Medtronic **Statistical Analysis Plan**	
Clinical Investigation Plan Title	Lead EvaluAtion for Defibrillation and Reliability (LEADR)
Clinical Investigation Plan Identifier	MDT19004
Clinical Investigation Plan Version	Version 4.0
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted], Principal Statistician [redacted], Sr Principal Statistician
2.0	• Section 5: updated enrollment cap specifications to align with CIP version 4.0 • Section 5.1: Clarification on time point of second decision point • Section 6.1.: added two-sided for clarification in "Comparisons between a Kaplan-Meier analysis and the planned Bayesian show that the lower bound of the 95% two-sided confidence interval from the Kaplan-Meier analysis at 6 months exceeded the 95% lower two-sided credible interval bound in the majority of simulations (see Figure 1 below, lower panels)". • Section 7.1.3: clarification on main analysis cohort for primary efficacy objective and how to handle study deviations with regard to defibrillation protocol • Section 7.1.3: added per protocol analysis cohort for primary efficacy objective • Section 7.3: updated enrollment cap specifications to align with CIP version 4.0 • Section 7.9.1.2: added clarification on when null hypothesis will be rejected based on posterior probability for primary safety objective • Section 7.9.1.4: Kaplan Meier estimate through 6 months and 95% two-sided confidence interval will always be provided instead of conditional • Section 7.9.2.2: added clarification on when null hypothesis will be rejected based on posterior probability for primary efficacy objective	[redacted] Principal Statistician [redacted], Sr Principal Statistician

Version	Summary of Changes	Author(s)/Title
	• Section 7.9.2.4: added “or successful termination should be confirmed by the episode review committee” • Section 7.9.2.6: added clarification on main analysis cohort for primary efficacy objective and how to handle study deviations with regard to defibrillation protocol • Section 7.9.2.6: added per protocol analysis cohort for primary efficacy objective	

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ACC	American College of Cardiology
AE	Adverse Event
AHA	American Heart Association
ATP	Anti-Tachycardia Pacing
CASE	Clinical Adjudication System
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
CRT-D	Cardiac Resynchronization Therapy - Defibrillator
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
EMEA	Europe, Middle East, and Africa
ERC	Episode Review Committee
ESC	European Society of Cardiology
FDA	Food and Drug Administration
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IDE	Investigational Device Exemption
LSE	Lead System Event
MedDRA	Medical Dictionary for Regulatory Activities
OC	Oracle Clinical
PCT	Pacing Capture Threshold
PMA	Pre-Market Application
PT	Preferred Term
RDC	Remote Data Capture
RV	Right Ventricle/Ventricular
SAP	Statistical Analysis Plan
SCD	Sudden Cardiac Death
SSVA	Sustained Shockable Ventricular Arrhythmia
US	United States

3. Introduction

Implantable cardioverter defibrillator (ICD) systems are indicated for patients who are at risk for sudden cardiac death (SCD), have exhibited life threatening tachyarrhythmia, or have compromised heart function associated with heart failure. Despite enhancements in design and technologies, the ICD lead is typically the most vulnerable component of the ICD system. Lower profile leads with the same or greater reliability can provide alternatives for physicians to serve patients with challenging or small anatomies.

Current Medtronic market released transvenous defibrillator leads (Sprint Quattro™ lead portfolio) have a lead body diameter of 8.6 Fr. To address needs for long term reliability, reduced defibrillation lead diameter, and ease of extraction for a defibrillation lead, Medtronic has developed a next generation defibrillation lead: The Model 093000 lead (further referenced as the 'Next Generation ICD lead'). The Next Generation ICD lead is built off the reliable and experienced platform of the Medtronic SelectSecure Model 3830 bradycardia lead.

