Subcutaneous Implantable Cardioverter Defibrillator

Group 8

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I. Phase I Device Concept

A. User Needs (Reece)

The list of users for ICDs primarily includes two broad categories; patients and healthcare providers. Healthcare providers range from people who have direct contact with the device to administrative staff in hospitals or private practices as well as insurance providers. Note that it does not necessarily include the manufacturers, engineers, or salespeople who work with the company that creates the device. Within hospitals or private practice, the responsibility of ordering necessary supplies falls under the purview of material management departments or procurement departments. These departments are responsible for managing, sourcing, purchasing and distribution of all supplies, including ICD, that are essential to the proper function of their business. This includes medical supplies, equipment, pharmaceuticals, and anything else required. They also work closely with suppliers and vendors to negotiate contracts, monitor inventory levels, track shipments, and manage the overall supply chain.

These departments work closely with other stakeholders, namely the physicians, nurses, and administrative staff to determine their supply needs. The primary party that decides which supplies to buy are the physicians who are also responsible for keeping up to date with the scientific literature to determine the best equipment for optimal treatment. The administrative team in conjunction with physicians will decide on the quantity needed. It is worth noting that biotech companies will reach out to physicians to perform clinical trials and advocate their devices to physicians. The teams who test devices with physicians as well as aid in the installation can be considered stakeholders as well, but they can be considered a distinct entity from the company's sales team. These specific engineering teams do consider themselves users but derive a significant portion of their needs and considerations from the input of physicians and patients.

Patients are perhaps the most classically considered stakeholder for ICDs. They include individuals with life-threatening abnormal heart rhythms or those who are at risk of having a harmful rhythm again. They also include people who have been tested, usually via echocardiograms, of being at risk of having threatening rhythms that are frequently the result of cardiomyopathies, genetic issues, or other syndromes and conditions. Lastly, they include heart failure patients that are at risk of developing life threatening rhythms.

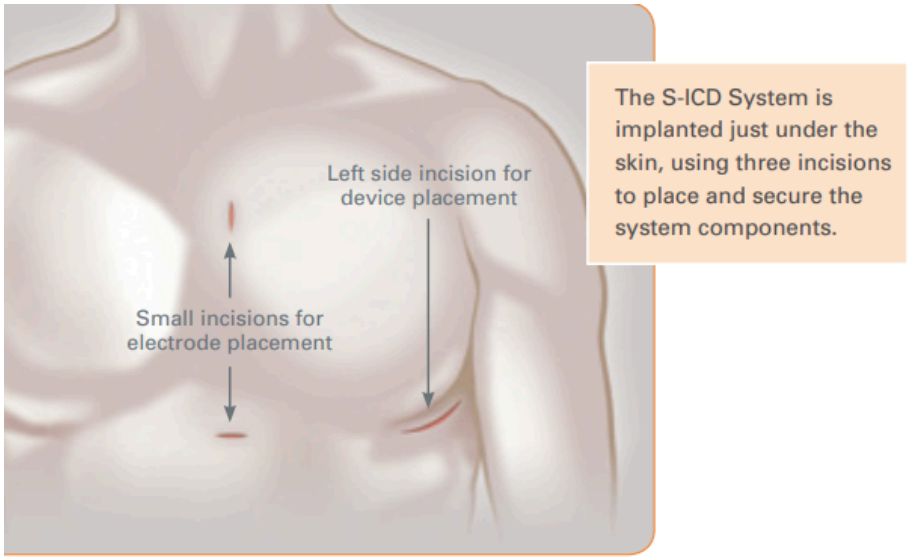
ICDs have an overarching goal of regulating and ensuring a healthy heartbeat. They send electrical signals to regulate arrhythmias using their own internal electrical signal, by sending electrical signals to the heart, causing it to contract and pump blood. When ICDs detect a dangerous rhythm they send one of three treatments. They can pace with a series of frequent low voltage beats, perform cardioversion with small electrical shocks, or defibrillate with large electrical shocks.

Pertaining to the needs of the users with particular consideration for the patients, ICDs need to be safe and reliable and able to accurately and consistently prevent dangerous arrhythmias via proper detection and shock delivery. They need to have long battery life and

require infrequent replacements. There needs to be a low risk of infection which is feasible through easy surgical implementation, proper sanitation, and full biocompatibility. They need to improve patients' quality of life and mitigate the diminishment of their lifestyle, so they need to be electromagnetically compatible.

B. Clinical Objectives (Ben)

For the subcutaneous cardioverter defibrillator to address the user needs, critical clinical objectives support the ease of implantation and efficacy and reliability of shock appropriate shock delivery. The main purpose of this device is to keep its users alive by providing necessary shocks to the heart in an event of cardiac fibrillation. However, this device is only for patients who have life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with antitachycardia pacing. If this device were implanted in patients with those conditions, the battery would deplete prematurely due to the constant use. For the objective of easy installation, surgeons only need to create 3 incisions to fully implant the device and these are shown picture 1. This design makes it much easier for surgeons to implant the device compared to the normal TV-ICD which involves fluoroscopy to introduce the leads into the chambers of the heart. This subcutaneous design also allows physicians easy access to the pulse generator and electrode in event of device malfunction/battery failure. Since this is an implanted device that can receive software updates electronically, it is critical that the device can not be tampered with from an outside source and only authorized physicians can make changes to the device. Being able to withstand multiple uses is another critical clinical objective as some of these patients may experience episodes of multiple arrhythmias in a few days. It would be ineffective if the ICD providing life saving shocks to the heart which is surgically implanted did not last years for a patient. With more surgery comes more of a risk for infection. Due to this device being implanted under the skin, the materials that make the device need to be biocompatible for the safety of the patient and effectiveness of the device itself. The materials need to be durable to withstand the multiple shocks it will create as well as not erode when it comes into contact with the environment of the inside of the body. It can also not degrade the surrounding skin and structures around it. The ICD must be able to accurately and continuously sense arrhythmias and administer appropriate shocks to the heart in a timely manner. This is the primary use of the device, to keep the patient alive by providing these shocks. It is important that these shocks have the correct power as to not damage surrounding tissues and to only serve as a mechanism to restart the heart. Overall, S-ICD functionality is crucial to the success of keeping the patient alive; with rigorously tested software that can accurately detect arrhythmias and deliver shocks at the correct power, created from durable biocompatible materials, the S-ICD system can improve the quality of life of its users.



