Human Use Condition Study- Fluoroscopic Evaluation of 3D Curvature of Implanted Right Ventricular Leads in Humans

SHORT TITLE: HUCS

CLINICAL INVESTIGATION PLAN

Final Protocol Version 3.0

January 5, 2021

Sponsored By

Duke Clinical Research Institute

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Human Use Condition Study (HUCS)

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the HUCS Study protocol and any attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed: _____

Name (please print)

_____ _____

Signature Date

2. Protocol Synopsis

Human Use Condition Study- Fluoroscopic Evaluation of 3D Curvature of Implanted Leads in Humans SHORT TITLE: HUCS	
Study Design and Objective(s)	The AAMI Human Use Condition Study (HUCS) is a prospective, observational, multi-center clinical study intended to determine whether Right Ventricular (RV) lead curvature in vivo is a function of lead stiffness. The results of this study will comprise a reference dataset to be used in a new international standard for conductor flexural fatigue performance of implantable CIED (Cardiac Implantable Electrical Device) RV leads. The HUCS study objectives are as follows: 1. Measure dynamic *in vivo* curvature of RV pacing and defibrillator leads in the extravenous and intracardiac anatomy 2. Measure the relationship between lead bending stiffness and *in vivo* curvature 3. Assess the relationship between subject and implant variables and lead curvature
Primary Endpoints	Three primary endpoints will assess the relationship between lead stiffness and curvature – one endpoint each for three different regions of the lead. 1. *In vivo* cyclic curvature and mean curvature of pacing and defibrillation leads in the <u>extravenous</u> region will be determined during specified arm movements. 2. *In vivo* cyclic curvature and mean curvature of pacing and defibrillation leads in the <u>intracardiac</u> region will be determined during two or more cardiac cycles. 3. *In vivo* cyclic curvature and mean curvature of pacing and defibrillation leads in the <u>connector</u> region will be determined during specified arm movements. The relationship between lead stiffness and curvature will be evaluated for all three Primary Endpoints.
Subject Population	The study will enroll at least 80 and up to 120 subjects with one of four different market-released lead families identified in the tables below.

<table>
<tr><td></td><td>The leads are from all four CIED manufacturers participating in this protocol. Approximately 30 leads from each manufacturer's lead family will be required.</td></tr>
<tr><td>ICD Leads of Interest</td><td>
<table>
<tr><th>Manufacturer</th><th>Model(s)</th><th>Description</th></tr>
<tr><td>Abbott</td><td>LDA 210Q
LDA 220Q
LDA 230Q</td><td>Optisure Single Coil Defibrillation Lead
Optisure Dual Coil Defibrillation Lead
Optisure Dual Coil Defibrillation Lead</td></tr>
<tr><td>Medtronic</td><td>6935M</td><td>Quattro Secure Single Coil Defibrillation Lead</td></tr>
</table>
</td></tr>
<tr><td>Pacing Leads of Interest</td><td>
<table>
<tr><th>Manufacturer</th><th>Model(s)</th><th>Description</th></tr>
<tr><td>Biotronik</td><td>Siello S, Solia S</td><td>Active Fixation Leads</td></tr>
<tr><td>Boston Scientific</td><td>4452, 4453, 4456, 4457</td><td>FINELINE II/ FINELINE II Sterox Passive Fixation (polyurethane)</td></tr>
<tr><td>Boston Scientific</td><td>4463/4464/4465 4469/4470/4471</td><td>FINELINE II/ FINELINE II Sterox EZ Positive Fixation (polyurethane)</td></tr>
</table>
</td></tr>
<tr><td>Inclusion Criteria</td><td>1. Patients with RV leads included in the scope of this study whose system has been implanted for at least 3 calendar months
2. Patients at least 18 years of age and capable of providing informed consent
3. Patients who can physically perform range of arm motion and breath-holding described in the imaging protocol (section 11.1.1)
4. Patients who are willing and able to comply with instruction related to the imaging protocol</td></tr>
<tr><td>Exclusion Criteria</td><td>1. Planned lead modification
2. Patients with abandoned leads (includes: RV/RA/LV)
3. Patients undergoing second or subsequent pulse generator change
4. Patient has permanent atrial arrhythmias
5. Limited life expectancy or medical condition that would not allow completion of the study
6. Patient is known to be pregnant or breastfeeding at time of consent
7. Limited range of mobility of the implant location arm</td></tr>
</table>

	8. Patient is unable to climb on and off an examination table unassisted 9. Patients deemed hemodynamically unstable
Study Overview and Follow-up Schedule	The study will consist of imaging sessions conducted at least 3 months post-implant. The image data will be processed using custom 3D reconstruction software to produce data for lead curvature. Subject demographic information, disease state, implant technique details (access, implant site, etc.) will be collected. Enrollment → Acquire Imaging
Study Duration	Enrollment is expected to be completed in approximately 6 months; therefore, the total study duration is estimated to be approximately 12 months.
Subject Duration	The study duration for each subject is expected to be approximately one month.
Planned Number of Investigational Sites	Up to 10 U.S. centers will participate

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4. Introduction

4.1. Background

The implantable leads are the only elements of the implantable cardioverter-defibrillator (ICD) system that are meant to last the life of the patient without repair or replacement. However, survival of ICD leads may be as low as 85% after 5 years and 60% after 8 years.[1] Like all engineered systems, implantable leads are subject to degradation and possible failure from the effects of stresses imposed by the use environment. Conductor fracture caused by metal fatigue is one of the more serious and common failure mechanisms for transvenous ICD leads.

Fatigue life can be quantified in bench tests based on the stress-life method. In fatigue testing of ICD leads and in the *in vivo* use condition, conductor stress,σ, is proportional to curvature (C) and alternating stress, *S*, is proportional to cyclic (alternating) curvature (ΔC). For this reason, alternating stress, *S*, in lead fatigue studies is customarily reported as cyclic curvature with units of cm^{-1} or $inch^{-1}$.

To develop physiologically relevant bench tests for conductor fatigue performance of ICD and pacing leads, valid data on *in vivo* lead motion is needed - specifically cyclic curvature (ΔC) in the intracardiac, extravenous, and connector regions. Preliminary studies have demonstrated the feasibility of acquiring these data by 3D reconstruction of bi-plane cine fluoroscopy images.[2] [3] [4] However, these studies were not randomized and did not control for effects of lead routing from the pulse generator implant site to the venous access site. None were powered to provide sufficient data for the purpose defined for the present study.

The stress-life (commonly denoted "S-N" in the literature on fatigue failure of materials) method was the first approach used to understand and quantify metal fatigue. It has been the standard design method for almost 100 years. The S-N approach is still widely used in design applications where applied stress is primarily within the elastic range of the material and the resultant lives (cycles to failure) are long, such as power transmission shafts.[5]

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1 Kleemann et al, Circulation 2007;115:2474-2480

2 W Baxter, N Skadsberg, et. al., New Unanticipated Insights on Peak Lead Bending During Pectoralis Flexure. HRS 2010

3 Pau, W Baxter, et. al., Lead Use Conditions Imaging: A Noninvasive Upper Thoracic and Intracardiac Lead Mechanics Investigation, CARDIOSTIM, June2014

4 Hoffmann KR, Williams BB, Esthappan J, Chen SY, Carroll JD, Harauchi H, Doerr V, Kay GN, Eberhardt A, Overland M: Determination of 3D positions of pacemaker leads from biplane angiographic sequences. Med Phys 24:1854-1862, 1997

5 Bannantine, Julie, Fundamentals of Metal Fatigue Analysis. Upper Saddle River, New Jersey, U.S.A, Prentice-Hall, Inc., 1990

The basis of the stress-life method is the Wöhler or S-N diagram, which is a plot of alternating stress, *S*, versus cycles to failure, *N*. Alternating stress is defined as half of the cyclic stress range, or 0.5 × (maximum stress – minimum stress). Figure 1 is an example of an S-N diagram for steel, plotting alternating stress against cycles to failure on logarithmic scales for both quantities.[6]

Figure 1: S-N Plot

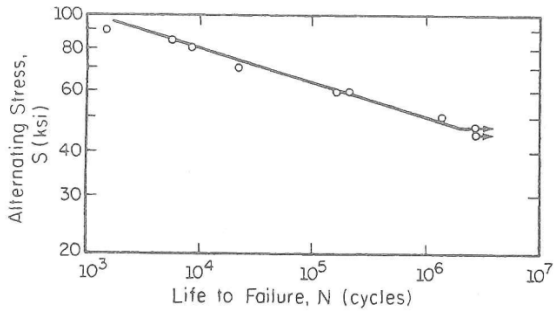

Figure 2 shows an example of S-N data for a Boston Scientific defibrillation lead. A 2-cm section of the lead body was repeatedly bent between high and low curvature values for up to 20 million cycles, and the cathode conductor coil was monitored to determine at what cycle of bending the coil fractured. Circles indicate test specimens which experienced coil fracture; crosses indicate specimens in which no coil fracture occurred during the test.[7] Fatigue models based on cyclic curvature have been used successfully to model *in vivo* lead survival with respect to fatigue fracture in the Medtronic Sprint Quattro and Sprint Fidelis ICD leads.[8]

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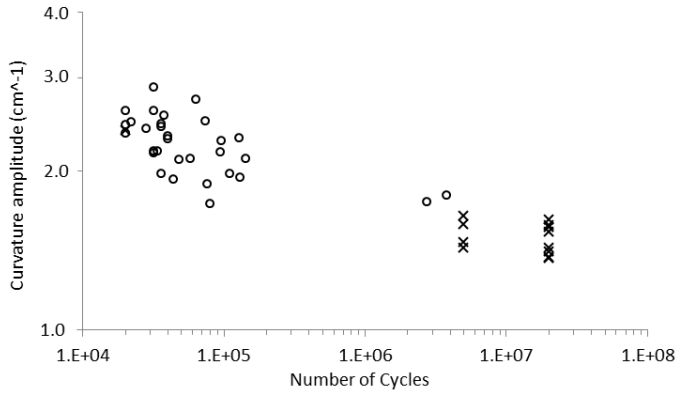
6 Shigley, Mechanical Engineering Design, New York, New York, U.S.A., McGraw-Hill Book Company, Third Edition,1977

7 D Smith, AAMI_PC_WG1_N213_ . Preliminary Fatigue Testing at Boston Scientific, AAMI CRMD Committee PC/WG1, Transvenous Cardiac Leads Working Group, 08-Apr-2014

8 T Haddad, A Himes and M Campbell. Fracture Prediction of Cardiac Lead Medical Devices Using Bayesian Networks. Reliability Engineering and System Safety.123(2014). p145–157.

