STUDY PLAN
FOR THE

OPTISURE STUDY
OPTISURE LEAD POST APPROVAL STUDY

December 12, 2013

Table of Contents

Table of Tables

1.0 Introduction

The Optisure™ Lead Post Approval Study (Optisure Lead Study) is a multi-center post-approval study of the Optisure family of high voltage (HV) leads.

The product under study is a St. Jude Medical lead available with a DF1 or DF4 connector, active or passive fixation method and single or dual shocking coils. The goal of this post approval study is to characterize the chronic performance of the St Jude Medical (SJM) Optisure family of right ventricular (RV) HV leads.

2.0 Purpose

The purpose of this post approval study is to characterize the chronic performance of the SJM Optisure family of HV leads in patients that have an approved indication, as per ACC/AHA/HRS/ESC guidelines, for implantation of an ICD or CRT-D system for treatment of heart failure or life-threatening ventricular tachyarrhythmia, and who meet all the inclusion/exclusion criteria. The Optisure lead study will be performed in compliance with the Conditions for Approval as agreed upon with the FDA. If during the course of the study a future generation of the Optisure RV lead is approved, these devices may be included in the study upon agreement with the FDA.

The following objectives will be evaluated in the post approval study:

1. To determine the Optisure lead related complication free rate at 5 years
2. To document all Optisure lead related adverse events

Additionally, the following objectives will be evaluated in a subset of patients in the Optisure lead study who agree to participate in a sub-study:

1. To determine the incidence of externalized conductors after enrollment
2. To determine the incidence of other visual lead anomalies by each subcategory per Appendix A after enrollment
3. To determine the incidence of electrical dysfunction[§] after enrollment
4. To evaluate the 30-day adverse event rate associated with lead revision procedures (include lead extractions or abandonments with or without lead replacement)
5. To determine the prevalence of "other insulation anomalies" in returned Optisure leads:
    - Internal abrasion short under RV shock coil
    - Internal abrasion short under SVC shock coil
    - Exposed conductors defined as a breach of the outer insulation and/or breach of the internal silicone lumen tubing, but the conductor cable is contained within the lead body diameter.

[§]"Electrical dysfunction" is determined to be present after adjudication of the following cases of potential electrical failures that led to the lead being either surgically capped/extracted or electrically abandoned. Potential electrical failures include the following:

- Presence of non-physiologic noise not due to external interference
- Rise in pace/sense (p/s) conductor impedance to > 2000 Ω or increase of more than 200 Ω over previous 6 months or increase of 400 Ω over any period of time
- Decrease of more than 200 Ω over previous 6 months or to impedance < 200 Ω from baseline impedance > 300 Ω or decrease of 400 Ω over any period of time
- Change in any high voltage coil impedance of > 25 Ω or to > 125 Ω or < 20 Ω
- Capture threshold > 5 V or an increase of > 2 V from baseline (all measurements) of < 1 V
  NOTE: In all cases, external sources of "noise" and other header-connector causes would be excluded. Functional abnormalities, including exit block and physiologic oversensing in the presence of an electrically intact lead are not electrical failures.

3.0 Description of Device

The Optisure HV lead is an 8 French, transvenous, steroid eluting, bipolar lead intended for the permanent sensing and pacing of the right ventricle, and the delivery of cardioversion/defibrillation therapy when used with a compatible SJM ICD or CRT-D device.

Optisure Model Number	Connector Type	Fixation	Single/Dual Coil
LDA220 LDA220Q	DF-1/IS-1 DF4	Active	Dual
LDA230 LDA230Q	DF-1/IS-1 DF4	Active	Dual
LDA210 LDA210Q	DF-1/IS-1 DF4	Active	Single
LDP220 LDP220Q	DF-1/IS-1 DF4	Passive	Dual
LDP230 LDP230Q	DF-1/IS-1 DF4	Passive	Dual

As compared to the Durata leads, the Optisure HV dual coil leads have an increased Optim sheath thickness of 0.0070" (from 0.0035") between the connector boot and the SVC defibrillation coil. In order to accommodate the increase in the thickness of the Optim sheath, minor modifications have been made to increase the inner dimensions of the suture sleeve. The Optisure HV dual coil leads also have an Optim sheath underneath the SVC defibrillation coil. In order to accommodate the Optim sheath underneath the SVC defibrillation coil, the SVC defibrillation coil has an increased diameter of 0.100" (from 0.092").

As compared to the Durata leads, the Optim sheath thickness in the Optisure family of HV single coil leads has been increased by 0.0035" between the connector boot and the proximal portion of the lead body, which is 9.85" from the distal tip of the lead.

4.0 Clinical Protocol

4.1 Study Design and Scope

The Optisure lead study is a multi-center, post-approval study that will be performed in compliance with the Conditions for Approval, as agreed upon with the FDA. Patients will be permitted to enroll in the study up to 30 days post-implant of the Optisure lead. Following a successful implant, patients will be followed every 6 months until 60 months (5 years). After patients complete 60 months of follow-up, their participation in the study will end. Patients who are consented prior to implant and for whom an implant is unsuccessful will be followed for 30 days for any adverse events and then withdrawn from the study, or may have an implant reattempted if the physician and patient choose to do so.

Patients who meet inclusion/exclusion criteria, sign an IRB/MEC approved informed consent, and have an implanted Optisure RV lead or attempted implant of the Optisure RV lead will be considered to be enrolled in the study. A total of 1725 patients will be enrolled at a maximum of 60 centers. Enrollment is expected to be completed between 20 and 24 months depending on the rate of enrollment.

Enrollment will be proportional to actual sales, and enrollment duration will not exceed 24 months. If implantation at the study sites is higher than the projected estimates (see section 4.5), then the study enrollment period will be decreased proportionately. Reporting will occur per section 6.0 of the protocol. In order to accomplish this, the study will be conducted at a maximum of 60 study centers.

4.2 Definitions

The following definitions will be used in the Optisure lead study.

- **Abnormal Lead Defibrillation Impedance**: Measured high voltage impedances with values $\leq 20\ \Omega$ or $\geq 100\ \Omega$
- **Abnormal Lead Pacing Impedance**: Measured pacing impedances with values $\leq 200\ \Omega$ or $\geq 2000\ \Omega$
- **Adverse Event**: Any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a patient caused by or associated with a study device or intervention. Adverse events are classified as complications or observations.
- **Cardiac Tamponade**: Confirmed or suspected accumulation of fluid in the pericardial space leading to hemodynamic compromise.

- **Cardiac Perforation**: An excursion of the lead through themyocardium. Signs and symptoms of perforation by an intra-cardiac lead may include radiographic evidence of excursion of the lead into the pericardial sac, abnormal echocardiography indicative of a perforation, the accumulation of fluid in the pericardium, cardiac tamponade, or patient symptoms..
- **Complication**: An adverse event that requires invasive intervention to resolve (e.g., lead fracture)
- **Diaphragmatic/Phrenic Nerve Stimulation**: Electrical activation of the diaphragm muscle by the device output pulse. The abrupt diaphragmatic contraction is noted clinically as hiccups associated with each pacing stimulus. The pacing stimulus may stimulate the diaphragm either directly or indirectly via the phrenic nerve.
- **Elevated Pacing Thresholds**: Voltage thresholds > 3.0V at implant or 2-fold increase between visits (after lead maturation) leading to a threshold greater than 3.5V at follow up. This definition is intended to serve as a guideline and it is understood that individual patients may have unique situations.
- **Externalized Conductor**: The appearance on x-ray or fluoroscopy of conductors outside of the lead body due to an abrasion-related breach of the outer insulation.
- **Generator Malfunction**: A confirmed failure of the device to perform as indicated.
- **Lead Dislodgement**: The movement of a pacing lead from its originally implanted position; often associated with changes in pacing and/or sensing thresholds including loss of sensing and/or capture. Dislodgement can often be confirmed by radiographic studies.
- **Lead Fracture**: A break in a conduction cable or coil of a pacing or defibrillation lead typically evidenced by an increase in impedance, intermittent or complete loss of capture, intermittent or complete loss of sensing, noise on the intra-cardiac electrogram and rarely, by visual signs of conductor coil fracture on x-ray.
- **Lead Insulation Damage**: A disruption to the integrity of the lead insulation without disruption of the conductor cable(s) or coil observed visually, electrically, or radiographically. An insulation break may be indicated by a drop in impedance, and can cause loss of capture or high voltage therapy delivery or sensing problems.
- **Loss of Capture**: The inability of the device's output pulse to result in depolarization and contraction of the appropriate cardiac chamber. Causes include insufficient stimulus strength, separation of the electrode from the myocardium, some anti-arrhythmic medications and placement of the stimulating electrode in contact with a non-responsive portion of the myocardium such as scar tissue. Delivery of an output pulse at a time when the myocardium is physiologically refractory is not loss of capture, since capture is not physiologically feasible.
- **Loss of Sensing**: A condition in which the pulse generator is unable to sense intrinsic cardiac signals (applicable to RA and RV leads).

- **Observation**: Adverse events that can be managed without invasive intervention (e.g., oversensing or loss of pacing capture, which is remedied by reprogramming of the pulse generator).
- **Oversensing**: The detection of inappropriate electrical signals by the pulse generator's sense amplifier. These signals, such as myopotentials, electromagnetic interference, T waves or crosstalk between atrial and ventricular channels, must be of sufficient duration to interfere with normal device function (applicable to RA and RV leads).
- **Pneumothorax**: An accumulation of air in the pleural cavity due to a disruption of the pleural lining.
- **Re-Attempted Implant**: Implant is being re-attempted in a new procedure due to previous failed implant of the Optisure lead
- **Re-Implant**: Implant is being attempted in a new procedure because of a previous removal of the Optisure lead implanted at enrollment, e.g. due to infection.
- **Successful implant**: An Optisure lead is implanted.
- **Undersensing**: The failure of the pulse generator to sense P or R waves, causing delivery of inappropriately timed, asynchronous or competitive output pulses. Undersensing can sometimes be corrected by programming the device to a more sensitive setting, i.e., decreasing the millivolt (mV) value. (Applicable to RA and RV leads).
- **Unsuccessful implant**: An attempted implant that does not result in a successful Optisure lead implant.

4.3 Sub-Study Design and Scope

This sub-study will determine the incidence of externalized conductors and other visual lead anomalies (as evidenced by imaging) and the risk of progression to electrical dysfunction in patients implanted with an Optisure HV lead. A minimum of 200 subjects who consent to participate in this sub-study will undergo cinefluoroscopy (AP, LAO 45° or the best possible LAO view, RAO 45° or the best possible RAO view) at the 24, 36, 48 and 60 month follow-up visits.

