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# Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD: Design and Rationale of the EFFORTLESS S-ICD Registry

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**Background:** Leads in and on the heart of the transvenous implantable cardioverter defibrillator (ICD) form the Achilles' heel of this system due to potential for peri- and postimplant complications. The S-ICD is a newer generation of the ICD that does not require leads on the heart or in the vasculature. We present the rationale and study design of the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry which was designed to evaluate the long-term performance of the S-ICD including patient quality of life and long-term resource utilization.

**Methods:** The Registry is an observational, nonrandomized, standard of care evaluation to be conducted at approximately 50 investigational centers in Europe and New Zealand where the S-ICD is approved for use and distribution. Clinical Registry endpoints include perioperative (30 days postimplant) complication-free rate, 360-day complication-free rate, and percentage of inappropriate shocks for atrial fibrillation and supraventricular ventricular tachyarrhythmia. Other endpoints include patient-reported outcomes (e.g., quality of life) and hospital personnel implant and follow-up experience with the S-ICD system.

**Conclusions:** Results from EFFORTLESS will build on and expand the initial published experience with the S-ICD, which demonstrated that the device successfully and consistently detects and treats episodes of sustained ventricular tachyarrhythmias. The Registry will also evaluate the patients' perspective of how it is to live with an S-ICD as compared to a contemporary transvenous system and track the experience of implanting physicians and personnel performing patient follow-up with a completely subcutaneous system. (PACE 2012; 1–6)

**implantable cardioverter defibrillator, subcutaneous, physician survey, quality of life, registry**

## Introduction

Implantable cardioverter defibrillator (ICD) therapy has superior survival benefits as compared to antiarrhythmic drugs for the prevention of sudden cardiac death for both primary and secondary prevention in subsets of patients.<sup>1,2</sup> However, ICD therapy is associated with a number of adverse events, including infection, inappropriate shocks, and other procedure- and system-

related complications, which have contributed to an ardent debate in the arrhythmia community surrounding the utilization and cost-effectiveness of the ICD.<sup>3,4</sup> Peri- and postimplant complications, such as pericardial effusion, tamponade, perforation, and pneumothorax, can primarily be attributed to leads that are implanted in or on the heart in the conventional transvenous ICD system. Repositioning and extraction of leads in the event of dislodgement, fracture, or other associated mechanical events further adds to the risk of complications including death.<sup>5</sup> Lead failure rates are estimated to be up to 20% at 10 years.<sup>6</sup> This essentially means that although such devices can be life-saving they introduce significant long-term cumulative morbidities to the patient who may require protection from arrhythmias over many decades.

The entirely subcutaneous ICD system (S-ICD<sup>®</sup>, Cameron Health Inc., San Clemente,

Disclosures: All coauthors serve as Steering Committee members on the EFFORTLESS S-ICD Registry.

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CA, USA) was developed to address some of the concerns related to transvenous ICD systems. Procedure-related complications are minimized, as the implantation is less invasive and does not automatically require fluoroscopy, thus avoiding radiation exposure and its potential consequences.<sup>7</sup> No leads are implanted in or on the heart, thereby preserving the vasculature.<sup>7</sup> The S-ICD can be a useful option in children and young adults, who may be faced with a long career as a device patient and the potential for more lead-related complications and extractions, although likely only in children weighing at least 25–30 kg due to the size of the S-ICD.<sup>8</sup> A potential disadvantage of the S-ICD system is the lack of bradycardia and antitachycardia pacing (ATP). It could be postulated that the absence of ATP may increase the number of therapeutic shocks that a patient receives, which can have an impact on the quality of life and well being of patients.<sup>9</sup>

The initial evaluation of the S-ICD indicates that the device successfully and consistently detects and treats episodes of sustained ventricular tachyarrhythmias.<sup>7,10</sup> Although the less invasive S-ICD implantation procedure should remove some of the complications historically associated with conventional transvenous leads, such as tamponade and perforation, the actual longevity of subcutaneous leads is not yet well established nor the long-term performance of this new device. Further information is required not only on the sensitivity and specificity of the device to detect and treat ventricular tachyarrhythmias but also the early and long-term complication rates, incidence of both appropriate and inappropriate ICD therapies, and the longevity of the system (i.e., lead and pulse generator). Pertinent information is also lacking on the experiences of physicians and hospital personnel with respect to the implantation and follow-up of the S-ICD system as compared to transvenous ICD systems and the experience of patients living with an S-ICD system as compared to patients implanted with a transvenous system. In their recommendations for improving the health care system of the 21st century to a system that provides consistent and high-quality care, the American Institute of Medicine has set out guidelines advocating that all treatment and care fulfill the six criteria of being safe, effective, timely, equitable, efficient, and patient-centered.<sup>11</sup> In the device community, others have also considered the inclusion of the patient perspective (e.g., quality of life and well being of patients) timely.<sup>12,13</sup>