Figure 2: S-N Plot for Boston Scientific Defibrillation Lead.

(Circles indicate test specimens which experienced coil fracture; crosses indicate specimens in which no coil fracture occurred during the test.)



The current ISO standard for fatigue performance[9] of transvenous defibrillation leads has proven to be insufficiently sensitive, since certain leads that met the ISO standard demonstrated poor reliability performance in service[10] and were ultimately withdrawn from use.

One limitation of the current standard is that it does not account for effects of *use stresses* on fatigue life. In general, reliability of a population of apparently similar devices is affected by both variability in the strength of the device and variability in the stresses imposed on the device. The stress-strength theory of reliability[11] accounts for both aspects. A statistical method for quantifying lead fatigue life utilizing the stress-strength theory of reliability and Bayesian network analysis has been proposed[12] and is currently under consideration for an improved standard for lead fatigue performance.[13]

The Association for Advancement of Medical Instrumentation (AAMI) Cardiac Rhythm Management Device (CRMD) Committee is the organization responsible for developing standards for CIEDs. The AAMI CRMD Committee, through their Leads Working Group (WG1), is responsible for developing a new fatigue standard based on the Bayesian network analysis method.[14]

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9 ISO 14708-6, Implants for surgery — Active implantable medical devices — Part 6: Particular requirements for active implantable medical devices intended to treat tachyarrhythmia (including implantable defibrillators), 2008

10 R G Hauser, W H Maisel, et.al., Longevity of Sprint Fidelis Implantable Cardioverter-Defibrillator Leads and Risk Factors for Failure - Implications for Patient Management, Circulation, 123: 358-363, 2010

11 Kotz, S., Lumelskii, Y, and Pensky, M. (2003) The Stress-Strength Model and Its Generalizations: Theory and Applications, World Scientific Publishing Co. Pte. Ltd. Singapore

12 T.Haddad, et.al, Fracture Prediction of Cardiac Lead Medical Devices Using Bayesian Networks, Reliability Engineering and System Safety, 123(2014) 145–157

13 AAMI_PC_WG1_N169 Outline of Requirements for Fatigue Performance of Cardiac Rhythm Management Leads

14 Cooke D, Himes A, Swerdlow C. Improved engineering standards for transvenous cardiac leads: A progress report from the Association for the Advancement of Medical Instrumentation Cardiac Rhythm Management Device Committee Leads Working Group, Heart Rhythm Journal, 2019; 16: 958–959

4.2. Study Rationale

The purpose of this study is to obtain in vivo data for the dynamic flexing experienced by defibrillation and RV pacing leads in humans. This data will be used to develop an improved international standard method for evaluating fatigue performance.

The current ISO standard for fatigue performance of transvenous defibrillation leads is insufficiently sensitive, since certain leads that met this standard have demonstrated poor reliability and were ultimately withdrawn from use. A limitation of the current standard is that it does not account for stresses due to the in vivo environment.

The AAMI Cardiac Rhythm Management Committee Transvenous Cardiac Leads Working Group has developed a new methodology based on a combination of bench testing and in vivo lead curvature data. This method requires data from multiple defibrillator and pacing lead models.

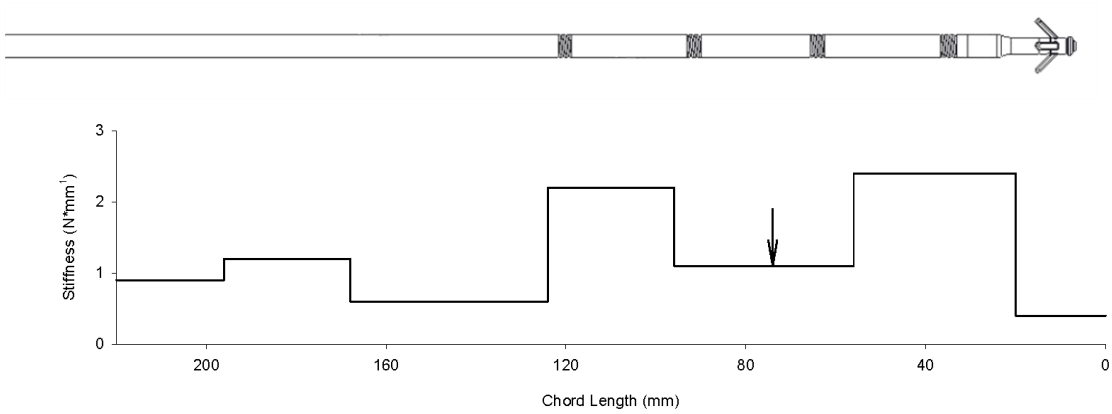
The proposed study will produce the data needed to complete the development of the new standard fatigue test methodology.

4.3. Overview of Data Acquisition and Analysis

4.3.1. Determine Lead Stiffness

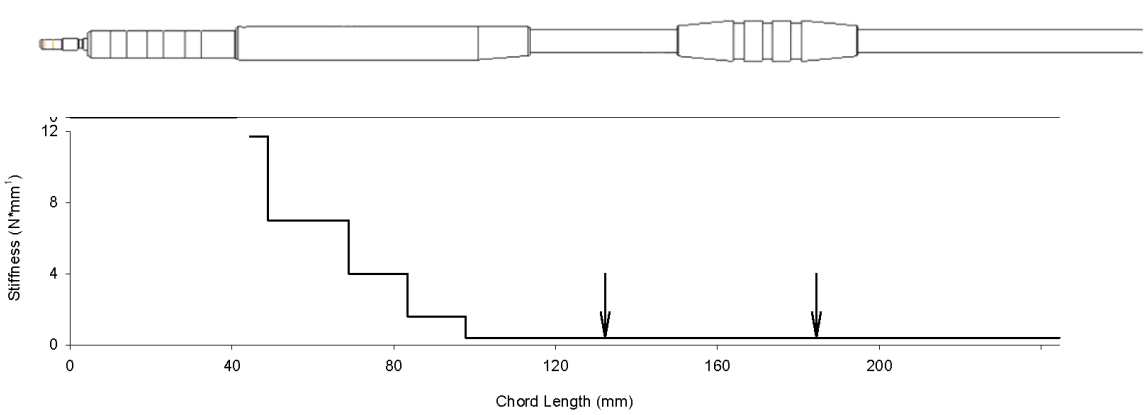
The funding CIED lead manufacturers will determine lead stiffness for the pacing and defibrillator leads included in this study in accordance with pre-defined requirements. (AAMI_PC_WG1_N169 Outline of Requirements for Fatigue Performance of Cardiac Rhythm Management Leads). Examples of these measurements are shown in Figure 3, and Figure 4.

Figure 3: Example Plot – Stiffness in Intracardiac Region



Arrows indicate maximum value for ΔC and corresponding stiffness for the intracardiac region.

Figure 4: Example Plot – Stiffness in Connector and Extravenous Regions

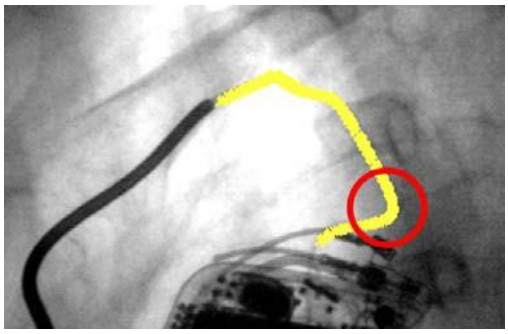


Arrows indicate maximum value for ΔC and corresponding stiffness for the intracardiac region.

4.3.2. Acquire cine fluoroscopy data (DICOM files)

For each subject, cine fluoroscopy data (DICOM files) shown in Figure 5, for the pacing or defibrillator leads will be acquired for 3 regions– the intracardiac region, extravenous region, and connector region. The intracardiac region will be imaged for two or more cardiac cycles; the extravenous region and connector regions will be imaged while the subject executes prescribed arm motions.

Figure 5: Cine Fluoroscopy Example



4.3.3. Perform 3-D reconstruction of Lead Trajectories

For each subject, cine fluoroscopy data (DICOM file) for the RV pacing or defibrillator lead will be reconstructed to generate 3D trajectories in time and spacing in accordance with the method described in AAMI_PC_WG1_N726 Methodology for 3-D Reconstruction of Lead Trajectories from Bi-Plane Fluoroscopy DICOMs. An example of a 3-D lead trajectory is shown in Figure 5.