Picture 1: Incision Diagram for Surgery

C. Clinical Design Hypothesis (Colten)

Installation of the S-ICD will result in the lead sensors detecting arrhythmias which the electronic components in the Can will decipher to determine when an 80J shock needs to be administered to the chest cavity. The patient's cardiac rhythm will then return to normal and after taking 10 seconds to recharge its capacitors the system will constantly monitor the patient for other arrhythmia occurrences without complications in the device's 5 year lifespan.

D. Design Inputs (Reece)

In order for the device to perform its function and carve out a role within the realm of medical technology, there are design inputs that have to be fulfilled. Since this device is implantable that needs to remain stable for years at a time, it needs to follow the biocompatibility standards per the FDA. Namely sections pertaining towards evaluation and testing, animal welfare requirements, tests for genotoxicity, carcinogenicity, and reproductive toxicity, selection of tests for interaction with blood, tests for cytotoxicity, in vitro methods, tests for local effects after implantation, ethylene oxide sterilization residuals, tests for irritation and delayed-type hypersensitivity, tests for systemic toxicity, sample preparation and reference materials, identification and quantification of degradation products from polymeric devices, chemical characterization of materials, as well as chronic toxicity. Additionally it is important that ICDs are sterile and follow the ISO 11137 standard for the sterilization of healthcare products.

Along with the chronic toxicity and general material degradation, more factors are needed to assess the longevity of the device. To perform more specific degradation testing relevant to this particular device, ISO standards 5832 and 5999 for titanium and polyurethane, respectively, must be adhered to in order to test the specific materials that come into contact with

the body. Furthermore, the battery is an important potential limitation for the durability of ICDs. The battery must adhere to the IEC 62619 standard to ensure a long enough lifespan. It is worth noting that at the time of manufacture ICDs typically have enough charge to deliver 100 shocks, far exceeding the typical expected number of shocks needed at 21 over a 5 year period.

Regulation of the detection of arrhythmias is a tricky aspect to regulate yet vitally important. The IEC 62304 standard for medical device software provides substantial regulation with regard to certain potential errors such as glitches in the code or the device spontaneously shutting down, but little to do with correctly identifying arrhythmias. Instead there have been clinical trials conducted to ensure appropriate behavior. One notable study conducted with 294 patients had ICDs deliver 809 shocks. It was retroactively determined that 808 of the shocks were in fact necessary, proving a high success rate. Additionally, after the device is installed, it actually induces a ventricular arrhythmia for a short window of time to test and see whether or not it is able to detect the electrical signaling of an arrhythmia. This is done in a controlled setting but this is unique testing that this device endures after it is installed and therefore worth mentioning. ICDs run a dual algorithm which means that while they continually run an electrocardiogram on the patient it cross references the most recent heartbeat (current) with both that of the previous heartbeat (past) as well as a standard template. Any significant deviation is considered a potential indicator for an arrhythmia and tells the system to prepare for a shock. During this charging period, the ICD continues to evaluate whether or not a shock is truly required, and often corrects itself and determines that a shock is no longer needed. This self correcting mechanism is a highly effective tool that limits the number of false positives detected and unnecessary shocks delivered.

In order to provide proper therapy a precise shock is needed. For defibrillations, a 65 joule shock is administered initially with 80 joule shocks delivered subsequently, as or if needed. Other arrhythmias generally require a shock in the 10-30 joule range, but that is highly individual and circumstantial. In order to verify correct electrical output the IEC standard for the safety and performance standard for portable lithium batteries is to be followed.

This last design input is that of electromagnetic compatibility. This needs to be kept to a minimum in order to prevent unwanted interaction with other devices. Generally this limit is thought to be 10 gauss and the IEC 61233 standard is followed.

E. Summary Table of A-D (Reece)

Table 1: Device Concept

User Needs	**Clinical Objectives**	**Design Inputs**
Biocompatibility	Biocompatibility	ISO 10993
Longevity	Withstand multiple uses and last years	Titanium and polyurethane stability and adequate battery life per ISO 5832, ISO 5999, and 62619
Able to deliver therapy	Accurately and continuously sense arrhythmias and administer an appropriate shock to the heart	Precise joule delivery and timing per IEC 61233
Electromagnetically compatible with life	Keep user alive	10 Gauss limit per ISO 14117
Able to detect arrhythmias	Surgically implanted	IEC 62304

Table 1: Device Concept Summary

There is an apparently clear relationship between user needs, clinical objectives, and design outputs for most devices, and this rule is true for ICDs. The user needs focus on the patients in which the device is intended to be installed within and are derived from the conditions that it addresses directly. Two two most difficult needs are the ability to detect arrhythmias and then to correct them as they arise. Other needs are essentially but don't directly address the issue. For example, the device needs to be compatible with the body in order to be used in a living human, but simply the ability to exist inside of someone without harming them does not mean that it will be able to treat anything.

The clinical objectives are determined from the user needs. The goal of creating a device that can withstand many uses and last for years arose from the desire of longevity from the user needs, and the overall goal for the device to continually detect arrhythmias and administer appropriate shocks along with keeping the patient alive arose from the need to detect irregular heartbeats, as well as the need for treating them. The biocompatibility clinical objective matches the biocompatibility need.

Design inputs are the quantifiable goals of clinical objectives. Adhering to the ISO compatibility sections that correspond to the device will ensure the fulfillment of the biocompatibility clinical objective. Same dynamic between the ISO 5832, 5999, and IEC 62619 standards with the objective of withstanding multiple uses and lasting years. The quantifiable

goals of accurately and continually sensing arrhythmias and administering appropriate shocks to the heart are delineated with IEC standards 61233 and 62304.

