

Trial Designs

The Extravascular Implantable Cardioverter-Defibrillator: The Pivotal Study Plan

Ian Crozier, MB CHB^a, David O'Donnell, MBBS^b, Lucas Boersma, MD, PhD^c, Francis Murgatroyd, FRCP^d, Jaimie Manlucu, MD^e, Bradley P. Knight, MD^f, Ulrika Maria Birgersdotter-Green, MD^f, Christophe Leclercq, MD, PhD^g, Amy Thompson, MS, MBA^h, Robert Sawchuk, BSEE, MBA^h, Sarah Willey, MPH^h, Christopher Wiggenhorn, PhD^h, Paul Friedman, MD, FHRSⁱ.

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Author affiliations:

- ^aChristchurch Hospital, Christchurch, New Zealand
- ^bAustin Health, Heidelberg, Victoria, Australia
- ^cSt. Antonius Hospital Nieuwegein and Amsterdam UMC, Netherlands
- ^dKing's College Hospital, London, United Kingdom
- ^eLondon Health Sciences Centre, London, Ontario, Canada
- ^fNorthwestern University, Chicago, IL, USA
- ^fUniversity of California San Diego, San Diego, CA, USA
- ^gCHU de Rennes - Hôpital Pontchaillou France
- ^hMedtronic plc, Mounds View, Minneapolis, MN, U.S.
- ⁱMayo Clinic, Rochester, MN, USA

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- Dr. Crozier is a consultant for and receives research support and fellow support from Medtronic plc and grants from Boston Scientific Corp. (ian.crozier@cdhb.health.nz)
- Dr. O'Donnell has received research support and/or served as consultant to Abbott and Medtronic. (odonnell_research@hotmail.com)
- Prof. Boersma is a consultant for Medtronic, Boston Scientific, Philips, Acutus, and Adagio and his institution receives grant support from Medtronic and Boston Scientific (l.boersma@antoniuziekenhuis.nl)
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- Dr. Manlucu is a consultant for and receives research and fellowship support from Medtronic. She also has received research support from and/or served as consultant to Abbott, Boston Scientific and Baylis Medical (Jaimie.Manlucu@lhsc.on.ca)
- Dr. Knight is a consultant for and receives research support and fellowship support from Medtronic. He also has received research support from and/or served as consultant to Abbott, Boston Scientific, Biotronik, CVRx, Baylis, and Philips. (bradley.knight@nm.org)

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Corresponding author:

Ian Crozier, MD
Department of Cardiology
Christchurch Hospital
Christchurch
New Zealand

Abbreviations and Acronyms:

AE: Adverse Event
AP: Anterior Posterior
ATP: Antitachycardia pacing
EV: Extravascular
ICD: Implantable Cardioverter-Defibrillator
PHD: Pre Hospital Discharge
TV: Transvenous
VF: Ventricular Fibrillation
MRI: Magnetic Resonance Imaging

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Abstract:

Background: Transvenous implantable cardiac defibrillators (TV ICD) provide life-saving therapy for millions of patients worldwide. However, they are susceptible to several potential short- and long-term complications including cardiac perforation and pneumothorax, lead dislodgement, venous obstruction, and infection. The extravascular ICD (EV ICD) system's novel design and substernal implant approach avoids the risks associated with TV ICDs while still providing pacing features and similar generator size to TV ICDs.

Study Design: The EV ICD pivotal study is a prospective, multi-center, single-arm, non-randomized, pre-market clinical study designed to examine the safety and acute efficacy of the system. This study will enroll up to 400 patients with a Class I or IIa indication for implantation of an ICD. Implanted subjects will be followed up to approximately 3.5 years, depending on when the patient is enrolled.

Objective: The clinical trial is designed to demonstrate safety and effectiveness of the EV ICD system in human use. The safety endpoint is freedom from major complications, while the efficacy endpoint is defibrillation success. Both endpoints will be assessed against prespecified criteria. Additionally, this study will evaluate antitachycardia pacing (ATP) performance, electrical performance, extracardiac pacing sensation, asystole pacing, appropriate and inappropriate shocks, as well as a summary of adverse events.

