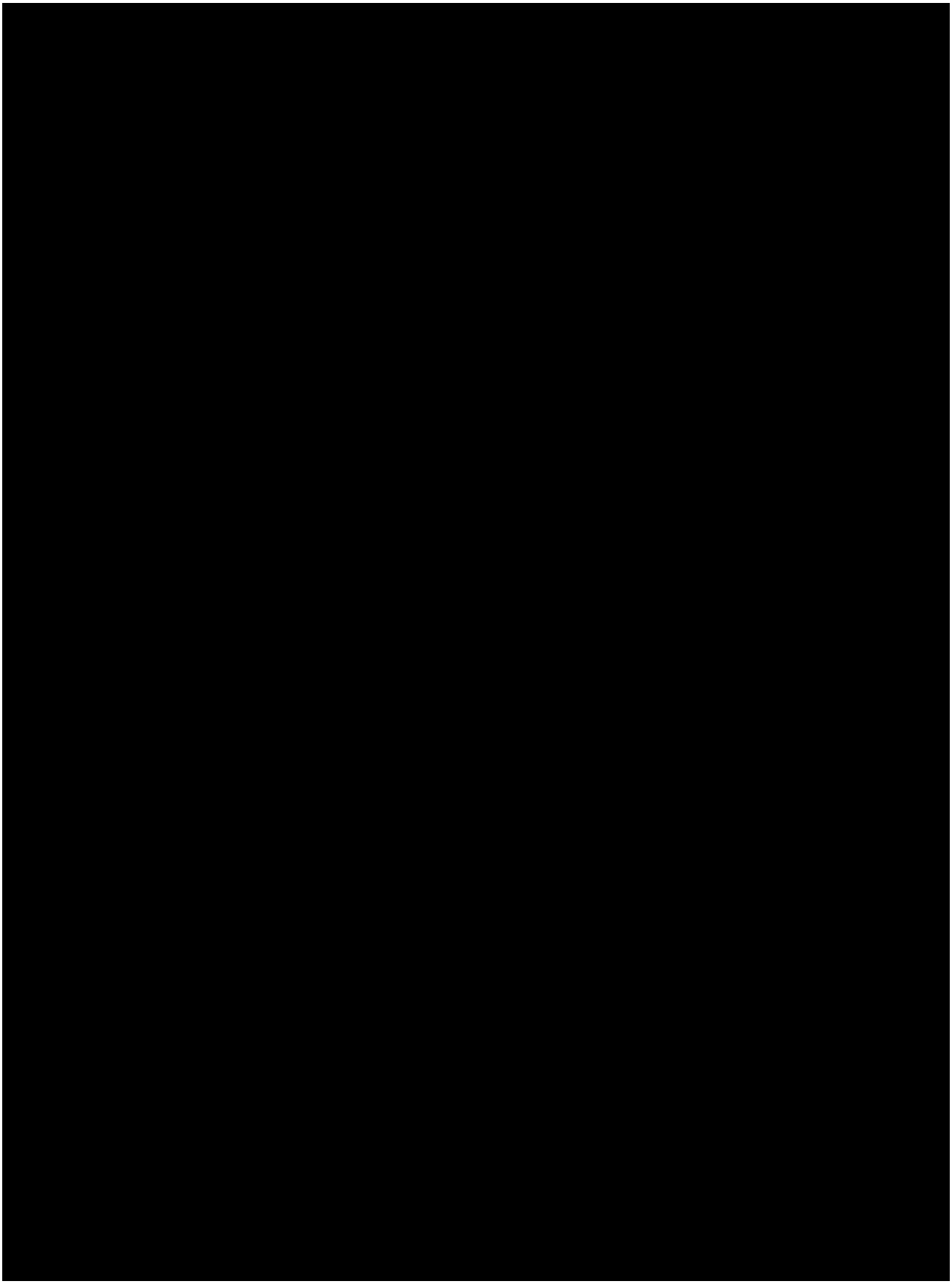
The training of applicable clinical site personnel will be the responsibility of the Sponsor. Prior to initiating subject enrollment at a site, appropriate study training will be provided. Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation with balloon and/or focal ablation catheters. Investigators will undergo device training in accordance with the physician training charter.

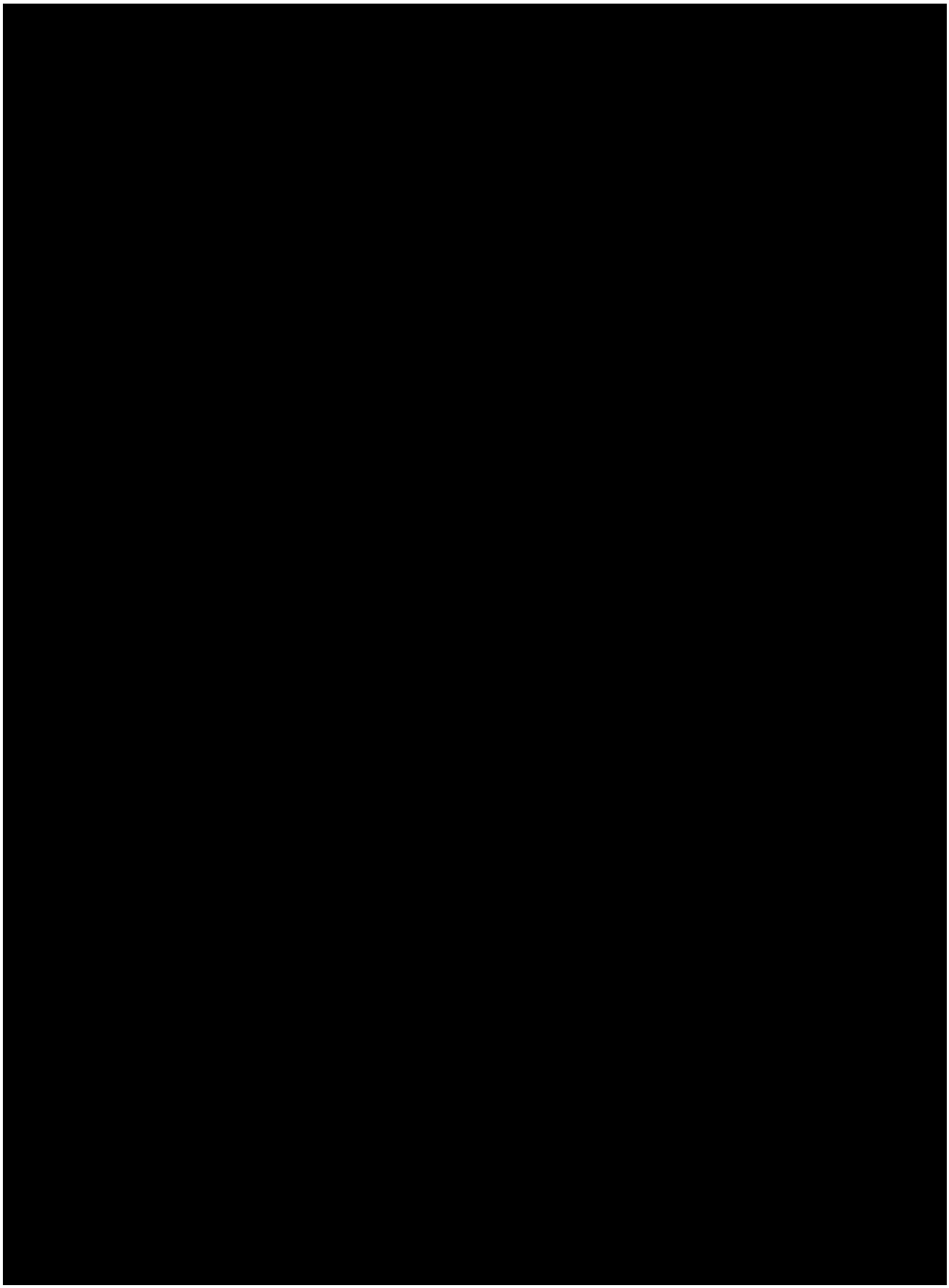
To ensure uniform data collection and protocol compliance, the Sponsor will conduct a training session that will include reviewing the protocol, eCRF and data collection process, and the adverse event reporting process. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