F. FMEA Risk Analysis (Ben)

Failure Mode	**Causes of Failure**	**Failure Effect**	**Frequency of Occurences**	**Severity**	**Chances of Detection**	**Risk Factor**	**Action**	**Design Validation**
Inaccurate Arrhythmia Detection Software Crash	Software algorithm failure	Failure to detect false detection of arrhythmia	3	10	5	150	Improve algorithm accuracy, implement redundant checks	Extensive software testing and simulations
	Electromagnetic interference	False detection or missed arrhythmia	4	7	5	140	Shielding, intense signal processing	EMI testing and validation
	Bugs or corruption in software	Complete device failure/ unpredictability	1	10	2	20	Thorough software development and validation process	Comprehensive software testing and verification
Battery Depletion	Normal use	Device shutdown or reduced functionality	8	8	1	64	Use high-capacity batteries, low power consumption design	Long-term battery life testing
	Malfunction, premature depletion	Device shutdown or reduced functionality	2	8	3	48	Use high-capacity batteries, low power consumption design	Long-term battery life testing
Pulse Generator	Component malfunction	Failure to deliver shock	1	10	5	50	Use high quality	Component reliability

Failure							components, redundant circuit	testing, redundancy verification
Device Migration	Poor execution in procedure	Displacement of device from implant site	2	7	5	70	Secure fixation methods, good ergonomic design	Post-implantation monitoring, lifestyle changes
Infection at implant Site	Surgical procedure or materials used in device	Infection	2	6	7	84	Use biocompatible materials, sterile surgical procedures	Biocompatibility testing, post-surgical follow up
Packaging	Contamination of sterile packaging	Infection may lead to device failure and additional treatment	3	3	2	18	Testing packaging process, robustness of seal, storage methods	Test Report
	Not stored in appropriate environment	Materials degrade, device efficacy decreases	3	3	1	9	Test extremes to determine failure conditions	Test Report

Table 2: Quantitative FEMA Risk

G. Device Regulatory Classification (Colten)

Subcutaneous Implantable Cardiodefibrilators are considered Class III devices. The device has a Premarket approval number P110042 which was granted due to the success of preclinical and clinical trials. S-ICD's are reviewed under the committee of Cardiovascular.

II. Phase IA Pre-Sub Document (Ben)

A. Pre-Sub Table of Contents

1. Cover letter
    a. Contact information: Company name, address, and contact person(s) including title(s), phone number(s), fax number(s), and email address (es).
    b. Q-sub Type: Presubmission
    c. If meeting required, draft agenda and attendees

2. Purpose: Get FDA feedback for device PMA submission
3. Device or Product Description
4. Proposed Indication for Use or Intended Use
5. Mechanism of Action on the Body
6. Technological Characteristics
7. Planned Testing Strategy
8. Pre-Sub questions

B. Scientific Principles of Device Operation

The Subcutaneous-ICD relies on several scientific principles to continuously monitor a patient's heart rhythm and deliver lifesaving shocks when necessary. The S-ICD implant contains an electrode that is 8 cm long positioned near the heart that detects the electrical activity of the heart muscle. This electrode picks up minute electrical signals generated by the heart with each beat.

Sophisticated signal processing algorithms analyze these signals to identify the heart rhythm. The S-ICD continuously monitors the heart rhythm for abnormal patterns. The algorithms are programmed to differentiate between normal heartbeats and potentially dangerous arrhythmias like ventricular tachycardia (VT) or ventricular fibrillation (VF). These arrhythmias can lead to sudden cardiac arrest (SCA) if left untreated. The system has two ways of comparing the live heartbeats to detect arrhythmias. This first is, the physician can input normal heart function used as a baseline for the device that is based on the patient's history and the second is, the system keeps track of the patient's heart rate and compares it to the previous normal heart functions. The device takes all of these factors into consideration to analyze arrhythmias and determine if a shock is necessary. If the S-ICD detects a pre-programmed arrhythmia, it initiates the shock delivery system. A high-voltage electrical pulse of 65 joules is delivered through the electrode directly to the heart. This shock disrupts the abnormal electrical activity and helps restore a normal heart rhythm. The S-ICD delivers a biphasic shock waveform, which is designed to be more effective and cause less damage to the heart tissue compared to older monophasic shocks.

The device carefully controls the energy level of the shock to be effective in stopping the arrhythmia while minimizing the risk of damage to surrounding tissues. The S-ICD is powered by a long-lasting internal battery. The device employs sophisticated power management techniques to optimize battery life and ensure continuous monitoring and shock delivery capability.