Conclusion: The EV ICD pivotal study is designed to provide clear evidence addressing the safety and efficacy performance of the EV ICD System.

Key Words (5-10):

Anterior mediastinum, defibrillation, extravascular, ICD, substernal, subcutaneous

Manuscript:

Introduction:

Transvenous defibrillators (TV ICD) are effective protective devices against sudden arrhythmic death. However, they are limited by various implantation risks including vascular injury, cardiac perforation and pneumothorax.¹ Venous obstruction, lead failure and infection are longer term complications that may occur years after the original implant.^{2,3} Device infections can be serious, with the potential for bacteremia or endocarditis due to the physical conduit between the TV ICD subcutaneous pocket and the ICD lead extending into the heart and systemic circulation. For these, and various other reasons, transvenous leads may ultimately require extraction, a relatively high-risk procedure associated with the potential for significant morbidity and mortality.⁴⁻⁶ Therefore, alternatives to TV ICDs are desired to reduce morbidity associated with endovascular and/or endocardial lead placement. The Extravascular ICD System with its substernal lead placement may offer an alternative to transvenous systems while positioning a lead close to the heart. The EV ICD has been purposely designed to provide life-saving defibrillator therapy, whilst addressing some of the concerns of conventional transvenous and subcutaneous implantable defibrillators.

The subcutaneous defibrillator (S-ICD), implanted extravascularly, was previously developed to avoid the vascular risks of TV ICDs.^{7,8} In a recent comparison with TV ICDs, S-ICD device complications tended to be fewer whilst offering similar protection from sudden arrhythmic death and until recently the inappropriate shock rate tended to be higher (with the first generation without the new algorithm to discriminate SVT from VT).^{9,10} However, since the S-ICD lead is placed above the sternum and some distance from the myocardium, the energy required for defibrillation is high relative to TV ICD, necessitating a large device (60 cc) with compromised longevity (projected 7.3 years with normal use).¹¹ Furthermore, because of the distance between the electrical lead and the heart, the only pacing possible is limited to 30s of post shock support.⁷ Moreover ATP is not possible with this device.

A number of case reports have described placing leads in the retrosternal space to achieve defibrillation. In 2007, Tung *et al.* reported implant of a “transvenous” lead into the retrosternal space from a superior (manubrial) approach in three patients with venous occlusion or refusing transvenous hardware and achieved successful defibrillation with a 10-Joule (J) safety margin using standard transvenous ICD device energy outputs.¹² Subsequently, multiple examples of successful “subcutaneous” lead placement in the retrosternal space have been reported.¹³⁻¹⁷

The EV ICD System, a product of a development program initiated in 2012 by Medtronic, is comprised of a pulse generator implanted subcutaneously over the serratus anterior in the left mid-axillary line and a high voltage lead in the substernal space. A series of animal studies and proof-of-concept studies confirmed a lead could be positioned in the anterior mediastinal space, allowing for defibrillation with energies lower than those required by the S-ICD, and demonstrating feasibility of ventricular pacing from this site.^{18,19}

The first human clinical feasibility study, The Acute Substernal Defibrillation (ASD) study, showed substernal defibrillation was feasible with the energy available in current TV ICDs, with defibrillation successful in 13 of 14 subjects at 35J.²⁰ In the second human clinical feasibility study, the Substernal Pacing Acute Clinical Evaluation (SPACE), 26 subjects underwent pacing evaluation, using a substernal decapolar catheter placed temporarily at the time of planned cardiac procedures. It showed that pacing is possible in nearly all patients from the substernal location.^{21,22} The third human clinical feasibility study, The Acute Extravascular Defibrillation, Pacing and Electrogram Study (ASD2), further assessed pacing thresholds and defibrillation efficacy via substernal therapy delivery in a larger cohort with an EV ICD lead designed for sensing, pacing and defibrillation in the substernal space. In 79 patients, the median lead implantation time was 12.0 ± 9.0 min. Ventricular pacing was

successful in at least 1 vector in 76 of 78 patients (97.4%), and a 30-J shock successfully terminated 104 of 128 episodes (81.3%) of ventricular fibrillation in 69 patients.²³