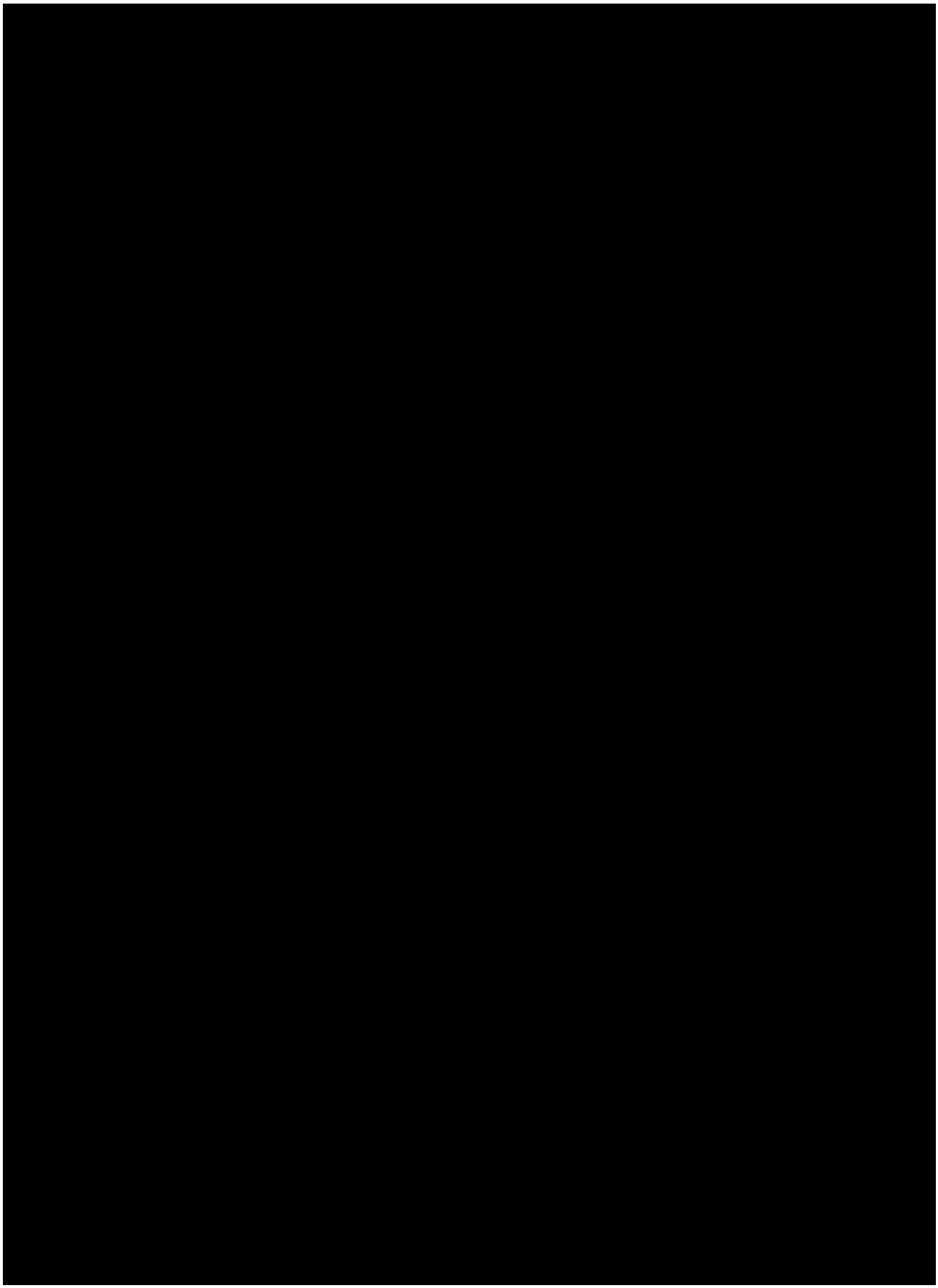


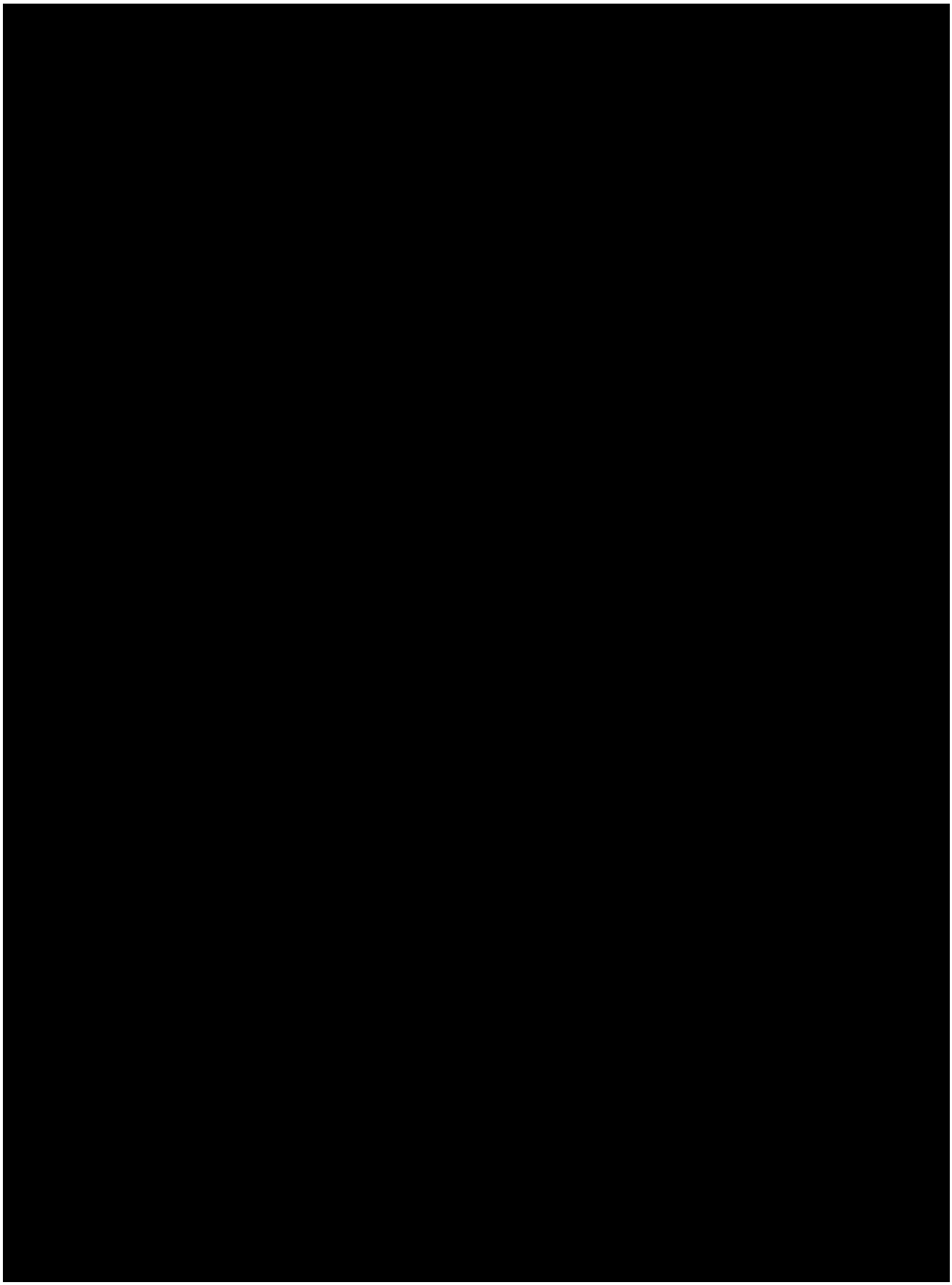


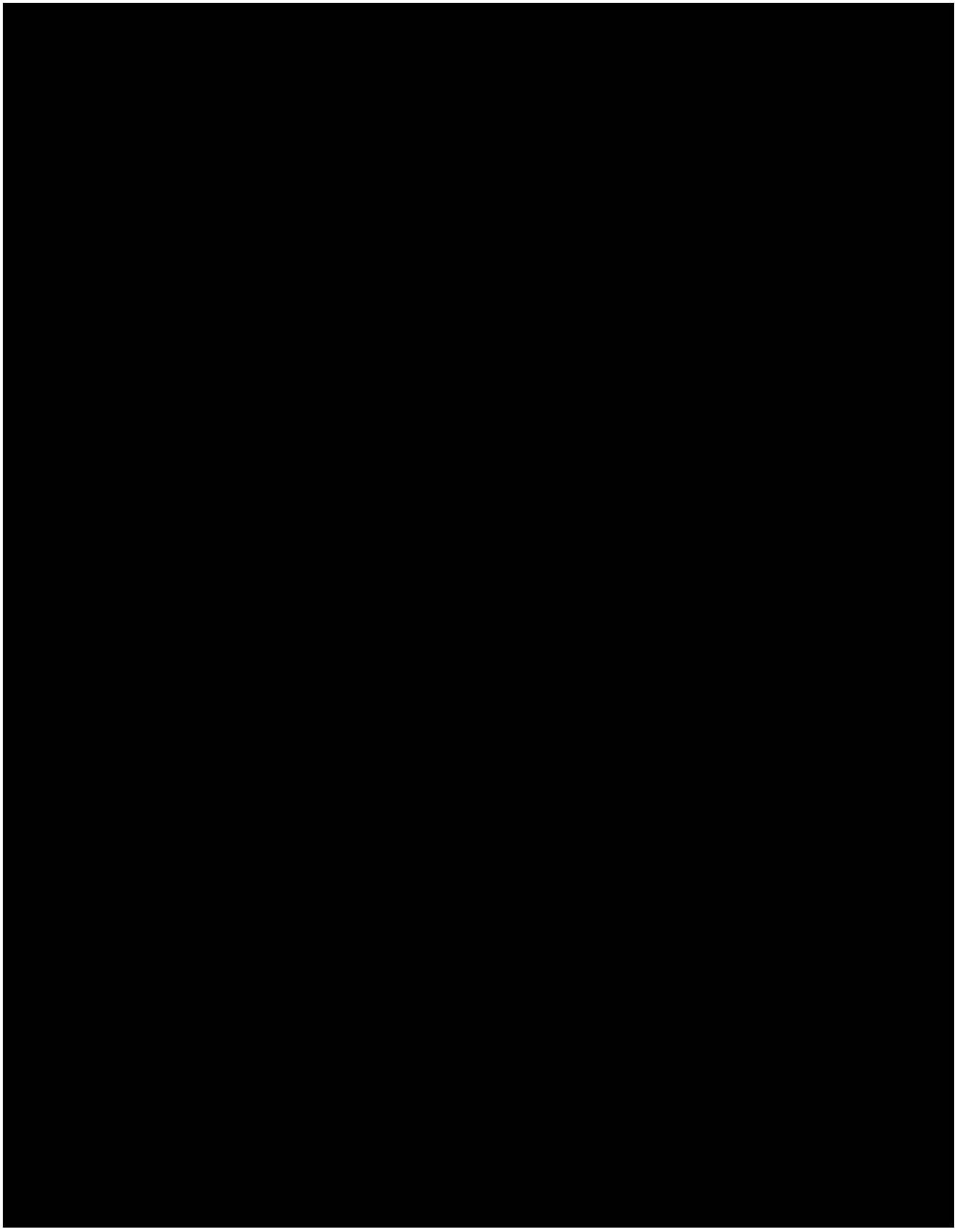


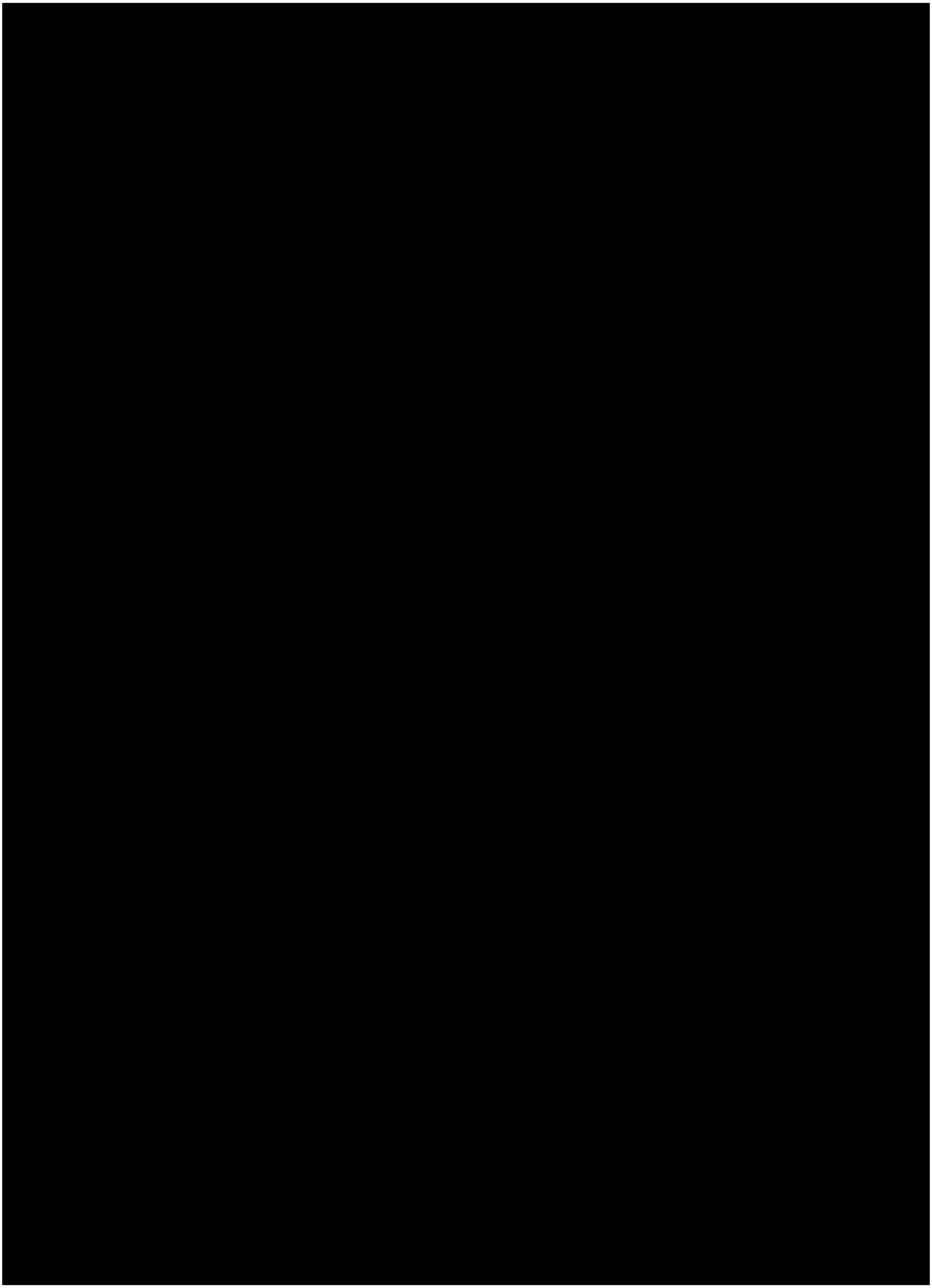












7. Study Medications

7.1. Antiarrhythmic drugs

During this study, current AF management guidelines and the institution's standard of care practices are to be followed as closely as possible for AAD therapy.

A Class I and/or Class III AAD can be administered for AF and terminated before the end of the 3-month follow-up visit window (i.e., day 104). If a Class I/III AAD is prescribed /administered after day 104 post procedure or oral amiodarone is prescribed/administered at any time post procedure, it MUST be accompanied by documentation of arrhythmia. If a Class I and/or Class III AAD is continued or started past Day 104, the subject will be considered a primary effectiveness failure. If oral Amiodarone is prescribed and/or taken at any time post index ablation procedure, the subject will be considered a primary effectiveness failure.

Table 7.1A illustrates the corresponding status of primary effectiveness endpoints based on AAD therapy administered in the blanking and post-blanking periods.

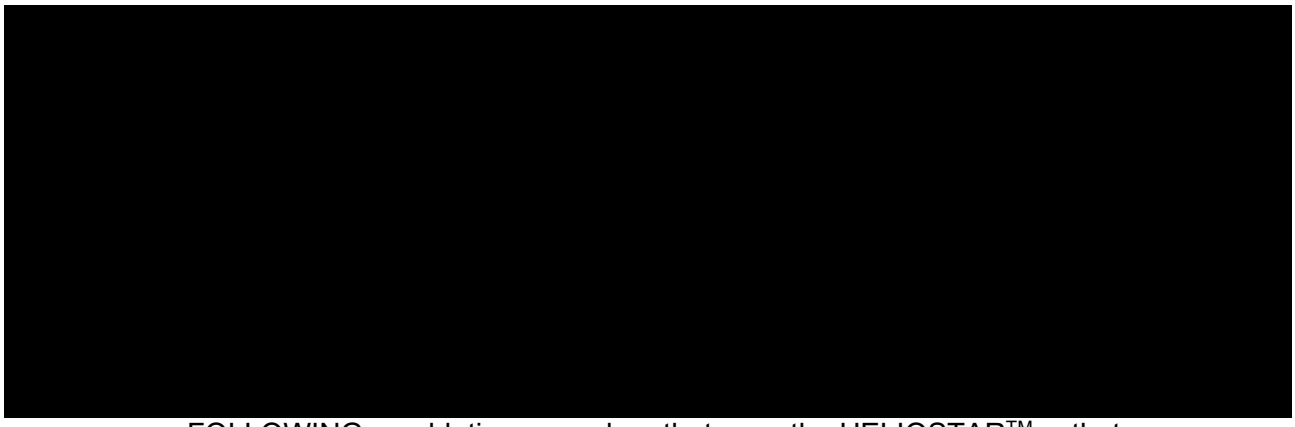
Table 7.1A: AAD Usage and Impact on Primary Effectiveness Classification

	≤ 104 days post procedure	> 104 days post procedure
Class I and/or Class III AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose as long as the AAD is **stopped on or before day 104 post procedure** and subject will not be classified as a primary effectiveness failure.	If initiated for the treatment of **AF**; subject will be classified as a primary effectiveness **failure**. If initiated for the treatment of **AF** prior to and continued past Day 104; Subject will be classified as a primary effectiveness **failure** **Can** be initiated, continued from Day 104, or increased if drug is NOT for the treatment of atrial arrhythmia (e.g. premature ventricular contractions, ventricular arrhythmias,) other than CTI dependent AFL and subject will not be classified as a primary effectiveness failure.
Class II and/or Class IV AAD	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.	**Can** be initiated, continued from prior to study enrollment, or increased in dose and subject will not be classified as a primary effectiveness failure.
Amiodarone (oral)	If prescribed and/or taken post index ablation procedure subject will be considered a **primary effectiveness failure**.	

7.2. Study specific anticoagulation requirements

- PRIOR to an ablation procedure that uses the HELIOSTAR™ catheter
  - Uninterrupted anticoagulation therapy **MUST** be in place at least 1 month prior to ablation procedure for warfarin/coumadin and 3 weeks for novel oral anticoagulation (NOAC) therapy.
    - If a subject is receiving warfarin/coumadin therapy, they **MUST** be maintained on warfarin/coumadin for at **least 4 weeks** prior to treatment with a weekly international normalized ratio (INR) ≥ 2 (to be confirmed maximum 48 hours pre-procedure). Any INR < 2 within 3 weeks prior to ablation will lead to exclusion of the subject or postponement of the study procedure until the INR is ≥ 2 for at least 3 weeks prior to treatment.
      - NOTE: If a subject is receiving warfarin/coumadin therapy and the anticoagulation therapy is changed to heparin or an equivalent agent due to documented elevated INR, this will be considered continuous anticoagulation therapy and the subject may proceed with the study procedure even if the INR falls below 2 while the subject is still receiving alternate therapy.
    - If a subject is receiving NOAC therapy, they **MUST** be maintained on recommended doses of anticoagulation for at least 3 weeks prior to the procedure day

[redacted]



- FOLLOWING an ablation procedure that uses the HELIOSTAR™ catheter
  - Anticoagulation therapy is strongly recommended for at least 2 months following ablation.
  - Decisions regarding continuation of systemic anticoagulation beyond 2 months post ablation should be based on the subject's stroke risk profile.
  - Systemic anticoagulation **will be** continued beyond two months post-procedure in subjects with a CHA_2DS_2-VASc score of ≥ 2 (unless deemed contraindicated based on clinical considerations).

8. Study Schedule, Procedures, and Assessments

8.1. Screening and Informed Consent

The Patient ICFs used must have approval from Biosense Webster and the study site's IRB/EC prior to patient enrollment in the study. An approved Patient ICF may be translated as appropriate. A copy of a blank approved Patient ICF must be maintained by each investigator in a designated study administrative file.

Patients presenting to the institution with symptomatic PAF and who are considered for an ablation procedure should be pre-screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria that can be evaluated as part of the patients' standard of care. Sites should pre-screen all patients who require a documented ablation procedure for symptomatic PAF without regard to sex or race. A pre-screening log will be used to document all patients who were reviewed for potential inclusion into the study.

The study investigator or designee will obtain written informed consent from the patient, or patient's legal representative if applicable, prior to the patient's participation in the study. The patient should NOT undergo any study specific tests or examinations that fall outside the standard of care without first signing the Patient ICF for this clinical investigation. Patients should be made aware that by signing the ICF, they are granting approval for study personnel to review their medical records and to collect/analyze personal medical information. Patients should also be informed that study personnel will maintain confidentiality of the medical records at all times. The background of the proposed study and the potential benefits and risks of the study should be explained to the patient before the ICF is signed.

If a patient is unable to read or write, informed consent shall be obtained through the aid of an independent witness who will be present throughout the process. The written Patient ICF and any other information shall be read aloud and explained to the prospective patient and, whenever possible, the patient shall sign and date the ICF. The independent witness

must also sign and date the ICF attesting that the information was accurately explained and that consent was freely given.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the patient's source documents. The voluntary process of informed consent confirms the patient's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with GCP, 21 CFR Part 50, ISO14155, and with applicable local and federal regulations. If new information becomes available that can significantly affect a study subject's future health and/or medical care, this information shall be provided to the subject(s) affected. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing an amended Patient ICF.

8.2. Pre-Procedure/Baseline Assessments, Evaluations and Procedures

Assessments and data that **MUST** be collected prior to the ablation procedure are described below. Assessments/data should be completed within 90 days prior to the study ablation procedure, unless otherwise specified.

- **Demographics:** Including but not limited to age, race (where allowed), ethnicity (where allowed), and gender.
- **Medical History:** Including arrhythmia, heart disease, thromboembolic events, lung/respiratory problems, etc.
- **AF History:** Including the first evidence of AF, number of episodes, symptoms, etc.
- **NYHA:** NYHA Classification will be used to assess the extent of heart failure for subjects with congestive heart failure.
- **CHA_2DS_2 VASc Score:** Will be used to assess the risk of stroke.
- **Medication History**: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records following enrolment but prior to the ablation procedure and should be recorded in the eCRF.
- **Anticoagulation Therapy**: Anticoagulation therapy information shall be gathered by interview or collected from medical records following enrolment but prior to the ablation procedure.
- **Height and weight** will be measured.
- **Physical Exam (including standardized neurological assessment and cardiovascular/ pulmonary examination):** Exam should be performed by a physician prior to the ablation procedure. The following items will be evaluated as part of the standardized neurological assessment: vision, hearing, speech, level of consciousness, orientation and ability to move all extremities.
- **Electrocardiogram:** Data from 12-lead ECG recordings will be collected if available.
- **Transthoracic Echocardiogram (TTE):** TTE will be used to determine the atrial size and left ventricle ejection fraction (LVEF). Equivalent exams may be substituted if needed and clinically acceptable.
- **Cardiac Multi Slice Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image:** CT/MRA **MUST** be of sufficient quality to evaluate the number, size and anatomy of the pulmonary veins and the left atrial anatomy. It is mandatory to conduct the CT/MRA assessment within 6 months prior to the study ablation procedure. All CT/MRA images collected for the study should be sent to the study core lab. For subjects in the CT/MRA subset and those with symptoms of PV stenosis, a core lab will determine the following measurements:

  - Major axis (mm)
  - Minor axis (mm)
  - Average diameter (mm)
- **Left Atrial Thrombus Detection**: Imaging for detection of left atrial thrombus or other structural contraindications to an ablation procedure is mandatory the day before or the day of the ablation procedure. Presence of a thrombus will require postponement of the ablation procedure or exclusion of the subject from further study involvement. The imaging methods to be used for atrial thrombus detection are TEE or ICE.
- **Pregnancy Test: MUST** be done for all women of childbearing age and potential within 72 hours prior to the ablation procedure.
- **Quality of Life (AFEQT™):** AFEQT™ **MUST** be collected prior to procedure.
- **Adverse Events:** AEs **MUST** be collected from the time the subject signs the informed consent onwards.
- **Neurological Assessment (NAE Subjects only):** The following assessment are required to be performed within 72 hours pre-procedure for subjects included in the NAE subset, including:
  - Cerebral MRI (see appendix A for methodology)
  - Neurological Exam
  - National Institutes of Health Stroke Scale (NIHSS)
  - Modified Rankin Scale (mRS)
  - Mini-Mental State Examination (MMSE)

  NIHSS and mRS assessments will be performed by a site staff certified in the administration of the assessments. The MMSE will be performed by site staff with documented training in the administration of such tools. A certified neurologist, blinded to the cerebral MRI data, will perform neurologic exams. Cerebral MRIs will be analyzed by a central core lab to determine the frequency, size, and anatomical location of cerebral micro-emboli, if any.