Expected Attrition in patients with high voltage leads

Withdrawals due to death

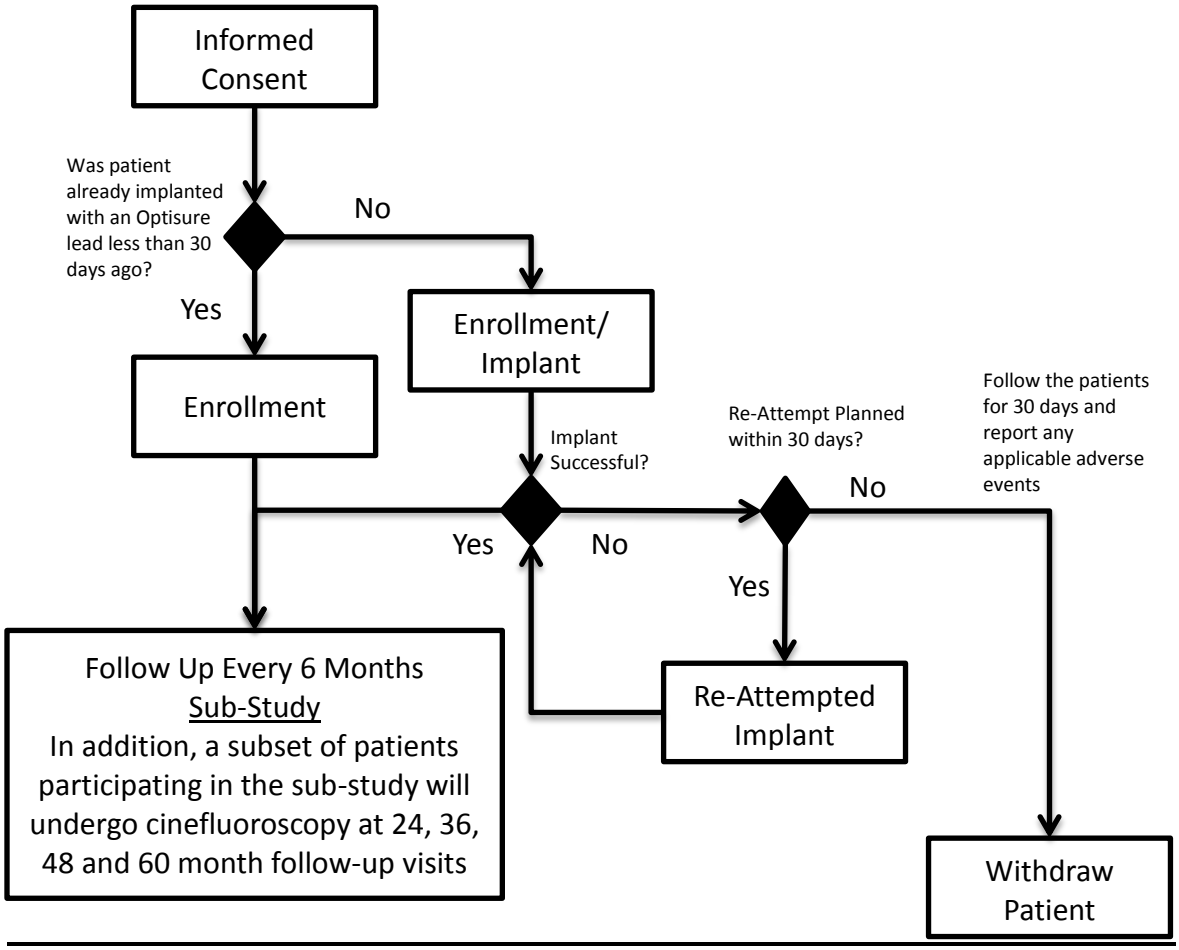
Assuming an annual mortality of 7% in the ICD patient population, the mortality at 5 years is 30% [1 – (1-0.07)^5] In the recent RHYTHM ICD/QuickSite 1056K left heart lead study using CRT-D devices, the annual mortality was 12.8%, which would result in a mortality of 49% [1 – (1-0.128)^5] at 5 years. If the ICD:CRT-D device mix is 60%:40% then the expected overall mortality in this study at 5 years is 38% (=0.6×0.30+0.4×0.49).

Withdrawals due to reasons other than death

In an ongoing St. Jude Medical post-approval study consisting of CRT devices and LV leads, 102 patients have been withdrawn for reasons other than death during an average of 22 months of follow-up. This translates to an attrition of 22% over 5 years.

Assuming that deaths and withdrawals are independent events, the total attrition is expected to be approximately 52% (= 1-(1-0.38)×(1-0.22)) over 5 years. With an expected attrition at 5 years to be 52%, a total of 417 subjects who consent to participate in this sub-study will be enrolled in order to have at least 200 subjects with fluoroscopy data available at the 60 month follow-up visit.

4.4 Study Flow Diagram



4.5 Optisure Projected Study Timeline

A timeline for the Optisure Lead Post Approval study is provided below. This timeline may change the actual enrollment rate.

Time = 0; month 1 *FDA Approval*	**Time = month 2**	**Time = month 3**	**Time = month 4**	**Time = month 5**	**Time = month 6**	**Time = month 7**	**Time = month 8**	**Time = month 9**	**Time = month 10**	**Time = month 11**	**Time = month 12**
▪ Study Initiation			▪ 10 sites with IRB approval ▪ First enrollment	▪ Enrollment & follow-up				▪ 60 sites with IRB approval			
			▪ Estimated enrollment = 20	▪ Estimated enrollment = 30	▪ Estimated enrollment = 40	▪ Estimated enrollment = 50	▪ Estimated enrollment = 60	▪ Estimated enrollment = 70	▪ Estimated enrollment = 80	▪ Estimated enrollment = 90	▪ Estimated enrollment = 100
		Cumulative enrollment	▪ 20	▪ 50	▪ 90	▪ 140	▪ 200	▪ 270	▪ 350	▪ 440	▪ 540

Time = month 13	**Time = month 14**	**Time = month 15**	**Time = month 16**	**Time = month 17**	**Time = month 18**	**Time = month 19**	**Time = month 20**	**Time = month 21**	**Time = month 22**	**Time = month 23**	**Time = month 24**
▪ Anticipated enrollment of 100/mo after month 12											▪ Enrollment completed
Cumulative enrollment	▪ 740	▪ 840	▪ 940	▪ 1040	▪ 1140	▪ 1240	▪ 1340	▪ 1440	▪ 1540	▪ 1640	▪ 1725

Time = month 25	**Time = month 26**	**Time = month 27**	**Time = month 28**	**Time = month 29**	**Time = month 30**	**Time = month 31**	**Time = month 32**	**Time = month 33**	**Time = month 34**	**Time = month 35**	**Time = month 36**
▪ Patient follow-up											

Time = month 37	**Time = month 38**	**Time = month 39**	**Time = month 40**	**Time = month 41**	**Time = month 42**	// *Elapsed time of 42 months*	**Time = month 84**	**Time = month 85**	**Time = month 86**	**Time = month 87**
▪ Patient follow-up						//	▪ Follow-up completed	▪ Complete Monitoring	▪ Data Analysis	▪ Final report submission

Enrollment for the sub-study (target sample size = 417) is expected to be completed by month 14 assuming that approximately 55% patients will provide consent to participate in the sub-study. Final follow-up visit (60 month visit) in the sub-study is expected to be done in month 84. Results from the sub-study will be included in the progress reports submitted to FDA.

5.0 Study Outcome Measures

5.1 Primary Outcome Measure

5.1.1 Freedom from RV Lead Related Complications

The primary outcome measure for the Optisure Lead Post Approval study is the complication free survival rate at 5 years for complications related to the Optisure RV leads.

The hypothesis is as follows:

H0: Complication free survival at 5 years ≤ 92.5%
H1: Complication free survival at 5 years > 92.5%

The desired outcome is to reject the null hypothesis. The null hypothesis will be rejected at the 5% significance level if the 95% Lower Confidence Bound (LCB) for the freedom from complications is greater than 92.5%.

Sample Size
Assuming that the time to first complication follows an exponential distribution and the complication-free survival at 5 years is 95%, a sample size of 645 patients provides 80% power to reject the null hypothesis of 92.5% complication-free survival years at the 5% significance level (See Appendix D for detailed sample size calculations).

Patient Group
All patients who had an attempted implant of the Optisure RV lead will be included in the analysis of this endpoint.

Analysis
All complications will be classified as related to the Optisure RV lead or unrelated.

The following complications will be included in this analysis:

- Cardiac perforation
- Lead dislodgement that occurred greater than 30 days after implant
- Lead insulation damage
- Lead fracture
- Abnormal RV lead performance (abnormal lead defibrillation impedance, abnormal lead pacing impedance, elevated pacing thresholds, loss of capture, failure to deliver therapy, loss of sensing, oversensing, undersensing)

- Other unexpected complications that are considered related to the RV lead

The survival time for all patients will be calculated as the number of days from implant or attempted implant to the date the complication was first discovered. For patients who do not experience a complication related to the Optisure RV lead at the time of their withdrawal, the survival time will be censored on the date of their withdrawal. For patients who have not experienced any complication related to the Optisure RV lead at the time of analysis, the survival time will be censored on the date of analysis. The endpoint will be evaluated using the Kaplan-Meier method and the 95% lower confidence bound (LCB) will be obtained by transformation from its log scale, based on Peto et al[1]. The null hypothesis will be rejected if the 95% LCB is greater than 92.5%.

Kaplan-Meier curves will also be presented for each adverse event category of complication listed above.

5.2 Secondary Outcome Measures

5.2.1 Optisure Lead-Related Complication Rates

The objective is to characterize the complication rate of the Optisure lead, and to perform a trend analysis of all complications. All complications will be evaluated for their relationship to the RV lead, reported and summarized.