Subsequently, 21 permanent EV ICD implants were performed in 2018 in the first-in-human chronic EV ICD Pilot study.²⁴ In the Pilot study, 20 patients had the device successfully implanted, of which 18 patients (90%) had induced ventricular arrhythmias successfully terminated by the EV ICD system. Pacing capture was achieved in 95% of study patients at implant. There were no intraprocedural complications, perhaps resulting from measures to facilitate a safe procedure, including a mandatory hands-on training program for implanters, cardiothoracic surgical proctoring, blunt dissection to access the substernal space, and use of fluoroscopic guidance in two views (lateral and AP). This study confirmed the potential of the EV ICD System to be implanted safely and provide effective defibrillator therapy, thus leading to the start of the EV ICD Pivotal trial.

Methods:

Study Design:

The EV ICD Pivotal study is a prospective, multi-center, single-arm, non-randomized, pre-market clinical study, conducted in accordance with the ethical principles of the Declaration of Helsinki at up to 60 sites worldwide, intended to include ANZ (Australia and New Zealand), Canada, EMEA (Europe, Middle East, and Africa), Hong Kong, Japan, and the United States. Up to 400 subject enrollments will allow at least 292 subjects to complete defibrillation testing of the implanted system. The study commenced in September 2019, and enrollments are expected to be completed mid-2021. At the time of manuscript submission, over 150 subjects have been enrolled.

The EV ICD System:

The EV ICD System (Figure 1) was designed for the substernal space; the device is a modified and enhanced version of the Evera MRI System, the size of a transvenous defibrillator (33 cm³) and

capable of delivering up to 40J of defibrillation energy. The EV ICD lead uses an epsilon-shaped design for passive fixation within the substernal space, and to intentionally orient the available electrodes to the left to optimize sensing and pacing therapies and the coils to the right to facilitate defibrillation therapy. There are two pace/sense electrodes and two defibrillation coil segments that are electrically coupled during defibrillation to form an 8cm defibrillation coil. There are three sensing and three pacing vectors available in the EV ICD system.²³

Implantation Procedure:

All implanting investigators will complete a formal training program on the recommended implant technique for the EV ICD system to establish skills in safe access and tunneling within the substernal space. Implants will be performed by the trained investigator with cardiothoracic surgical backup available. General anesthesia is recommended, and external defibrillation pads will be placed outside the surgical field for rescue defibrillation if required. Chest x-rays (AP and lateral) will be collected at baseline for all patients, and computerized tomography (CT) scans or magnetic resonance imaging (MRI) will be recommended for the first three implants; imaging may help in pre-procedure planning and assessment of anatomy. To access the substernal space, an incision (approximately 3 cm) will be made between the inferior point of the xiphoid and the left costal margin. Blunt dissection is then performed beyond the rectus fascia and through the diaphragmatic attachments. The dedicated implant tunneling tool will be placed within a peel-away introducer sheath and then be introduced and advanced utilizing lateral fluoroscopy to ensure the tip of the tunneling tool is in close proximity to, or direct contact with, the posterior surface of the sternum to avoid cardiac injury. The tunneling path will extend to the upper border of the heart silhouette as marked by the lower margin of the carina using AP fluoroscopy, and between the midline and left sternal margin. The EV ICD lead will be inserted into the substernal space via the peel-away introducer sheath once the tunneling tool is removed. After deployment of the lead, acute sensing measurements will be collected with the requirement of R-wave amplitudes ≥ 1 mV and P wave

≤0.2mV. If need be, the lead can be repositioned to achieve the sensing targets. The lead will then be anchored to the fascia in the sub-xiphoid incision. The proximal portion of the lead will be tunneled to a left lateral subcutaneous device pocket near the mid-axillary line. The device will be placed against the fascia and sutured within the pocket. Following hemostasis, the incisions will be closed using standard closure techniques (Figure 2: EV ICD System in Situ). Programming recommendations and requirements at discharge are provided (Appendix I).