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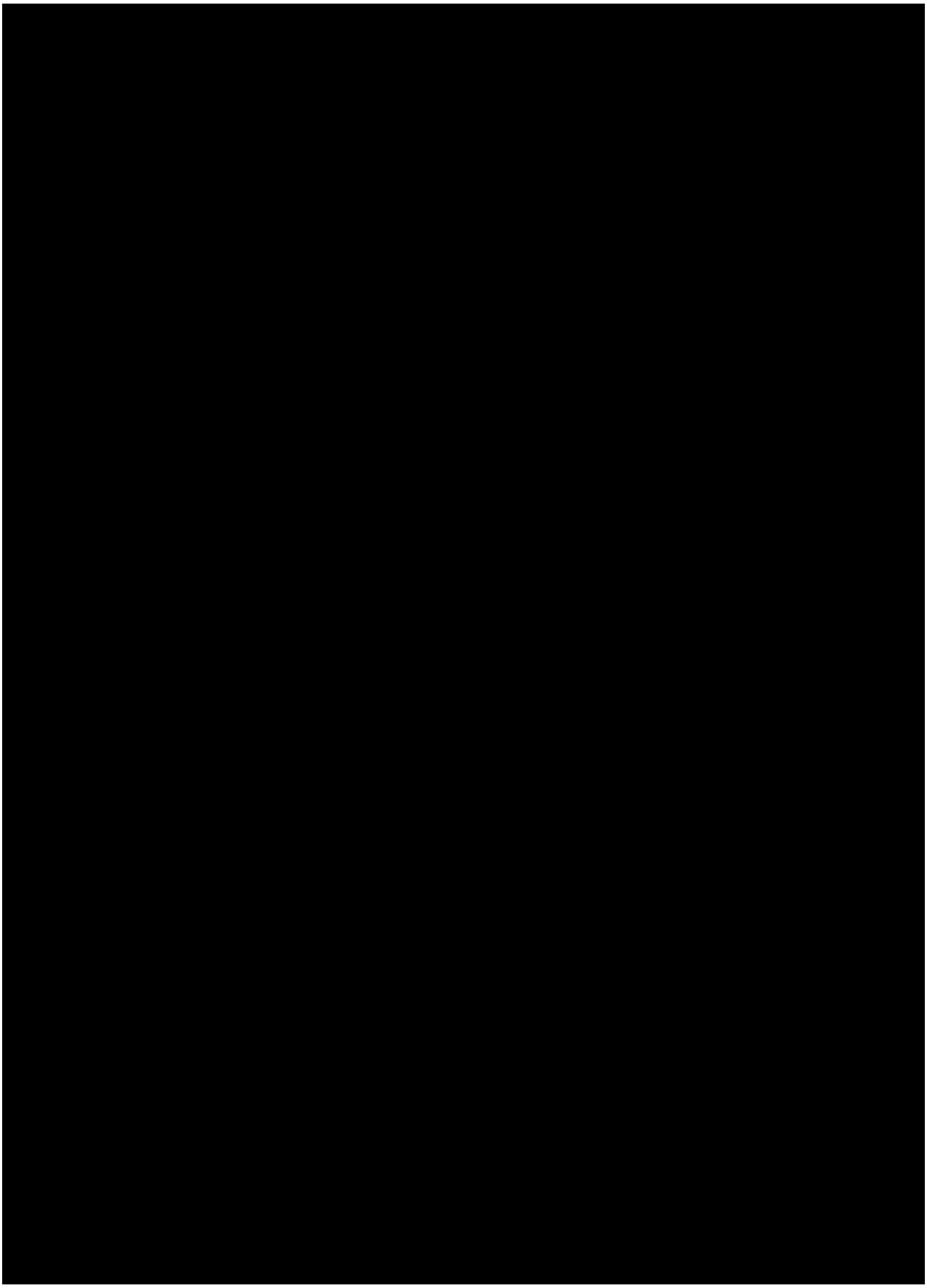
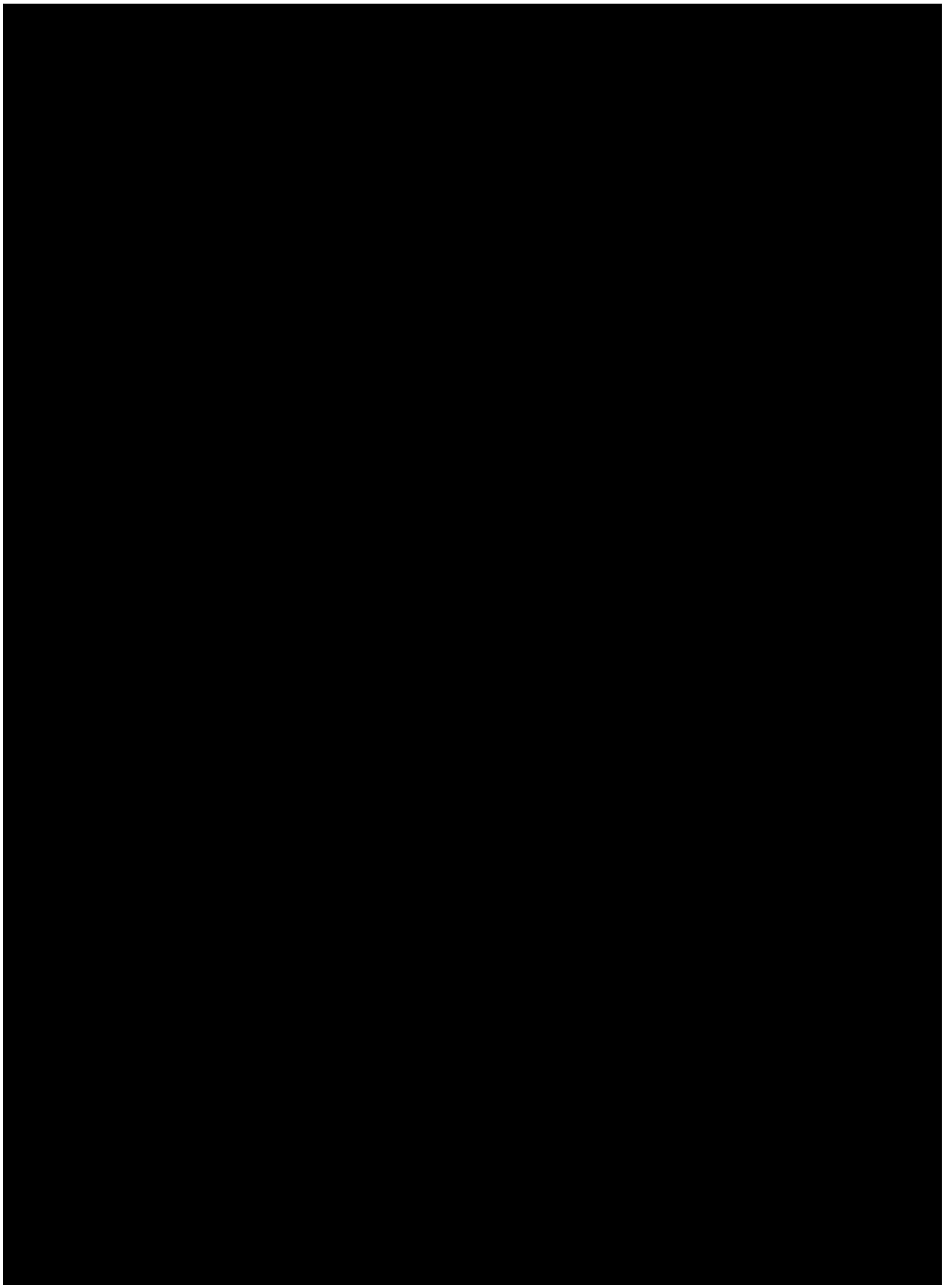
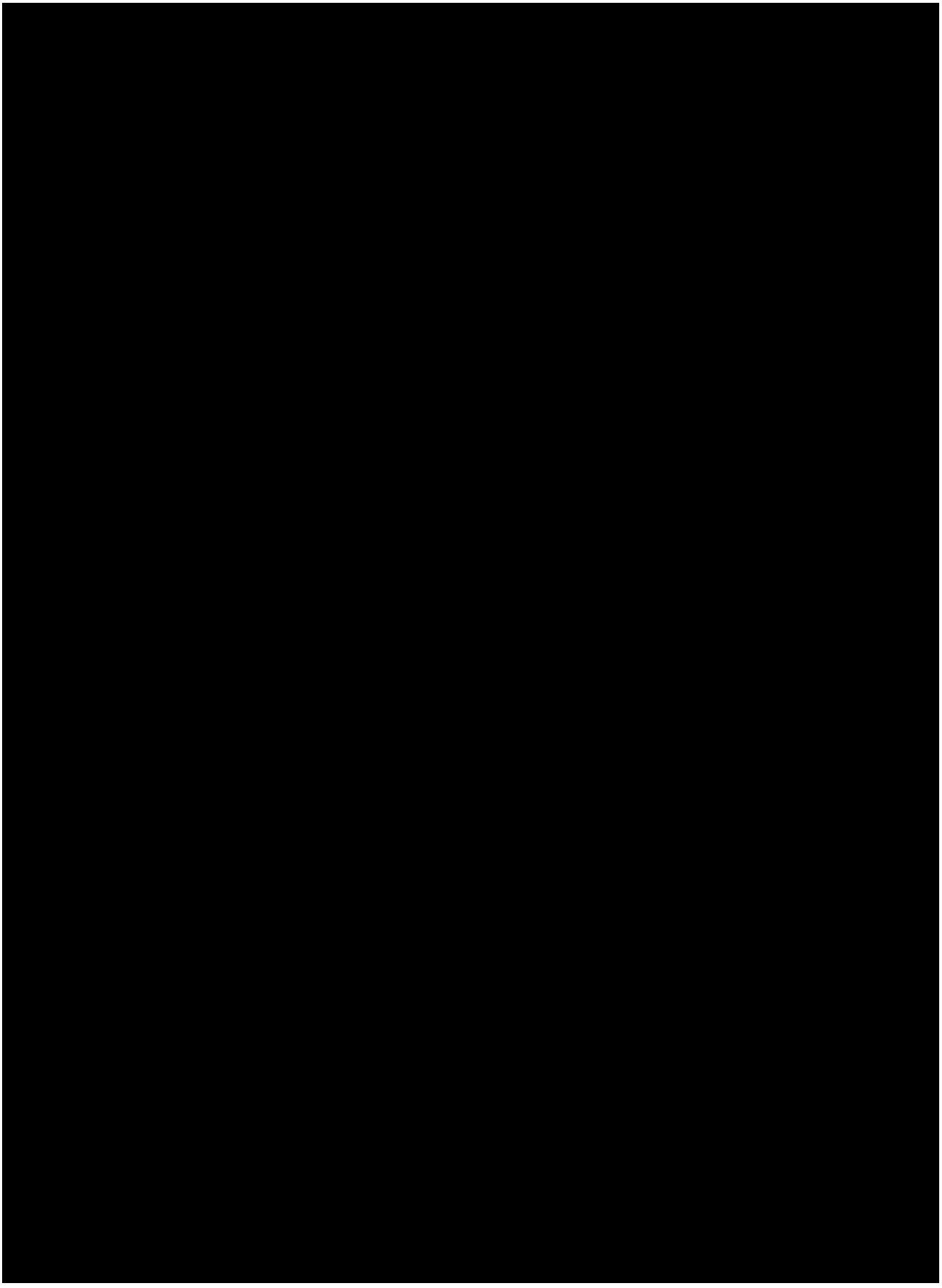






8.5. Repeat Procedures

Repeat procedures may be performed at the discretion of the investigator. Repeat procedures during the blanking period (90 days post index procedure) must be conducted with the investigational device, with or without focal touch-up, if the arrhythmia is due to PV triggers. Repeat procedures performed after the blanking period may be managed per investigator discretion using a commercially available ablation catheter and generator. The follow-up schedule will remain based on the initial ablation procedure. All pre-discharge and 7-day post-ablation assessments as summarized in Table 8.8A are to be collected for repeat procedures.

8.6. Pre-Discharge and Follow-up Assessments

The subject will be required to complete follow up visits through 12 months post index ablation procedure. Discharged subjects will receive a telephone call at 7 days post ablation procedure to assess any occurrence of Adverse Events; otherwise, any Adverse Events can be found in subjects' in-hospital source records. Additional follow-up visits are to be conducted at 1 month, 3 months, 6 months, and 12 months post index procedure.
Follow-up visits and/or calls should be scheduled according to the following timeframes: 7 day (7D, day 7-14), 1 month ± 7 days (1M, day 23-37), 3 month ± 14 days (3M, day 76-104), 6 months ± 30 days (6M, day 150-210), and 12 month ± 45 days (12M, day 315-405). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure.

Pre-Discharge / Follow-up assessments and data to be collected are described below.

- **Cardiac Medication Regimen:** All cardiac medication prescribed since the ablation procedure until the end of follow-up will be recorded, including the type and name of the medication, associated indications, start and end dates, etc. Data will be collected at the pre-discharge visit, the 7 day, 1M, 3M, 6M, and 12M follow-up, and at any unscheduled visits.
- **Anticoagulation Medication Regimen:** Information is to be collected at the pre-discharge visit, 1M, 3M, 6M, and 12M follow-up, and at any unscheduled visits.
- **Physical Exam (including standardized neurological assessment and cardiovascular/ pulmonary examination):** Physical Exam is to be performed by a physician at discharge and physician, physician assistant, or nurse practitioner at subsequent clinical visits (1M, 3M, 6M (if clinical visit), and 12M visits). The following items will be evaluated as part of the standardized neurological assessment: vision, hearing, speech, level of consciousness, orientation and ability to move all extremities. If the neurological assessment demonstrates abnormal findings, the subject should have a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI), used to confirm any suspected diagnosis of stroke.

- **Quality of Life questionnaire: AFEQT™** is to be collected at the 3M, 6M (if clinical visit), and 12M visits.
- **Transthoracic Echo (TTE):** TTE should be conducted within 48 hours of the index procedure. Equivalent exams may be substituted if needed and clinically acceptable.
- **Electrocardiogram** (12-Lead ECG): Data from 12-lead ECG recordings will be collected at the 3M and 12M follow-up visit. ECG data will be collected at baseline, pre-discharge, 1M follow-up visit, and unscheduled visits if completed as standard of care and at 6M if a clinical visit occurs and ECG is completed as standard of care. If an ECG is unable to be obtained (e.g. due to telemedicine visit), subjects will be instructed to transmit 1 TTM transmission (60 seconds) in lieu of an ECG recording at the time of the follow-up visit. Any 12-lead ECG tracings obtained beyond 3 months (90 days) showing an arrhythmia will be reviewed and adjudicated by an independent cardiologist.
- **Transtelephonic Monitoring (TTM):** Subjects will be provided with a TTM device no later than at the 1M follow-up visit (TTM device may be provided at discharge if collected as standard of care) and required to record and transmit a minimum of 1 transmission (60 seconds) every week through the end of month 5 of follow-up. Starting at month 6 of follow-up, subjects will be required to record and transmit a minimum of 1 transmission (60 seconds) every month until the effectiveness evaluation period is completed (12 months post index procedure). Subjects will also be instructed to transmit any symptom-triggered episode that occurs from the time they receive the TTM device through the 12M follow-up visit. A core lab will be used to evaluate and assess the TTM tracings.
- **24 Hour Holter:** Holter monitor will be used at the 12M follow-up visit to monitor the subjects' heart rhythm for 24 hours continuously. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.
- **Cardiac Multi Slice CT/MRA Image:** CT/MRA will be completed at the 3M follow-up visit for subjects in the CT/MRA subset. In addition, any subjects who have symptoms suggestive of PV stenosis should undergo CT/MRA imaging. Post procedure CT/MRA should be performed with contrast, unless there is a contraindication, and must be of sufficient quality to evaluate the number, size and anatomy of the pulmonary veins. All CT/MRA images collected for the study should be sent to the study core lab.
- **Adverse Events:** AEs must be collected from the time the subject signs the informed consent onwards.
- **AFL/AT/AF recurrence:** Any post-procedure atrial arrhythmia that is documented by devices other than the sponsor provided TTM/Holter Monitor and/or ECG will be recorded at 1M, 3M, 6M, and 12M follow-up as well as at any unscheduled visits.
- **Repeat Ablation:** Any ablation procedure performed after the index procedure will be recorded at 1M, 3M, 6M, and 12M follow-up as well as at any unscheduled visits.

For NAE subjects:

- **Cerebral MRI** is required to be performed between 12-48 hours (preferably between 24-48 hours) post index procedure to evaluate the presence/absence of cerebral lesions and/or neurological defects. If there are findings noted on the post-ablation cerebral MRI, a follow-up MRI will be required at each follow-up visit until resolution is observed. Cerebral MRIs will be analyzed by a central core lab to

determine the number, size, and anatomical location of cerebral micro-emboli, if any. See appendix A for methodology.