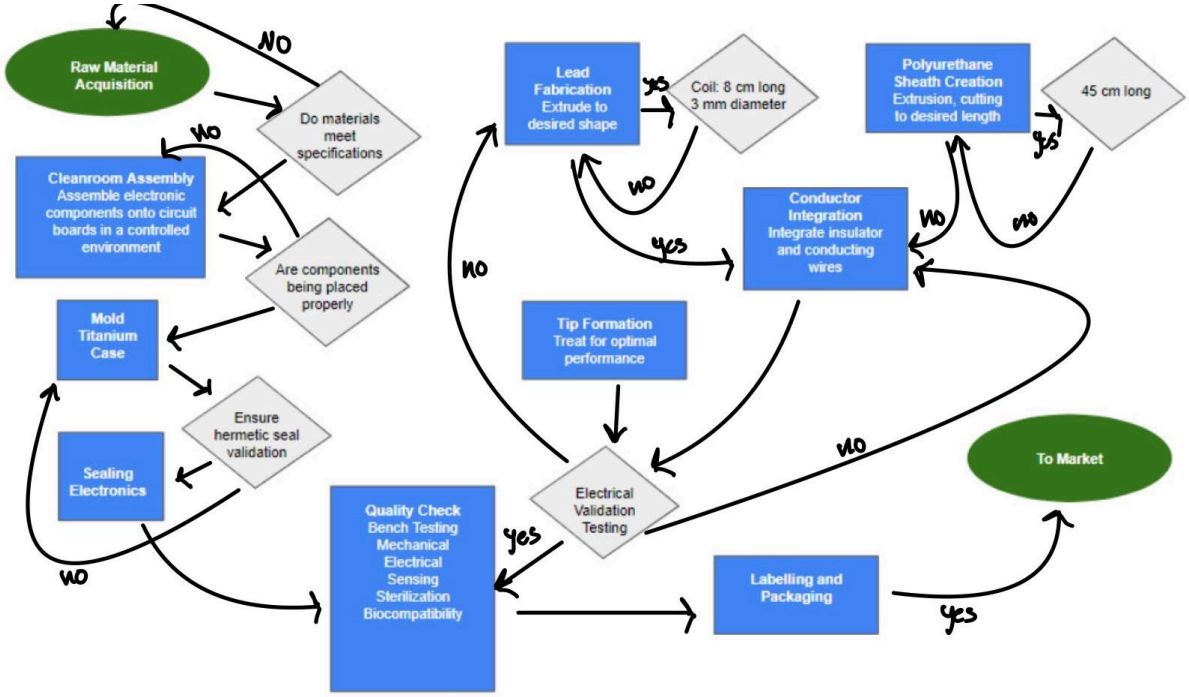
C. Pre-Sub Questions

Questions to obtain targeted feedback from the FDA to ensure tha the S-ICD meets necessary and safety standard suitable for its intended use:

1. What are the most critical safety concerns that the FDA identifies for the S-ICD, and what measures should be taken to address those concerns?

2. Is the intended use of the S-ICD in line with the regulatory requirements for medical devices that concern our clinical problem?
3. For evaluating acute use of ICD in a porcine and canine model acceptable to the FDA? Does the agency agree that this model will accurately depict what will happen in a human study if allowed to proceed?
4. For the pulse generator, we have designed it to be able to administer more than 100 shocks with its battery which should last the patient around 5 years. Is this duration of time long enough for the device? If not, please provide further guidance
5. Currently, the canine model for testing the continued performance of the ICD as well as algorithm operation is only going to run for 36 months. We are also going to run simulated aging testing on the device for more than 5 years. Is this satisfactory with the FDA standard's?

III. Phase II Manufacturing Processes (Ben/Colten)



As seen in the figures below, the main components of the S-ICD are the pulse generator (produces the shock) and the electrode (administers the shock). The external layers of both components need to be biocompatible. This housing for the pulse generator is made of titanium which was chosen for strength, durability, and ability to safely interact with the body for extended periods. The internal circuitry uses high-reliability components like microprocessors, capacitors, and resistors. These components are miniaturized for space efficiency and hermetically sealed to prevent moisture corrupting the system. A long-lasting lithium battery provides power to the device. The pulse generator is assembled in a meticulously controlled

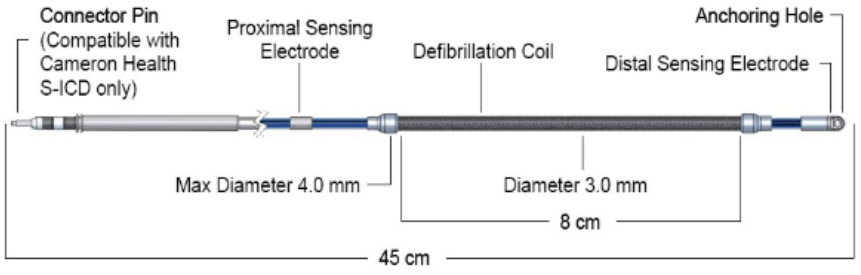
cleanroom environment to minimize contamination risk. High-precision robotic systems likely place and solder the intricate electronic components onto circuit boards. For the electrode, the lead body is constructed from a flexible, silicone and polyurethane polymer. This material allows for conformability to the patient's anatomy. High- conductivity wires, made from platinum-iridium, are used to transmit electrical signals. The electrode tip, responsible for sensing electrical activity and delivering shocks is made from a nickel alloy, MP35N.

Most of the manufacturing processes are automated like the lead body is extruded to the desired shape and size. The insulated conductor wires are carefully integrated into the lead body, ensuring proper electrical connection and structural integrity. The distal tip is formed and treated using specialized techniques to achieve optimal electrical performance and biocompatibility. The completed electrode undergoes a validated sterilization process, using gamma irradiation and ethylene oxide gas with different percentages for each component to ensure sterility before implantation.

Processes with most Variability (Sensors and Shock Coil)

Sensor installation in the lead will have the most variability. They will be placed by hand and being that they come from third party vendors although most of the time they work perfectly fine little differences in readings will need to be calibrated. This is to make it so from device to device the sensing range for arrhythmias will be standardized. Coming out of the sensor manufacturer it is unlikely that all will be precisely the same so the calibration will be a necessary step.

Shock coils will have the same issues as sensors as there has to be very precise shock impulses. The shock coil which is placed in the lead by hand will come from a third party vendor so the materials may have slightly varying properties. The precise location in the lead will also have some variety from device to device as it is a hand installation process. This location needs to be within certain tolerances as there is a desired location in comparison to the heart where it should be delivered. Keeping this location consistent and the calibration of the shock value will need to occur to keep device variability low.



Picture 2: Electrode

Picture 3: Pulse Generator

Process Verification or Validation

Process	**Verification or Validation**	**Rationale**
Battery	Verify	Batteries are very consistent from manufacturer, but the capacity and performance will need to be verified.
Shock coil	Validate	Shock coil will need to be validated to make sure it can administer 80 J of energy
Titanium Shell	Verify	The shell will be consistently made so the dimensions and material origins will need to be verified
PCB electronic circuit board	Validate	The electronic components will need to be validated after they are created and the programming as well to make sure it can detect and administer shocks with

		correct timing
Wiring	Verify	The wiring will need to be verified that it was correctly installed and no short circuits or other failures occur.
Sensors	Validate	The sensors will have to be calibrated and validated so they can measure the electrical signals the heart produces and send the correct signals to the circuit board.