Study Population:

Patients with a Class I or IIa indication for implantation of an ICD according to the ACC/AHA/HRS/ESC Guidelines^{25,26}; who are at least 18 years of age; are geographically stable and willing and able to complete the study procedures and follow-up will be enrolled after providing written informed consent. Patients will be excluded from the first generation of the system if they have indications for bradycardia pacing or cardiac resynchronization therapy. Additionally, key study exclusions included patients with an existing system, leads, or neurostimulator or other chronically implanted device which delivers current; patients with medical interventions which might increase surgical risk to patient during the tunneling procedure (e.g., prior or planned sternotomy, prior chest radiotherapy), patients with medical conditions or abnormalities which might increase procedure risk, infection risk, or risk of potential comorbidities which might impact the evaluation of the system during a clinical study (e.g., pectus excavatum, decompensated heart failure), patients who might be more vulnerable to potential increased risk during the evaluation of the clinical study defibrillation protocol (e.g., hemodynamic instability, current intracardiac left atrial or left ventricular thrombus, left ventricular ejection fraction <20%) or contraindication for temporary suspension of oral/systemic anticoagulation.

Study Objectives and Endpoints:

The main purpose of the study is to test the safety and acute efficacy of the EV ICD System. The primary safety objective is to demonstrate the freedom from major complications related to the EV ICD System and/or procedure up to 6 months post-implant, defined as a subject's first occurrence of a major complication related to the EV ICD System and/or procedure as adjudicated by an independent Clinical Events Committee. The study will meet the prespecified objective performance criterion if the freedom from major complications exceeds 79% (i.e., the lower bound of a two-sided 95% confidence interval exceeds 79%). (Appendix II. Safety endpoint definition)

The primary efficacy objective is to demonstrate defibrillation efficacy at implant of the EV ICD system. Sustained shockable ventricular arrhythmias (SSVA) (e.g., ventricular fibrillation, polymorphic ventricular tachycardia, rapid ventricular tachycardia) will be induced at implant using burst induction (20Hz), T-shock (up to 20J), or other methods at the discretion of the investigator. Testing is deemed successful if a ≥ 10 J defibrillation safety margin is present with the 40J system, and defined as termination of an SSVA with either a single 20J shock or on two consecutive episodes of SSVA at 30J shock in the final configuration (Appendix III. Defibrillation Protocol at Implant). If the patient is successfully defibrillated at 20J, defibrillation efficacy will be assessed at 15J. The study protocol incorporates shock polarity reversal and revision of lead and/or pulse generator position in the event of initial failure. If defibrillation success is not achieved, the EV ICD system will be explanted. The study will meet the pre-specified objective performance criterion if the defibrillation success at implant is greater than 88% (i.e., the lower bound of a two-sided 95% confidence interval exceeds 88%).

Ancillary objectives will include characterization of appropriate and inappropriate shocks; electrical performance (pacing capture thresholds, pacing impedance, sensing amplitudes) over time; extracardiac pacing sensation; asystole pacing; ATP performance with spontaneous arrhythmias and

summary of adverse events. In a subgroup of up to 34 patients that prospectively consent to this, chronic defibrillation efficacy will be evaluated at 6 months post implant; subjects will be induced to produce up to two episodes of VF, with detection and termination at either 30 or 40J regarded as successful.

Follow-up Plan:

Patients will be evaluated during follow up at 2 weeks, 3 months, 6 months and then every 6 months until completion of the trial (Figure 3. Study overview). Assessments will include device interrogation; electrical testing (sensing, impedance, and pacing tests); adverse event rate and type; device deficiency rate and type; healthcare utilizations; and medications. Chest radiographs (anteroposterior and lateral) will be obtained prior to discharge and at 6 months.

Study Organization:

Study oversight includes a Steering Committee with members from various geographies, responsible for advising on study design and execution. An independent Clinical Events Committee (CEC) will review and adjudicate all system- and procedure-related events, as well as death classifications. An Episode Review Committee (ERC), which includes independent physicians, will evaluate and adjudicate device-treated ventricular episodes and appropriateness of therapy. An independent data monitoring committee (DMC) will review incidents and trends of adverse events and make recommendations to Medtronic and/or the Steering Committee regarding study conduct and subject safety.