- **Neurological Exam** is required to be performed between 24-48 hours post index procedure to evaluate the neurological condition and presence of neurological deficits occurring post study ablation procedure. The Neurological Exam may be performed earlier than 24 hours if neurological symptoms/signs developed post ablation. If there are findings of microemboli/neurologic deficits, a follow-up neurologic exam will be required at each follow-up visit until resolution is observed. A certified/qualified neurologist, blinded to the MRI data, must perform neurologic exams.
- **National Institutes of Health Stroke Scale (NIHSS)** assessment is required to be performed between 24-48 hours post index procedure to evaluate the neurological condition and presence of neurological deficits of the subject's post study ablation procedure. The NIHSS can be administered earlier than 24 hours if neurological symptoms/signs developed post ablation. If there are findings of microemboli/neurologic deficits, a follow-up NIHSS assessments will be required at each follow-up visit until resolution is observed. This assessment will be performed by site staff certified in the administration of the NIHSS
- **Modified Rankin Scale (mRS)** assessment is required to be performed at the 1 month follow-up visit to evaluate the neurological condition and presence of neurological deficits occurring post study ablation procedure. If there are findings of microemboli/neurologic deficits, follow-up mRS assessments will be required at each follow-up visit until resolution is observed. This assessment will be performed by site staff certified in the administration of the mRS.
- **Mini-Mental State Examination (MMSE)** is required to be performed at the 1 month follow-up visit to assess changes in cognitive status post study ablation procedure. If there are findings of microemboli and/or new cognitive deficits, follow-up MMSE assessments will be required at each follow-up visit until resolution is observed. The MMSE will be performed by site staff with documented training in the administration of such tools.

8.7. Unscheduled visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 8.9A, the visit will be considered "unscheduled" (UNS). An Investigator may request an unscheduled visit in the presence of a new or worsening cardiovascular condition or neurological deficit. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule is based on the index ablation procedure. For all unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for their next scheduled study visit.

8.8. Schedule of Events Table

At each visit, the following assessments should be performed (Equivalent exams may be substituted if needed).

Table 8.8A: Summary of Subject Assessments

Assessments	Pre-Procedure	Pre-Discharge Post procedure - Discharge	D7[1] D7-14	M1 D23-37	M3 D76-104	M6[1] D150-210	M12 D315-405	UNS
Patient Informed Consent/ Demographics	●[2]							
Height and Weight	●[2]							
Physical exam	●[2]	●		●	●	●[3]	●	●
Medical/AF history	●[2]							
Cardiac Medication Regimen[4]	●[2]	●	●	●	●	●	●	●
Anti-coagulation Regimen[4]	●[2]	●		●	●	●	●	●
CHA_2DS_2-Vasc Score	●[2]							
NYHA functional Class Scale	●[2,5]							
Pregnancy Test	●[6]							
QoL (AFEQT™ questionnaire)[4]	●[2]				●	●[3]	●	
TTE	●[2]	●[7]						
LA thrombus detection (TEE/ICE)	●[8]							
ECG	●[2,9]	●[9]		●[9]	●	●[10]	●	●[9]
TTM[11]				●	●	●	●	●
24-hour Holter[4]							●	
Cardiac CT/MRA	●[12]				●[13]			●[15a]
Adverse events[4, 14, 15]	●	●	●	●	●	●	●	●
AFL/AT/AF recurrence [4]				●	●	●	●	●
Repeat Ablation				●	●	●	●	●
Cerebral MRI (NAE subjects only)	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
Neurological Exam (NAE subjects only)	●[16]	●[20]		●[18]	●[18]	●[18]	●[18]	●[19]
NIH Stroke Scale (NAE subjects only)	●[16]	●[20]		●[18]	●[18]	●[18]	●[18]	●[19]
mRS (NAE subjects only)	●[16]			●	●[18]	●[18]	●[18]	●[19]
MMSE (NAE subjects only)	●[16]			●	●[18]	●[18]	●[18]	●[19]

1. May be telephone call, virtual visit, or clinic visit.
2. Completed/Collected within 90 days prior to ablation procedure.
3. Required only for clinical visit
4. May be completed via telephone call or virtual visit when a clinic visit is not possible.
5. Completed/Collected in subjects with congestive heart failure.
6. In all women of childbearing age and potential. To be completed within 72-hours prior to ablation procedure.
7. To be completed within 48 hours post-index procedure.
8. To be completed the day before or the day of the study ablation procedure.
9. To be collected if completed as standard of care.
10. To be completed if a clinical visit occurs and if collected as standard of care
11. Refer to section 8.6, Pre-Discharge and Follow-up Assessments, for TTM transmission requirements
12. Completed/Collected within 6 months prior to ablation procedure
13. Required for subjects in the CT/MRA subset
14. If AE results in Hospitalization, associated cost data should be collected
15. Some adverse events may require specific tests/assessments to be conducted
    a. Subjects with symptoms suggestive of PV stenosis should undergo CT/MRA imaging
    b. Subjects with symptoms suggestive of thromboembolism, phrenic nerve paralysis, and/or stroke/CVA should undergo the assessments descr bed in the corresponding sections of Table 9.2.3A
    c. Subjects whose post-procedural fluoroscopic evaluation of the diaphragm demonstrates diaphragmatic paralysis should undergo appropriate follow-up test (e.g. sniff test or inspiration/expiration chest radiography) at discharge and subsequent follow-up visits until resolution of the diaphragmatic paralysis or the completion of the study (diaphragmatic paralysis is considered to be permanent when it is documented to be present 12 months).
16. To be completed within 72-hours prior to ablation procedure.
17. To be completed between 12-48-hours post-procedure.
18. To be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation (if undertaken, then clinical visit is needed).
19. To be completed only if a previous mandated test was missed, or if subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval.
20. To be completed between 24-48-hours post-procedure.

9. Assessment of Safety

9.1. Specific Safety Parameters

⸸ Pursuant MDR 2017/745, in the occasion relevant (local) regulations, guidance(s) and processes on safety determinations, definitions and reporting become in full force during the course of the study, the Sponsor shall adhere to the applicable definitions and processes.

9.2. Adverse Event Definitions

9.2.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a subject whether or not related to the investigational medical device. Specifically, an adverse event (AE) is any undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the device or procedure.

The following clinical events **will not be considered an adverse event for this clinical study**:

- Any medical condition that is present at the time of screening. Such conditions should be added to the medical history, if not previously reported. However, if the study subject's condition deteriorates at any time during the study, it should be recorded as an AE.
- A trace / trivial / minor pericardial effusion that is asymptomatic, requires no medical intervention, and does not extend hospitalization will not be considered an adverse event
- Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.
- Recurrence of pre-existing AF/AT/AFL
- AF/AFL/AT recurrence requiring DC cardioversion during the blanking period and/or pharmacological cardioversion at any time throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE.
- Re-ablation for AF or pre-existing AFL/AT itself is not an AE, however any complication associated with the repeat ablation procedures is considered an AE and shall be reported within the applicable timelines.

9.2.2. Serious Adverse Event (SAE)

A serious adverse event (SAE) is any event that meets one or more of the following criteria:

- Leads to a death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury
  - A permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of an existing hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
  - Chronic disease (MDR 2017/745) ⸸
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

*Planned hospitalization for a condition present prior to the subject's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" for seriousness if the event necessitated an admission to a health care facility (e.g., an overnight stay). Emergency

room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

9.2.3. Primary Adverse Event

A Primary AE is an event listed in Table 9.2.3A which occurs within the first week (7 days) of an ablation procedure which used one or more of the investigational device(s) unless otherwise indicated.

Table 9.2.3A: Primary Adverse Events

Primary Adverse Event	Description / Criteria
Death*	Subject death directly related to the device or procedure that occurs at any time during or after the procedure.
Atrio-Esophageal Fistula*	Defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
Myocardial Infarction	Presence of any one of the following criteria: • Detection of ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB]) which persist for more than 1 hour • Development of new pathological Q waves on ECG • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Cardiac Tamponade**/ Perforation	The development of a significant pericardial effusion during or within 30 days of undergoing the index AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. • Cardiac tamponade/perforation should also be classified as: o Early – diagnosed prior to discharge o Late – following initial discharge from the hospital
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow accompanied by clinical symptoms. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography. For the purposes of this study silent (asymptomatic) cerebral embolism will not be considered a PAE.

Primary Adverse Event	Description / Criteria
Transient Ischemic Attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
Pulmonary Vein Stenosis*	Severe PV stenosis (≥70% reduction in the diameter of the PV) will be considered a primary adverse event and major complication of AF ablation.
Phrenic Nerve Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Major Vascular Access Complication / Bleeding	**Major Vascular Access Complication:** Defined as a hematoma, an AV fistula or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission. **Major Bleeding:** A major complication of AF ablation if it requires and/or treated with transfusion or results in a 20% or greater fall in HCT.
Pericarditis	**Major:** results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 h, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation). Pneumonia (infiltrate, fever and leukocytosis) and Acute Respiratory Distress Syndrome are excluded from this definition.

Primary Adverse Event	Description / Criteria
Stroke/ Cerebrovascular Accident (CVA)	Diagnosis: • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. • Duration of a focal or global neurological deficit ≥ 24 h; or < 24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. • No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences).† • Confirmation of the diagnosis by at least one of the following: Neurology or neurosurgical specialist; Neuroimaging procedure (MRI or CT scan or cerebral angiography); Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage). Definition: Stroke: (diagnosis as above, preferably with positive neuroimaging study) • Minor—Modified Rankin score < 2 at 30 and 90 days†† • Major—Modified Rankin score ≥ 2 at 30 and 90 days
Hospitalization (initial or prolonged)	Device or procedure related serious adverse event that prolongs or requires in patient hospitalization for more than 48 hours. Excludes hospitalization (initial & prolonged) solely due to arrhythmia (AF/AFL/AT) recurrence or due to nonurgent cardioversion (pharmacological or electrical).

* Occurrence greater than one week (7 days) post-procedure shall be deemed Primary AE.
** Hemodynamic compromise or instability is defined as Systolic blood pressure < 80 mmHg
† Non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.
†† mRS assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day mRS, a final determination of major versus minor stroke will be adjudicated by an independent physician/committee.

9.2.4. Non-Serious Adverse Events

A non-serious AE is any event that results in minimal transient impairment of a body function or damage to a body structure and does not meet any of the serious adverse event criteria.

9.2.5. Adverse Device Effect / Serious Adverse Device Effect

An adverse device effect (ADE) is an adverse event related to the use of the investigational medical device.

NOTE 1- This includes any adverse event resulting from insufficiencies or

inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

A Serious Adverse Device Effects (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

9.2.6. Unanticipated (Serious) Adverse Device Effect

An unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or risk analysis report, or any other unanticipated serious problem associated with a device that relates to rights, safety, or welfare of subjects. Refer to Table 9.3.4A for a comprehensive list of foreseeable and anticipated adverse events.

9.2.7. Study Device Deficiency, Failure or Malfunction

A device has failed if it does not perform according to the IFU or fails to meet the expectations of the device and/or investigator (i.e., related to appearance of the device, performance, durability, safety, effectiveness, quality, reliability, labeling, ⸸ (MDR 2017/745) inadequacy in information supplied by the manufacturer, etc.). If a device failure is detected or suspected, it should be documented on the appropriate eCRFs and must be reported per the AE documentation and reporting requirements (Section 9.5.1).

9.3. Classification of an Adverse Event

9.3.1. Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

Table 9.3.1A Intensity or Severity Definitions

Mild	Awareness of signs, symptoms, or events that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring and ear easily tolerated.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure causing interference with usual activities, or that warrants possible intervention; such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure; or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

9.3.2. Causality

For all collected AEs, the clinician who examines and evaluates the subject will determine the AE's causality based on temporal relationship and his/her clinical judgment. The

degree of certainty about causality will be graded using the categories below (based on MEDDEV 2.7/3 Rev. 3):

Table 9.3.2A Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Definitely (Causal Relationship)	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained
	Possibly	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained (🌲 The Sponsor shall adhere to the new applicable definitions per MDR 2017/745 once the regulation is implemented in full force)
	Not related	Relationship to the investigational device can be excluded
Study Procedure	Definitely (Causal Relationship)	The event is associated with the study procedure beyond reasonable doubt
	Probable	The relationship with the study procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained
	Possibly	The relationship with the study procedure is weak but cannot be ruled out completely
	Unlikely	The relationship to the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained (🌲 The Sponsor shall adhere to the new applicable definitions per MDR 2017/745 once the regulation is implemented in full force)
	Not related	Relationship to the procedure can be excluded

9.3.3. Outcome

The outcome of each AE must be assessed according to the following classifications:

Table 9.3.3A Adverse Event Outcome Classifications

Classification	Definition

Recovered/Resolved	Subject fully recovered with no observable residual effects
Recovering/Resolving	Subject's condition is improving, but residual effects remain
Recovered/Resolved with sequelae	Subject recovered with observable residual effects
Not Recovered/Not Resolved	AE is ongoing without improvement in the overall condition
Fatal	Subject died as a result of the AE (whether or not the AE is related to the device or procedure)
Unknown	AE outcome is unknown (e.g., subject is lost to follow-up)

9.3.4. Expectedness

An anticipated Adverse Event is an effect which by nature, incidence, severity or outcome has been identified as a possible complication associated with the investigational medical device and/or intervention procedure.

Potential adverse events that are reasonably anticipated to occur during the cardiac electrophysiology procedure are listed in Table 9.3.4A. These events should be reported via the appropriate eCRF as anticipated AEs. Anticipated adverse events are to be reported to the sponsor via EDC as indicated in section 9.5.

Table 9.3.4A provides a comprehensive list of anticipated AEs.

Anticipated Adverse Events	
Acute Respiratory Distress Syndrome (ARDS)	Air embolism
Allergic reaction	Allergic reaction to Anesthesia (e.g., hair loss)
Anaphylactic shock	Anemia
Anesthesia reaction	Apnea - sedation induced
Arrhythmia: bradycardia	Arrhythmia: pro-arrhythmias
Arrhythmia: tachycardia	Aspiration pneumonia
Asthmatic attack	Asymptomatic Cerebral Lesion(s)
Atelectasis	Atrial fibrillation*
Atrio-Esophageal fistula	Atypical left atrial flutter
AV fistula	Bleeding complications
Bleeding requiring transfusion	Cardiac arrest
Cardiac perforation	Cardiac thrombo-embolism
Cerebro-vascular accident (CVA) / stroke	Chest pain/discomfort
Complete heart block, temporary or permanent	Conduction block: ongoing / resolved
Congestive Heart Failure (CHF)	Coronary artery dissection
Coronary artery occlusion	Coronary artery spasm
Coronary artery Thrombosis	Damage to the vascular system
Death	Deep venous thrombosis
Diaphragmatic paralysis	Dislodgement of permanent pacing leads
Disseminated Intravascular Coagulation	Dyspnoea
Endocarditis	Epistaxis

Anticipated Adverse Events	
Exacerbation of pre-existing arrhythmia*	Expressive aphasia
Fainting	Fatigue
Gastric reflux	Gastric hypomotility
Gastrointestinal diverticulosis	Gastro-intestinal NOS
Heart Failure	Hematoma (local) /ecchymosis
Hemorrhage	Hemothorax
High / increased creatine phosphokinase (CPK)	Hypotension
Hypoxia	Increase in frequency or duration of episodes of typical atrial flutter
Increased phosphokinase level	Infection, localized
Infection, systemic	Injury to skin, muscle, connective tissue due to body position, electrical cardioversion, etc.
Laceration	Leakage of air or blood into the lungs or other organs due to perforation
Liver toxicity	Local hematoma/ecchymosis
Mobile strands in Inferior Vena Cava	Myocardial Infarction
Nausea	Neurological disorders (headache)
Neurological disorders (poor coordination)	Neurological disorders (tremor)
Obstruction to the vascular system	Palpitations
Perforation to the vascular system	Pericardial effusion without tamponade
Pericardial effusion resulting in tamponade	Periesophageal vagal nerve injury
Peripheral embolus	Pericarditis
Peripheral thromboembolism	Peripheral nerve injury
Phrenic nerve damage	Phlebitis
Pneumothorax	Pleural effusion
Pulmonary edema	Pseudoaneurysm
Pulmonary hypertension	Pulmonary embolism
Pulmonary vein dissection	Pulmonary toxicity, like acute pulmonary syndrome
Pulmonary vein thrombus	Pulmonary vein Stenosis
Renal failure	Pump failure
Respiratory failure	Respiratory depression
Rhabdomyolysis, including produced by body position or propofol	Retroperitoneal hematoma
Seizure	Sedation induced CO_2 retention with lethargy and cholecystitis
Skin burns (due to cardioversion, tape, etc)	Sepsis
Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion	Skin discoloration
Tamponade	Skin rash
Thrombocytopenia	Temperature elevation
Thrombosis	Thromboembolism
Transient extremity numbness	Thyroid disorders

Anticipated Adverse Events	
Unintended complete or incomplete AV, Sinus node, or other heart block or damage	Transient ischemic attack (TIA)
Urinary tract injury or infection related to the urinary catheter	Urinary retention
Vasovagal reactions	Valvular damage/insufficiency
Volume overload	Vision change
X-ray radiation injury of skin, muscle and/or organ	Worsening obstructive, restrictive, or other form of pulmonary disease

*Atrial Fibrillation and exacerbation of an existing arrhythmia are anticipated adverse events. However, they will not be captured as such under this protocol, as they are considered recurrence of disease.