The following complications will be reported as related to the RV lead:

- Cardiac perforation
- Lead dislodgement that occurred greater than 30 days after implant
- Lead insulation damage
- Lead fracture
- Abnormal RV lead performance (abnormal lead defibrillation impedance, abnormal lead pacing impedance, elevated pacing thresholds, loss of capture, failure to deliver therapy, loss of sensing, oversensing, undersensing)
- Other unexpected complications that are considered related to the RV lead

Table 1: Summary of RV Lead Related Complications

Description of Complication	Number of Patients with Comp (No. of pts = X)	% of Patients with Comp	Number of Comps	# Comps/pt-years (Total pt-years =)
Cardiac perforation	X	X%	X	X
Lead dislodgement that occurred greater than 30 days after implant	X	X%	X	X
Lead insulation damage	X	X%	X	X
Lead fracture	X	X%	X	X
Abnormal RV lead performance	X	X%	X	X
Other unexpected complications that are considered related to the RV lead	X	X%	X	X
Total	X	X%	X	X

Sample Size

The sample size required to obtain a two-sided 95% upper confidence limit for the complication rate of no more than 5%, based on the Clopper-Pearson exact Binomial method[2], assuming an expected complication rate of 3.5%, is 828 patients (See Appendix D for detailed sample size calculations).

Sample size accounting for patient attrition

The following categories are included to account for patient attrition.

1. Unsuccessful Implant

A small proportion of the patients are expected to have an unsuccessful implant of the Optisure lead (less than 1%).

2. Mortality

The expected distribution of ICDs to CRT-Ds in this post-market surveillance study is 3:2[3]. The annual mortality in the ICD patient population varies between 5.6% and 7%, which are calculated from the published results of the SCD-HeFT and MADIT II trials[4,5]. Assuming an annual mortality of 7% in the ICD patient population, the mortality at 5 years is 30%. In the recent RHYTHM ICD/QuickSite 1056K left heart lead study[6], the annual mortality was 12.8%, which gives a mortality of 49% at 5 years. Hence the expected overall mortality in this post-approval study at 5 years is 38% (=0.6×0.30+0.4×0.49).

3. Withdrawal due to Lost-to-follow-up, system explant due to heart transplant/infection, patient/physician request

In the ongoing St. Jude Medical post-approval study consisting of CRT devices and LV leads[7], out of a total of 1127 enrollments, 102 patients have been withdrawn for reasons other than death during an average of 22 months of follow-up. This translates to an attrition of 22% over 5 years. It is assumed that attrition in the study over 5 years is 22%. This is a conservative assumption since the CRT Device System Post Approval Surveillance study solely enrolled patients indicated for CRT, while this study is expected to enroll patients receiving either a CRT-D or an ICD.

Assuming that deaths and withdrawals are independent events, the total attrition is thus expected to be approximately 52% (= 1-(1-0.38)×(1-0.22)) over 5 years. Thus, a minimum of 1725 patients will be enrolled in the post-approval study.

Patient Group
All patients who give consent for the study and undergo an attempted implant of the Optisure lead or had an Optisure lead implanted within 30 days of enrollment will be included in this analysis.

5.2.2 Optisure Lead Related Events

Adverse Events related to the Optisure lead will be classified and reported as complications or observations. RV lead related complications or observation are defined in section 5.2.1

5.3 Sub-study - Outcome Measures

5.3.1 The annual hazard rate of lead electrical dysfunction

Lead Population
All enrolled Optisure leads being followed in this sub-study.

Analysis:
The annual hazard rate will be assessed.

5.3.2 The annual hazard rate of externalized conductors (from enrollment)

Lead Population
All enrolled Optisure leads being followed in this sub-study.

Analysis:
The annual hazard rate will be assessed.

5.3.3 The annual hazard rate of other visual lead anomalies by each subcategory (from enrollment)

Lead Population
All enrolled Optisure leads being followed in this sub-study.

Analysis:
The annual hazard rate will be assessed.

5.3.4 Prevalence of "other insulation anomalies" in "returned leads" (as defined in section 2.0)

Lead Population
Any enrolled lead in the sub-study that is returned to St. Jude Medical for analysis.

Analysis:
The prevalence of "other insulation anomalies" will be calculated as the number of returned leads that have "other insulation anomalies" divided by the total number of returned leads in enrolled sub-study patients. The one-sided 95% UCB for prevalence will be calculated using Clopper-Pearson exact method.

5.3.5 Time from externalized conductors to electrical dysfunction

Lead Population
All Optisure leads with externalized conductors but without electrical dysfunction.

Analysis:
Time to electrical dysfunction will be analyzed using the Kaplan-Meier method. The zero time will be the date at which externalized conductor was detected. Those patients who experience an externalized conductor after enrollment, but do not experience an electrical dysfunction will be censored 3 years after enrollment in this trial.

5.3.6 Time from other visual lead anomalies by each subcategory to electrical dysfunction

Lead Population
All Optisure leads with other visual lead anomalies (by each subcategory) but without electrical dysfunction.

Analysis:
Time to electrical dysfunction will be analyzed using the Kaplan-Meier method. The zero time will be the date at which other visual lead anomaly (by each subcategory) was detected. Those patients who experience other visual lead anomaly (by each subcategory) after enrollment, but do not experience an electrical dysfunction will be censored 3 years after enrollment in this trial.

5.3.7 Adverse Event rate through 30 days post-intervention for lead (e.g. extraction, abandonment, revision, other)

Lead Population
All Optisure leads that require an intervention/revision (e.g. extraction, abandonment, other).

Analysis
The 30-day adverse event rate will be calculated as the number of adverse events within 30 days associated with lead related interventions divided by total lead related interventions.

5.3.8 Time from externalized conductors to clinical intervention

Lead Population
All Optisure leads with externalized conductors.

Analysis:
Time to clinical intervention will be analyzed using the Kaplan-Meier method. The zero time will be the date at which externalized conductor was detected. Those patients who experience externalized conductor after enrollment but do not experience clinical intervention will be censored 3 years after enrollment in this trial.

5.3.9 Time from other visual lead anomalies by each subcategory to clinical intervention

Lead Population
All Optisure leads with other visual lead anomalies (by each sub category).

Analysis:
Time to clinical intervention will be analyzed using the Kaplan-Meier method. The zero time will be the date at which other visual lead anomaly (by each subcategory) was detected. Those patients who experience other visual lead anomaly (by each subcategory) after enrollment but do not experience clinical intervention will be censored 3 years after enrollment in this trial.

5.3.10 Comparison of patients with lead compromise as evidenced by imaging (includes externalized conductors and other visual lead anomalies) to those without lead compromise

Patient Population
All the patients implanted with Optisure leads.

Analysis
Demographic and clinical parameters will be compared between patients who experience lead compromise as evidenced by imaging and those who do not experience lead compromise. Specifically, the variables age, gender, body mass index, lead size, lead model, and implant factors such as venous access site, number of other leads in the vasculature, fixation location in the right ventricle, level of activity (based on functional NYHA class scale I, II, III, IV), level of therapy that patient received (no ATP/shock, ATP or shock) and slack (grades 0, 1, 2, 3, 4 based on the scale described by Ha et al., 2010[8]) in the lead will be used for the comparison. Continuous variables such as age or body mass index will be compared using Student's T-tests while categorical variables such as gender or lead models will be compared using Pearson's Chi-square statistic. Point estimates and p-values will be provided from these analyses.

5.3.11 Comparison of patients with electrical dysfunction to those without electrical dysfunction.

Patient Population
All the patients implanted with Optisure leads.

Analysis
Demographic and clinical parameters will be compared between patients who experience electrical dysfunction and those who do not experience electrical dysfunction. Specifically, the variables age, gender body mass index, lead size, lead model, and implant factors such as venous access site, number of other leads in the vasculature, fixation location in the right ventricle, level of activity (based on functional NYHA class scale I, II, III, IV), level of therapy that patient received (no ATP/shock, ATP or shock) and slack in the lead (grades 0, 1, 2, 3, 4 based on the scale described by Ha et al, 2010[8]) will be used for the comparison. Continuous variables such as age or body mass index will be compared using Student's T-tests while categorical variables such as gender or lead models will be compared using Pearson's Chi-square statistic. Point estimates and p-values will be provided from these analyses.

6.0 Analysis and Reporting

6.1 Interim Reports and Trend Analysis

Interim reports will be submitted to FDA every 6 months for the first 2 years and yearly thereafter.

The observed number of enrollments in the study and the sub-study at participating centers, number of implants at participating centers and number of overall US implants will be included in the progress reports until enrollment is completed.

Other data summarized in the progress reports will include:

- Demographic data including gender, age, NYHA functional classification, left ventricular ejection fraction, and indication for device. Continuous variables will be summarized by average and standard deviation. Categorical variables will be summarized by frequency and percentage
- Complications and observations related to the Optisure RV lead will be summarized and reported
- Complications or observations that are unrelated to the RV lead (shown in Table 2) will be summarized and reported
- Signal amplitude measurements for Optisure leads at implant/enrollment, as appropriate, and at each follow-up visit (if available) will be summarized and reported.
- Capture thresholds for Optisure leads at implant/enrollment, as appropriate, and at each follow-up visit will be summarized and reported.

- Pacing lead impedance for Optisure leads at implant/enrollment, as appropriate, and at each follow-up will be summarized and reported.
- High voltage lead impedance for Optisure leads at implant/enrollment, as appropriate, and at each follow-up will be summarized and reported.
- The rate of successful Optisure RV lead implants will be reported (only applicable to patients enrolled at or before implant)
- Total implant procedure time (skin to skin) – the average and standard deviation for successful Optisure lead implants will be reported (only applicable to patients enrolled at or before implant)
- Implant approach (site of venous access) (only applicable to patients enrolled at or before implant)
- Percentage of leads with externalized conductors, other visual lead anomalies at different time points (24, 36, 48 and 60 months)
- Type, location and extent of externalized conductors and other visual lead anomalies
- Percentage of leads with electrical dysfunction in the sub-study
- Prevalence of "other insulation anomalies" in returned Optisure leads

Table 2: Complications or Observations That Are Unrelated To the RV Lead

Pneumothorax
Lead dislodgement occurring in the peri-operative period (within 30 days of implant)
Elevated pacing thresholds due to patient physiology
Loss of capture unrelated to lead fracture or dislodgement
Loss of sensing unrelated to lead fracture or dislodgement
Oversensing due to a change in patient physiology
Undersensing due to a change in patient physiology
Generator malfunction
Abnormal lead pacing impedance ($\leq 200\ \Omega$ or $\geq 2000\ \Omega$) unrelated to lead fracture or dislodgement
Abnormal lead defibrillation impedance ($\leq 20\ \Omega$ or $\geq 100\ \Omega$) unrelated to lead fracture or dislodgement
Failure to detect VT/VF due to a cause unrelated to the Optisure RV lead
Complications related to other implanted leads (right atrial or left ventricular)

A trend analysis for the complications listed in Table 1 will be summarized by quarter with the first analysis carried out after 100 patients have been enrolled and followed for a minimum of 6 months. Each interim report will include a plot of quarterly trend analyses of % of Patients with Complications and # of Complications/patient-year from all preceding analyses.