The objectives of the Evaluation of Factors Impacting Clinical Outcome and Cost Effectiveness of the S-ICD (EFFORTLESS S-ICD) Registry are to: (1) Document the complication

rate, incidence of inappropriate therapy, and the extrapolated costs associated with the S-ICD system; (2) Compare patients implanted with an S-ICD system to patients with a contemporary transvenous ICD system on patient-reported outcomes (PROs; e.g., quality of life, anxiety, and depression); (3) Document hospital personnel implant and follow-up experience with the S-ICD as compared to contemporary transvenous ICD systems.

## Methods

### Study Design

The EFFORTLESS S-ICD Registry is an observational, nonrandomized, standard of care evaluation to be conducted at approximately 50 investigational centers in Europe and New Zealand where the S-ICD is approved for use and distribution. Participating countries include the Czech Republic, Denmark, Germany, Italy, New Zealand, Portugal, Slovakia, the Netherlands, and the United Kingdom. The EFFORTLESS S-ICD Registry has been registered on <http://www.ClinicalTrials.gov> (NCT01085435). The rules for medical ethics approval of such a standard of care protocol are followed for every participating country. The Registry will be conducted according to the Helsinki Declaration and ISO 14155:2009.

### Study Population and Eligibility Criteria

Patients from the investigators' general ICD patient population will be eligible to be enrolled in the Registry, provided that they meet all the inclusion criteria and none of the exclusion criteria. Retrospective enrollments are allowed provided that minimal data requirements are met, as per protocol, but this subset of patients is not eligible for participation in the PRO substudy that focuses on the patient perspective. In addition to the original protocol of the Registry, an amendment is available allowing the option of the participating center to include patients below the age of 18 years. The inclusion and exclusion criteria listed later apply to patients below and above the age of 18 years. Only adult, prospective patients will participate in the PRO substudy of the Registry.

#### *Inclusion Criteria*

Eligible for implantation of an S-ICD system per local clinical guidelines or currently implanted with an S-ICD system (SW version 1.59.0 or later; Cameron Health Inc.); primary or secondary prevention indication for ICD implant; willing and able to provide written informed consent or have informed consent provided by a legal representative in case of patients below 18

years of age; patients currently implanted must meet minimal data set requirements to be enrolled as described in the Registry protocol.

#### *Exclusion Criteria*

Participation in any other investigational study that may interfere with interpretation of the Registry results; incessant ventricular tachycardia and/or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing; patients with an indication for cardiac resynchronization therapy; patients with unipolar pacemakers or implanted systems that revert to unipolar pacing. Retrospective patients are ineligible for participation in the PRO substudy.

#### **Sample Size**

A target sample size of 1,000 patients is to be enrolled into the general Registry with 250 patients also participating in the PRO substudy (although more are allowed). Since the study is a single-arm observational study, the target sample size was statistically derived based on an acceptable 95% confidence interval width. Based on reported complication rates for conventional ICD technology,<sup>6</sup> estimates of the anticipated range of complication-free rates for the S-ICD were made for both 30- and 360-day postimplant. Data will be presented with the corresponding 95% confidence intervals based on exact confidence intervals for the 30-day postimplant estimate and the Kaplan-Meier method using the Peto standard error for the 360-day postimplant. Assuming an attrition rate of 10%, the 95% confidence interval width for the 30-day complication-free rate should be no wider than 4% for estimated values of 90% or higher and no wider than 6% for estimated values of 70% or higher in regards to the 360-day complication-free rate.

#### **Study Procedure and Follow-Up**

A member of staff (e.g., electrophysiologist, research coordinator, etc.) at each participating center who has been approved by the center to take informed consent and do the enrollment will approach patients for participation in the Registry. Written informed consent of prospective patients will be obtained before the S-ICD implantation. In the case of retrospective inclusion in the Registry, the respective patients will normally be approached at a scheduled follow-up visit. Following implant, data will be collected from each patient's scheduled and unscheduled follow-up visits for at least 360 days postimplant per the standard of care follow-up schedule as defined by their implanting center or the center that performs the clinical follow-up visits. Once the 360 days of

follow-up have been completed for all enrolled patients, they will continue to be followed per institutional standard of care but data will then only be collected once annually for the subsequent 48 months. All complications, hospitalizations and clinical events that occur between annual follow-ups will be reported. This will ensure that at least 60 months' data are available on postimplant system status and clinical events. The follow-up duration for the PRO substudy is 12 months from baseline. See also Figure 1. A reminder system is coupled to the PRO substudy, such that patients are sent a reminder with a new questionnaire if not returned within 2 weeks.