9.4. Time Period and Frequency for Event Assessment and Follow-up

The investigator, or designated individual, will record all events for a subject in the eCRF with start dates occurring any time after informed consent is obtained until the subjects' last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed until the event resolves (with or without sequelae) or stabilizes. All required treatments and outcomes of the SAE must be recorded in the eCRF.

9.5. Reporting Procedures

9.5.1. Adverse Event Documentation and Reporting Requirements

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g., "How was your health been since last visit?"). Anytime during the study, the subject may volunteer information that resembles an AE.

The investigator is responsible for ensuring that all AEs, observed by the investigator/study staff or reported by the subject, that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the AEs, Adverse Device Effects and Device Deficiencies section of this protocol. Adverse events are to be documented in the subject's medical record and recorded on appropriate eCRFs by the investigator or designee throughout the study and provided to the Sponsor. Each investigator shall provide source documentation as requested by the Sponsor to facilitate reporting and adjudication of these events. All AEs will be monitored until they are adequately resolved, stabilized, or explained.

Anonymized documentation pertaining to the AE (e.g., laboratory tests, consultation reports, post-mortem reports, new information relating to a previously reported AE, correspondence with the local EC, etc.) will be provided by the investigator to the sponsor or designee in a timely manner, when requested. Follow-up information relative to the subject's subsequent course must be submitted to the sponsor or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes. If the subject is withdrawn from the study because of the AE, the information must be included on the appropriate eCRFs.

The sponsor is responsible for reviewing AEs (causality, classification, seriousness…) and for ongoing safety evaluations in accordance with the study safety management plan. In case of disagreement between the sponsor and the principal investigator(s) that remain

after query resolution, the sponsor shall communicate both opinions to the concerned parties.

Biosense Webster will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related, probably device-related, or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious adverse device effects and device deficiencies that might have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventive action is required.

Adverse event reporting should occur within the timeframes noted in table 9.5.1A or per local country requirements, whichever is earlier.

Table 9.5.1A AE Reporting Requirements

Type of Adverse Event	Reporting Requirements
Serious Adverse Events	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
UADE, USADE & SADE	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
Study device deficiency associated with an AE	Report both study device deficiency and AE to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
Study device failure/malfunction that might have led to a SAE	Report to Sponsor as soon as possible but no later than 72 hours upon awareness of the event
All other Adverse Events	Routine reporting via eCRF as soon as possible but no later than 2 weeks upon awareness of the event

9.5.2. Serious Adverse Events Reporting

All SAEs, whether or not they are related to the device or procedure, **must be reported** to the Sponsor, via eCRF, **as soon as possible but no later than 72 hours upon awareness of the event** by the study site personnel.

The study investigator shall report the SAE to the reviewing IRB/EC in accordance with the local IRB/EC requirements. Biosense Webster will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely device-related or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious device effects and device deficiencies that might have led to serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

The sponsor will submit, as per site specific requirements, an update of all SAEs and all device deficiencies that might have led to a SAE to all participating clinical investigators with sites located in the EU and China. Event reporting to relevant regulatory authorities within the EU for non CE-marked devices per MEDDEV 2.7/3 Rev3 guidelines will occur by the sponsor and if indicated per local country requirements by the investigator. Pursuant to EN ISO 14155 all SAEs will be fully recorded and reported by the Sponsor to

the regulating Ministry of Health (MoH) as well as the EC according to the deadlines in force.

9.5.3. Unanticipated Device Effect Reporting

All UADE/SADE/USADE **must be reported** to the Sponsor, via eCRF, **as soon as possible but no later than 72 hours upon awareness of the event** by the study site personnel. An investigator shall submit to the reviewing IRB/EC a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but no later than 10 working days after the investigator first learns of the effect, where applicable.

9.5.4. Events of Special Interest

All Study device deficiencies that resulted or may have resulted in a SAE **must be reported** to the Sponsor, via eCRF, **as soon as possible but no later than 72 hours upon awareness of the event** (or per local country requirements, whichever is earlier) by the study site personnel. If a device deficiency is detected or suspected, it should be documented on the eCRF and the device returned to the Sponsor.

Complaints related to marketed products manufactured and/or distributed by Biosense Webster used during the procedure, are to be reported per current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC policies, and local regulations). Investigators are instructed to return devices in accordance with current company procedures and other relevant regulations.

A device deficiency related to a medical device not manufactured by Biosense Webster should be reported by the investigator to their respective manufacturer as per relevant regulation. Complaints related to non-Biosense Webster, Inc. products must be handled per institutional policies, EC policies, and local regulations.

Event reporting to relevant competent authorities in accordance with the jurisdictional regulations will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done in EU per MEDDEV 2.12/1 guidelines for CE-marked devices manufactured by Biosense Webster and per MEDDEV 2.7/3 guidelines for non CE-marked devices manufactured by Biosense Webster.

9.6. Safety Oversight

Safety oversight will be conducted as described in the safety management plan. Aggregate safety data will be reviewed regularly throughout the course of the study by the study safety lead or designee to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety. Under the rules of an approved study-specific charter, safety data will also be reviewed by an established DMC which may recommend appropriate action(s) to ensure subject safety. A Clinical Events Committee (CEC) will be implemented to adjudicate the primary safety endpoint events. The CEC will operate as described in the CEC Charter.

10. Deviations from the Clinical Study Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures and evaluations described in this protocol. The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations, and shall identify any issues of non-compliance with regulations or guidelines.

Issues of non-compliance include but are not limited to repeated protocol deviations, failure to obtain proper informed consent, non-conformance to IRB/EC requirements, failure to report Adverse Events/product malfunctions/other product issues, and other non-conformance to GCP.

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g., missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria). Investigators are not allowed to deviate from the protocol. Protocol deviations will be monitored closely and may require reporting to the IRB/EC and/or regulatory authority per IRB/EC/regulatory authority requirements.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed. Such deviations shall be documented as protocol deviations in the eCRF and reported to the IRB/EC/regulatory authority as required.

11. Investigational Product Materials and Accountability

11.1. Materials

Biosense Webster, Inc., Irwindale, CA USA, is the manufacturer of the catheters to be used in this study. Biosense Webster implements manufacturing precautions to protect the health and safety of subjects who undergo procedures with the investigational catheters. The investigational catheters are built in a clean room environment, and sterilized using EtO gas, in a manner similar to standard, commercially approved Biosense Webster products.

Complete manufacturing records of every lot of catheter manufactured for human use during this study are maintained at Biosense Webster, Inc. Each lot of catheters is released for human use under a Confirmation of Conformity from Regulatory Affairs that will certify that the investigational catheters meet all Essential Requirements for product release except those features that are being investigated in this clinical investigation.

11.2. Device Acquisition and Accountability

The study site will receive the necessary amount of study-related materials prior to commencement. Study-related devices (investigational and non-investigational) will be shipped to the site after completion of required documentation (essential regulatory documents, Clinical trial agreement, IRB/EC approval, regulatory agency approval). Investigational Study Devices will be labeled as Investigational and are only to be used for subjects enrolled in this clinical study. Study-related materials may be augmented throughout the study on an as needed basis.

The Sponsor will keep records of all investigational devices shipped to the site. Investigational site personnel are responsible for ensuring that appropriate device logging is completed.

The following information should be recorded in the Device Accountability Log:

- Date of receipt
- Person in receipt of the devices
- Quantity received
- Packing Slip Verification

- Catalog number for catheters
- Serial/lot numbers
- Expiry Date
- Date devices was used
- Subject ID on whom device was used
- Date of return
- Reason for return (i.e. used without issue, malfunction, expired, end of study…)

11.3. Device Returns

All Investigational Devices (**used and unused**) will be returned to the Sponsor's attention per the instructions on the investigational device return forms. Device deficiencies should be documented by completing the appropriate eCRF. All returned devices should be labeled with at minimum: Study name (STELLAR), subject identification number, if there was a complaint (adverse event)/malfunction or not. Tracking information should be retained in the event the package has been lost and requires tracking.

12. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Each site will undergo periodic monitoring of the study, which may involve visits from a Sponsor representative qualified to perform such visit. Monitoring activities may include, but are not limited to, the following:

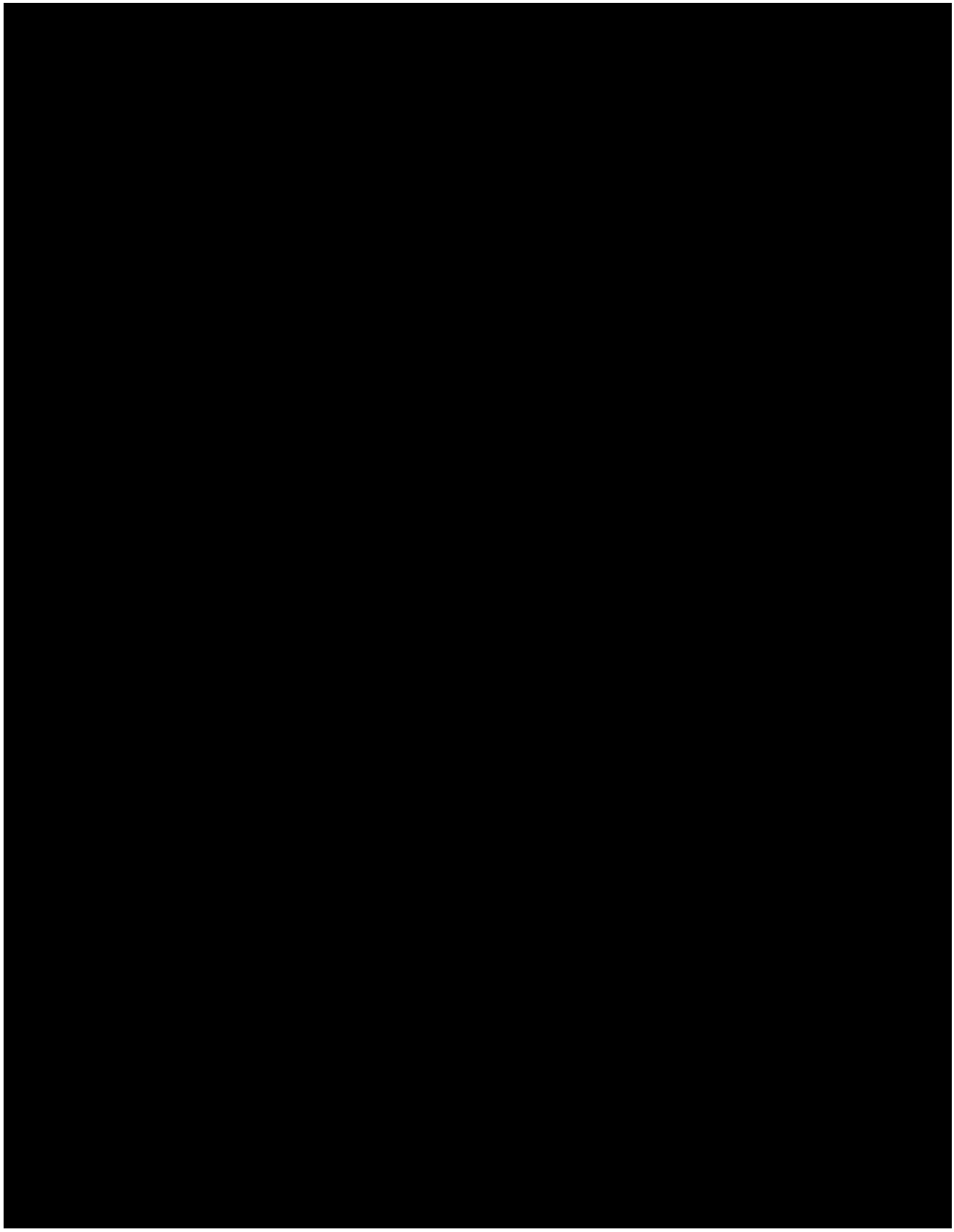
- Protocol adherence
- Source documentation verification and accuracy of the eCRFs
- Verification that informed consent is being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the Regulatory Binder
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

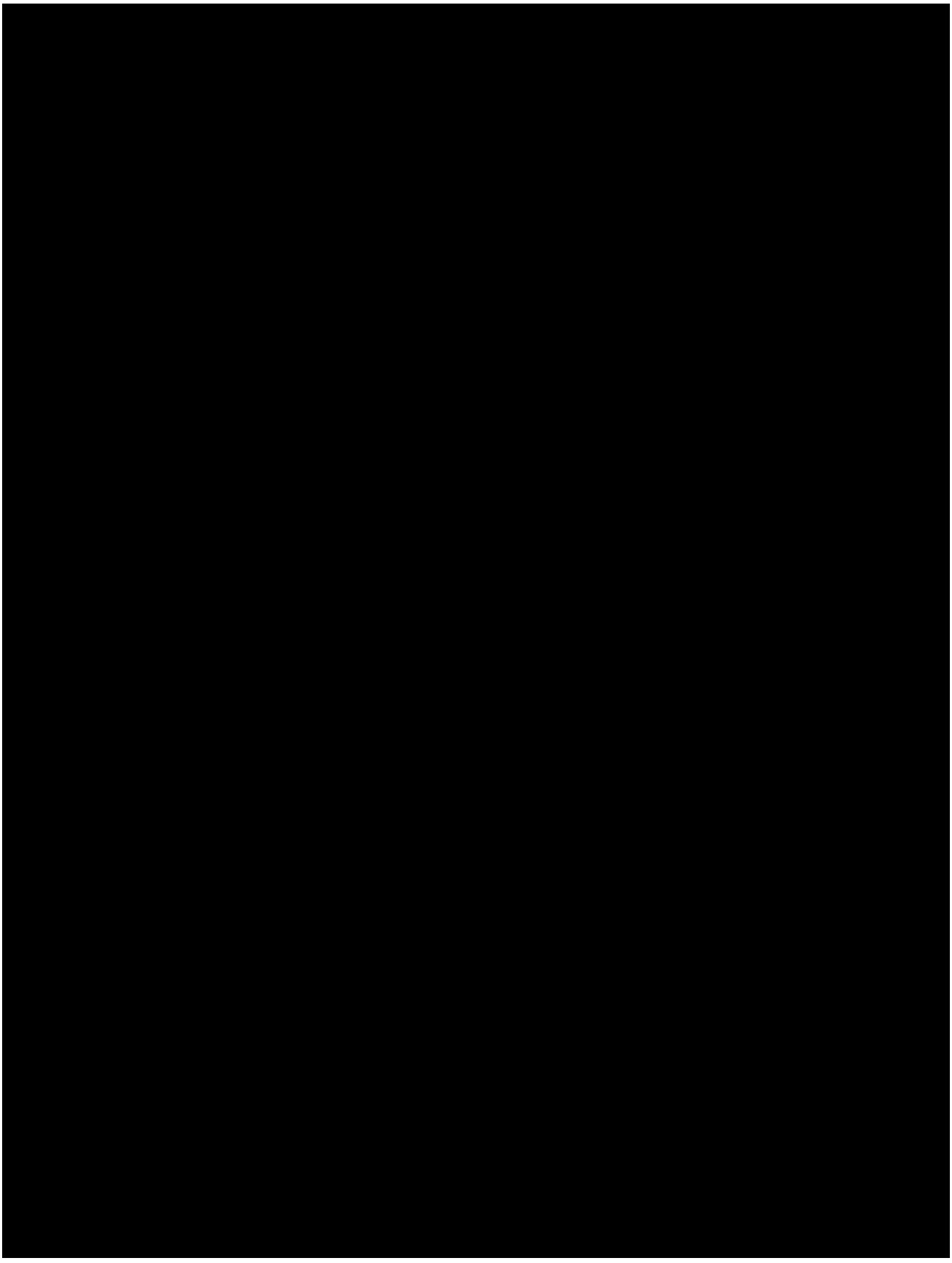
Data are to be submitted as soon as possible after collection via e-CRF. Missing or unclear data will be corrected as necessary throughout the trial. Biosense Webster may request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported.