6.2 Final Study Report

In addition to the summaries described in section 6.1, the following will also be included in the final report: The number and proportion of patients who experience each type of complication in Table 1 at 5 years will be presented along with the 95% confidence intervals for the proportion based on the Clopper-Pearson exact Binomial method. A Kaplan-Meier analysis will be performed for all-cause death for the final report.

7.0 Site Selection

Centers will be selected for participation in the study and sub-study based on their ability to screen and enroll eligible patients, and perform the required study procedures outlined in section 9.0. SJM will attempt to have a diversified group of centers participating in the study, including academic and non-academic institutions, and anticipates participation to be in the order of approximately 25-30 percent from academic institutions. To ensure a widespread distribution of data and minimize site bias, a maximum of approximately 15% of the total enrollment will be allowed at a single site.

8.0 Patient Selection

8.1 Inclusion Criteria

Eligible patients will meet all of the following:

1. Have an approved indication, as per ACC/AHA/HRS/ESC guidelines, for implantation of an ICD or CRT-D system for treatment of heart failure or life-threatening ventricular tachyarrhythmia(s).
2. Have been implanted with a St. Jude Medical Optisure lead in the last 30 days or are scheduled for an Optisure lead implant.
3. Have the ability to provide informed consent for study participation and be willing and able to comply with the prescribed follow-up tests and schedule of evaluations.
4. Are 18 years or above, or of legal age to give informed consent specific to state and national law.

8.2 Exclusion Criteria

Patients will be excluded if they meet any of the following:

1. Enrolled or intend to participate in a clinical drug and/or device study, which could confound the results of this trial as determined by SJM, during the course of this clinical study.
2. Have a life expectancy of less than 5 years due to any condition.

8.3 Sub-study Enrollment Criteria

Patients enrolled in the main study who provide their consent to participate in the sub-study will be enrolled until 417 patients are enrolled.

9.0 Study Procedures

All required study procedures at each specified interval are outlined in the sections below.

Table 3: Schedule of Evaluations Summary

Evaluation	Enrollment*	Every 6 months thereafter until 5 years	24, 36, 48 and 60 month follow-up visits
Inclusion/Exclusion Criteria Evaluation	√		
Record capture threshold, signal amplitude, pacing lead impedance and high voltage lead impedance measurements on Optisure lead	√	√	
RV Lead Handling Characteristics (only applicable to patients enrolled at or before implant)	√		
Cinefluoroscopy (AP, LAO 45° or the best possible LAO view, RAO 45° or the best possible RAO view)			√**

* Enrollment can occur up to 30 days post implant
**Only applies to patients participating in the sub-study

9.1 Data Entry

Each study center will capture all study-related data and submit via an Electronic Data Capture (EDC) system. All study data will be entered and submitted through this system, including device data. The device session record data will be submitted through the SJM EDC system using the device data upload portal. The SJM EDC system complies with regulatory requirements to protect patient privacy and maintain data integrity.

Patient-specific device print-outs may be placed in the provided Patient Binders. Alternatively, print-outs may be stored electronically on the thumb drive provided to the centers specifically for the purpose of data collection and retention. The thumb drives will be stored in a secure location and made available to the sponsor representatives as required. The thumb drives will be returned or destroyed at sponsor request at the end of the study. All other study training material will be placed in the provided study Regulatory Binder.

Training for the EDC system will be provided by SJM.

9.2 Enrollment Requirements

9.2.1 Enrollment

Patients will undergo screening evaluations as outlined by the inclusion/exclusion criteria. To ensure enrollment of a diverse patient population into the Optisure lead study, centers will be instructed to approach and invite all patients who meet all of the inclusion and none of the exclusion criteria for participation in the study.

Data will be collected on the patient's gender, age, indication for device implantation, NYHA functional classification, and left ventricular ejection fraction.

Patients who meet inclusion/exclusion criteria, sign an IRB/MEC approved informed consent, and have an Optisure lead implant or attempted implant of the Optisure lead will be considered enrolled in the study. Enrolled patients who provide consent to participate in the sub-study will be included in the sub-study.

The following electrical measurements* must be performed: capture threshold testing for all implanted leads, signal amplitude measurements for the RV and RA leads, pacing lead impedance for all implanted leads and high voltage lead impedance for all implanted leads.

*Notes

1. If the patient is in atrial fibrillation or atrial flutter, RA electrical measurements are not required.
2. If the patient is pacemaker dependent, RV sensing amplitude is not required.
3. As referenced under the Definitions in section 4.2, abnormal pacing lead impedances are defined as measured pacing impedances with values $\leq 200\ \Omega$ or $\geq 2000\ \Omega$. RV lead pacing impedances have been observed in typical clinical settings to be in the range of 200-1200 Ω for the majority of patients. However, lead pacing impedances measured up to 1999 Ω are considered to be within the normal bounds of the performance of the RV lead because characteristics such as non-

viable myocardium, lead-to-tissue contact, etc., specific to each patient have been known to produce measured pacing impedances that are higher than the observed 1200 Ω noted above.

Device diagnostics and archives of RV lead impedance values may also be used to diagnose potential lead failures. Alternatively, investigators should consult the respective device and lead user manuals, St. Jude Medical technical support or other St. Jude Medical clinical support personnel to diagnose potential lead failures.

The enrollment date for patients in the study will be the date when all protocol defined enrollment procedures (consent, implant and lead measurements) are completed.

Complete an Enrollment, Implant and Lead Measurements Case Report Forms and record all results. Complete an Adverse Event Case Report Form (if applicable) for all adverse events which occurred since the implant of the Optisure lead. Submit the forms to St. Jude Medical using the EDC system. Complete an Out of Service Form for any product used but not implanted (e.g. contaminated, dropped or opened in error).

Upload the device session record including all stored IEGMs to St. Jude Medical using the SJM EDC Portal device data upload utility. If the patient is enrolled after implant, provide the session record from the enrollment visit.

9.2.2 Unsuccessful Implant– if applicable

Enrolled patients who have an unsuccessful implantation of a St. Jude Medical Optisure lead (see definition for successful Optisure lead implant in section 4.2) will be followed for a period of 30 days for adverse events and then withdrawn from the study unless the implant will be re-attempted within 30 days of the unsuccessful implant. The physician may re-attempt the implantation of a St. Jude Medical Optisure lead at his/her discretion.

In addition to the Forms identified in section 9.2.1 complete the Out of Service for any product used but not implanted (e.g. contaminated, dropped or opened in error) and record all results. After 30 days, if the patient has not had an implant re-attempted, complete a Withdrawal Case Report Form and record all results. Submit the forms to St. Jude Medical using the EDC system.

If the physician chooses to re-attempt the implantation of a St. Jude Medical Optisure lead within 30 days, complete Implant and Lead Measurements Case Report Forms, an Adverse Event Case Report Form (if applicable) and Out of Service Case Report Form (if applicable) and record all results. Submit the forms to St. Jude Medical using the EDC system.

9.3 System Revisions – if applicable

If the system revision procedure occurs more than 3 months after implant then obtain cinefluoroscopy views of the entire length of the implanted leads before repositioning or explanting the Optisure lead. Cinefluoroscopy should be performed in three views (AP, LAO 45° or the best possible LAO view, RAO 45° or the best possible RAO view) and submitted to St. Jude Medical. If the patient is unwilling then the imaging is not required.

For all lead revisions (e.g. replacement or repositioning of the lead) complete the applicable testing as outlined in section 9.2.1. Any explanted pulse generator or leads (including damaged leads, lead segments and lead fragments) should be returned to St. Jude Medical for analysis promptly.

Any changes to the status of a lead (i.e., capped, removed) will be documented on the Product Out of Service Case Report Form. Complete an Adverse Event (if applicable), System Revision, Imaging (if applicable), and Out of Service for any product used but not implanted (e.g. contaminated, dropped or opened in error) Case Report Form. Submit the forms to St. Jude Medical using the EDC system.

9.4 Follow-Up Requirements

Lead measurements and adverse events (if applicable) will be obtained every 6 months from patients who have a successfully implanted Optisure lead until they reach the 5 year follow-up.
The schedule of follow-ups is based on the date of a successful Optisure lead implant. Table 4 outlines the time window that is permitted for each of the study interval visits.

Table 4: Study Interval Time Windows

	Every 6 months thereafter until 5 years
	± 90 days

The following electrical measurements* will be obtained at each follow up: capture thresholds for all implanted leads, signal amplitude measurements for the RV and RA leads, pacing lead impedance for all implanted leads and high voltage lead impedance for all implanted leads.

*Notes

1. If patient is in atrial fibrillation or atrial flutter or RA lead is turned off, RA electrical measurements are not required.
2. If patient is pacemaker dependent, RV sensing amplitude is not required.

3. As referenced under the Definitions in section 4.2, abnormal pacing lead impedances are defined as measured pacing impedances with values ≤ 200 Ω or ≥ 2000 Ω. RV lead pacing impedances have been observed in typical clinical settings to be in the range of 200-1200 Ω for the majority of patients. However, lead pacing impedances measured up to 1999 Ω are considered to be within the normal bounds of the performance of the RV lead because characteristics such as non-viable myocardium, lead-to-tissue contact, etc., specific to each patient have been known to produce measured pacing impedances that are higher than the observed 1200 Ω noted above.

Device diagnostics and archives of RV lead impedance values may also be used to diagnose potential lead failures. Alternatively, investigators should consult the respective device and lead user manuals, St. Jude Medical technical support or other St. Jude Medical clinical support personnel to diagnose potential lead failures.

In the subset of patients participating in the sub-study, cinefluoroscopy (AP, LAO 45° or the best possible LAO view, RAO 45° or the best possible RAO view) of the entire lead length and the pocket area will be performed at the 24, 36, 48 and 60 month visits. Additionally, query the patient to determine whether the patient has had any chest x-rays or fluoroscopy of the implanted leads since the last visit. Whenever possible, obtain copies of any imaging done (x-ray or fluoroscopy). Review those images for signs of lead conductor externalization. Report those events, as applicable, on an adverse event form. Also, query the patient regarding any adverse events occurring between routine visits. Complete a Follow-up Case Report Form and record all results. Should any adverse event occur, complete an Adverse Event Case Report Form. If any images were obtained (especially for patients participating in the sub-study at the 24, 36, 48 and 60 month visits), complete an Imaging Case Report Form. Submit the forms to St. Jude Medical using the EDC system.