Statistical Methods:

The analysis of the primary safety objective will include all subjects with an implant attempt. The endpoint consists of major complications related to the EV ICD System and/or procedure within 182 days of implant attempt, as determined by an independent CEC (Appendix II. Safety endpoint

definition). Subjects not experiencing an event will be censored at their last point of contact. The 182-day freedom from major complication rate will be estimated using the Kaplan-Meier method, along with a two-sided 95% confidence interval based on a log-log transformation. If the lower bound of the confidence interval exceeds 79%, the primary safety objective will be met.

In estimating statistical power for the safety objective, the occurrence of major complications was modeled with a Weibull distribution, assuming an event-free rate of 90% at one month and 86% at 6 months. Attrition due to exit or death was also assumed to follow a Weibull distribution, at a rate of 9% at one month and 16% through one-year post-implant. Using these assumptions, the outcome of the trial was simulated 10,000 times. Each simulated sample included 292 subjects, with a simulated time to safety endpoint and time to attrition for each subject. Using these data, the 182-day Kaplan-Meier freedom from major complication rate and a 95% confidence interval was calculated for each simulation of the trial. The results of the simulation determined that a sample size of 292 subjects undergoing an implant attempt allowed for 90% power for this objective.

For the primary efficacy objective, each subject who completes the defibrillation protocol will be categorized as a success or failure. A two-sided exact binomial 95% confidence interval will be calculated for the proportion of successes, and the efficacy objective will be met if the lower bound of the confidence interval exceeds 88%. In calculating the sample size for this objective, it was assumed that the true success rate is 93.5%. Using the statistical software package PASS 2008, it was determined that 292 subjects completing the defibrillation protocol were required to achieve 90% power. To further account for subjects who enroll in the study but exit prior to an implant attempt, up to 400 subjects may be enrolled.

Discussion:

The EV ICD System uses a novel substernal lead implant location designed to avoid the risks associated with transvenous defibrillators and the limitations of the subcutaneous defibrillator. The study is designed to evaluate the safety and efficacy of the EV ICD system as well as features unavailable in the S-ICD system, such as ATP pacing and pause prevention pacing, with no requirement for pre-implant sensing evaluation screening. The study will also characterize appropriate and inappropriate shocks, which is of interest as the EV ICD lead does not have direct myocardial contact; as smaller R-waves have been reported previously for the S-ICD, the EV ICD system will be similarly evaluated for T-wave and non-cardiac sensing observations.²⁷

The success criterion (i.e., objective performance criterion (OPC)) of 79% was used to evaluate system-related complications in the pivotal trial for the S-ICD. By comparison, the EV ICD pivotal study is evaluating both system- and procedure-related complications using an OPC of 0.79 at 6 months to establish safety.

Similarly, the OPC threshold of 88% was used in the pivotal trial for S-ICD as the criterion for evaluating termination of induced ventricular rhythms at implant, and the EV ICD pivotal study uses the same criterion to evaluate efficacy. In a retrospective analysis of trends and in-hospital outcomes associated with early adoption of the S-ICD compared to single- and dual-chamber transvenous ICD implants, DFT testing efficacy among 2791 patients was shown to be 92.7% when a 15-J safety margin was used for S-ICD.²⁸ Additional studies and sub-analyses of defibrillation testing performance for S-ICD show evidence of defibrillation testing performance of less than the OPC of 88%, further justifying the clinical relevance of such a threshold.^{29,30}

In conclusion, the EV ICD System has similar capabilities to a single-chamber transvenous ICD system while avoiding leads in the heart and vasculature. Therefore, the EV ICD system may become the preferred option for many patients indicated for a single chamber ICD in the future. Compared to the current market-released non-transvenous subcutaneous ICDs, the EV ICD system includes a smaller device that uses less defibrillation energy which may result in longer battery life but with the additional capabilities to deliver pacing therapies such as ATP and pause prevention pacing from a single device. The EV ICD Pivotal study will demonstrate the efficacy and safety of the EV ICD System: a single-chamber extravascular ICD system with the lead implanted substernally.