For each lead, the maximum cyclic curvature, ΔCmax, and the corresponding value of lead stiffness will be determined by the lead manufacturer, for each region (intracardiac region, extravenous region, and connector region).

5. Device Description

The devices in this study are FDA approved, commercially available, Pacemaker (PM) systems and implantable cardioverter defibrillator (ICD) systems.

Pacemaker systems are composed of any approved, commercially available dual chamber or single chamber pacemaker and at least one implantable pacing lead implanted in the right ventricle. The pacing leads included in this study are listed in Table 1.

Table 1: RV Pacing Leads

Manufacturer	Model(s)	Description
Biotronik	Siello S, Solia S	Active Fixation Leads
Boston Scientific	4452, 4453, 4456, 4457	FINELINE II/FINELINE II Sterox Passive Fixation (polyurethane)
Boston Scientific	4463, 4464, 4465, 4469, 4470, 4471	FINELINE II/FINELINE II Sterox EZ Positive Fixation (polyurethane)

ICD systems are composed of any approved, commercially available dual chamber or single chamber ICD and at least one implantable defibrillation lead implanted in the right ventricle. The defibrillation leads included in this study are listed in Table 2.

Table 2: Defibrillation Leads

Manufacturer	Model(s)	Description
Abbott	LDA 210Q LDA 220Q LDA 230Q	Optisure Single Coil Defibrillation Lead Optisure Dual Coil Defibrillation Lead Optisure Dual Coil Defibrillation Lead
Medtronic	6935M	Quattro Secure Single Coil Defibrillation Lead

6. Required Imaging System

Center selection criteria include access to a biplane fluoroscopy system with capability of at least 15 frames per second (fps) and image portability using removable media or secure network. The following equipment must be available at each study site to support study activities;

- Biplane fluoroscopy system with:
  - capability of fluoroscopy (scout image) capture at 7.5 fps or less **and** Cine recording at 15 fps or more
  - capability of image recording in a DICOM format
  - if available, capability of simultaneous recording of the ECG signal as part of the DICOM header
- Secured Hard Drive for data storage and capabilities of nightly backup
- Computer system capable of high-speed network data transfer

7. Study Overview and Endpoints

7.1. Study Overview

The Human Use Condition Study (HUCS) is a prospective, observational, multi-center clinical study intended to determine whether lead curvature in vivo is a function of lead stiffness. The results of this study will comprise a reference dataset to be used in a new international standard for conductor flexural fatigue performance of implantable CIED leads.

The extravenous region and connector region for each subject enrolled in the study will be imaged by high resolution, bi-plane cine fluoroscopy while the subject executes prescribed arm motions. The intracardiac region will be imaged for two or more cardiac cycles.

Lead trajectories in DICOM file images will be manually identified in both views. For each frame, 3D lead trajectory will be generated using indicated 2D lead trajectories. Three dimensional reconstructions will be generated for the prescribed arm motions utilized in the imaging study.

7.2. Primary Endpoints

Three primary endpoints will assess the relationship between lead stiffness and curvature – one endpoint each for three different regions of the lead. Primary Endpoint 1 will evaluate the extravenous region. Primary Endpoint 2 will evaluate the intracardiac region. Primary Endpoint 3 will evaluate the connector region.

Failure to reject any of the null hypotheses does not indicate a failure of the study, but rather that no significant relationship between lead stiffness and lead curvature was observed. The results of the endpoint analyses will be used to inform the new lead standard.

7.2.1. Primary Endpoint 1 (Extravenous Region)

In vivo cyclic curvature (ΔC) and mean curvature (C_{mean}) of RV pacing and defibrillation leads in the extravenous region will be determined during specified arm movements. The relationship between lead stiffness and curvature will be evaluated.

7.2.1.1. Hypotheses

The following set of hypotheses will be used to evaluate the relationship between lead stiffness and curvature in the extravenous region:

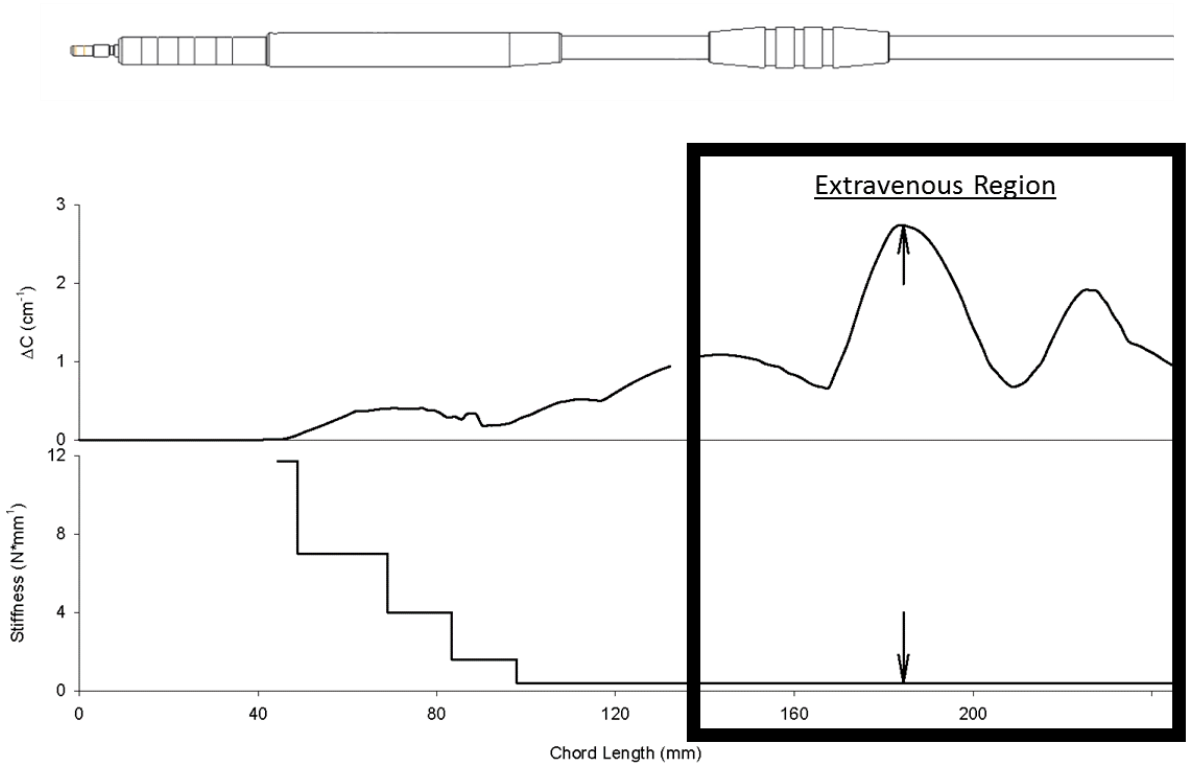
H_0: $a \geq 0$
H_a: $a < 0$
where a represents the coefficient for stiffness in the following model:
*log (curvature) = a*stiffness + b + normally distributed error.*

Prior studies of in-vivo curvature have shown that a lognormal distribution models the data well. The alternative hypothesis represents an inverse relationship between lead stiffness and curvature.

7.2.1.2. Statistical Methods

Each lead with lead stiffness and curvature data available in the extravenous region of the lead will be included in the analysis of Primary Endpoint 1. Each lead's curvature measurement used in the analysis will represent the maximum value of the curvature observed in the extravenous region. Each lead's stiffness measurement used in the analysis will represent the stiffness measurement at the location corresponding to the maximum value of the curvature (Figure 6).

Figure 6: Curvature and Stiffness Values used Primary Endpoint 1 Analyses



Arrows indicate maximum value for ΔC and corresponding stiffness for the extracardiac region.

The relationship between curvature and stiffness will be evaluated via a general linear model, treating log (curvature) as the outcome and stiffness as the predictor. The following model will be fit: log (curvature) = *a**stiffness + *b* + normally distributed error. The 90% upper confidence limit of the coefficient for stiffness, *a*, will be compared to 0. If the upper confidence limit is less than 0, the null hypothesis will be rejected, thereby establishing a significant relationship between curvature and stiffness in the extravenous region.

7.2.2. Primary Endpoint 2 (Intracardiac Region)

In vivo cyclic curvature (ΔC) and mean curvature (C_{mean}) of RV pacing and defibrillation leads in the intracardiac region will be determined during two or more cardiac cycles. The relationship between lead stiffness and curvature will be evaluated.