Upload the device session record including all stored IEGMs to St. Jude Medical using the SJM EDC Portal device data upload utility.

10.0 Protocol Deviations

Investigators are required to adhere to the protocol, signed Investigator's Agreement, applicable federal (national) or state/local, laws and regulations, and any conditions required by the IRB/MEC or applicable regulatory authorities.

A protocol deviation is used to describe situations in which the clinical protocol was not followed. All deviations from the protocol must be reported to St. Jude Medical per 21 CFR §812.150. In addition, all deviations must be reported to the reviewing IRB/MEC per the IRB/MEC's reporting requirements.

The investigator must notify St. Jude Medical and the reviewing IRB/MEC of any deviation from the protocol plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but not later than 5 working days after the deviation has occurred, or no later than 5 working days after the investigator becomes aware of the deviation.

Should a deviation occur, complete a Deviation Case Report Form and submit to St. Jude Medical using the EDC system. If a deviation occurs between scheduled visits, the event should be reported at the next scheduled visit. Visits will be considered missed if they are outside of the visit window.

11.0 Adverse Events

Adverse events are any unfavorable clinical event which impacts, or has the potential to impact the health or safety of a patient caused by or associated with a study device or intervention. Adverse events will be classified as complication or observations.

Complications: Adverse events that require invasive intervention (e.g., lead fracture) with the exception of RV lead perforations. All adverse events reported as RV lead perforations (managed with or without an invasive intervention) will be considered a complication. Each complication will be reported in one of the following categories for analysis purposes:

- RV lead related complication: A complication that is related to the RV lead.
- Device related: A complication related to the device
- Other lead related complication: A complication that is related to the LV or RA lead.
- Procedure related complication: A complication related to an implant or system revision procedure.
- Other complication: Any complication that does not fall into one of the categories listed above.

Observations: Adverse events that can be managed without invasive intervention (e.g., oversensing or loss of pacing capture, which is remedied by reprogramming of the pulse generator). Observations will be reported in one of the following categories:

- RV lead observation: An observation that is related to the RV lead.
- Device related: An observation that is related to the device.
- Other lead related observation: An observation that is related to the LV or RA lead.
- Procedure related observation: An observation that is related to an implant or system revision procedure.
- Other observation: Any observation that does not fall into one of the categories listed above.

Should an adverse event occur at any time between implant and withdrawal, complete an Adverse Event form and submit to St. Jude Medical using the EDC system as soon as possible or within 10 days from the date the site became aware of an event. If an adverse event occurs between scheduled visits, the event should be reported at the next scheduled

visit. Report the adverse event to the IRB/MEC per the IRB/MEC policy. Any explanted devices or leads should be returned to St. Jude Medical for analysis.

Possible adverse events (in alphabetical order) associated with leads, devices or implant and/or system revision procedure may include, but are not limited to the following:

- Abnormal lead defibrillation impedance
- Abnormal lead pacing impedance
- Acceleration of arrhythmias (caused by the device)
- Air embolism
- Allergic reaction
- Bleeding
- Cardiac perforation
- Cardiac tamponade
- Chronic nerve damage
- Decompensated heart failure
- Elevated pacing thresholds
- Erosion
- Exacerbation of heart failure
- Excessive fibrotic tissue growth
- Extracardiac stimulation (phrenic nerve, diaphragm, chest wall)
- Failure to detect VT/VF
- Fluid accumulation
- Formation of hematomas or cysts
- Generator malfunction
- Hemothorax
- Inappropriate shocks
- Infection
- Lead/port damage
- Lead fracture
- Lead insulation damage
- Lead migration/dislodgement
- Lead Noise
- Loss of capture
- Failure to deliver therapy
- Loss of sensing
- Myocardial Infarction (MI)
- Oversensing
- Pectoral Stimulation
- Pericardial Effusion
- Pneumothorax
- Thromboemboli
- Undersensing
- Venous occlusion

Patients susceptible to frequent shocks despite antiarrhythmic medical management may develop psychological intolerance to an ICD or CRT-D system that may include the following:

- Dependency
- Depression
- Fear of premature battery depletion
- Fear of shocking while conscious
- Fear that shocking capability may be lost
- Imagined shocking (phantom shock)

For unexpected failure modes or unexpected adverse events, the site should follow their standard reporting practices for medical device reporting (MDR). As defined in 21 CFR 803, a MDR reportable event (or reportable event) means: An event that device user facilities become aware of that reasonably suggests that a device has or may have caused or contributed to a death or serious injury. A device user facility must report deaths and serious injuries that a device has or may have caused or contributed to, establish and maintain adverse event files, and submit summary annual reports to FDA.

12.0 Other Reported Events

Other Reported Events are any other clinical event that is submitted by the investigator which is not caused by or associated with the study device and/or system component(s) and/or defined as an adverse event in section 11.0.

13.0 Health Care Utilization/Hospitalization Visits

All inpatient, urgent care, ER, observational or outpatient visits for cardiac or suspected heart failure reasons which occur after a successful implant of the Optisure RV lead must be reported using the Health Care Utilization Case Report Form.

A Health Care Utilization/Hospitalization Case Report Form must be completed and submitted along with supporting documentation (i.e. Admission/Discharge Summary) to St. Jude Medical using the EDC system.

14.0 Deaths

All patient deaths that occur during this investigation must be reported to St. Jude Medical as soon as possible. Notification of death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the appropriate case report forms (Death form, Withdrawal form, and Product Out of Service form). A Mortality Committee will review and classify all patient deaths. It is the investigator's responsibility to notify the IRB/MEC per the IRB/MEC policy. Details of death and the following information, if available, should be provided in a letter to St. Jude Medical by the investigator summarizing the patient's course since enrollment in the study:

- Date and time of death

- Place death occurred (e.g., hospital, nursing home, patients home)
- If death was witnessed
- Identification of the rhythm at the time of death, if known (include any available documentation)
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event.
- Autopsy report (if performed)
- Whether it was device and/or procedure related
- Whether it was related to the study
- Device configuration at the time of death

Provide clinical notes and witness statements. If possible, interrogate the pulse generator. Retrieve and print all episode diagnostics, IEGMs, and programmed parameters. If applicable, the pulse generator should then be programmed OFF.

Every attempt should be made to explant the pulse generator and/or leads intact. Any explanted devices or leads (including damaged leads, lead segments and lead fragments) should be returned to St. Jude Medical for analysis promptly. In the event that the device is not explanted, the above procedure must be followed to retrieve the data. The reason the pulse generator and/or lead(s) are not being returned to St. Jude Medical must be stated clearly on the case report form.

15.0 Patient Relocation

If a patient moves from the geographic catchment area of their investigator, then St. Jude Medical (SJM) will first attempt to place the patient with another Optisure investigator. If it is not possible to place the patient with another Optisure investigator, then SJM will request that the patient's new physician forward the patient's study information to the investigator. If patient follow up information is not forwarded to the investigator the patient will be considered lost to follow up per the lost to follow up definition in section 16.0.

16.0 Withdrawals

Withdrawal is defined as termination of participation of a patient from a clinical study. All reasonable efforts should be made to retain the subject in the clinical study until completion of the clinical study. Reasons for withdrawal include, but are not limited to the following:

- Patient Death
- Patient and/or Family Request
- Patient Lost to Follow-Up - Defined as the following: Patient will be considered "lost to follow-up" after a minimum of two documented phone calls were made by personnel at the study center to the patient or emergency contact, a certified letter was sent to the last known address, and two consecutive visits pass without an investigator receiving data
- Patient Non-compliance

- Patient Participation terminated by Investigator
- Sponsor Request
- Unsuccessful Implant
- Heart transplant
- Optisure lead removed or capped without a Optisure lead replacement

A Withdrawal Case Report Form should be completed and submitted to St. Jude Medical using the EDC system. **If there is a potential withdrawal in the study, please contact a member of the study team to see if there is anything that can be done to keep the patient in the study.**

17.0 Returning Devices and Leads to St. Jude Medical

St. Jude Medical strongly encourages physicians to notify our Patient Records department (888-SJM-2763) each time a device or lead is removed from service for any reason. Additionally, all explanted products are requested to be returned to St. Jude Medical for laboratory evaluation whether or not a malfunction is suspected. To facilitate the return of explanted devices and leads, St. Jude Medical offers a no-cost Returned Products Kit comprised of a postage paid explant box with a shipping address label, a removed device information form, a biohazard bag, and biohazard labels to seal the explant box. This kit, #N0004, can be ordered free of charge by contacting St. Jude Medical Customer Service (888-SJM-2763).

18.0 Risk Analysis

The risks associated with the use of the Optisure lead are anticipated to be comparable to those associated with the use of other currently available ICD leads. Patients participating in this study are indicated for an ICD or CRT-D system as part of their standard medical management and are subject to the risks associated with these devices (refer to Section 11.0). There are no expected additional risks associated with this study beyond those found with testing at standard implant and follow up visits.

19.0 Committees

19.1 Cinefluoroscopy Adjudication Committee

Cinefluoroscopy Adjudication Committee (CAC) will be comprised of at least three Electrophysiologists or Cardiologists specially trained in using Cinefluoroscopy in this patient population. The role of the CAC is to adjudicate the cinefluoroscopy videos/images to determine the presence of lead compromise in the sub-study patient population. Committee members will be reviewing the cinefluoroscopy videos/images for the 24, 36, 48 and 60 month follow-up visits and any additional cinefluoroscopy videos/images

received during the course of the study. Data will be sent either electronically or on a disk to the committee members. Once the adjudication is complete, a cinefluoroscopy adjudication form will be collected per patient per study visit. If the presence of externalized conductors is deemed to be 'indeterminate' then the cinefluoroscopy will be further reviewed by two other CAC members. Sample pictures/fluoros/x-rays and other examples of "other visual lead anomalies" will be provided to the adjudication committee to aid the committee members in identifying these "other visual lead anomalies" on the cinefluoroscopy videos/images received from the site.

Only the adjudicated imaging data will be included in the progress reports. Percentage of leads with compromise, evidenced by imaging, will be presented in the report. The type, extent and location of lead compromise, as described in Appendix A, will also be included. As detailed in Appendix A, the HV lead is divided into different regions. Both the proximal as well as distal ends of externalization will be recorded by the cinefluoroscopy adjudication committee. The distribution of externalization (both absolute number and percentage) by each region of the lead will be presented for both proximal and distal ends of externalization. The distribution of "other visual lead anomalies" (both absolute number and percentage) by each region of the lead and each individual subcategory of "other visual lead anomalies" will be presented. The frequency (both absolute number as well as percentage) of individual subcategories will be reported for "other visual lead anomalies".