Table 3: Process Verification/Validation

IV. Device Verification

A. Design Outputs and Device Verification (Colten)

Design Output Tests:

ISO 10993 Biocompatibility Tests:

ISO 10993-1 outlines the general principles for the biological evaluation of medical devices within a risk management process. It provides guidelines for the assessment of biological hazards and the evaluation of the biological safety of the medical device.

Sensitization Testing: ISO 10993-10 is an in vivo test that evaluates the ability of leachables to cause Type IV Hypersensitivity.

Local Effects After Implantation: ISO 10993-6 specifies test methods for the assessment of the local effects after implantation of biomaterials intended for use in medical devices.

ISO 11137 Sterilization Tests:

ISO 11137-1 outlines the requirements for the development, validation, and routine control of a sterilization process for medical devices.

Sterility testing is an essential part of every sterilization validation program. ISO standards for both gamma and electron beam sterilization employ sterility testing as a measure of adequacy of sterilization parameters.

IEC 62304 Software Life Cycle Tests:

The standard outlines a systematic approach to software development, including requirements analysis, design, implementation, testing, integration, and maintenance. It emphasizes the importance of traceability, ensuring that each stage of development is linked to specific requirements.

IEC 62304 divides the software lifecycle into different phases: development, maintenance, and retirement. Each phase has defined activities and documentation requirements, ensuring that software updates and modifications are handled systematically.

Testing activities include functional testing, non-functional testing, and validation testing to ensure compliance with user requirements and regulatory standards outlined in IEC 623042.

Mechanical Verification Tests:

Fatigue Testing which measures how many bends of a patient's body the lead will be able to handle without breaking.

Dimensional testing of each component to make sure that everything fits together well.

Electrical Verification Tests:

PC69 Compatibility addresses the interaction of pacemakers and implantable cardioverter defibrillators (ICDs) with electromagnetic (EM) emitters operating across the EM spectrum.

The standard details test methods appropriate for the interference frequencies issues. It specifies performance limits or requires disclosure of performance in the presence of EM emitters, where indicated.

CENELEC standard 45502-2-2:2008.

The standard tests the safety of the device. This includes ensuring that the device does not cause harm to the patient when it is functioning. The standard tests the reliability of the device. This includes how consistently the device functions over time.The standard tests the device's resistance to interference. This includes ensuring that the device can function correctly in the presence of other electronic devices.

Design Verification Table

Design Inputs	Design Output Test	Acceptance Criteria	Rationale	Verified
Biocompatible for implantable use	Passes ISO 10993 26 week subcutaneous implantation	Each component must pass all standards and have no evidence of irritation or toxicity with 95% success after 26 weeks	Device will be inserted in body so must be safe	Pass
Sterilization packaging and shelf life	Passes ISO 11137 13 month shelf life after battery attached	Each piece must pass all standards and electrode stays sterilized for 2 years and pulse generator for 12 months before use	Device will sit on shelf before being inserted so it must hold its battery and keep sterilization while in storage	Pass

Design Inputs	Design Output Test	Acceptance Criteria	Rationale	Verified
Software and Firmware	Passes IEC 62304 medical device software life cycle processes	Support clinical release for design integration, algorithm validation, pulse generator firmware, simulated user validation	Programming must successfully detect arrhythmias, and be integrated with hardware to administer shock when necessary	Pass
Mechanical verification	Physical shock, vibration,rib compression, sharp edges, pressure on surrounding tissue are limited	Pulse generator and electrode must pass mechanical design requirements	Device will be inserted in body so must be comfortable, safe shock amount, and create no complications	Pass
Electrical verification	PC69 Electromagnetic Compatibility compliance standards are met. High voltage shock, threshold impedance, VF induction, pacing therapy and sensing categories are sufficient. CENELEC standard 45502-2-2:2008.	The Pulse generator and electrode components must both be in compliance with all standards and work with 1-140 KHz AC protection and RF interference of 450-3000 MHz. In compliance with CENELEC standards and ultrasound exposure. The nominal battery longevity of the pulse generator is 5.1 years.	Pulse generator must deliver the necessary shock at pacing intervals and not be interfered with by outside frequencies or EM effects. It must also last long enough in the body so that the patient won't have to keep undergoing surgery	Pass

B. Device Validation (Reece/Colten)

a. Animal Studies (Reece)

All animal studies follow the same general procedure with the primary difference being that of what is being evaluated. Each procedure is performed on a canine or a porcine.

Prior to surgery, a healthy animal is selected based on a variety of factors such as size and weight to ensure relevance to humans. The operating room is prepared with the device at hand and vitals taken on the animal as well as wound closure and relevant surgical equipment available. While the animal is under general anesthesia, the ICD is installed. For most tests,

Ventricular Fibrillation is induced to allow the ICD to both detect the arrhythmia and deliver a shock, but there is variability for this step. For the next 1-2 weeks there is a period of recovery from implantation. After recovery there is a period for data collection and analysis. After the study the animals continue with follow up and are cared for.