#### **Main Registry and Substudies**

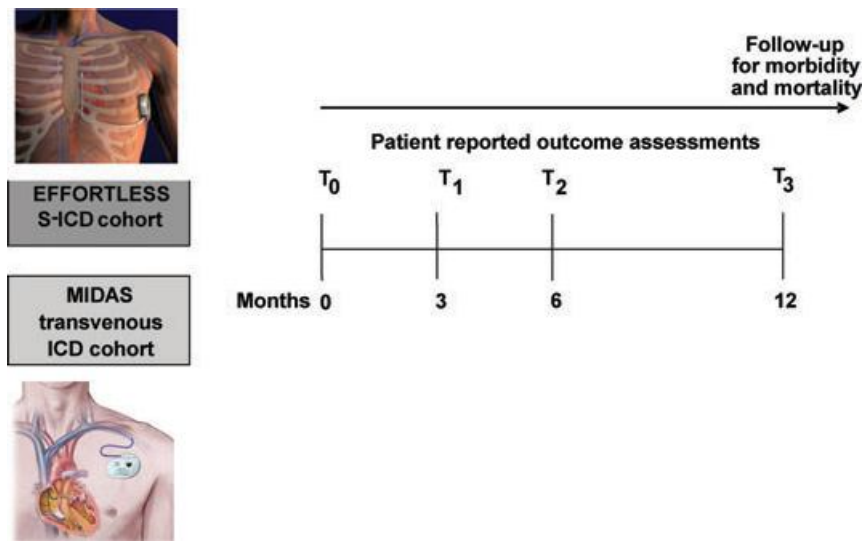
##### *Main Registry*

The endpoints of the main registry include perioperative (30 days postimplant) complication-free rate, 360-day complication-free rate, and percentage of inappropriate shocks for atrial fibrillation and supraventricular ventricular tachyarrhythmia and/or noise.

##### *PRO Substudy*

Quality of life and other PROs used to evaluate the patient perspective will be assessed with standardized and validated measures shown to have acceptable psychometric properties. These outcomes will be assessed at all time points, as presented in Figure 1, except for the Florida Patient Acceptance Survey which will not be assessed at baseline. Table I presents an overview of these measures. Generic measures include the Short Form Health Survey 12,<sup>14</sup> the EuroQol (EQ-5D),<sup>15</sup> the Hospital Anxiety and Depression Scale (HADS),<sup>16,17</sup> and the Type D Scale (DS14),<sup>18,19</sup> whereas disease-specific measures include the ICD Patient Concerns questionnaire (ICDC)<sup>20,21</sup> and the Florida Patient Acceptance Survey (FPAS).<sup>22,23</sup> If available for the specific patient group and PROs under study, it is paramount to include disease-specific measures, as they are more relevant for patients and are more sensitive to detect changes in scores over time.<sup>24</sup> The DS14 was included in the Registry, as Type D personality has been implicated in poor PROs but also in increased risk of ventricular tachyarrhythmias and premature death in ICD patients.<sup>21,25,26</sup> In addition to being used as a PRO, the EQ-5D can be used as a measure of cost-effectiveness.

As a comparison group for the EFFORTLESS S-ICD cohort on PROS, we will use the MIDAS (Mood and personality as precipitants of arrhythmia in patients with an Implantable cardioverter Defibrillator: A prospective Study) cohort, which is a consecutive cohort of patients implanted



**Figure 1.** The EFFORTLESS S-ICD Registry study design and time points for assessment of PROs.

**Table I.**

Patient Reported Outcomes and Psychological Factors Assessed in the EFFORTLESS S-ICD Registry

Construct	Number of Items		Questionnaire
Quality of life	12	SF-12*	Short Form Health Survey 12
	5 + VAS	EQ-5D*	EuroQol
ICD concerns	8	ICDC†	ICD Patient Concerns Questionnaire
ICD acceptance	18	FPAS†	Florida Patient Acceptance Survey
Anxiety/depression	14	HADS*	Hospital Anxiety and Depression Scale
Type D personality	14	DS14*	Type D Scale

VAS = visual analogue scale.