19.2 Electrical Data Adjudication Committee

Electrical Data Adjudication Committee (EDAC) will be comprised of at least three Electrophysiologists or Cardiologists experienced in analyzing and interpreting device data. The role of the EDAC is to adjudicate the device session records to determine the presence of electrical dysfunction in the Optisure lead sub-study patient population. Committee members will be reviewing device session records for all leads taken out of service during the course of the sub-study. Data will be sent either electronically or in a paper binder to the committee members. Once the adjudication is complete, an electrical data adjudication form will be collected per patient.

Only the adjudicated cases of electrical dysfunction will be included in the progress reports. Percentage of leads with electrical dysfunction (based on the definition in section 2.0) will be part of the reports.

20.0 Investigator Information

This post approval study will be conducted by investigators with experience and/or willingness to be trained in the use of ICD or CRT-D devices. A principal investigator should have experience in and/or will be responsible for:

- Conducting the clinical investigation in accordance with the signed agreement with St. Jude Medical, the protocol, all applicable FDA regulations (21 CFR Parts 50, 54, 56), GCP guidelines, and any conditions of approval imposed by the IRB/MEC
- Providing signed Investigator/Co-Investigator (s) Agreement
- Providing signed Financial Disclosure Form for Clinical Investigators
- Providing IRB/MEC Approved Informed Consent
- Collection and archiving of data obtained pursuant to the requirements of the protocol during the course of the study and after the study has been completed
- Strict adherence to the post approval study testing requirements
- Screening and selecting appropriate patients

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the post approval study and collecting all required data.

21.0 Monitoring Procedures

St. Jude Medical will serve as the "sponsor" of the Optisure lead study. It is the responsibility of St. Jude Medical as the "sponsor" of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met.

Prior to beginning the study, a St. Jude Medical monitor will contact the investigator or designee to discuss the protocol and to review the data requirements in detail. A St. Jude Medical monitor will visit the investigator or designee periodically during the study to monitor progress, to assist in gathering the required data and to answer any questions. During these visits, the clinical monitor will review the patient's records to verify that all records and files are up to date, and to ensure compliance with all requirements of the protocol and FDA regulations.

The investigator will make patient and study records available to the clinical monitor for periodic inspection. Clinical monitoring will be conducted under the St. Jude Medical standard operating procedure 9.4.3 (Clinical Monitoring Procedure) or, if developed, the study specific Monitoring Plan.

Responsibility for overall study management will be held by the Vice President of Clinical Affairs, St. Jude Medical.

Clinical Affairs
St. Jude Medical
15900 Valley View Court
Sylmar, CA 91342
TEL: (800) 423-5611 ext. 2739 or 2872
FAX: (800) 254-6411

22.0 FDA Inspections

The investigator and /or designee should contact St. Jude Medical in Sylmar, CA within 24 hours upon being notified of an impending FDA inspection. A clinical monitor may assist and review study documentation with the investigator and/or designee to prepare for the audit.

An investigator shall permit authorized FDA employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where post approval study devices are used and to inspect and copy all records relating to the study.

An investigator shall permit authorized FDA employees to inspect and copy records that identify subjects, upon notice that FDA has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB/MEC have not been submitted or are incomplete, inaccurate, false, or misleading.

23.0 Labeling

Please see the respective device and lead user manuals for appropriate handling and implant technique of the Optisure lead.

24.0 Consent Materials

See attached consent forms in Appendices B and C

Failure to obtain informed consent from a patient prior to study enrollment should be reported to St. Jude Medical within 5 working days and to the reviewing IRB/MEC consistent with the IRB/MEC's reporting requirements.

25.0 IRB/MEC Information

IRB/MEC approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB/MEC approval and corresponding informed consent must be forwarded to St. Jude Medical prior to authorization of the institution to begin the study. Any withdrawal of IRB/MEC approval should be reported to St. Jude Medical within 5 working days of the withdrawal of approval.

Institutional Review Board (IRB/MEC) for participating Institutions
A list of IRB/MEC's for Institutions participating in the Clinical Investigation will be provided upon request.

26.0 Other Institutions

The name and address of each institution, at which a part of the investigation may be conducted, that has not been identified under IRB/MEC information, will be provided upon request.

26.1 Records and Reports

Clinical investigators of post approval studies performed as a condition of FDA approval are required to maintain records, prepare and submit reports, and permit FDA Bioresearch Monitoring Inspections relating to the investigator's participation in and conduct of the study.

26.2 Custody

An investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them as described, including the requirements regarding FDA inspection. Notice of transfer shall be given to St. Jude Medical and FDA no later than ten working days after transfer occurs.

26.3 Retention Period

Clinical investigators in the Optisure lead study are required to maintain records during the investigation and for a period of at least two years after the date on which the post approval study is terminated or completed.

27.0 Publications

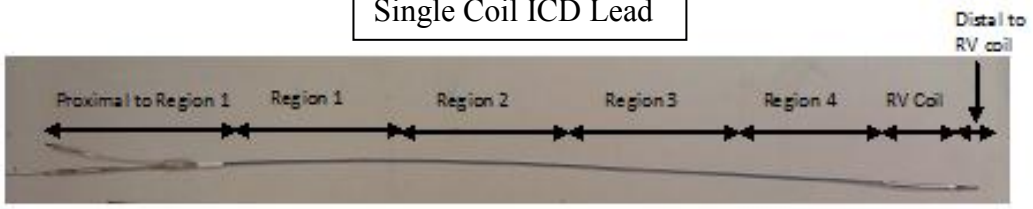
This study will be posted on ClinicalTrials.gov and results will be posted on ClinicalTrials.gov as required.

Appendix A: Lead Compromise Details

Lead Compromise as evidenced by imaging includes externalized conductors or other visual lead anomalies. The types, extent and location of these anomalies in high voltage (HV) leads are listed below:

Type	**Extent**	**Location on the lead (see figure below)**
Externalized Conductors	- Apparent width and length of externalized conductors on fluoroscopy	- Region 1 - Region 2 - Region 3 - Region 4
Other Visual Lead Anomalies	- Fracture - Subclavian crush - Kink - Other irregularities	- Region 1 - Region 2 - Region 3 - Region 4 - RV coil - SVC coil - Distal to RV coil - Proximal to region 1

Single Coil ICD Lead



Dual Coil ICD Lead

Appendix B: Study Consent Form

Statement of Informed Consent

Study Title: Optisure Lead Study

Introduction

You are being asked to participate in a post approval study involving research. This informed consent form explains why this study is being performed and what your role will be if you decide to participate. This form also describes the possible risks associated with being in this study. This study is sponsored by St. Jude Medical, Inc., a company that currently manufactures Cardiac Resynchronization Therapy Defibrillators (CRT-Ds), Implantable Cardiac Defibrillators (ICDs), pacemakers, lead systems, heart valves and catheters.

Please read this form and feel free to ask your doctor any questions you may have about the information provided. You will be given the opportunity to ask questions and have your questions answered before making a decision whether to take part in the study. Please take your time and discuss this information with your family, friends or family physician.

If you agree to be in the study, you will need to sign this consent form. You will be given a copy to keep. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled.

What is the purpose of this study?

This study is called the Optisure ^{TM} Lead study. You are being asked to participate because you either have been implanted with one of St. Jude Medical's family of high voltage right ventricular leads within the past 30-days or are having one of St. Jude Medical's family of high voltage right ventricular leads implanted. These products are already approved by the FDA and we are studying their long term performance.

These leads are currently being implanted in other patients not participating in this research study. The leads will be referred to as "the RV lead" (right ventricular lead). The implanted lead along with the CRT-D or ICD will be referred to as "the device system."

Even though your device system has been approved by the FDA, this study will allow St. Jude Medical to continue to monitor it for a period of up to five years from the date of your implant. You are being asked to take part in this study because your doctor (Dr. _____) has determined that you are a suitable candidate. Your participation in this study is voluntary.

Up to 1725 patients will be enrolled in this study. Patients will be enrolled at a maximum of 60 study centers.

What will happen if I take part in this post approval study?

Your doctor has determined that you are a suitable candidate to participate in the Optisure Lead Study because you will be or have already been implanted with a St. Jude Medical (SJM) Optisure lead within the past 30-days. Your device system will be tested using a programmer (computer) that will be used to communicate with your device system. You should not feel any discomfort during this procedure. It should take no longer than 15 minutes to gather information on your device.

If you decide to take part in this study prior to your implant procedure, the following describes what will happen. If you have already been implanted with the Optisure lead then this section does not apply to you and you may skip to the Follow-up requirements section below. The implant procedure will be the same as if you were receiving a device system and not participating in a study. The device system will be implanted during a procedure in the Electrophysiology Laboratory (EP Lab) or in the Operating Room (OR). The total estimated time for you to have the device put in is approximately 2 hours.

Prior to the procedure, the doctor will give you medicine to make you sleepy. This could involve general anesthesia or a local anesthesia and sedation, depending on your doctor's preference. The doctor will discuss this with you before surgery.

The device system will have one (1), two (2) or three (3) wires depending on the device that your doctor decides is right for you. The leads are inserted through your veins, positioned in your heart and, after testing, are connected to the ICD or CRT-D device. These wires allow information to travel between your heart and the device, and help the device monitor your heart. The study doctor will use x-rays to be sure that the wires are positioned correctly. The lead placement procedure and the location of the implanted leads will be the same as if you were receiving a device system and not participating in a study.

It is common practice for testing to be performed during the placement of your device. This is to confirm that the wires are placed in the position that would be most effective in pacing your heart and detecting and treating your heart rhythm problem(s). Testing of the device may cause your heart to beat very fast similar to what happens when you are having an arrhythmia. Your doctor will then use your device to return your heart to its regular rhythm. Throughout the procedure, there are back-up defibrillators readily available, if they should become necessary. After testing is finished, a pocket for the device will be made under the skin in the left or right upper-chest near the shoulder and the incision will be closed after the device is placed in the pocket. The St. Jude Medical CRT-D or ICD device and wires that will be used in the study are all legally marketed. This procedure and testing are the same regardless of whether you participate in this study or not.