Tests performed:

Study	**Animal Model**	**Objective**	**Results**
Chronic Canine	Canine	Evaluate performance of S-ICD as well as algorithm operation in a Canine	Successful continued operation of S-ICD through 34 months
Histology	Canine	Assess gross histological effect on subcutaneous tissue with regards to mechanical implant as well as shock from therapy	Typical finding when compared to other foreign materials installed surrounded by tissue
Acute Implant Performance	Porcine	Evaluate acute use of ICD in a porcine model prior to a human study	All tests passed without exception
Acute GLP Validation Study	Porcine	Validate in vivo function of I-ICD	All tests passed without exception
24-Hour Histology	Porcine	Asses potential for acute cardiac, lung, skeletal muscle and adjacent tissue injuries associated with shock delivery	
EIT / Electrode Performance Verification	Porcine	Verify EIT performance during an implant procedure	All tests passed without exception
X-ray ID Verification	Canine	Verify that an implanted pulse generator can be identified via x-ray	All requirements passed without exception
Electrode	Porcine	Evaluate the	Modified electrodes

Modification Analysis		performance of modified electrode design	outperformed unmodified electrodes with acceptable post-shock and post-pace characteristics
Acute Testing for Software Maintenance	Porcine	Validate acute use of S-ICD after software maintenance update	All tests passed without exception
Validation of User's Manual for Software Maintenance Release	Porcine	Confirm that following instructions for use allows for successful software updates	All tests passed without exception

Table 4: Animal Study Summary

b. Clinical Studies (Reece)

Three studies were performed in order to assess the feasibility of S-ICDs. The first clinical study was conducted that followed 6 patients in 2 centers in New Zealand for 30 days. The S-ICS system sensed and converted 12 consecutive induced ventricular fibrillations. Each patient met the criteria of 2 successful conversions of induced VF. All patients were discharged the same day following their surgery and have follow ups one week and one month after. There were 4 adverse events that occurred during this study: one patient had two inappropriately placed beats following an undersensed beat post shock. Three patients had the pulse generator rotate by 180 degrees after one month. None of these events had any undue effects on the patients.

In the CE study, the second study was conducted in 8 centers in New Zealand, the Netherlands, United Kingdom, and Italy. 55 patients were enrolled for 180 days. The ICD successfully converted 52/53 measurable induced VF episodes. The one failed conversion was due to the patient's significant hemodynamic instability. 100% of all arrhythmias were detected and correctly categorized as VF or VT episodes. 19 patients experienced 26 clinical events, and the events that occurred multiple times are as follows: 6 inappropriate shocks, 4 electrode movements, 2 infections, 2 instances of discomfort, 2 instances of worsened heart failure. There were also a number of single events reported. All events were resolved without any long term clinical sequelae.

The third trial was the pivotal clinical trial in which the Clinical Investigation was performed in order to establish assurance of safety and effectiveness of the S-ICD system. The study was performed in the US, New Zealand, the Netherlands, and the United Kingdom under IDE G090013. 330 adult patients were indicated and pre screened before the study began. Chronic induced VT/VF data was collected for a minimum of 125 subjects. A target minimum of

100 implants were followed for 360 days. Prior to the study a Data Safety Monitoring Board (DSMB) was assembled consisting of experts in cardiology and biostatistics.

A primary safety endpoint was defined as the 180 S-ICD complication free rate evaluated by comparing the lower confidence bound of the observed rate to the performance goal of 79%. The primary effectiveness endpoint was defined as the Acute Ventricular Fibrillation Conversion Effectiveness Rate of induced episodes, evaluated by comparing the lower confidence bound of the observed rate to the performance goal of 88%. 321 patients had viable data. It is worth noting that clinical events caused by labeling or the system users manual (Type II), complications not caused by the device but would not have occurred had it not been present (Type III), or changes in the patient's condition (Type IV) were not included in the complication free rate. The only included compilations were that from the S-ICD when used as intended (Type I). A successful conversion was defined as two successful 65J shock conversions of induced episodes. The demographic of the study is as follows:

Demographic	Statistic/Category	N=321
Age (years)	Mean ± SD (Median) Range	51.9 ± 15.5 (53.8) 18.5-85.2
Gender (n, %)	Male	238 (74.1)
	Female	83 (25.9)
Race (n, %)	White or Caucasian	208 (64.8)
	Black or African American	76 (23.7)
	Hispanic or Latino	23 (7.2)
	Asian	6 (1.9)
	Asian Indian	3 (0.9)
	Maori	3 (0.9)
	Pacific Islander	2 (0.6)
Height (cm)	Mean ± SD (Median) Range	174.3 ± 10.2 (175.0) 142.2-200.7
Weight (kg)	Mean ± SD (Median) Range	90.5 ± 25.2 (86.6) 42.6-230.9
BMI	Mean ± SD (Median) Range	29.7 ± 7.2 (29.0) 15.2-69.0

Table 5: CE Study Demographic Summary

Despite the population being primarily large, white, geriatric men, it was determined that there was no bias. The indication information is as follows:

Indication Details	N=321 Patients n (%)
Left ventricular ejection fraction (LVEF) less than 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III	88 (27.4)
Non-ischemic DCM and an LVEF less than or equal to 35% and is in NYHA functional Class II or III	76 (23.7)
Survivor of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes	40 (12.5)
Hypertrophic Cardiomyopathy with risk for SCD	28 (8.7)
Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable	15 (4.7)
Left Ventricular (LV) dysfunction due to prior MI and is at least 40 days post-MI, has an LVEF less than 30%, and is in NYHA functional Class I	13 (4.0)
Cardiomyopathy with risk for SCD	13 (4.0)
Long-QT syndrome with risk of SCD	12 (3.7)
Brugada syndrome with risk for SCD	10 (3.1)
Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study	7 (2.2)
Familial cardiomyopathy associated with SCD	6 (1.9)
Cardiac sarcoidosis or Chagas disease	4 (1.2)
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) with risk for SCD	3 (0.9)
Nonsustained VT due to prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiological study	2 (0.6)
LV noncompaction	1 (0.3)
Catecholaminergic polymorphic VT	1 (0.3)
Sustained VT and normal or near-normal ventricular function	1 (0.3)
Symptomatic ventricular arrhythmia	1 (0.3)

Table 6: CE Study Event Summary

The Type I complication free rate was assessed in all patients with an S-ICD implant. A Type I complication is defined as a clinical event caused by the S-ICD system that requires intervention. The Type I complication free rate at 180 days was 99.0% with a lower 95%

confidence bound of 97.9%, qualifying the device as safe. Details of the Kaplan Meier analysis are below:

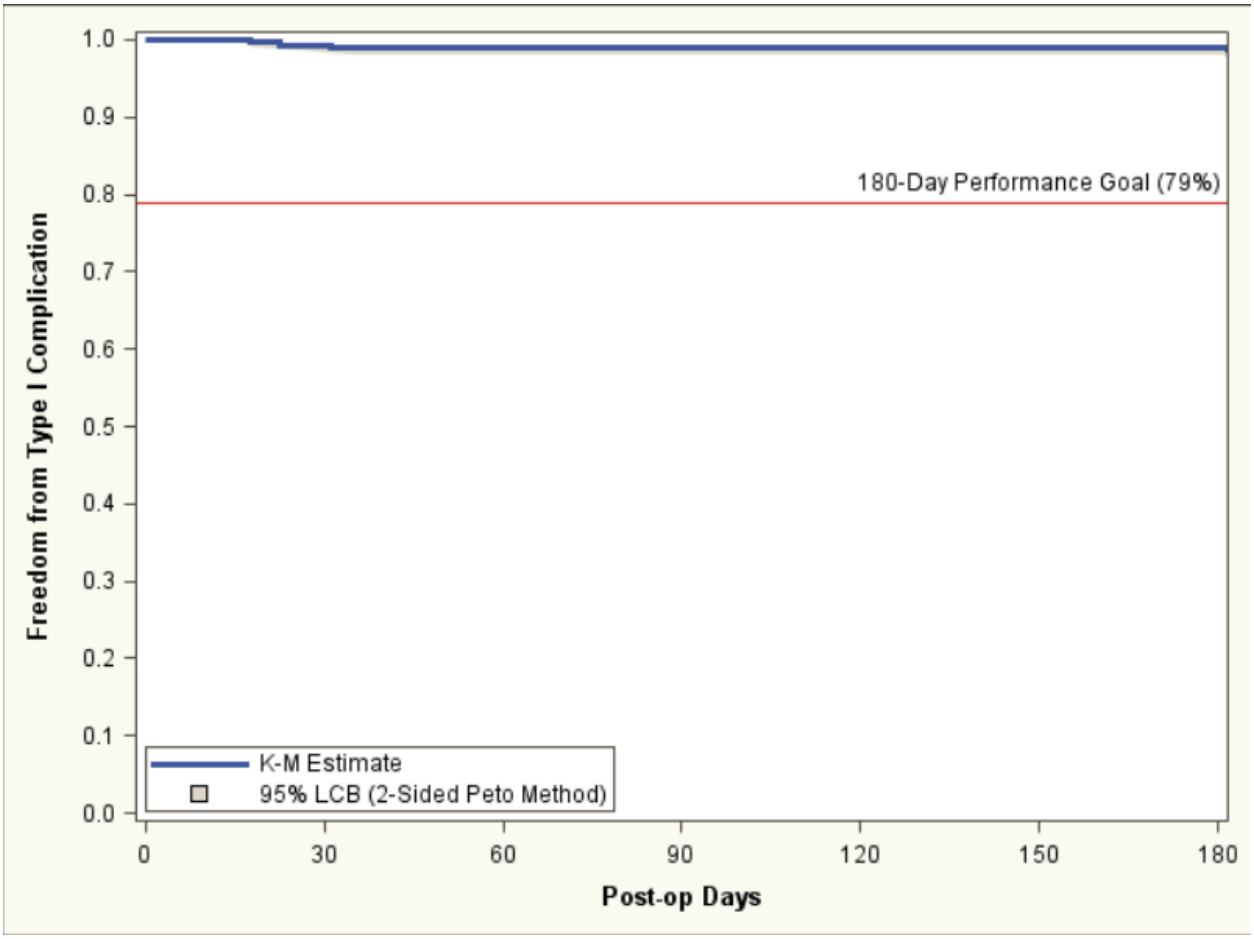


Table 6: Kaplan Meier Safety Results

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Discomfort	3	3 (0.9)	8	7 (2.2)	11	11 (3.4)
Inability to Communicate with the Device	2	2 (0.6)	0	0 (0.0)	2	2 (0.6)
Inappropriate Shock: Oversensing	5	5 (1.6)	25	21 (6.5)	30	25 (7.8)
Numbness at Device Site	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Premature Battery Depletion	2	2 (0.6)	0	0 (0.0)	2	2 (0.6)
Subcutaneous Emphysema	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
All Type I Clinical Events	12	11 (3.4)	35	30 (9.3)	47	39 (12.1)

Table 6: CE Study Clinical Event Summary

Of the 330 patients recruited,17 did not complete the study. 9 of which were deemed not compatible to receive the S-ICD and 8 deaths occurred. It was determined that there was no conclusive evidence that the ICD was the cause of death for 7 of the patients and one of the deaths was kept private.

Of the 320 patients who underwent acute VF conversion testing, 16 had no evaluable results due to incomplete protocol testing. Of the 304 evaluable results, the conversion success rate was 100% with a lower 95% confidence bound of 98.8%. It was determined that the device was effective.

Non-evaluable Results	**Evaluable Results**		**Estimate (%)**	**95% Clopper-Pearson Interval (%)**
	Successful	**Failure**		
16	304	0	100.0	(98.8-100.0)

Table 7: CE Study Efficacy Results

c. Outcome Metrics (Colten)

Outcome Metric	Clinical Objective	Measurement Technique	Acceptance Criteria/ Comparison
Comfortability Post Implantation Rate	Device after implantation presents little discomfort or affect on daily activities	Subjects monitored after surgery and discomfort rating given	A low secondary surgery rate due to discomfort and device placement 2% or less
Label, packaging success rate	Device is in working condition before it is implanted and identifiable	Package drop and burst tested and labeling visual and inspection performed	No impact from a 1m fall will disrupt sterilization and integrity of device passes IEC 60601-1
Battery Longevity	Device remains operational for a certain lifespan	Accelerated in body simulations as well as 26 week trials	Device must last the equivalent to 5.1 years under normal circumstances
Infection Risk/ Biocompatibility complication rate	Reduce infections after implantation and components don't present complications to body	Pass ISO 11137 standards for sterilization and ISO 10993 for biocompatibility while in patients	Both the Can and Lead components must meet standards aiming for 5% or less complication rate
Algorithm Validation for Simulated users	The device will not send inappropriate shocks or under sense arrhythmias despite being further from heart than other ICD styles	In vivo testing performed over a 26 week period with patients consistently monitored	A 20 second or less shock response time with 5% or less over sensing or under sensing occurrences
Software Calibration/ Firmware Validation	System is validated after a software update with successful arrhythmia detection and treatment	Arrhythmias of different types will be induced and then ICD will be used to convert patient	98% detection rate and 95% conversion effectiveness rate either due to device or natural fixes will be required