7.2.2.1. Hypotheses

The following set of hypotheses will be used to evaluate the relationship between lead stiffness and curvature in the intracardiac region:

H_0: $a \geq 0$

H_a: $a < 0$

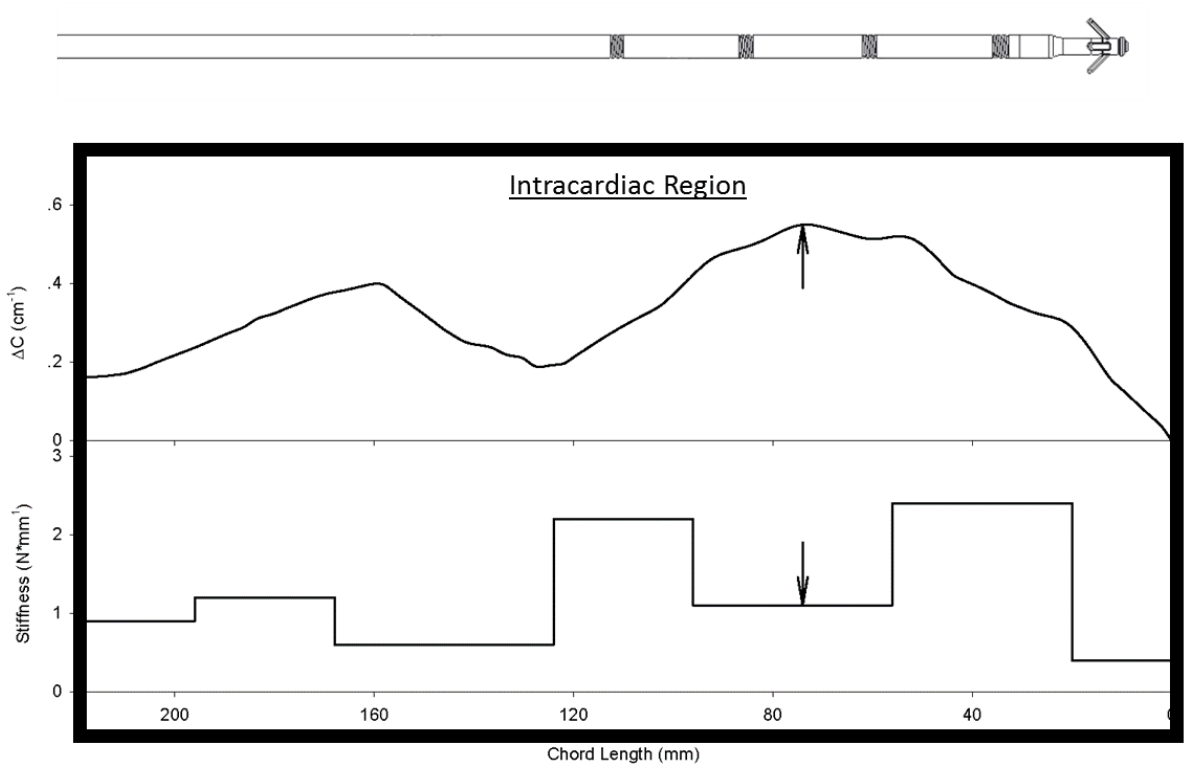
where a represents the coefficient for stiffness in the following model:
*log (curvature) = a*stiffness + b + normally distributed error.*

Prior studies of in-vivo curvature have shown that a lognormal distribution models the data well. The alternative hypothesis represents an inverse relationship between lead stiffness and curvature.

7.2.2.2. Statistical Methods

Each lead with lead stiffness and curvature data available in the intracardiac region of the lead will be included in the analysis of Primary Endpoint 2. Each lead's curvature measurement used in the analysis will represent the maximum value of the curvature observed in the intracardiac region. Each lead's stiffness measurement used in the analysis will represent the stiffness measurement at the location corresponding to the maximum value of the curvature
Figure 7).

Figure 7: Curvature and Stiffness Values used Primary Endpoint 2 Analyses



Arrows indicate maximum value for ΔC and corresponding stiffness for the intracardiac region.

The relationship between curvature and stiffness will be evaluated via a general linear model, treating log (curvature) as the outcome and stiffness as the predictor. The following model will be fit: log (curvature) = *a**stiffness + *b* + normally distributed error. The 90% upper confidence limit of the coefficient for stiffness, *a*, will be compared to 0. If the upper confidence limit is less than 0, the null hypothesis will be rejected, thereby establishing a significant relationship between curvature and stiffness in the intracardiac region.

7.2.3. Primary Endpoint 3 (Connector Region)

In vivo cyclic curvature (ΔC) and mean curvature (C_{mean}) of RV pacing and defibrillation leads in the connector region will be determined during specified arm movements. The relationship between lead stiffness and curvature will be evaluated.

7.2.3.1. Hypotheses

The following set of hypotheses will be used to evaluate the relationship between lead stiffness and curvature in the connector region:

H_0: $a \geq 0$

H_a: $a < 0$

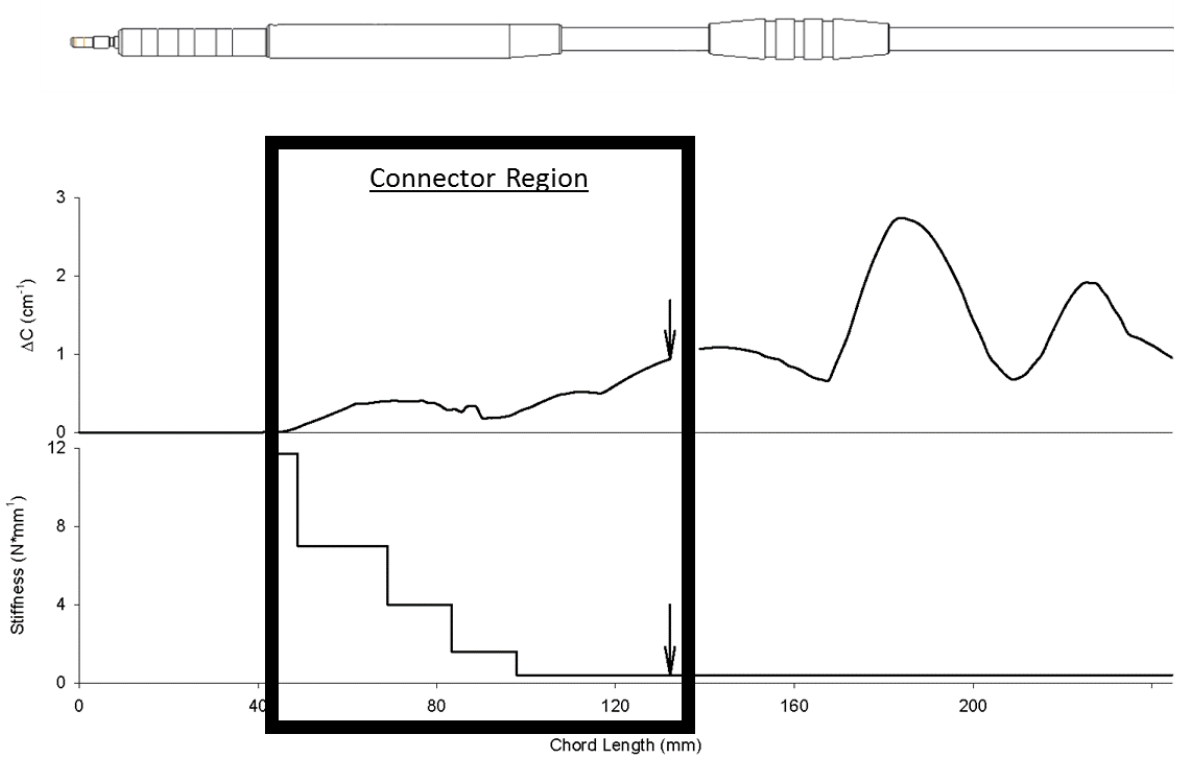
where a represents the coefficient for stiffness in the following model:
*log (curvature) = a*stiffness + b + normally distributed error.*

Prior studies of in-vivo curvature have shown that a lognormal distribution models the data well. The alternative hypothesis represents an inverse relationship between lead stiffness and curvature.

7.2.3.2. Statistical Methods

Each lead with lead stiffness and curvature data available in the connector region of the lead will be included in the analysis of Primary Endpoint 3. Each lead's curvature measurement used in the analysis will represent the maximum value of the curvature observed in the connector region. Each lead's stiffness measurement used in the analysis will represent the stiffness measurement at the location corresponding to the maximum value of the curvature (Figure 8).

Figure 8: Curvature and Stiffness Values used Primary Endpoint 3 Analyses



Arrows indicate maximum value for ΔC and corresponding stiffness for the connector

The relationship between curvature and stiffness will be evaluated via a general linear model, treating log (curvature) as the outcome and stiffness as the predictor. The following model will be fit: log (curvature) = *a**stiffness + *b* + normally distributed error. The 90% upper confidence limit of the coefficient for stiffness, *a*, will be compared to 0. If the upper confidence limit is less than 0, the null hypothesis will be rejected, thereby establishing a significant relationship between curvature and stiffness in the connector region.

7.3. Sample Size

To sufficiently power each of the three Primary Endpoints, a total of 30 subjects enrolled for each manufacturer's lead families is expected to yield at least 20 leads with usable endpoint data in the each of the 3 image regions. Monte Carlo simulations were performed to establish the sample size, using the following assumptions:

- Expected value for coefficient *a* = -0.23
- Alpha (one-sided) = 10% (corresponding to a one-sided 90% upper confidence limit)
- Power = 99%
- Missing data = 33%

Reasons for missing data includes, imaging and/or ECG data not collected, imaging data not optimal for analysis, and subject withdrawal/death. Enrollment may stop prior to 30 subjects if 20 useable data sets have been collected.

7.4. Additional Analyses

7.4.1. Multiple Measures per Region

In addition to the Primary Endpoint analyses, in which only one measurement per region will be assessed, analyses evaluating multiple measurements per region will be performed. Curvature and stiffness measurements obtained in millimeter intervals will be evaluated. Analyses will be performed separately for each of the three regions of the lead. To account for the within-subject correlation, a random effects general linear model will be used. These analyses will evaluate the relationship between curvature and stiffness across the entire region of the lead.