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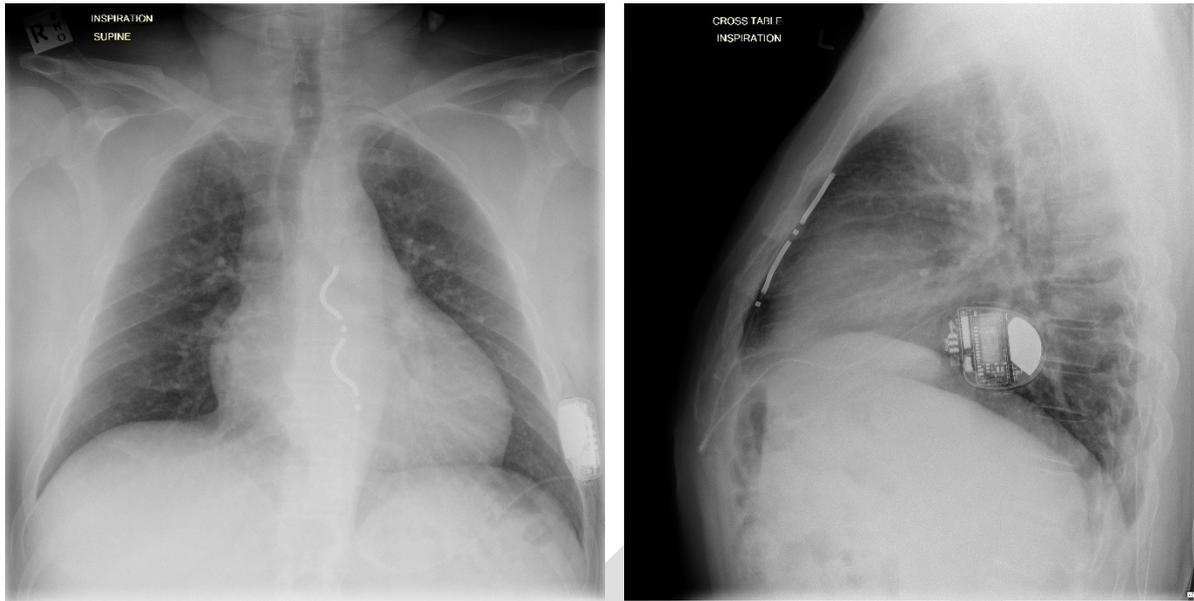
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Figures:

Figure 1. EV ICD System. Extravascular Implantable Cardioverter Defibrillator (EV ICD) and EV ICD quadripolar lead with passive fixation.