Follow-up Requirements

If you decide to take part in this study, you will be required to return for follow-up visits. The function of your device system will be checked at each of these visits. The follow-up visits required for this study will occur every 6 months after you leave the hospital until you have completed 5 years of visits. After your 5 year visit, your participation in the study is complete.

These 6 month follow-ups will occur in-clinic.

At each in-clinic follow-up visit, you will have the following testing done by the research staff.

• Your device system will be tested using a programmer (computer) that will be used to communicate with your device system. You should not feel any discomfort during this procedure. It should take no longer than 15 minutes to gather information on your device.

• Your study doctor or nurse will ask you questions regarding your health.

The testing and information collected at these follow up visits is no different than if you were not participating in this study.

You will be required to carry an identification card indicating that you have a St. Jude Medical device system. If you are hospitalized during your participation in this study, please inform the treating doctor that you are enrolled in this post approval study and show the doctor your identification card. If you have any changes in your address or telephone number over the length of this study, please report those changes to your study doctor and to St. Jude Medical Patient Tracking at 1-800-423-5611.

What are the possible discomforts, side effects, and risks?

Since your RV lead is already approved by the FDA, the risks associated with your participation will not be different than if you chose not to participate in this study. If any significant new findings are identified during the study that would affect your willingness to participate, your doctor will inform you of this new information. Any risks that may occur because you are having a device system implanted will be explained in a separate consent.

What are the possible benefits to you or to others?

The information obtained through this study will add to the overall knowledge of the long term performance of the lead. We cannot and do not guarantee that you will receive any benefits from taking part in this study.

If you do not want to take part in this study, what other options are available to you?

Your participation in this study is voluntary. You are free to refuse to be in the study, and your refusal will not influence your current or future relationship with your doctor. If you choose not to be in the study, your doctor will still follow your progress in a similar manner. However, no data will be submitted to SJM.

How will your privacy and the confidentiality of your research records be protected?

If you choose to take part in this study, your medical records will be kept confidential to the extent provided by federal, state and local law. Nothing about you, your illness or your treatment will be made public. The information obtained from the study will be submitted to St. Jude Medical. The data will then be presented in a report to the applicable governmental agencies (for example: the Food and Drug Administration). Your personal information will be kept confidential. Any publications using the information collected during the study will not include your name or any information that can identify you. Your name will not be included in mailing lists or used for marketing purposes. Only information about your medical condition as it pertains to the study will be provided to St. Jude Medical. Information from this study may be exported to countries where different data protection laws apply. Professional standards of confidentiality and data protection will be maintained. In order to verify study data, monitors from governmental agencies (for example: the Food and Drug Administration), St. Jude Medical, and the hospital's Institutional Review Board will have the right to review your medical records as they pertain to this study.

If you receive medical care at another location while still being followed in this study, you agree to allow copies of your medical records from the location to be made available for collection of data related to the study.

If you choose to take part in this study, will it cost you anything?

All test and procedures, as well as the cost of your device implantation will be the responsibility of you and your insurance company. There is no guarantee that your insurance company will cover 100% of the expenses. You are encouraged to check with your insurance company to verify coverage or payments of these procedures. The testing procedures listed in the follow-up requirements section of this consent form are all considered standard of care.

What if the device needs to be removed?

In the event your device system or any part has to be removed, you agree to have the removed device system components returned to St. Jude Medical for analysis. In the event of your death, you agree that your implanted device system may be removed and returned to St. Jude Medical for analysis. Should you withdraw from this study and choose to have your device system or any part of it removed, the cost will be your responsibility.

Who can you contact for study information?

If you have any questions regarding your participation in this study, please contact Dr. _____ at ___-___-_____.

In addition, if you have questions about your rights as a research patient, or if you have complaints, concerns, or questions about the research, please contact _____ the Institutional Review Board Administrator at ___-___-_____.

What if you are injured because of the study?

In the event of injury to you resulting directly from your participation in this study, medical treatment shall be available to you. You or your insurance company shall be responsible for all costs as a result of that treatment. No other arrangement has been made for financial payments or other forms of compensation (such as lost wages, lost time or discomfort) with

respect to such injuries. However, you do not waive any legal rights by signing this consent form.

During the study, if you experience any medical problems or illnesses, please contact Dr. _____ at ___-___-_____.

What are your rights if you decide to participate in this study?

Your signature on this consent form means that you have received information about this study and that you agree to be a part of the study. If you decide to participate, you are free to discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to stop your participation in this post approval study for any reason, you should contact Dr. _____ at ___-___-_____. A decision to withdraw or to not take part in the study will not affect the quality of medical care that you receive. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled or affect your future medical care.

Your doctor or the sponsor, St Jude Medical, may decide to withdraw you from the study at any time without your consent. If certain circumstances arise and it is felt to be in your best interest, or if the study is discontinued, your doctor may withdraw you from this research. If you experience side effects as described in the risks section or if you become ill during the research, you may have to be withdrawn from the study, even if you would like to continue. Your study doctor will make this decision.

Participation in the study is strictly voluntary. Your decision whether or not to participate will not affect the quality of medical care that you receive or your future relations with your doctor.

If significant new findings are developed during the course of this study, your doctor will be notified immediately by St. Jude Medical and will advise you of such developments that may affect your willingness to continue your participation in this study.
You will be a given a copy of this form to keep.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You are making a decision as to whether or not to participate in the study. Your signature indicates that you have read the information provided above and have decided to participate in the study. You may withdraw at any time after signing this form should you no longer want to participate in this study.

Printed Name of Subject:_____

Signature of Subject:_____

Date (must be written in by Subject):_____

_____
Name of Person Obtaining Consent

Date of Consent:_____

Appendix C: Sub-Study Consent Form

Statement of Informed Consent

Study Title: Optisure Lead Sub-Study

Introduction

You are being asked to participate in a sub-study involving research. This informed consent form explains why this sub-study is being performed and what your role will be if you decide to participate. This form also describes the possible risks associated with being in this sub-study. This sub-study is sponsored by St. Jude Medical, Inc., a company that currently manufactures Cardiac Resynchronization Therapy Defibrillators (CRT-Ds), Implantable Cardiac Defibrillators (ICDs), pacemakers, lead systems, heart valves and catheters.

Please read this form and feel free to ask your doctor any questions you may have about the information provided. You will be given the opportunity to ask questions and have your questions answered before making a decision whether to take part in the study. Please take your time and discuss this information with your family, friends or family physician.

If you agree to be in the sub-study, you will need to sign this consent form. You will be given a copy to keep. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled. You may also refuse to participate in this sub-study and still participate in the Optisure ™ Lead Post Approval Study.

What is the purpose of this sub-study?

This sub-study is called the Optisure ™ Lead sub-study. You are being asked to participate because you have agreed to participate in the Optisure ™ Lead Post Approval Study.

You are being asked to take part in this sub-study because your doctor (Dr. _____) has determined that you are a suitable candidate. Your participation in this sub-study is voluntary.

Up to 318 patients will be enrolled in this sub-study. Patients will be enrolled at a maximum of 60 study centers.

The purpose of this sub-study is to determine the incidence of wires being visible outside the lead insulation body (externalized conductors) or other forms of visual compromise in the Optisure ICD leads. In order to evaluate the incidence of externalized conductors or other forms of visual compromise in the Optisure ICD leads, cinefluoroscopy (i.e. video or x-ray) will be taken to determine the incidence of externalized conductors or other forms of visual compromise of the lead.

What will happen if I take part in this sub-study?

Your doctor has determined that you are a suitable candidate to participate in the Optisure Lead Sub-Study because you are participating in the Optisure ™ Lead Post Approval Study. You will be screened for evidence of externalized conductors, forms of visual compromise of the lead through cinefluoroscopy (i.e. X-ray, video, etc.), demographics (gender, age, medical history, history of electrical malfunctions in the past, etc.) and lead electrical performance will also be evaluated.

There may be a representative of the sponsor at your study visits and the representative and the sponsor's representative will work under the direction of your study doctor or other care provider.

Follow-up Requirements

You will be screened for evidence of externalized conductors or other forms of visual compromise of the lead through cinefluoroscopy (i.e. X-ray, video, etc.) every 12 months starting 24 months post lead implant up to 60 months post lead implant. None of the test required in this sub-study are experimental in nature.

You will be required to carry an identification card indicating that you have a St. Jude Medical device system. If you are hospitalized during your participation in this study, please inform the treating doctor that you are enrolled in this sub-study and show the doctor your identification card. If you have any changes in your address or telephone number over the length of this study, please report those changes to your study doctor and to St. Jude Medical Patient Tracking at 1-800-423-5611.

What are the possible discomforts, side effects, and risks?

Since your RV lead is already approved by the FDA, the risks associated with your participation will not be different than if you chose not to participate in this sub-study. If any significant new findings are identified during the sub-study that would affect your willingness to participate, your doctor will inform you of this new information.

There may be risks that are unforeseeable. In addition, there may be risks associated with (a small amount of radiation) exposure to cinefluoroscopy (required in the sub-study) which may increase your risk of cancer. The estimated fluoroscopy time required is approximately 45 seconds per visit.

What are the possible benefits to you or to others?

If you decide to take part in the sub-study, you may encounter an additional benefit if the incidence of externalized conductors is identified. You may also be more closely monitored by your physician.

If you do not want to take part in this sub-study, what other options are available to you?

Your participation in this sub-study is voluntary. You are free to refuse to be in this sub-study, and your refusal will not influence your current or future relationship with your doctor nor will it influence your participation in the Optisure ™ Lead Post Approval Study. If you choose not to be in the study, your doctor will still follow your progress in a similar manner and your decision will not result in any penalty or loss of benefits to which you are otherwise entitled or affect your future medical care. However, no data will be submitted to SJM. Should you choose not to participate in this sub-study, you may discuss alternatives with your physician that may include no screening or screening at intervals other than what is required by the sub-study.

How will your privacy and the confidentiality of your research records be protected?

If you choose to take part in this sub-study, your medical records will be kept confidential to the extent provided by federal, state and local law. Nothing about you, your illness or your treatment will be made public. The information obtained from the sub-study will be submitted to St. Jude Medical. The data will then be presented in a report to the applicable governmental agencies (for example: the Food and Drug Administration). Your personal information will be kept confidential. Any publications using the information collected during the sub-study will not include your name or any information that can identify you. Your name will not be included in mailing lists or used for marketing purposes. Only information about your medical condition as it pertains to the sub-study will be provided to St. Jude Medical. Information from this sub-study may be exported to countries where different data protection laws apply. Professional standards of confidentiality and data protection will be maintained. In order to verify sub-study data, monitors from governmental agencies (for example: the Food and Drug Administration), St. Jude Medical, and the hospital's Institutional Review Board will have the right to review your medical records as they pertain to this sub-study.