7.4.2. Interaction Analyses

Each of the three Primary Endpoints will be assessed for its association with various lead, procedural and subject characteristics. The interaction between each characteristic and stiffness will be assessed using a general linear model. Each characteristic will be assessed separately. The list of characteristics includes, but is not limited to:

Product Level Characteristics

- Model/serial of pulse generator and leads
- Lead related information:
    - Septal / apical positioning of lead
    - Active / passive fixation
    - Dual / single coil defibrillator lead
    - Manufacturer
    - Implant date(s) of leads
- Pulse generator information:
    - Implant date of pulse generator

- Manufacturer
- Pulse generator position

Implant Procedure Related Characteristics

- Access technique (axillary, cephalic, subclavian intra-thoracic, subclavian extra-thoracic)
- Lead configuration determined from retrospective AP/PA Chest X-rays collected post implant

Subject Level Characteristics

- Subject birth date, gender, race, ethnicity, height, weight
- Ejection fraction, implant indication

7.4.3. Multivariable Analyses

The association between curvature and stiffness will be evaluated in the presence of other potential confounding variables, including but not limited to the characteristics listed above. A multivariable general linear model for each endpoint will be analyzed, treating curvature as the outcome and stiffness and other characteristics as the predictors. To minimize the potential for overfitting the multivariable model, a subset of characteristics will be included in the model. To select which characteristics are included in the multivariable model, each characteristic's association with curvature will be assessed via a univariable model. Characteristics significantly associated with curvature in the univariable models will be included in the multivariable model. A separate multivariable model will be analyzed for each endpoint.

7.5. Changes to Planned Analyses

Any changes to the planned statistical analyses outlined in this protocol will be documented in the statistical analysis plan and/ or clinical study reports along with a reason for the deviation.

7.6. Handling of Missing, Unused, or Spurious Data

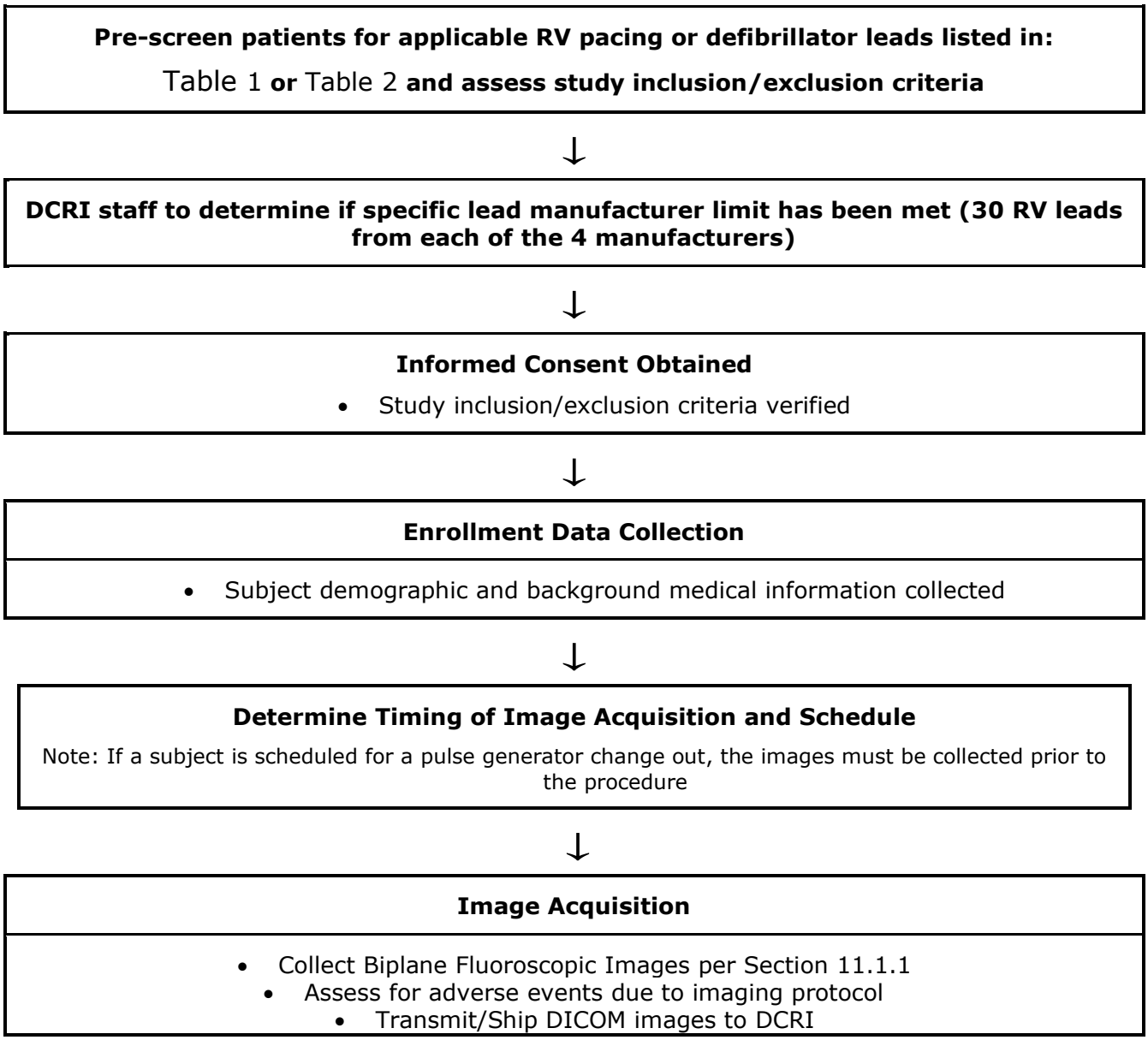
The respective centers will be contacted by Duke Clinical Research Institute (DCRI) to remedy any missing, unused, or spurious data in the case report forms (CRFs). In case of missing imaging/ECG data, the respective centers will confirm the availability of the data. If parts of the imaging/ECG data are missing or spurious, the analysis of the data set may be excluded, if the missing or spurious data prevents appropriate analysis of the data set.

8. Study Design

HUCS is a prospective, observational, multi-centre clinical study. A previous publication hypothesized that, in the extravenous region, curvature in vivo is a function of lead stiffness. [15] The present study is intended to determine whether this phenomenon is evident in the intracardiac region and connector region as well as the extravenous region, and for leads having a wider range of stiffness.

[15] W Baxter, N Skadsberg, et. al., New Unanticipated Insights on Peak Lead Bending During Pectoralis Flexure. HRS 2010

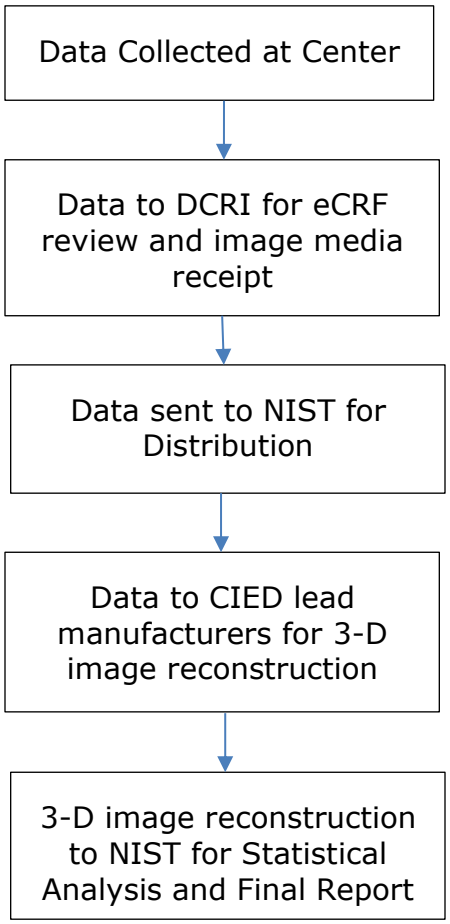
Figure 9: Study Flowchart



8.1. Data Flow

The data collected by the implanting centers will be transferred to DCRI, NIST, and lead manufacturers as shown in the flowchart below (Figure 10).

Figure 10: Data Flow



8.1.1. Data Collected by Center

All subjects will be imaged by high-resolution bi-plane fluoroscopy in the intra-cardiac region through 2 or more cardiac cycles, and in the extravenous region while the performing prescribed arm motions. NOTE: All imaging **must** be de-identified prior to saving to the DICOM media. All Media must be labeled clearly on the outside with the subject identifier. Case Report Form data will be entered by the site staff into an electronic data capture system (EDC).

8.1.2. Data Sent to DCRI

The imaging media will be sent to DCRI via pre-specified shipping/transfer method and receipt verified. Enrollment data specified in section 7.4 will be provided to DCRI for review through entry in the EDC. Case report form data will be reviewed for completion and quality.

8.1.3. Data Sent to NIST

The images and de-identified subject data (see section 7.4) are transferred to NIST by DCRI. Data will include identification of the lead design, eCRF data and the DICOM media.

8.1.4. Data Transfer from NIST to Lead Manufacturers

NIST will transfer a copy of the DICOM file and subject data to the individual lead manufacturers for datasets containing their respective leads for 3-D reconstruction. Each DICOM file will be reconstructed two times, once by the individual lead manufacturer, and a second time by one of the other lead manufacturers.