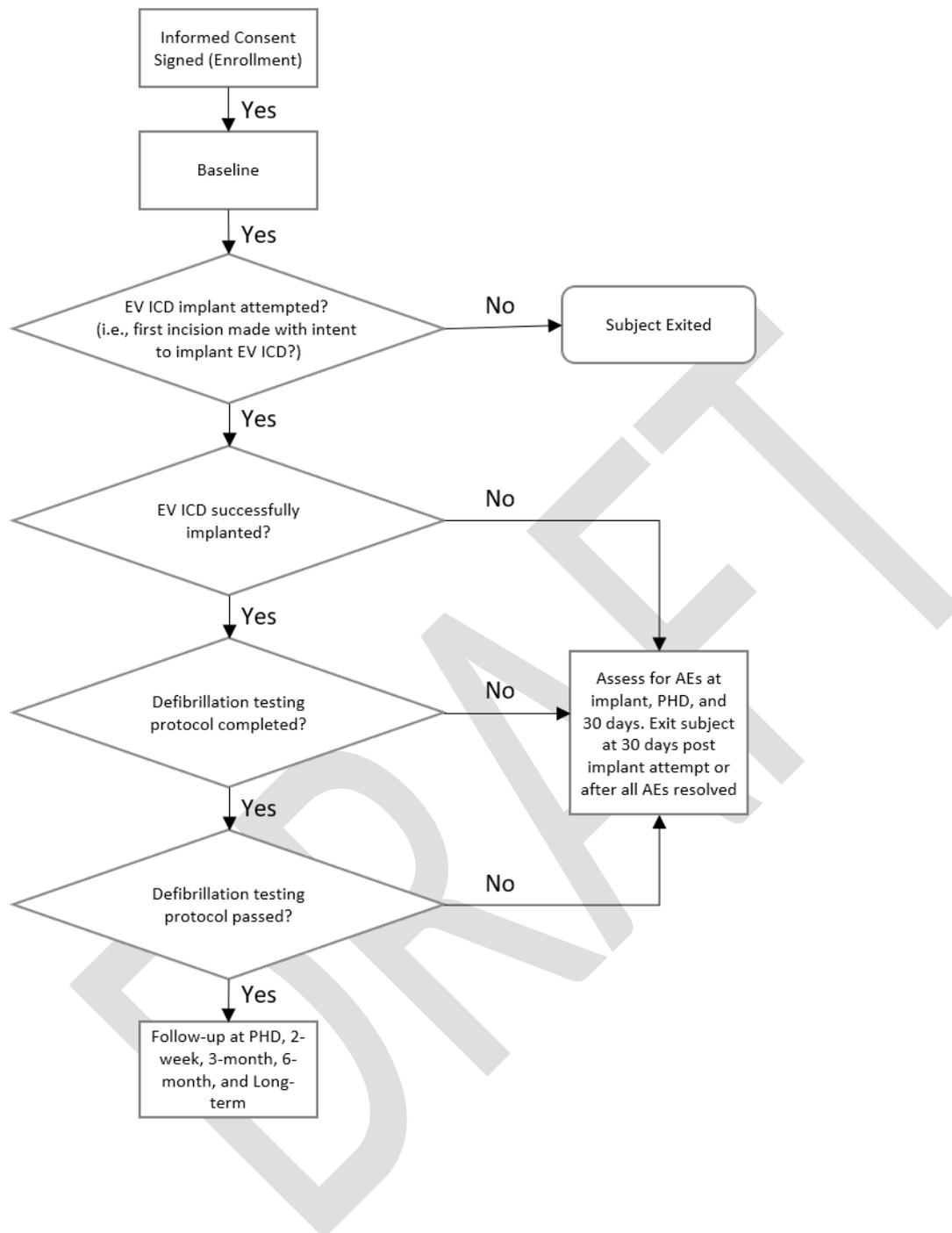


Figure 2. EV ICD System in situ. Anteroposterior (left) and lateral (right) fluoroscopic images of fully implanted system (Image from EV ICD Pilot study patient).



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Figure 3. Study Overview. (Abbreviations: PHD =Pre-hospital discharge, AE =adverse event)



Appendices:

Appendix I: Pre-Hospital Discharge (PHD) Programming Requirements and Recommendations for patients who have undergone implantation with an EV ICD System.

Required Programming		Recommended Programming	
Initial NID for VF Therapies	Minimum 30/40	VF Sensing	Per implant testing results (most sensitive setting)
All Rx	40 J	VF Sensing if PHD Troubleshooting is required	Per PHD testing results (most sensitive setting)
Pause Prevention	Monitor, 5 s	Post Shock Pacing	Per physician recommendation; 4 V margin minimum
		ATP	At physician discretion; 4 V margin minimum

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Appendix II - Safety Endpoint Definitions