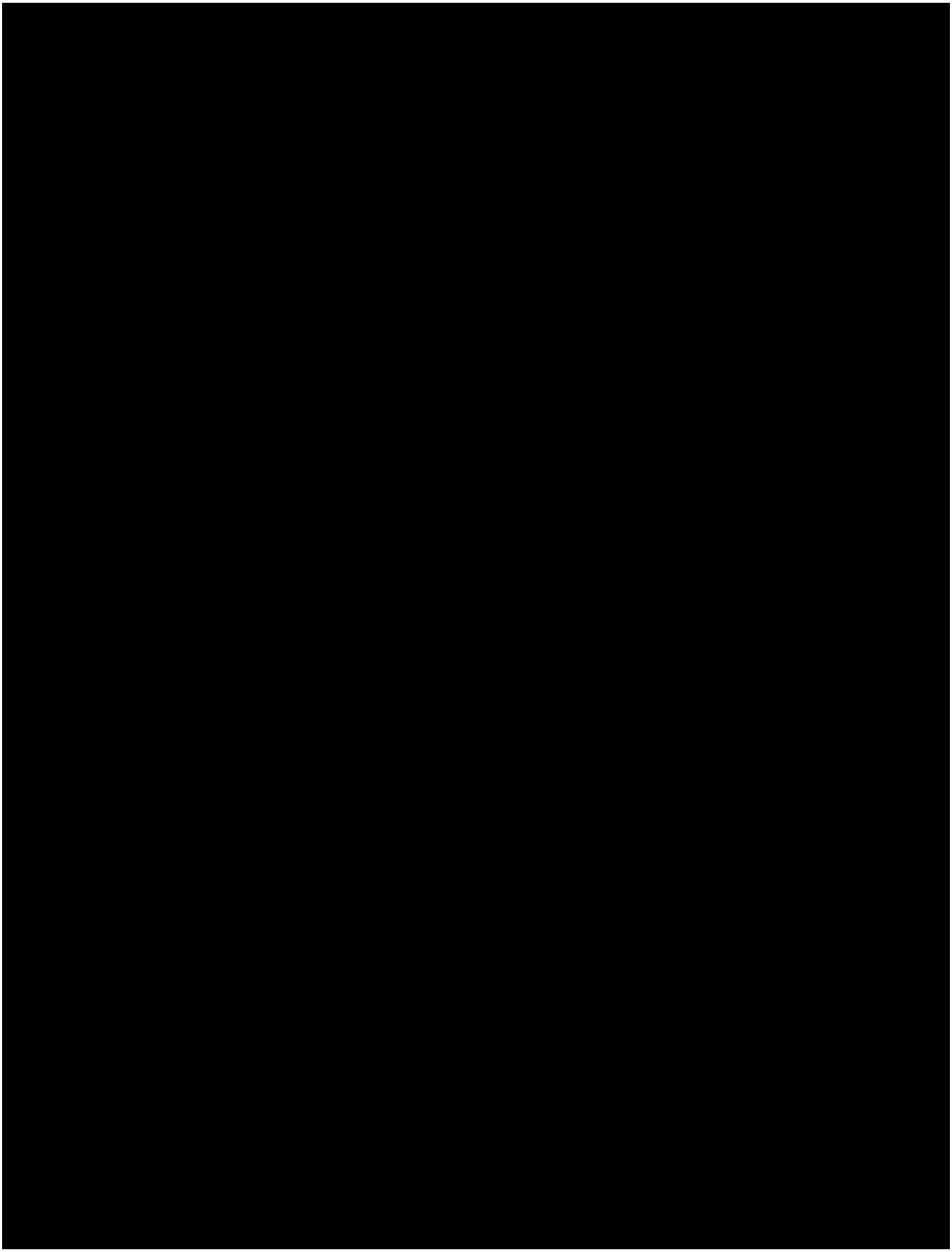
Further details on clinical monitoring are provided in the study specific monitoring plan.

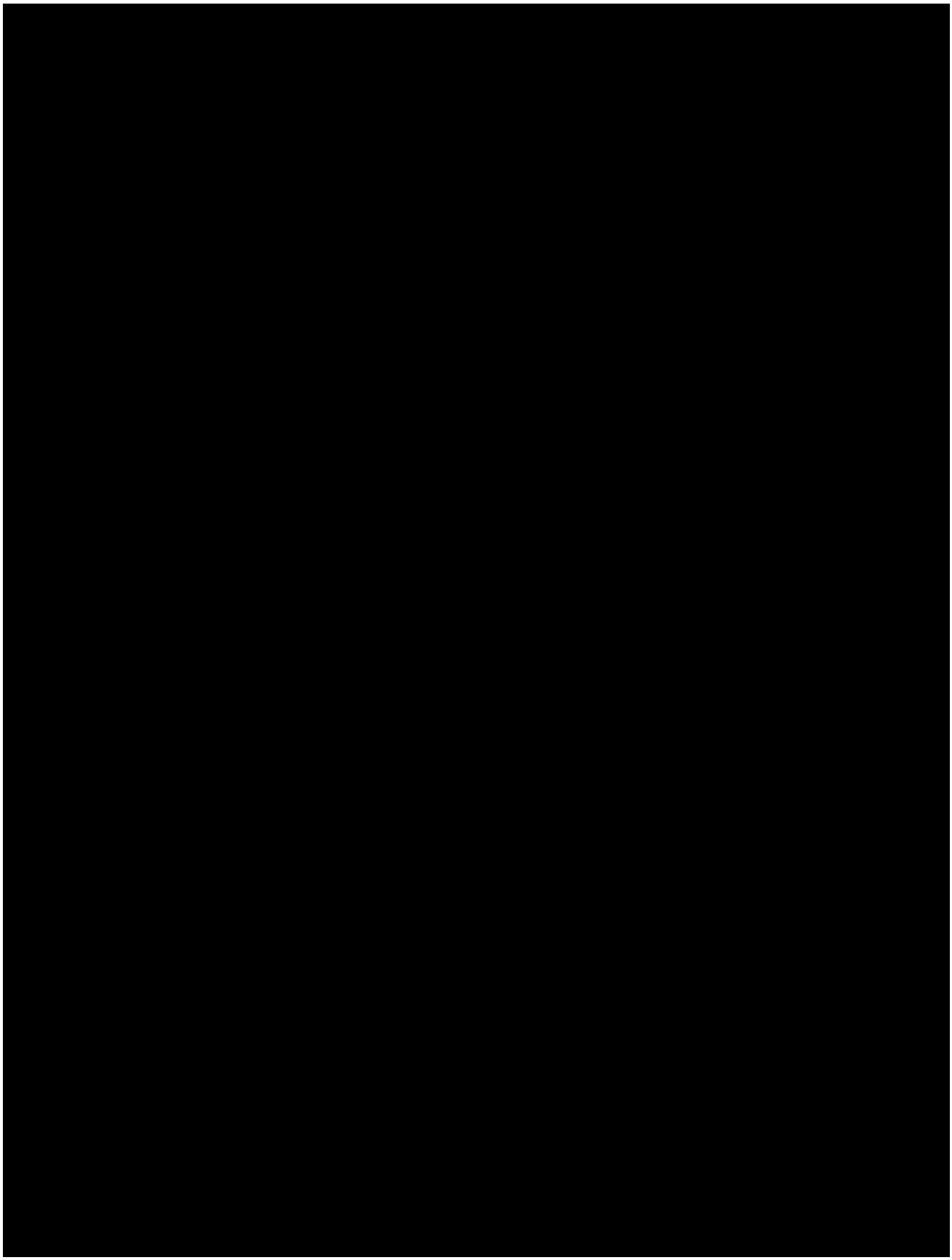
12.1. Early Termination Monitoring Visit

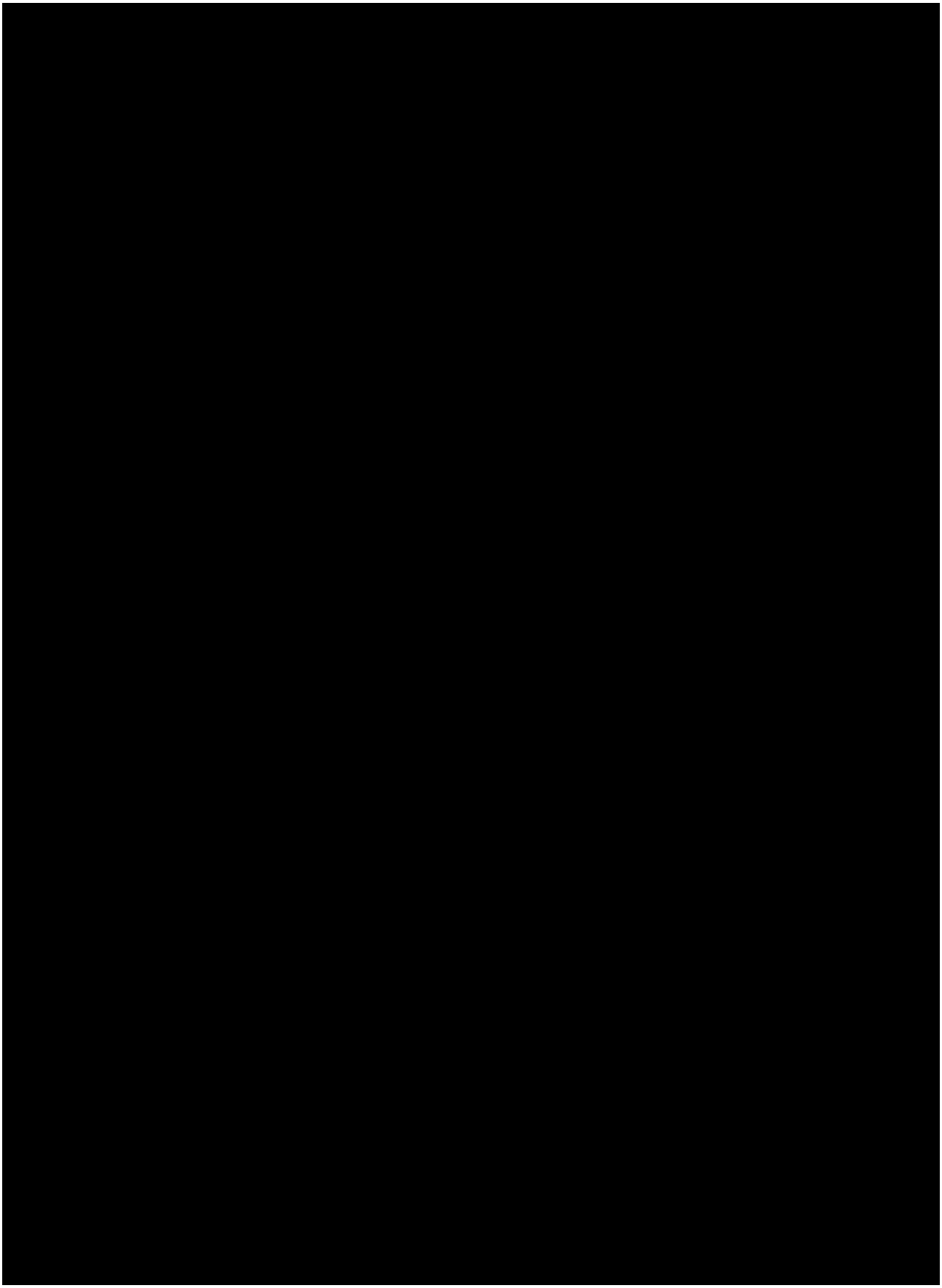
If early termination of the study is required, each site will undergo a monitoring visit as described in the monitoring plan to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Subjects will be notified of the termination of the study. Any enrolled subjects will continue to be followed per the study protocol requirements until a study closeout plan is implemented that outlines alternative follow-up procedures.