8.1.5. 3-D Reconstruction of Lead Trajectories

Each lead manufacturer will perform 3-D reconstruction of the lead trajectories per the 3-D reconstruction protocols (AAMI_PC_WG1_N726 Methodology for 3-D Reconstruction of Lead Trajectories from Bi-Plane Fluoroscopy DICOMs).

3-D reconstruction will be sent to NIST for statistical analyses and reporting per the statistical analyses plan (AAMI_PC_WG1_N725 HUCS Statistical Analysis Plan).

8.2. Scale and Duration

The HUCS study will enroll at least 80 and up to 120 subjects, with at least 20 and up to approximately 30 subjects per lead family specified in Section 5. Enrollment is expected to be completed in approximately 6 months; therefore, the total study duration is estimated to be approximately 12 months. The study duration for each subject is expected to be approximately 1 month to account for time from enrollment to completing the imaging protocol. Subject participation will be considered complete after image has been acquired. Up to 10 U.S. centers will participate.

8.3. Justification for the Study Design

The purpose of this study is to improve the safety profile of transvenous leads, through the development of a new lead safety requirements standard. The data collected in this study is required for the development of the standard. Furthermore, the study poses no significant risks to the participants of the study.

9. Subject Selection

9.1. Study Population and Eligibility

At least 80 and up to 120 subjects will be enrolled based on their willingness, and consent to participate in this study, at centers with approved bi-plane fluoroscopy capabilities. Subjects may be either male, or female, and must meet all of the inclusion criteria in Table 3 and none of the exclusion criteria in Table 4.

9.2. Inclusion Criteria

Subjects who meet all of the following criteria (see Table 3) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Table 4) is met.

Table 3: Inclusion Criteria

Inclusion Criteria	1. Patients with RV leads included in the scope of this study whose system has been implanted for at least 3 calendar months. 2. Patients at least 18 years of age and capable of providing informed consent 3. Patients who can physically perform range of arm motion and breath-holding described in the imaging protocol (section 11.1.1) 4. Patients are willing and able to comply with instruction related to imaging protocol

9.3. Exclusion Criteria

Subjects who meet any one of the following criteria (Table 4) cannot be included in this study or will be excluded from this clinical study.

Table 4: Exclusion Criteria

Exclusion Criteria	1. Planned lead modification 2. Patients with abandoned leads (includes: RV/RA/LV) 3. Patients undergoing second or subsequent pulse generator change 4. Patient has permanent atrial arrhythmias 5. Limited life expectancy or medical condition that would not allow completion of the study 6. Patient is known to be pregnant or breastfeeding at the time of consent 7. Limited range of mobility of the implant location arm 8. Patient is unable to climb on and off an examination table unassisted 9. Patients deemed hemodynamically unstable

10. Subject Accountability

10.1. Point of Enrollment

Subjects will be considered enrolled once they meet all the inclusion criteria (Table 3), and none of the exclusion criteria (Table 4), and they have signed the informed consent form. Note: All subjects must be consented after they have had their device system implanted for three months.

10.2. Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported in the eCRF.

11. Study Methods

11.1. Data Collection

The data collection schedule is shown in Table 5.

Table 5: Study Data Collection

Procedure/Assessment	**Screening and Enrollment**	**Imaging***
Informed Consent Process (Includes signature/date and documentation)	X	
Physical Assessment (Including recent Weight and Height)	X^	
Pregnancy test***	X	
Implant procedure information (Including date of implant, venous access technique)	X^	
All currently implanted lead details (Including Lead Type, model/serial number, manufacturer, positioning of the lead, and age of existing lead)	X^	
Currently implanted pulse generator details (Including Pulse Generator type, model/serial, manufacturer, position of pulse generator)	X^	
Medical History (Including birthdate, race, ethnicity, gender, most recent ejection fraction)	X^	
Most recent Chest X-ray**	X^	
Schedule Imaging Procedure*	X	
Intra-Cardiac Imaging		X
Calibration Object Imaging		X
Shoulder Movement-1 Imaging		X
Calibration Object Imaging		X
Shoulder Movement-2 Imaging		X
Calibration Object Imaging		X
Adverse Events Assessment		X

* Imaging procedure must occur at least 3 months post implant

** Provide most recent AP/PA Chest X-ray post implant of current system, if available

*** Women of childbearing potential must have a pregnancy test within 7 days prior to required imaging to confirm study eligibility

^ Specific data items should be collected, if available

11.1.1. Imaging Protocol

Prior to the protocol required imaging, the biplane fluoroscopy imaging cameras will be positioned at the head end of the table. Collection of images should be conducted by a site staff member qualified to obtain fluoroscopy and trained on the protocol.

For each image sequence, the subject will lay on the table in a supine position and exit the table once the image sequence is complete. After the subject image is taken, a calibration object (AAMI_PC_WG1_N741, HUCS Calibration Object) will be placed on the table and imaged in the same fashion.

Note: Incidental findings (i.e. lead dislodgement noted prior to start of arm movement or an unknown mass of tissue in the area of the imaging) will be reported to the subject's primary care provider or following physician per medical discretion. Incidental findings will not be discussed or collected as a part of the study.

***Image Sequence* 1:**

Intra-cardiac Imaging Protocol

1. Subjects will be asked to assume a supine position with their arms by their sides (Figure 11A) in the biplane system field of view and coached to perform a breath-hold maneuver for a period of 5 seconds and be given specific instructions on when to do so.
2. Subjects will have ECG electrodes placed, and the signal continually recorded.
3. Short taps of the fluoroscopy pedal (scout films) will be used to optimize both Image Intensifier (II) positions to ensure adequate visualization of the RV lead through its intra-cardiac course. Image Intensifiers shall be at an angle of 90°±45° to each other. Lowest intensity exposure at 7.5 frames/ second or less will be used for this purpose. (Approximately 4 seconds) Note: It is required that for each image sequence the entire intracardiac region must be visible throughout the entire image sequence.
4. A breath-hold biplane cine-fluoroscopy capture (15 frames/ second or more) of two cardiac cycles (3 seconds) will be acquired.
5. At this time disconnect the ECG cables and have the subject leave the imaging field without moving the x-ray cameras (image intensifiers).
6. A calibration object will be placed in the field of view, and adjusted without moving the x-ray camera, until a minimum of 12 markers are visible in both views.
7. The calibration object will be imaged without moving the biplane system (approximately 1 second)

Image Sequence 2:

Shoulder movement-1 (Arm along body movement) Imaging Protocol

Note: If the PG is implanted on the left, the left arm will be in motion; if implanted on the right, the right arm will be in motion.

1. Subjects will be asked to assume a supine position in the biplane system field of view, and coached to perform a movement at a starting point with the arm on the table alongside the body (Figure 11A) to follow a course along the long axis of the body as high as possible (Figure 11B).
2. Short taps of fluoroscopy will be used to optimize adequate visualization of the suture-sleeve and connector regions of the defibrillator/pacing lead in the center of the imaging plane of both Image Intensifiers during this arm movement. Image Intensifiers shall be at an angle of 90°±45° to each other. Lowest intensity exposure at 7.5 frames/ second or less will be used for this purpose. (Approximately 4 seconds each) Note: It is required that for each image sequence the PG and entire extracardiac region (including the venous access site) must be visible throughout the entire image sequence.
3. A cine- fluoroscopy exposure capture (15 frames/second or more) of the defibrillator/pacing lead will be acquired during the arm along body movement. (3 seconds)
4. Have the subject leave the imaging field without moving the x-ray cameras.
5. A calibration object will be placed in the field of view, and adjusted without moving the x-ray camera, until a minimum of 12 markers are visible in both views.
6. The calibration object will be imaged without moving the biplane system (approximately 1 second)

Image Sequence 3:

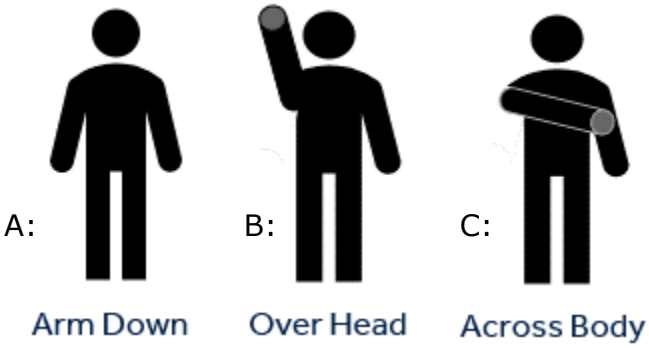
Shoulder movement-2 (Cross-chest movement) Imaging Protocol

1. Note: If the PG is implanted on the left, the left arm will be in motion; if implanted on the right, the right arm will be in motion. Subjects will be asked to assume a supine position in the biplane system field of view, and coached to perform a movement at a starting point with the arm on the table alongside the body (Figure 11A) to follow a course across the chest (Figure 11C).