If you receive medical care at another location while still being followed in this sub-study, you agree to allow copies of your medical records from the location to be made available for collection of data related to the sub-study.

If you choose to take part in this sub-study, will it cost you anything?

All the tests for this sub-study will be paid by the sponsor.

What if the device needs to be removed?

In the event your device system or any part has to be removed, you agree to have the removed device system components returned to St. Jude Medical for analysis. In the event of your death, you agree that your implanted device system may be removed and returned to St. Jude Medical for analysis. Should you withdraw from this sub-study and choose to have your device system or any part of it removed, the cost will be your responsibility.

Who can you contact for study information?

If you have any questions regarding your participation in this sub-study, please contact Dr. _____ at ___-___-_____.
In addition, if you have questions about your rights as a research patient, or if you have complaints, concerns, or questions about the research, please contact _____ the Institutional Review Board Administrator at ___-___-_____.

What if you are injured because of the sub-study?

In the event of injury to you resulting directly from your participation in this sub-study, medical treatment shall be available to you. You or your insurance company shall be responsible for all costs as a result of that treatment. No other arrangement has been made for financial payments or other forms of compensation (such as lost wages, lost time or discomfort) with respect to such injuries. However, you do not waive any legal rights by signing this consent form.

During the sub-study, if you experience any medical problems or illnesses, please contact Dr. _____ at ___-___-_____.

What are your rights if you decide to participate in this sub-study?

Your signature on this consent form means that you have received information about this sub-study and that you agree to be a part of the sub-study. If you decide to participate, you are free to discontinue participation at any time without penalty or loss of benefits to which you are otherwise entitled. If you wish to stop your participation in this sub- study for any reason, you should contact Dr. _____ at ___-___-_____. A decision to withdraw or to not take part in the sub-study will not affect the quality of medical care that you receive or your ability to continue your participation in the Optisure ™ Lead Post Approval Study. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled or affect your future medical care.

Your doctor or the sponsor, St Jude Medical, may decide to withdraw you from the sub-study at any time without your consent. If certain circumstances arise and it is felt to be in your best interest, or if the sub-study is discontinued, your doctor may withdraw you from this research. If you experience side effects as described in the risks section or if you become ill during the research, you may have to be withdrawn from the sub-study, even if you would like to continue. Your sub-study doctor will make this decision.

Participation in the sub-study is strictly voluntary. Your decision whether or not to participate will not affect the quality of medical care that you receive or your future relations with your doctor.

If significant new findings are developed during the course of this sub-study, your doctor will be notified immediately by St. Jude Medical and will advise you of such developments that may affect your willingness to continue your participation in this sub-study.
You will be a given a copy of this form to keep.

A description of this clinical trial will be available on http://www.Clinical Trials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

You are making a decision as to whether or not to participate in the sub-study. Your signature indicates that you have read the information provided above and have decided to participate in the sub-study. You may withdraw at any time after signing this form should you no longer want to participate in this sub-study.

Printed Name of Subject:_____

Signature of Subject:_____

Date (must be written in by Subject):_____

_____
Name of Person Obtaining Consent

Date of Consent:_____

Appendix D: Detailed Sample Size Calculations for Complication Free Survival Endpoint

The sample size is calculated assuming that the time to first complication follows an exponential distribution. For a given sample size (N), N samples of time to first complication are generated from an exponential distribution with rate of (-log(0.95)/5 = 0.0103). The 95% lower confidence bound for the survival probability at 5 years is calculated by transformation from its log-survival scale based on Peto et al. For each sample size N, this is repeated 10,000 times and the power is estimated as the number of times the 95% lower confidence bound is greater than 0.925. This process is repeated and the power is estimated for different values of N, and the sample size is chosen as the smallest N for which the estimated power is > 80%. Simulations were carried out in R version 2.7.1 and the code is provided below:

```
# Power calculation for exponential assumption
p.nul <- 0.925
p.exp <- 0.95
l.exp <- -log(p.exp)/5

N <- seq(630,660,5)
P <- numeric(length(N))

for (i in 1:length(N)){
   n <- N[i]
   l <- NULL
   for (j in 1:10000) {
      print(j)
      x <- data.frame(time=rexp(n, l.exp), event=1)
      s.fit <- summary(survfit(Surv(time, event)~1, data=x, conf.int=0.9,
   conf.lower="peto", conf.type="log-log"))
      idx <- sum(s.fit$time<=5)
      l <- c(l, ifelse(idx==0, 1, s.fit$lower[idx]))
   }
   P[i] <- mean(l>p.nul,na.rm=T)
}
res <- cbind(N, P)
dimnames(res)[[2]] <- c("N", "Power")
```

Output:

```
> cbind(N, Power)
[1,] 630 0.8257
[2,] 635 0.8046
[3,] 640 0.7909
[4,] 645 0.8324
[5,] 650 0.8132
[6,] 655 0.8067
[7,] 660 0.8399
```

Detailed Sample Size Calculations for Complication rate

The 95% confidence interval for the Binomial proportion is calculated based on the Clopper-Pearson exact Binomial method. For a given observed value *x*, of the random variable *X*, which has a Binomial*(n,p)* distribution, the 100(1-α)% confidence interval for *p* is given by (L,U), where [1]:

$$L = \begin{cases} 0 \ for \ \ x = 0 \\ \dfrac{x}{x + (n - x + 1)F_{1-\alpha/2;2n-2x+2,2x}} \ for \ 0 < x < n \\ \left(\dfrac{\alpha}{2}\right)^{1/n} \ for \ \ x = n \end{cases}$$

$$U = \begin{cases} 1 - \left(\dfrac{\alpha}{2}\right)^{1/n} \ for \ x = 0 \\ \dfrac{(x+1)F_{1-\alpha/2;2x+2,\,2n-2x}}{(n-x) + (x+1)F_{1-\alpha/2;\,2x+2,\,2n-2x}} \ for \ 0 < x < n \\ 1 \ for \ x = n \end{cases}$$

Simulations for safety endpoint:
For a particular sample size (*n*), generate 10,000 random binomial samples with $p = 0.4\%$.
Calculate the 95% Clopper-Pearson confidence interval for each sample.
The mean of the 95% Upper Confidence Limit is estimated by the average UCL from the 10,000 samples.

The above process was repeated for different values of *n*, and the sample size was chosen as the smallest *n* such that the mean 95% UCL is no more than 1% for any sample size larger than *n*.
Simulations were carried out in R version 2.5.1 and the code is provided below:

```
# Clopper-Pearson interval
intcp <- function(x, n, alpha) {
       fl <- rep(1, length(x))
       fu <- rep(1, length(x))

       fl[x>0] <- qf(1-alpha/2, 2*(n-x[x>0]+1), 2*x[x>0])
       l <- x/(x+(n-x+1)*fl)
       fu[x<n] <- qf(1-alpha/2, 2*(x[x<n]+1), 2*(n-x[x<n]))
       u <- (x+1)*fu/(n-x+(x+1)*fu)

       l[x==n] <- (alpha/2)^(1/n)
       u[x==0] <- 1 - (alpha/2)^(1/n)
       return(u)
}

N <- seq(800, 900, by=1)
W <- numeric(length(N))
p.exp <- 0.035
alpha <- 0.05
```

```
for (i in 1:length(N)){
       n <- N[i]
       x <- rbinom(10000, n, p.exp)
       W[i] <- mean(intcp(x,n,alpha))
}

res <- cbind(N, W)
dimnames(res)[[2]] <- c("N", "UCL_CP")
```

Output:

```
        N     UCL_CP
  [1,] 800 0.05017309
  [2,] 801 0.05024370
  [3,] 802 0.05012932
  [4,] 803 0.05018507
  [5,] 804 0.05014391
  [6,] 805 0.04987072
  [7,] 806 0.04995208
  [8,] 807 0.05000009
  [9,] 808 0.05003701
 [10,] 809 0.04995956
 [11,] 810 0.05008931
 [12,] 811 0.04996120
 [13,] 812 0.04996724
 [14,] 813 0.04991788
 [15,] 814 0.04996942
 [16,] 815 0.04987241
 [17,] 816 0.04994953
 [18,] 817 0.04987100
 [19,] 818 0.05001757
 [20,] 819 0.04988905
 [21,] 820 0.04999551
 [22,] 821 0.04991874
 [23,] 822 0.04984346
 [24,] 823 0.04982024
 [25,] 824 0.04987433
 [26,] 825 0.04984522
 [27,] 826 0.04986564
 [28,] 827 0.05003381
 [29,] 828 0.04979808
 [30,] 829 0.04988435
 [31,] 830 0.04986327
 [32,] 831 0.04984702
 [33,] 832 0.04976303
 [34,] 833 0.04985150
 [35,] 834 0.04983886
 [36,] 835 0.04980120
 [37,] 836 0.04974487
 [38,] 837 0.04983173
 [39,] 838 0.04974888
 [40,] 839 0.04968908
 [41,] 840 0.04959278
 [42,] 841 0.04955788
 [43,] 842 0.04969887
 [44,] 843 0.04967408
 [45,] 844 0.04966207
```

References

[1] Peto R, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient: II. Analysis and examples. *British Journal Cancer* 1977, 35:1-39

[2] Hahn, G.J. and Meeker, W.Q. Statistical Intervals: A Guide for Practitioners. Wiley Series in Probability and Mathematical Statistics. 1991.

[3] Stephen CH et al. *Heart Rhythm* (2007), 4:1260-1263.

[4] Bardy GH et al *NEJM* (2005), Amiodarone or an Implantable Defibrillator-Cardioverter for Congestive Heart Failure, 352: 225-237.

[5] Moss AJ et al *NEJM* (2002), Prophylactic Implantation of a Defibrillator in Patients with Myocardial Infarction and Reduced Ejection Fraction, 346: 877-883.

[6] RHYTHM ICD/QuickSite 1056K left heart lead study final report (IDE G020114).

[7] Biventricular Cardiac Pacing System and Cardiac Resynchronization Therapy Defibrillator System post-approval study approved under P030035/S002 and P030054/S002.

[8] Ha A, Vezi BZ, Keren A, et al. Predictors of Fracture Risk of a Small Caliber Implantable Cardioverter Defibrillator Lead. *PACE*, 2010;33(4):437-443.