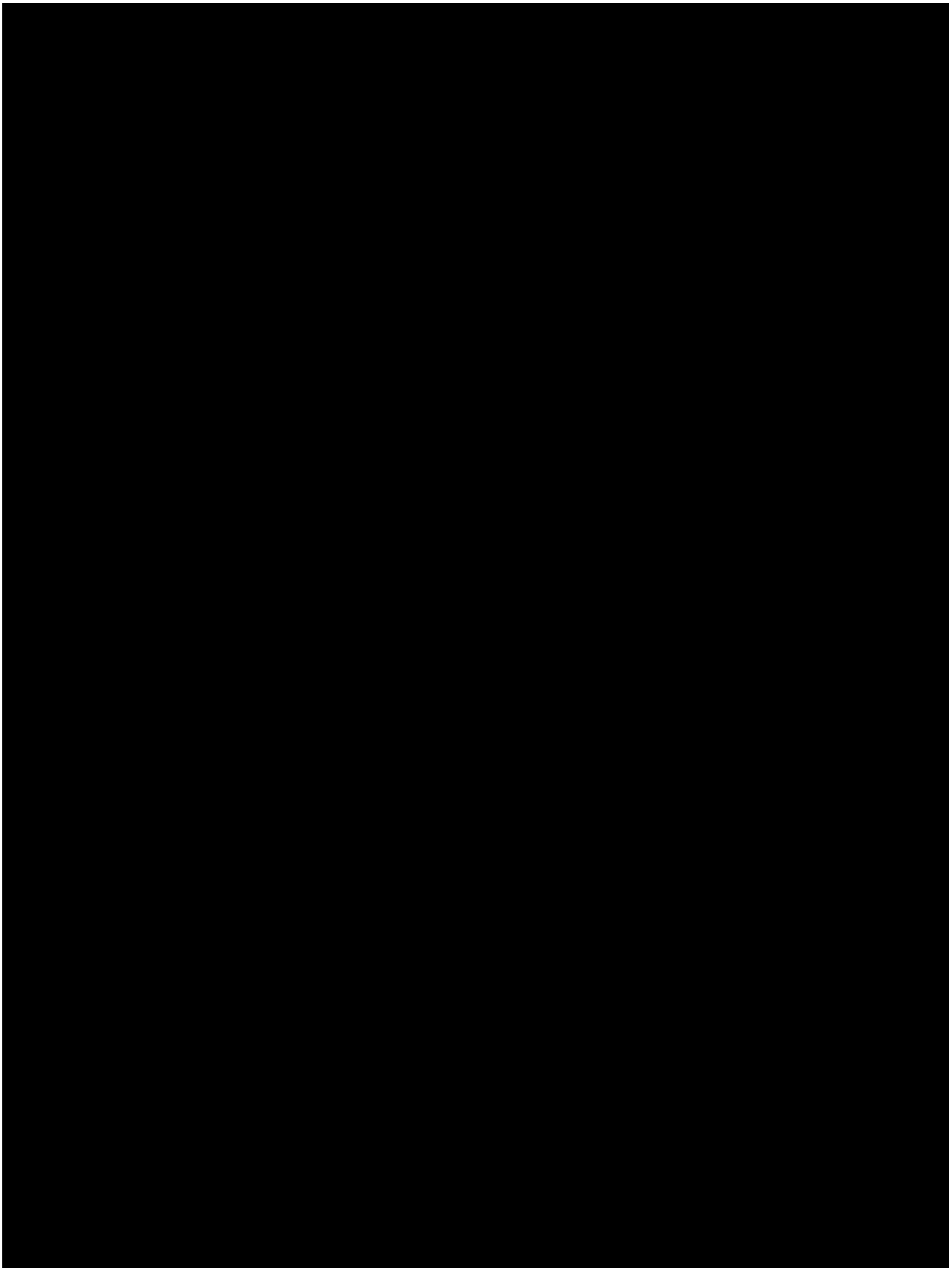


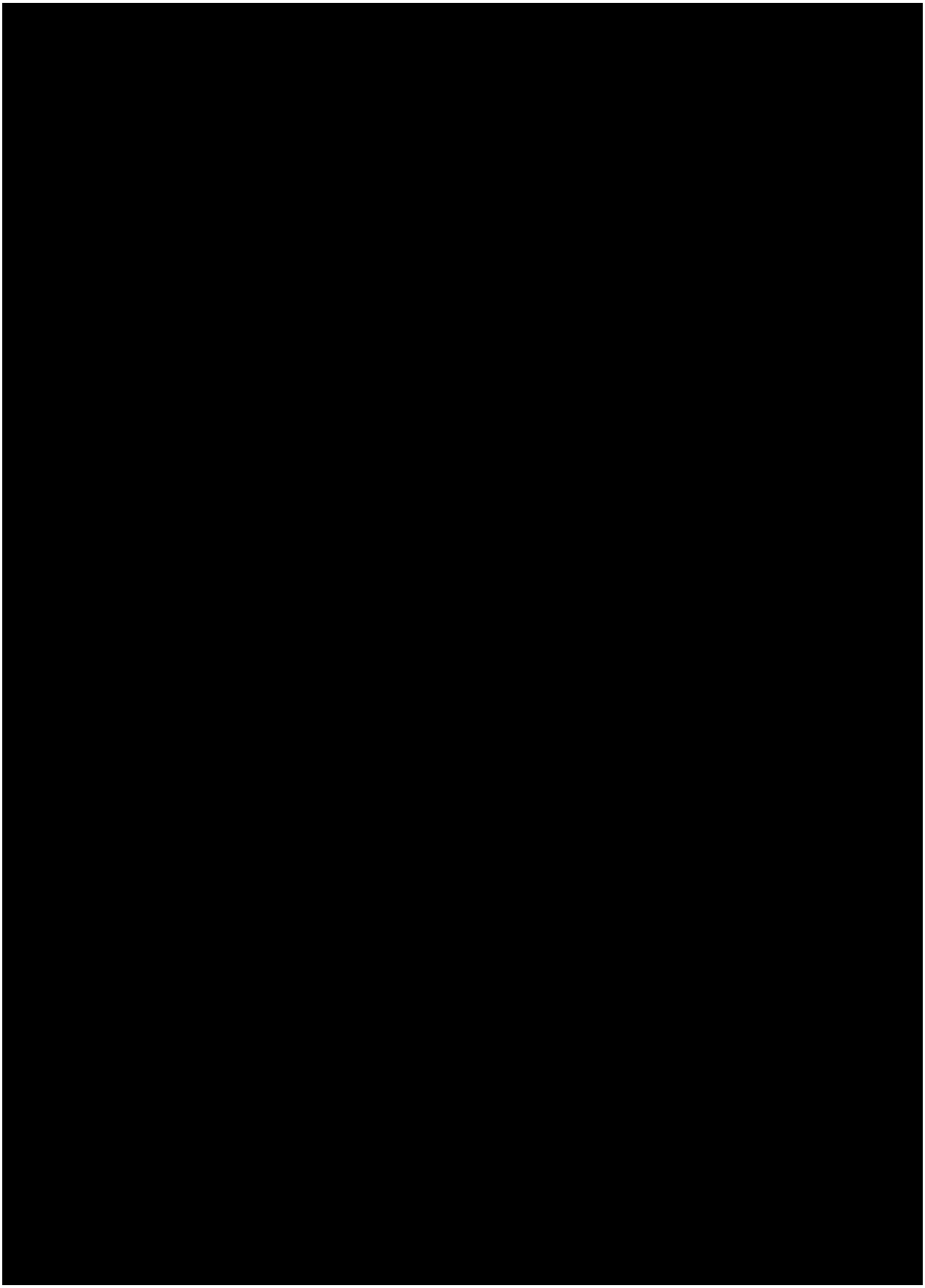


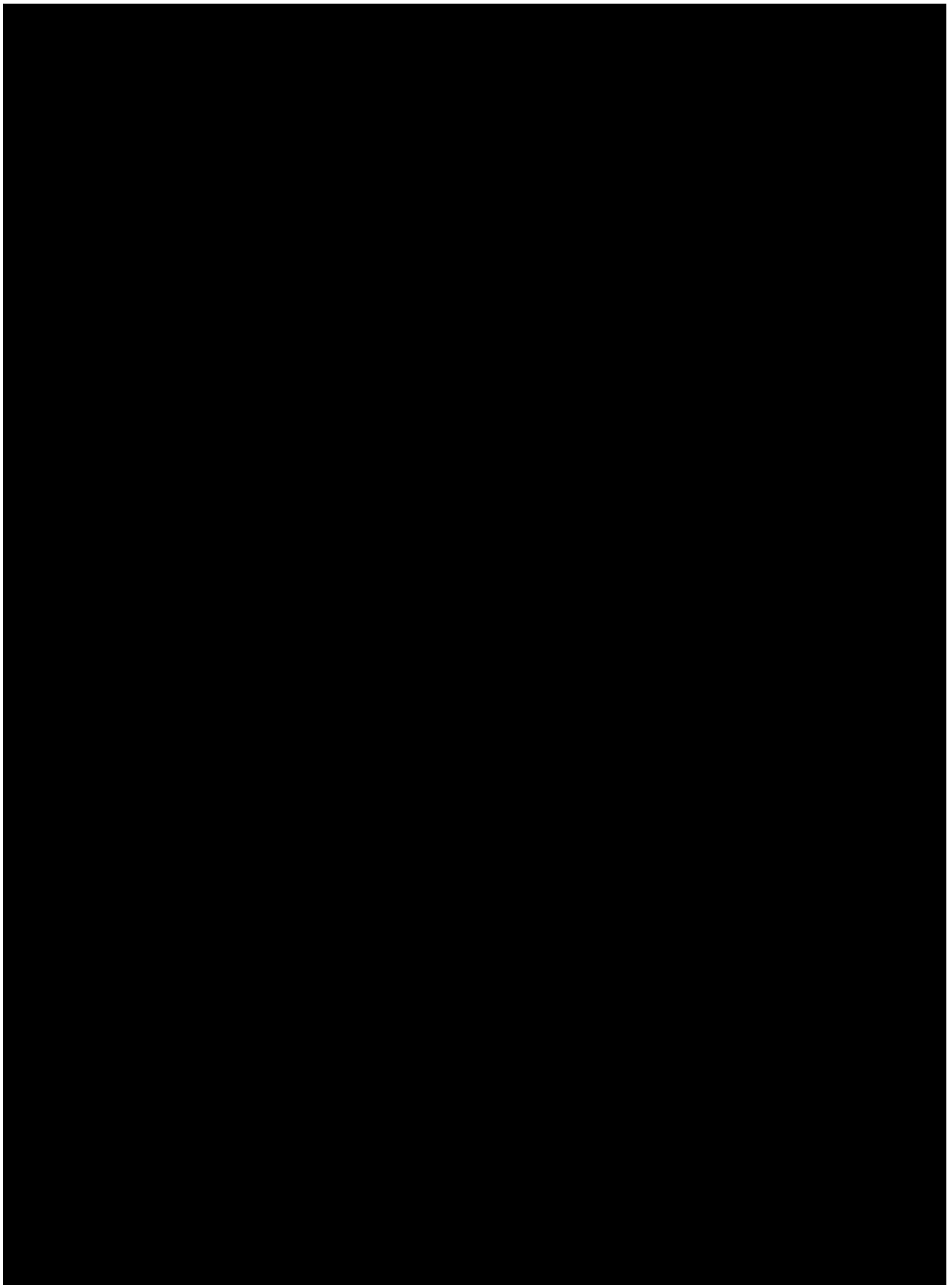


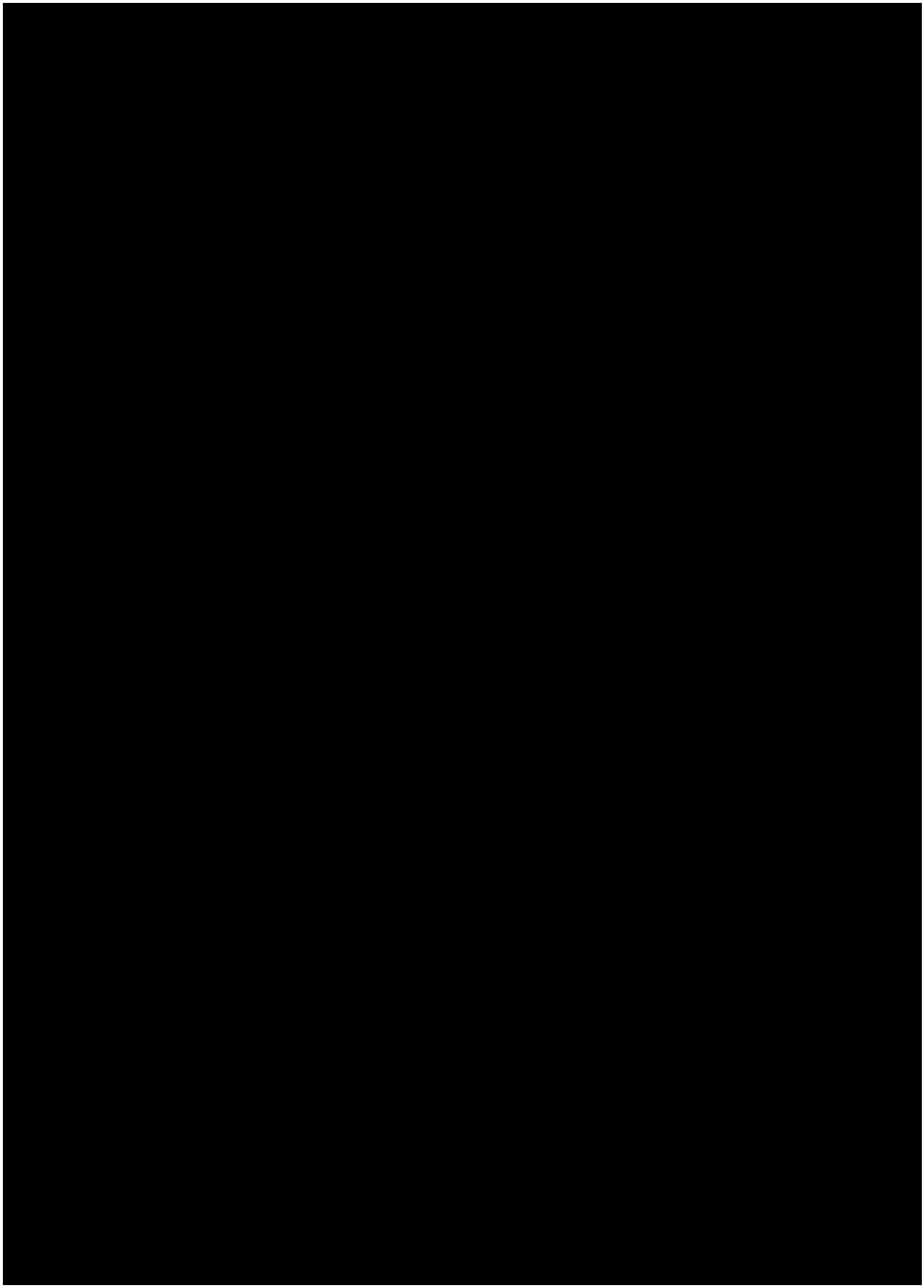


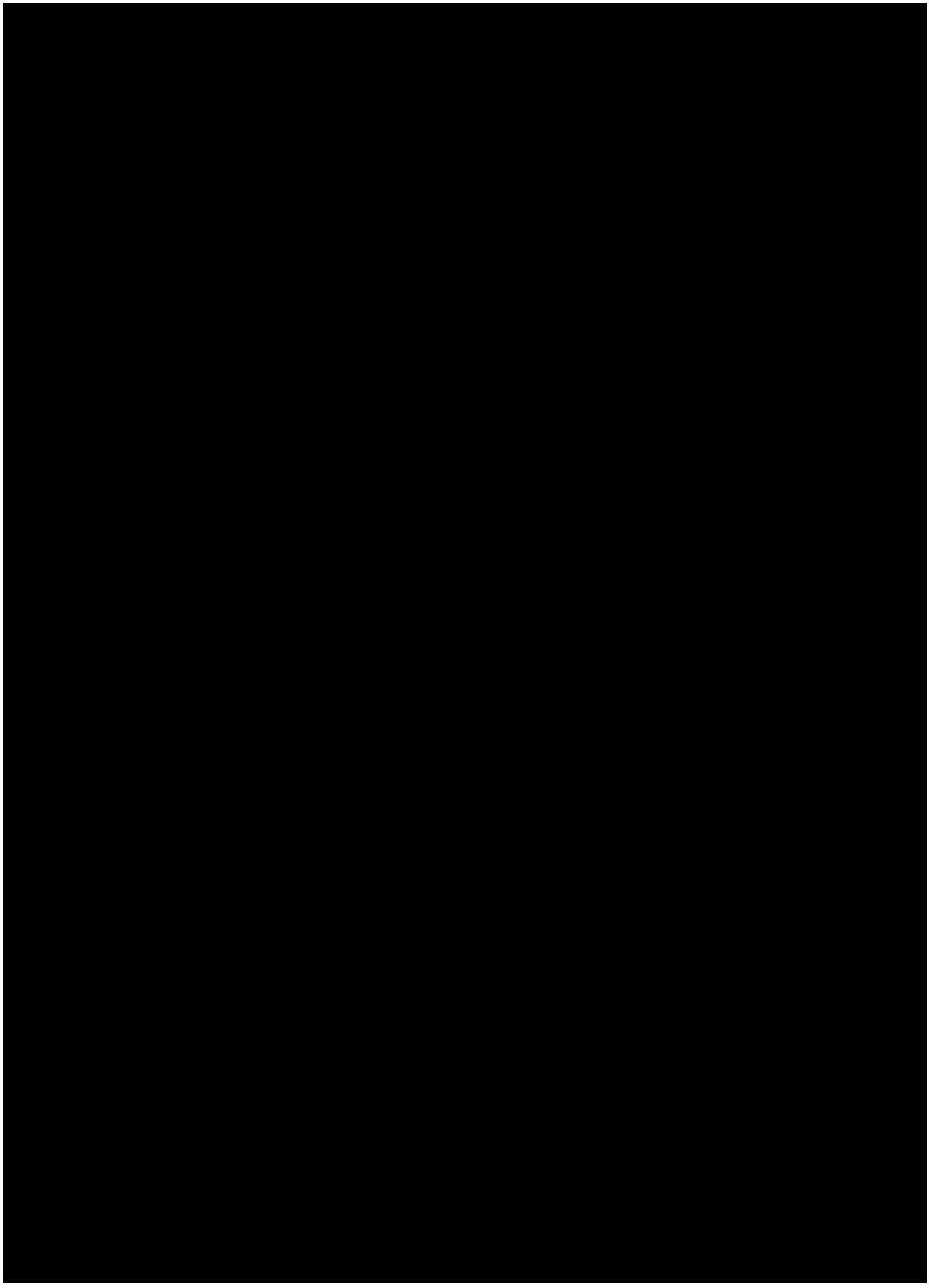


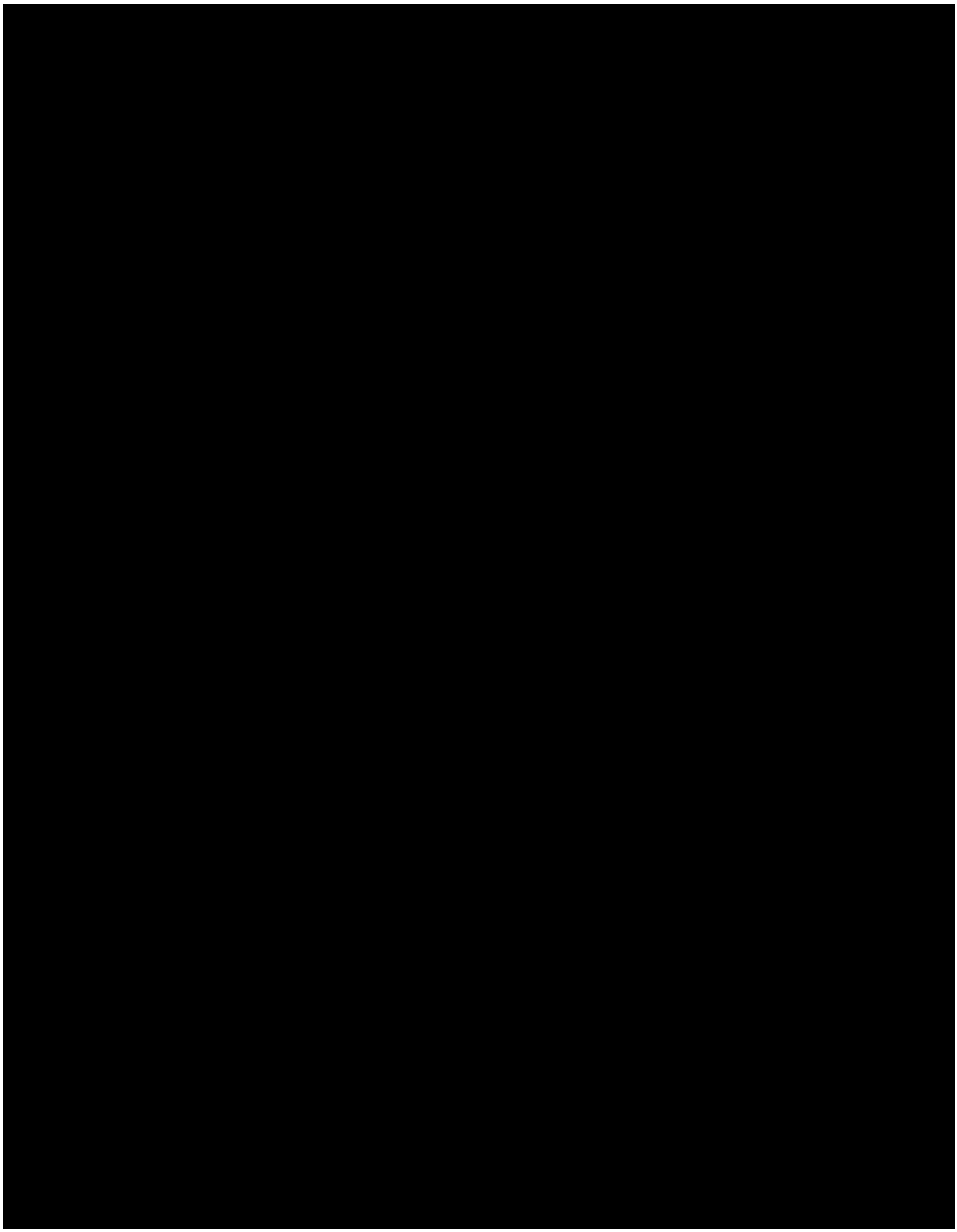


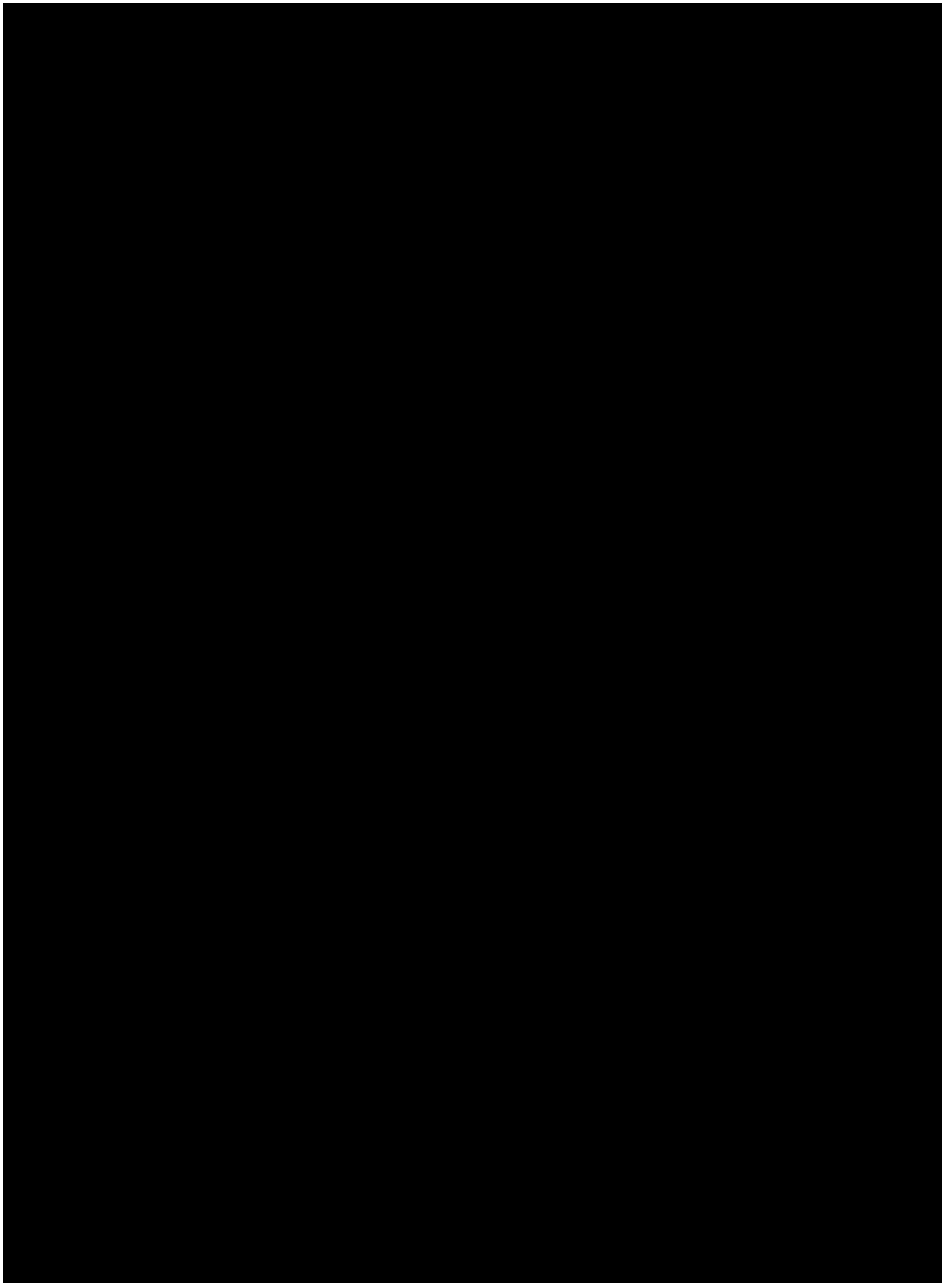


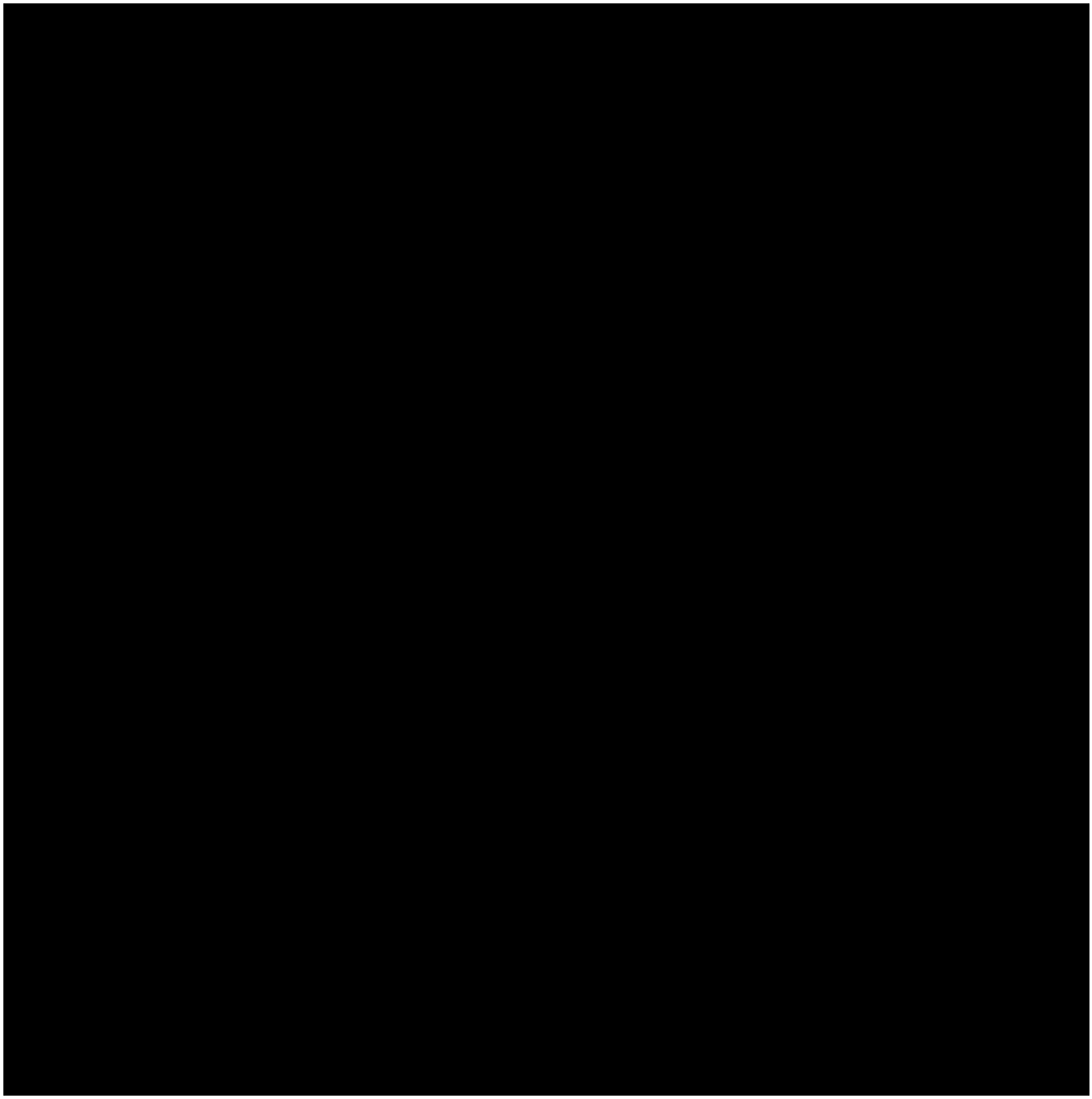












14. Ethics and Protection of Human Subjects

14.1. Ethical Standard

As the Sponsor of this study, Biosense Webster has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration and the MDD 93/42/EC and the local government. The Sponsor will also maintain compliance with Good Clinical Practice (ICH version 6, revision 2, 11 June 2015), the European standard EN ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Brazil, October 2013), Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]),

maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b])], and to local regulations where required.

- General Duties
  Biosense Webster's general duties consist of submitting the IDE application to appropriate regulatory agencies, assuring that sites have received IRB/EC approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and verifying that subject informed consent is obtained.

- Data Quality and Reporting
  Biosense Webster is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated adverse events and deviations from the protocol.

- Selection of Investigators
  Potential investigational sites will undergo an evaluation to ensure that the site has the appropriate facilities and personnel to conduct the study in compliance with the clinical investigational plan. Based on outcome of evaluation process, Biosense Webster will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

- Supplemental Applications
  As appropriate, Biosense Webster will submit changes in the Clinical Investigation Plan to the investigators to obtain applicable re-approvals from IRBs/ECs.

- Maintaining Records
  Biosense Webster will maintain copies of correspondence, data, adverse device effects and other records related to the study. Biosense Webster will maintain records related to the signed Investigator Agreements.

- Submitting Reports
  Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This includes unanticipated adverse device effects, withdrawal of IRB/EC approval, current investigators list, annual progress reports, recall information, final reports and protocol deviations.

14.2. Institutional Review Board/Ethics Committee

The investigator will obtain written and dated approval from the responsible IRB/EC for the study protocol (or amendment[s]) and informed consent before enrolling study subjects. Biosense Webster and the IRB/EC must approve in writing any changes to the protocol that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study.

A copy of the IRB/EC approval letter addressed to the investigator must be sent to Biosense Webster certifying study approval prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local requirements) of the study by their IRB/EC.

14.3. Informed Consent Process

14.3.1. Consent/Assent and Other Informational Documents Provided to Subjects

Patient informed consent must be obtained and documented according to the principles of informed consent in the latest version of the Declaration of Helsinki (Brazil, 2013), ISO 14155, using the document approved by the reviewing IRB/EC. Informed consent is mandatory and must be obtained from all subjects prior to their participation in the study.

14.3.2. Consent Procedure and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Discussion of risks and possible benefits of participation will be provided to the patients as part of the informed consent process. Consent forms will be IRB/EC-approved and the patient will be asked to read and review the document. The investigator, or designee, will explain the research study to the patient and answer any questions that may arise. All patients will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Information should be given to the patient in a language and at a level of complexity understandable to the patient in both oral and written form by the principal investigator or designee. Patients will have ample opportunity to review the written consent form and to ask questions prior to signing.

Prior to participation in the trial, the Patient ICF should be signed and personally dated by the patient or his/her legal representative. If a witness is used for an illiterate or compromised patient, the witness should also sign the consent form, attesting that informed consent was freely given by the patient or his/her legal representative. The patients may withdraw consent at any time throughout the course of the trial. The rights and welfare of the patient will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study. A signed and dated copy of the Patient ICF must be collected from each enrolled subject and kept in the study subject files and medical records. The site should provide each subject with a copy of their fully executed ICF.

Biosense Webster, Competent Authority (where applicable), and the reviewing IRB/EC must approve any modifications to the Patient ICF for this clinical investigation. A copy of the IRB/EC approved Patient ICF must be maintained by each investigator.

Documentation of the consent process for each subject should be maintained by each investigator.

Patients should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial.

14.4. Subject and Data Confidentiality

During this clinical investigation, representatives of the Sponsor will comply with in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Biosense Webster concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Biosense Webster personnel or representatives (including contracted service providers,

i.e. Core Lab, Clinical Research Associate, CRO, etc.) and/or representatives of the FDA or Competent Authorities acting in their official capacities will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, ECG reports, admissions/discharge summaries for hospital admission occurring during a subjects study participation and autopsy reports for deaths occurring during the clinical investigation). Some of the countries to which the study subjects and investigators personal data may be transferred may not offer as comprehensive a level of protection of personal data as within the European Union but Sponsor will put adequate measures in place to act in compliance with regional policies and requirements and to ensure a sufficient level of data protection. All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

14.4.1. Research use of Stored Data

- Intended Use: Data collected under this protocol may be used to study Atrial Fibrillation.
- Storage: Access to stored data will be limited. Data will be stored using codes assigned by the sponsor. Data will be kept in password-protected computers. Only investigators and the sponsor will have access to the data.

15. Source Documents and Access to Source Data/Documents