2. Short taps of fluoroscopy will be used to optimize adequate visualization of the suture-sleeve and connector regions of the defibrillator/pacing lead in the center of the imaging plane of both Image Intensifiers during this arm movement. Image Intensifiers shall be at an angle of 90°±45° to each other. Lowest intensity exposure at 7.5 frames/ second or less will be used for this purpose. (approximately 4 seconds each) Note: It is required that for each image sequence the PG and entire extracardiac region (including the venous access site) must be visible throughout the entire image sequence.
3. A cine- fluoroscopy exposure capture (15 frames/second or more) of the RV lead will be acquired during the arm along body movement. (3 seconds)
4. Have the subject leave the imaging field without moving the x-ray cameras for the final time.
5. A calibration object will be placed in the field of view, and adjusted without moving the x-ray camera, until a minimum of 12 markers are visible in both views.
6. The calibration object will be imaged without moving the biplane system (approximately 1 second)

Figure 11: Illustrations of prescribed arm positions

A: Arms down, B: Arm overhead, and C: Arm across chest



11.2. Imaging Data recorded

1. For the intra-cardiac region, DICOM data files (with ECG signal, if available) shall be reported for each frame.
2. For the extra-venous region, DICOM data files shall be reported for each frame.
3. For the connector region, DICOM data files shall be reported for each frame.

Note: all images for one subject should be placed on the same DICOM media.

11.3. Informed Consent

Prior to initiation of any study specific procedures including data collection, an institutional review board (IRB) approved Informed Consent Form must be signed and dated by the subject. Documentation of the informed consent process is required for each subject and should be maintained within the electronic medical record, per hospital policy.

If informed consent is obtained the same day the subject begins participating in study-related procedures, it should be documented that informed consent was obtained prior to participation in any study-related procedures. The signed Informed Consent Form must be kept in the hospital/clinic medical chart or with the study subject documentation and be available for monitoring and auditing, if applicable. A copy of the Informed Consent Form must be given to the subject.

11.4. Source Documents

It is preferable that original source documents are maintained at the center, when available. Where copies of the original source document as well as printouts of original electronic source are retained, these shall be signed and dated by a member of the study team. All source documentation that is provided to DCRI must have the personal health identifiers redacted and be labeled with the subject study identifier. Source documentation includes but is not limited to those items noted in Table 6.

Table 6: Source Documentation Requirements

Requirement	Disposition
Medical history, physical assessment and Implant/Lead related data	Retain at site
Biplane Fluoroscopy DICOM	Retain original at site, and provide a copy to DCRI
Synced ECG data (if available)	Retain original at site, and provide a copy to DCRI
Historical and Implant related X-ray images (AP/PA view), if available	Retain original at site, and provide a copy to DCRI

12. Data Management

12.1. Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

The EDC database will reside on a production server hosted by a system specified by DCRI. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Any data changes to forms previously signed by the investigator will require new signatures by the investigator, acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

12.2. Data Retention

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and DCRI must receive written notification of this custodial change. Sites are required to inform DCRI in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3. External Laboratories

The National Institute of Standards and Technology, NIST will perform the final data analysis for the lead imaging collected during the HUCS study. NIST will prepare the lead analyses, which will be reviewed by the members of the AAMI CRMD Committee Leads Working Group and approved by the lead manufacturers. This report will be codified into a new AAMI Standard for pacing and defibrillator leads.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify DCRI and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using the study EDC system. Sites may also be required to report deviations to the IRB, per local guidelines and government regulations.

14. Compliance

14.1. Statement of Compliance

This study has been determined by the sponsor to be a nonsignificant risk device study subject to the abbreviated requirements specified by 21 CFR Part 812.2(b), in addition conformance to Part 50, 54, and 56 will be required. The study may not begin until the required IRB approval is obtained. Additionally, the site may not begin participation until formal authorization to enroll is provided by DCRI.

14.2. Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator’s responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study through up-to-date curriculum vitae or other relevant documentation.

- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during potential monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to DCRI in the eCRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the procedure) every adverse event as applicable per the protocol.
- Report to DCRI, per the protocol requirements, all adverse events (includes AE, SAEs).
- Allow DCRI to perform monitoring and auditing activities if applicable and be accessible to the clinical research monitor or auditor and respond to questions during potential monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, are competent to perform the tasks they have been delegated and adequate supervision of those to whom tasks are delegated. Where there is a sub investigator at a site, the sub investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. Institutional Review Board

The investigational site will obtain the written and dated approval/favorable opinion of the IRB for the clinical investigation inclusive of an approved informed consent document before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the IRB approval and ICF must be received by DCRI before recruitment of subjects into the study.

Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the ICF must be IRB approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.

Annual IRB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB requirements. Copies of the study reports and the IRB continuance of approval must be provided to DCRI.

14.4. Sponsor Responsibilities

All information and data sent to DCRI concerning subjects or their participation in this study will be considered confidential by DCRI and will be kept confidential in accordance with all applicable laws and regulations. Only authorized DCRI personnel and/or a NIST representative, the applicable CIED lead manufacturer's representatives, and AAMI will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by AAMI for the purposes of this study, publication, and to support future standards. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

15. Monitoring

All data is collected at the time of enrollment and imaging; therefore, no on-site monitoring is planned.

16. Potential Risks and Benefits

16.1. Anticipated Adverse Events

The following potential adverse events (AE) have been identified for the study related to the imaging procedure and requirements. This study will not report adverse events associated with the pulse generator or lead implant procedure as subjects will already be implanted. Adverse events associated with the pulse generator will not be collected as a part of this trial as the imaging procedure will not affect the device. **Table 7** indicates potential adverse events related to participation in this study.

Table 7: **Potential Adverse Events**

Potential Adverse Events
Adverse or allergic reaction to adhesive from ECG tabs (i.e. rash, redness etc.)
Pain or discomfort from required shoulder movement
Dislodgement of the lead (RA/LV/RV)
Adverse reaction to the imaging procedure radiation (See section 16.2.1)

16.2. Risks Associated with Participation in the Clinical Study

This study involves minimal risk to subjects. Including by not limited to fluoroscopy/radiation exposure. It is estimated that it will take approximately 10 minutes of time to optimally position cameras and acquire images. See specifics below. The risk is considered very low and clinically acceptable.

16.2.1. Radiation Exposure

All study participants will receive standard biplane fluoroscopy x-radiation. X-ray exposure has been shown to increase the risk of cancer, as well as excessive radiation exposure can cause skin injury, the severity of which depends on dose to skin and ranges from hair loss, to skin irritation, to severe skin burns. However, the incremental amount of x-ray used in this study is expected to be minimal and is not expected to have significant, if any clinical consequence for the subject.

In a standard x-ray exposure (2D fluoroscopy), the x-ray tube is stationary. This directs the x-radiation to a limited area of skin as it enters the body, reducing the potential risk of adverse effects.

Radiation exposure can be quantified as "absorbed dose to skin", in units of Gray (Gy). The National Council on Radiation Protection & Measurement[16] provides guidance for 2D exposure that can cause injury. A dose of <2000 mGy is considered insignificant or very low. A dose of 2000 mGy can cause early transient erythema (reddening of the skin).[17]

A previous lead imaging study performed in the same manner as the study imaging procedure in section 11.1.1 showed the absorbed dose to skin, as < 300 mGy (range 45-287) for an exposure time ≤ 45 seconds (range 22-45).[18] This exposure time is the same as what is expected for the HUCS study subjects.

To put this dose of radiation into perspective, the following comparisons are provided:

1. The absorbed dose to skin for a diagnostic coronary angiography procedure has been reported as 1350 mGy (range 900-1910).[19]
2. The absorbed does to skin for a percutaneous transluminal coronary angioplasty (PTCA) is 3760 mGy (range 2400 - 5560). [20]

The radiation exposure is not expected to have any acute adverse effects or any discernable effects from the low level of exposure. However, it is possible that following the fluoroscopic procedure, the skin area exposed to the x-rays could react to produce an effect similar to a sun burn.

16.3. Risk Minimization

To minimize radiation exposure the principal investigator will train other investigators/site staff on optimal techniques to acquire images. Only short taps of fluoroscopy will be utilized for scout images.

To minimize procedural time on the table, laboratory staff will be trained on optimal setup procedures.

These procedures will be done in a clinical or hospital setting. If unforeseen issues arise during the procedures (i.e. subject becomes unstable or experiences a medical emergency), medical personnel will be available.

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[16] NCRP Report No. 168, Radiation Dose Management for Fluoroscopically-Guided Interventional Medical Procedures, Table 2.5, National Council on Radiation Protection and Measurements, 7910 Woodmont Avenue, Suite 400, Bethesda, MD 20814-3095

[17] NCRP Report No. 168, Radiation Dose Management for Fluoroscopically-Guided Interventional Medical Procedures, Table 2.5, National Council on Radiation Protection and Measurements, 7910 Woodmont Avenue, Suite 400, Bethesda, MD 20814-3095

[18] Internal Medtronic Data (Unpublished)

[19] Mahesh, M. (2001). Fluoroscopy: patient radiation exposure issues. Radiographics, 21(4), 1033-1045

[20] Mahesh, M. (2001). Fluoroscopy: patient radiation exposure issues. Radiographics, 21(4), 1033-1045

16.4. Anticipated Benefits

There are no benefits to study subjects participating in the study. The study results could benefit future patients who receive defibrillator or pacing leads by improving on current test methods and future lead designs.

No data exists in regard to the use conditions experienced by implanted leads in the human population. Defibrillation and Pacing leads are life-saving and life-sustaining devices that have to withstand the rigors of the human environment to function adequately. The gap in this knowledge-base has resulted in multiple large-scale recalls with currently existing test methods being unable to predict reliable lead performance with new designs with resultant patient deaths, morbidity and financial burden on the health care delivery system. It is important that a study such as this be performed for the following potential positive outcomes:

Investigate the relationship between lead stiffness and curvature evident by imaging in implanted leads which would permit the development of ISO standards. The development of these standards will lead to qualifying safer products for human implantation.