C. Meeting Panel Recommendations and FDA Post Panel Action (Reece)

An advisory meeting was held on April 26, 2012 and the Circulatory System Devices Panel voted 8-0 that the device is safe and 7-1 that it is effective. They also ruled 7-1 that the benefits outweigh the risks for patients. The specific additional recommendations by the panel include:

- Post-Approval Study: A 5 year post approval study is recommended to collect more information on spontaneous episodes and to treat a more diverse "real world" population. They advised that the study should be more rigorous.
- Labeling: The panel recommended that implant VF induction and 65J shock conversion testing be routinely performed and included in the instruction to ensure adequate implant configuration.
- Training: The implant physician is required to have training and experience sufficient to manage an appropriate selection of patients for the S-ICD as well as long term device and arrhythmia management.

The FDA worked with the firm to make the same recommendations with minor modifications.

V. Design Review Response (Colten)

Phase 1 User Needs/Design Inputs

Summary:

The main questions that came up in response to our first design review dealt with data transferring, how the software would recognize arrhythmias, and what risks could occur from the leads. We were also asked about the specific ISO standards that our device would need to follow and what type of patients would be using the ICD.

Adaptations:

There are a couple different adaptations of this device, one with a wireless transmitter where a reading device can be placed on the side of the body where the can is located and then data can be transmitted that way, and there is another version where the device is stand alone and the data can only be monitored if it is taken out of the body. This procedure is not too difficult, but requires the surgery mentioned below. Cyber security actions that will be in place will follow the CENELEC 45502-2-2:2008 standards of safety and the decision would be made either to have a stand alone frequency for this device to only be able to communicate with proprietary readers, a password or some other way to limit the changing of settings if it were allowed to communicate with a patients cellphone or other device if live data was desired.

There is a baseline for typical arrhythmias including ventricular fibrillation and atrial fibrillation that the device will compare the sensor data to. The bounds will vary depending on the patient as the device has a memory that stores a log of the patients typical heart rhythm patterns and from there if an anomaly is detected and it models that of the preprogrammed arrhythmia algorithms within a given range for example 10% a shock will be administered.

We chose to go with the subcutaneous ICD so the leads are not directly inserted into the heart. Instead they are placed besides the heart in the chest cavity with small incisions. This way there is only one lead and fatigue failure is much less common. If it does occur then the lead and ICD system can be taken out easily by reopening the two incisions one for the lead and the other for the can and further action can be taken to replace the lead or other malfunctioning part.
We go into depth on the iso standards during phase 2 of the project.

The ICD would be able to work for all body types regarding the shocks, but the size of the can and lead may cause issues in smaller patients. For this reason some companies have different size ICD's that are smaller and better suited for women and children.

Phase 2 Manufacturing Processes

Summary:

The response we got from our second design review was very positive, with that, the two things that were mentioned the most were talking more about the variation in manufacturing. People asked for specific values in manufacturing as well as for the quality control needed to keep the device consistent.

Adaptations:

We included more values when talking about the validation and gave a range of 90% or better for successful validation. We also looked into more of the variability values for each of the materials. From there it was determined that the sensors and the shock administering portions would have the most significant effect in variations and therefore they must be validated before implantation. The can and electrode have tight tolerances in order to fit the electronic components they must adhere to these. But if they are a little off the result will not have the same devastating effect as if the sensing or electronic components were to have variation. For the manufacturing process tolerances will vary by the component, but things like the shell and wiring will need to be in tolerance but the range will vary slightly more then the sensing and shocking components.

Phase 3 Device Verification/Validation
Summary:

This final phase about device verification and validation went pretty good with some general comments for improvement. One thing that came up a few times was regarding our animal study, more information on what differentiates the animal studies from those done on

humans. Another thing that was mentioned was a better explanation of the differences between S-ICD devices and TV-ICD devices and the complications that occur with both. The last comments we got were about explaining the PMA table of contents better and what section of it applies to each part of the device design process.

Adaptations:

More time was spent going into the animal testing specifics. For example animal testing was conducted first before the clinical trials and in this x-ray tests, 65 J ventricular fibrillation conversion tests, and a 35 month study was preformed. These tests are talked about in further detail in our animal study portion. Regarding the TV-ICD vs S-ICD, the difference lies in the leads. For TV-ICD multiple leads are fed through arteries and into the heart. They are then attached to the ventricles and arterial walls with barbs so that they do not come out. The problem with this is that if the lead fails due to too much bending or general movement in the heart, scar tissue is formed around the lead and it is too dangerous to remove. This is the reason that if one fails surgeons tend to just leave that lead in the patient and add another lead and attach it to the can as a replacement. The beauty of the S-ICD system is that it only requires 3 incisions one along the side of the body where the can will be placed. One in the middle of the chest and one in the middle of the chest at heart level. The lead will then be attached to the can and it will be slid into the cavity under the rib and besides the heart. It is never in contact with the heart as it is secured to the tissue of the underside of the chest. This is the reason why a higher energy shock is required for S-ICD's since they are farther away from the heart and the shock has to go through the chest cavity before it reaches the heart. Through testing it was determined that this delay can be beneficial as the TV-ICD will sometimes prematurely shock patients when the heart would have other reset itself naturally with the S-ICD system. The S-ICD system also only has the one lead so there is less of a chance for lead failure due to the location it is placed and having less leads involved. The table of contents was also updated and can be seen in the phase 1a pre sub section for greater details.

VI. References

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