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, other hospital or investigator office/clinic documents, and system data (CARTO®, generator). If unique study parameters are not documented on standard hospital or office reports, a worksheet may be developed to record this information. The worksheet shall be signed by the PI or authorized designee and will serve as the basis for monitoring the eCRFs. Electronic subject records will be considered as source documents. A print-out of a completed eCRF cannot be used as source documentation.

Investigators should maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained.

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes from the day of entry into the study including the study Sponsor (Biosense Webster), protocol number, clinical site, subject number assigned and a statement that consent to participate in the study was obtained.
- Dated and signed notes from each study visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- Reports on AEs and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results.
- Notes regarding protocol-required medication and prescription medications taken during the study (including start and stop dates).
- Notes on subject's condition upon completion of or withdrawal from the study.

Only authorized Biosense Webster personnel or representatives, authorized site personnel, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

16. Quality Assurance and Quality Control

QC procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

17. Data Handling and Record Keeping

17.1. Data Collection and Management Responsibilities

The Sponsor will be responsible for all data management activities. These activities include development of an electronic data collection (EDC) system and utilizing a validated EDC system into which all study data will be entered. The Sponsor will be responsible for reviewing all data to ensure the overall integrity of the database.

17.1.1. Data Collection

Electronic Case Report Forms (eCRFs) will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this clinical investigation Plan. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and the monitor will ask the site representative to correct if necessary to match the source documents. Changes made to the data will be tracked in the electronic audit trail. The investigator will be required to sign designated eCRFs as verification that they have been reviewed and the data entered are correct. Data from these eCRFs will be sent to the Sponsor, and/or 3rd party affiliate acting on behalf of the Sponsor, and used in the analysis of clinical investigation results.

At the completion of the study ablation procedure, two back-up copies of the CARTO® and generator log files will be made. One copy should be kept at the site within the investigator site or subject binders, and one fully anonymized copy will be provided to / collected by the Sponsor.

If performed and recorded, a copy of the fully anonymized angiography images (preferably with contrast), confirming position of the balloon and occlusion of the PVs will be provided to / collected by the Sponsor.

17.1.2. Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are properly recorded on each subject's eCRF and related documents. Completed eCRF will be reviewed and monitored by the sponsor personnel, or an appropriately qualified and trained designee, throughout the clinical investigation. To this end, the Investigator and institution must permit inspection of the trial files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the governing IRB/EC and/or Biosense Webster.

Table 17.1.2A. Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator For	Time of Notification
Subject withdrawal	Biosense Webster	Should report within 5 working days
Withdrawal of IRB/EC approval	Biosense Webster	Should report within 5 working days
Final report	Biosense Webster, IRB/EC	Will prepare a final report for the clinical investigation as required per national regulations.
Informed consent not obtained from subject	Biosense Webster, IRB/EC (per IRB/EC requirements)	Should report within 5 working days

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical investigation protocol (section 9.5).

17.1.3. Data Verification and Review

Biosense Webster will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data will be queried as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device deficiencies are observed and reported. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

17.1.4. Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

17.2. Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 2 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed. This documentation must be accessible upon request by the regulatory authorities, the sponsor, or a designee. The sponsor must approve archiving, transfer, and destruction of the documentation, in writing, prior to the actual archiving, transfer, and destruction. The investigator must notify the sponsor, in writing, of transfer location, duration, and the procedure for accessing the study documentation.

If the investigator retires, relocates, or withdraws from assuming primary responsibility for keeping the study records, custody transfer per written notice must be submitted to the sponsor indicating the name and address of the person accepting primary responsibility. The IRB/EC must be notified in writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

18. Study Suspension or Termination

This study may be temporarily suspended or prematurely terminated at the discretion of the Sponsor. The Sponsor may also terminate a site prior to study completion if the Sponsor believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by IRB/EC). If the study is prematurely terminated or suspended, the PI will promptly inform the IRB/EC and will provide the reason(s) for the termination or suspension.

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 shall keep each other informed of any communication received from either the IRB/EC or the regulatory authority.

If early termination of the study is required due to safety concerns or the occurrence of unanticipated adverse or device events, each site will undergo a monitoring visit to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Any enrolled subjects will continue to be followed per the study protocol requirements.

If, for any reason, the sponsor suspends or prematurely terminates the study at an individual study site, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the IRB/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.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the sponsor, IRB/EC and/or regulatory agency.

19. Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated between Biosense Webster, Inc. and the clinical investigation author(s). Authorship will be determined prior to development of any manuscript. All information concerning the study, investigational medical device, sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the sponsor.

20. Document Filing

A copy of all approved versions of the Investigation Protocol will be kept by the site in the Investigator Site File and will be kept by the sponsor in the Sponsor Trial Master File.

21. Scientific References

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