Provide manufacturers with quantifiable information across different lead designs on the effects of physical stress impacted by shoulder motion, and cardiac contraction across variable physical conditions and implanting physician techniques.

Three-D reconstruction of fluoroscopy-derived images on a background of cardiac anatomy and implant technique will provide insights into the propensity to lead failure over time.

16.5. Risk to Benefit Rationale

Although there is radiation exposure to the subjects participating in this study, the radiation dosage is not enough to cause skin burns or significant increase in cancer risk.

The learnings from this will result in the development of a new standard, which is expected to improve the lead reliability of transvenous leads.

17. Adverse Event Reporting

17.1. Reportable Events by investigational site to DCRI

The investigator will be required to assess and classify each AE that occurs during the time of the imaging procedure. AEs that occur following consent, but prior to the imaging procedure will not be collected.

Events collected during this study will include adverse events, serious adverse events and unanticipated adverse events (inclusive of serious) **specific to the imaging procedure duration**. When possible, the medical diagnosis should be reported as the event term, not individual symptoms. Adverse events must be recorded in the eCRF. Underlying diseases are not reported as an adverse event.

17.2. Definitions

17.2.1. Adverse Event Definitions

An adverse event (AE) is defined as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects that occurs during the course of the study (defined as occurring during the imaging procedure), whether or not directly related to the imaging procedure.

Adverse Events are classified as a serious adverse event (SAE) as defined by *MEDDEV 2.7/3* if one or more of the following consequences are fulfilled:

- led to death
- led to serious deterioration in the health of the subject as defined by either:
    - a life-threatening illness or injury or
    - a permanent impairment of a body structure or function or
    - in-patient hospitalization (>24 hours) or prolongation of existing hospitalization or
    - a medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function
- led to fetal distress, fetal death, or a congenital abnormality or birth defect

17.3. Relationship to Study Procedure

The Investigator must assess the relationship of the reportable AE to the study procedure. See criteria in Table 8.

Table 8: Criteria for Assessing Relationship of Study Procedure to Adverse Event

Classification	Description
Not Related *Def based off intent of MEDDEV 2.7/3*	Relationship to the procedures can be excluded when: - the event is not a known side effect of the procedures; - the event has no temporal relationship with the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of it (or increase of the level of activation/exposure), do not impact the serious event; - the event involves a body-site or an organ not expected to be affected by the procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of procedures and the serious event.
Unlikely Related *Def based off intent of MEDDEV 2.7/3*	The relationship with the procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Def based off intent of MEDDEV 2.7/3*	The relationship with the procedure is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Def based off intent of MEDDEV 2.7/3*	The relationship with the procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Classification	Description
Causal Relationship *Def based off intent of MEDDEV 2.7/3*	The serious event is associated with the procedures beyond reasonable doubt when: - the event is a known side effect of the procedures; - the event has a temporal relationship with procedures; - the event involves a body-site or organ that the procedures are applied to; -the procedures have an effect on; - the discontinuation of the procedure (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. Adverse Event Reporting to DCRI

The investigator shall report to DCRI, by completing the Adverse Event eCRF:

- AEs that are classified by the investigator as related to the imaging procedure
- AEs that occur following imaging that are classified by the investigator as related to the imaging procedure

17.5. Investigator Reporting Requirements

The requirements for investigators to report relevant adverse events (see section 16.1) to DCRI are as shown in Table 9.

Table 9: Communication requirements for reporting to DCRI

Event Classification	Communication Method	Communication Timeline
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	Within 3 calendar days of first becoming aware of the event or as per local/regional regulations. Reporting required through the end of the study participation
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	At request of DCRI
Adverse Event	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device. Provide all relevant source documentation (de-identified/pseudonymized) for reported event.	In a timely manner (e.g. Recommend within 10 business days) after becoming aware of the information Reporting required through the end of the study subject participation.

The requirements for investigators to report other information to DCRI are as shown in Table 10.

Table 10: **Additional Investigator Reporting Responsibilities**

Type of Report	Report to DCRI	Report to IRB	Time Constraints of Notification
Subject Withdrawal	Required	As Required	Within 5 working days after notification of the event
Withdrawal of IRB Approval	Required	N/A	Within 5 working days of receipt of notice of withdrawal of approval
Progress Report	Required	Required	At, minimum annually

Significant Deviations from Investigational Plan	Required	Required	Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by DCRI is required
Informed Consent Not Obtained	Required	Required	Within 5 working days of occurrence

17.6. Reporting Responsibilities to IRB

DCRI is responsible for reporting summary adverse event information to all participating investigators and IRBs, as applicable (refer to Table 11).

The Principal Investigator is responsible for informing the IRB of SAE and other applicable information as required by local/regional regulations.

17.7. DCRI Records and Reports

DCRI will maintain the following records:

- All correspondence with the investigator(s) and IRBs that pertains to the study
- Protocol signature page, delegation/signature logs and curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical investigation protocol and report of prior investigations
- Clinical progress reports
- Any other information upon the request of an IRB or regulatory authority
- Table 11 outlines the responsibilities, including time constraints, for sponsor reports.

Table 11: DCRI Sponsor Reporting Responsibilities

Type of Report	Prepared by DCRI for	Time Constraints of Notification
Withdrawal of IRB approval	All reviewing IRBs, participating investigators, AAMI Project Lead	Within 5 working days of receipt of notice of withdrawal of approval
Progress report	All reviewing IRBs, AAMI Project Lead	Submitted at least annually
Final report	All reviewing IRBs, participating investigators, AAMI Project Lead	A final report will be submitted within 6 months after completion or termination of the study
Informed consent not obtained	Overseeing IRB	Within 5 working days of notification of occurrence

18. Additional Study Conditions

18.1. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the study-required imaging procedures and/or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, and the reviewing IRB The ICF must be accepted by the and approved by the site's IRB or central IRB, if applicable.

DCRI will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB. Any modification requires acceptance from DCRI prior to use of the form. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study
- avoid any coercion of or undue influence of subjects to participate

- not waive or appear to waive subject's legal rights
- use native language that is non-technical and understandable to the subject
- provide ample time for the subject to consider participation and ask questions if necessary
- ensure important new information is provided to new and existing subjects throughout the clinical study

The ICF shall always be signed and personally dated by the subject competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by DCRI to the applicable regulatory authority according to their requirements (e.g., specific IRB reporting time frame). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. IRB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB. The new version of the ICF must be approved by the IRB. Acceptance by DCRI is required if changes to the revised ICF are requested by the site's IRB. The IRB will determine the subject population to be re-consented.

18.2. Termination of Study Participation by the Investigator or Withdrawal of IRB Approval

Any investigator, or associated IRB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to DCRI. Investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

18.3. Requirements for Documentation and Subject Follow-up

In the event of premature study termination, a written statement as to why the premature termination has occurred will be provided to DCRI. The IRB and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB terminates participation in the study, participating investigators, associated IRBs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by DCRI.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by DCRI.

The Principal Investigator or his/her designee must return all study-related documents to DCRI, unless this action would jeopardize the rights, safety, or welfare of the subjects.

18.4. Criteria for Suspending/Terminating a Study Site

DCRI reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

The IRB and regulatory authorities, as applicable, will be notified. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

19. Publication Policy

AAMI CRMD Committee Leads Working Group requires disclosure of its involvement as a financial supporter in any publication or presentation relating to an AAMI CRMD Committee Leads Working Group study or its results. AAMI CRMD Committee Leads Working Group will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. AAMI CRMD Committee Leads Working Group adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org).

In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, AAMI CRMD Committee Leads Working Group personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- AAMI CRMD Committee Leads Working Group involvement in the publication preparation and the AAMI CRMD Committee Leads Working Group Publication Policy should be discussed with the Principal Investigator(s) at the onset of the project.

- The CIED lead manufacturers are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers on approval from all the lead manufacturers.

20. Abbreviations and Definitions

20.1. Abbreviations

AE:	Adverse Event
AAMI:	Association for Advancement of Medical Instrumentation
AAMI CRMD:	Association for the Advancement of Medical Instrumentation Cardiac Rhythm Management Device Committee
AAMI WG01:	Association for the Advancement of Medical Instrumentation Technical Working Group 1
ABT:	Abbott
BIO:	Biotronik
BSC:	Boston Scientific Corporation
CIED:	Cardiac implantable electrical device
Co-I:	Co Investigator
CRC:	Clinical Research Coordinator
CSA:	Clinical Study Agreement
DCRI:	Duke Clinical Research Institute
DICOM:	Digital Imaging and Communications in Medicine
eCRF:	Electronic Case Report Form
ECG:	Electrocardiogram
FDA:	Food and Drug Administration
Fps:	Frames per second
HUCS:	Human Use Condition Study
ICD:	Implantable Cardioverter Defibrillator
ICF:	Informed Consent Form
II:	Image Intensifier
IRB:	Institutional Review Board
ISO:	International Standards Organization
MDT:	Medtronic

mGy:	milligray
NIST:	National Institute of Standards and Technology
PI:	Principal Investigator
RV:	Right Ventricular
SAE:	Serious Adverse Event
SADE:	Serious Adverse Device Effect
SDO:	Standards Developing Organization
2D:	Two-Dimensional
3D:	Three-Dimensional