\*Generic measure.

†Disease-specific measure.

with a first-time transvenous system between August 2003 and February 2010 at the Erasmus Medical Center, Rotterdam, the Netherlands.<sup>21,25</sup> The inclusion criteria for the MIDAS cohort were similar to those for the EFFORTLESS S-ICD cohort, apart from MIDAS patients being implanted with a transvenous system. The MIDAS cohort completed the same PROs at the same time points as the EFFORTLESS S-ICD cohort, except for the EQ-5D.

**Hospital Personnel Implant and Follow-Up Experience Substudy**

Hospital personnel experience with implantation of the S-ICD compared to a transvenous system and follow-up experience with the S-ICD will be assessed with a purpose-designed survey that was developed by the first (SSP), sixth (HR), and the last author (DAMJT). The survey consists of three sections tapping into (1) general character-

istics of the respondent (e.g., position, experience with implantation in general, knowledge of the S-ICD, and transvenous systems), (2) opinions about the S-ICD system (e.g., “I am comfortable with the simplified programming options of the S-ICD system”) rated on a 5-point Likert scale from “completely agree” to “completely disagree,” and (3) a section allowing implanting hospital personnel to provide additional information to elaborate on their answers and their experience. Implanting hospital personnel are eligible to participate in the survey, if they have implanted or performed clinical follow-up of the S-ICD as part of the EFFORTLESS S-ICD Registry. Implanting physicians and personnel responsible for patient follow-up will complete the survey at two time points: (1) At baseline (after the enrollment and implant of the first prospective patient) and (2) at the end of the Registry.

**Table II.**

## Observational Data Collected in the EFFORTLESS S-ICD Registry

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<ul style="list-style-type: none"> <li>● Clinical indications for implant</li> <li>● Patient demographics</li> <li>● Type of anesthesia/analgesia</li> <li>● Implant procedure duration</li> <li>● Use of fluoroscopy and x-ray</li> <li>● Shock conversion efficacies (spontaneous and induced)</li> <li>● All-cause therapies (appropriate and inappropriate)</li> <li>● Total shock burden</li> </ul>	<ul style="list-style-type: none"> <li>● Overall complication rates with time</li> <li>● Frequency of scheduled/unscheduled follow-ups/hospitalizations</li> <li>● All-cause mortality</li> <li>● Length of hospital stay (implant procedure and follow-ups)</li> <li>● All clinical events</li> <li>● Clinical event rates over time</li> <li>● Quality of life</li> <li>● Hospital personnel implant and follow-up experience (using surveys)</li> </ul>
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**Observational Data Collected**

A list of observational data collected for the Registry is presented in Table II.

**Study Organization and Analysis of Data**

Data are captured using a web-based electronic data capture system, and the Registry is entirely funded by Cameron Health Inc. Two separate committees that are independent of Cameron Health Inc. have been formed: (1) A clinical events committee, which will review all spontaneous episodes and serious device-related events; and (2) A steering committee, which will review all data. Data analyses for the PRO substudy will be performed by members of the steering committee, and if applicable with the assistance of an independent statistician.

**Discussion**

The EFFORTLESS S-ICD Registry is an observational, nonrandomized, standard of care evaluation that will include patients from approximately 50 investigational centers in Europe and New Zealand where the S-ICD is approved for use and distribution. Participating countries include the Czech Republic, Denmark, Germany, Italy, New Zealand, Portugal, Slovakia, the Netherlands,

and the United Kingdom. The Registry is set up to extend the initial period of evaluation of the S-ICD, which has indicated that the device successfully and consistently detects and treats episodes of sustained ventricular tachyarrhythmias.<sup>7,10</sup> In addition to expanding on the clinical evaluation of the S-ICD system, for the first time, the Registry will evaluate the patient perspective as to how it is to live with an S-ICD system as compared to a transvenous system and the experience of implanting physicians and personnel performing patient follow-up with a completely subcutaneous system. The inclusion of the patient perspective is advocated by the American Institute of Medicine as a means to improve the health care system of the 21st century,<sup>11</sup> but has also been advocated by physicians from the device field<sup>13</sup>: *“To move the care of patients with ICDs, and the entire field of cardiology for that matter, into the next strata of quality, the field must become more patient-centered. Patients’ perspectives, goals, and values should guide all medical trials, guidelines, and decisions.”*<sup>13</sup> As such, inclusion of the patient perspective seems appropriate when evaluating any new technology developed to improve the management and care of patients, such as the S-ICD system.

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