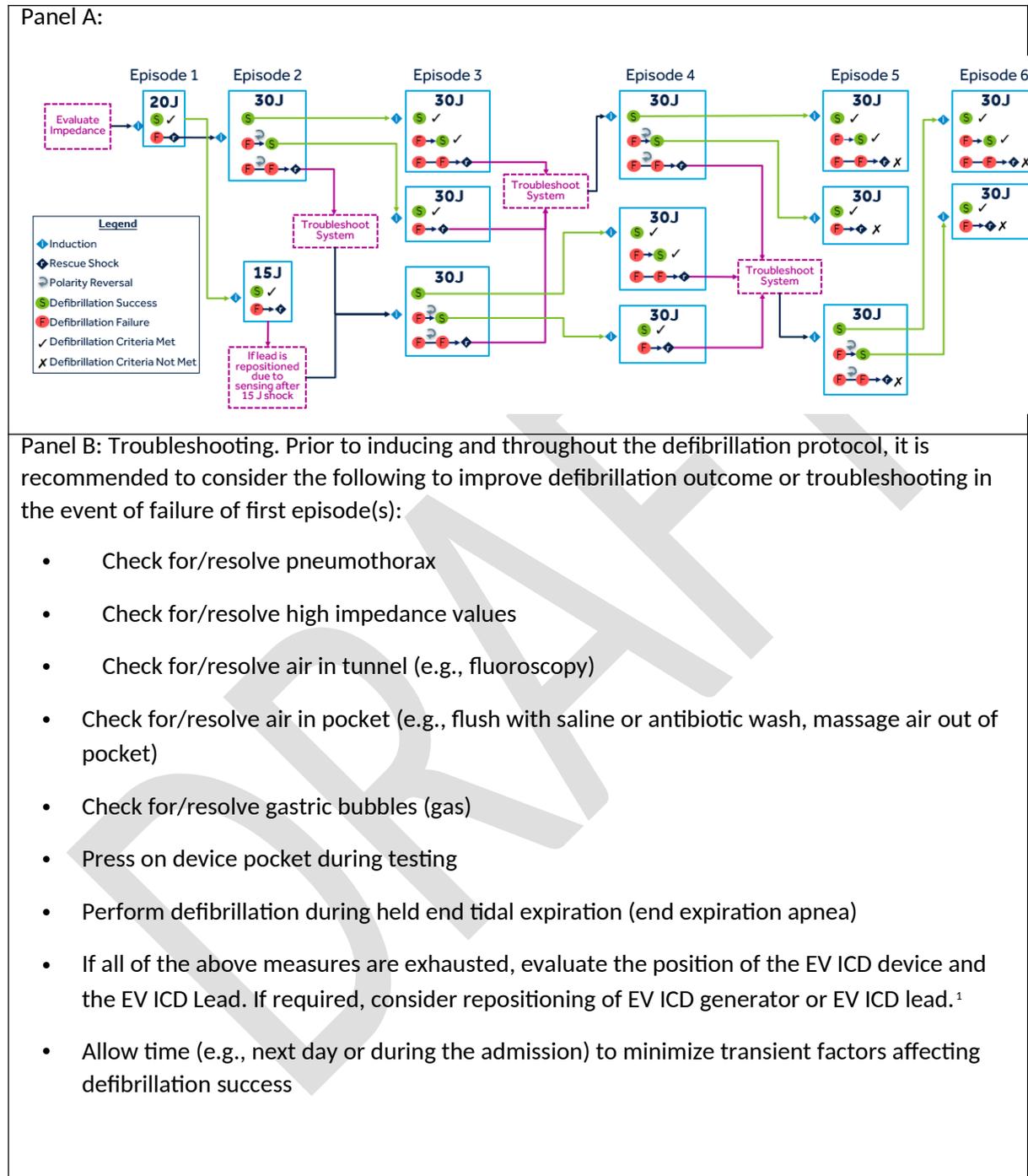
For an adverse event to meet the endpoint, the event must have occurred within 182 days (inclusive) of the EV ICD System implant and be adjudicated by the Clinical Events Committee as being a major complication related (causal relationship) to the EV ICD System and/or procedure. Major complications are those complications resulting in:

- Death
- Permanent loss of defibrillation function (specifically shock) due to mechanical or electrical dysfunction of the device
- Hospitalization
- Prolongation of an existing hospitalization by at least 48 hours
- System revision (reposition, replacement, explant)

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Appendix III - Defibrillation Protocol at Implant

Defibrillation testing protocol at implant procedure, outlining (Panel A): the process of SSVA induction and defibrillation testing and (Panel B): troubleshooting recommendations in the event of failure of first episode.



¹ Lead revision is not permitted if the subject has resumed anticoagulation. Post-procedure anticoagulation should be resumed as soon as possible unless clinically contraindicated (e.g. effusion observed) in subjects who have had atrial fibrillation for ≥ 48 hours in duration prior to the implant procedure and who convert to sinus rhythm during defibrillation testing to diminish the risk of peri-procedural stroke.