The Next Generation ICD lead is a 4.7 Fr, steroid-eluting, catheter delivered, active fixation, polyurethane insulated, integrated bipolar single coil defibrillation lead. The lead is designed for pacing, sensing, cardioversion, and defibrillation therapies. The right ventricular (RV) coil delivers cardioversion and defibrillation therapies. Pacing and sensing occur between the helix and RV coil electrode. No new materials are being used in the Next Generation ICD lead. It has the same insulation materials, inner conductor and insulation, helix fixation, and implant procedure as the commercially available SelectSecure Model 3830 bradycardia lead as well as the SI polyimide coating utilized in Medtronic's left heart leads.

The components and materials in the Next Generation ICD lead have been used for 10+ years in other lead designs with acceptable field performance. This experience gives Medtronic knowledge of possible fracture mechanisms of the Next Generation ICD lead. With a fatigue survival engineering model that utilizes simulations to provide virtual patient modeling of predicted fracture survival, Medtronic has gained confidence in the expected high fatigue reliability of the Next Generation ICD lead. The virtual patient model incorporates current and planned use condition assessments with bench fatigue testing and numerical modeling, that replicate clinical use conditions over ten years of use. The virtual patient model has been validated against clinical data. The virtual patient model will be incorporated with the clinical data using a Bayesian piecewise exponential model for fracture free survival. Incorporation of the virtual patient data will supplement the clinical data allowing increased precision for the prediction of the Next Generation ICD lead's fracture free rate. The contribution of virtual patient data derived from the fatigue survival engineering model for the estimation of the Next Generation ICD lead failure rate will not exceed the contribution of actual patients enrolled in the LEADR study. Additionally, the contribution of the virtual patient data may be discounted if the predictions based on the fatigue survival engineering model differ from the clinical data.

This Statistical Analysis Plan (SAP) details the methods used to analyze the study's objectives. The SAP has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports for the LEADR clinical study. This SAP does not limit the analysis in reports. Additional analysis of the study data beyond this plan may be needed.

The following documents were used to create this SAP:

- CIP LEADR Version 4

4. Study Objectives

While the primary endpoints are consistent across all geographies, the timing for the evaluation of the safety endpoint does vary between US and non-US countries.

A pre-market application will be submitted in the US following evaluation of the study's primary safety and efficacy objectives.

4.1 Primary Safety Objective

Demonstrate that the freedom from major complications related to the Next Generation ICD lead at 6 months post-implant exceeds a pre-specified threshold of 90%.

4.2 Primary Efficacy Objective

Demonstrate the percentage of patients successfully defibrillated at implant with the Next Generation ICD lead exceeds a pre-specified threshold of 88%.

4.3 Secondary Objective

The secondary objective (safety) is to estimate the fracture-free rate of the Next Generation ICD lead throughout the study duration.

4.4 Ancillary Objectives

- [redacted]
- [redacted]
- [redacted]

4.5 Stage 1 Safety Objective

Estimate the 3-month RV lead-related major complication-free rate.

The stage 1 safety objective will be used to support marketing applications in countries outside the US where applicable.

5. Investigation Plan

The LEADR Clinical Study is a pre-market, prospective, multi-center, single-arm, non-randomized, Bayesian, adaptive study design, interventional pivotal clinical study. The LEADR clinical study aims to evaluate the efficacy and safety of the Next Generation ICD lead. The study is expected to be conducted at up to approximately 60 study sites. Participating geographies are expected to include but are not limited to: Australia, China, Hong Kong, Malaysia, Singapore, Japan, EMEA (Europe, Middle East, and Africa), Canada, Puerto Rico, and the United States.

The expected total study duration is approximately three years from the study's first enrollment. The enrollment period is expected to take approximately 15 months. Individual subjects may be participating in the study for a period of minimum 18 months to approximately 3 years. Subjects will undergo assessments at baseline, implant, pre-hospital discharge, 3 months, 6 months, and every 6 months thereafter until official study closure.

The Next Generation ICD Lead is indicated for the treatment of subjects who have experienced, or are at significant risk of developing, life-threatening ventricular tachyarrhythmias. The intended population to receive the Next Generation ICD Lead includes subjects who are indicated for implantation of a single or dual chamber ICD, or CRT-D according to current ACC/AHA/HRS or ESC guidelines.

The number of enrolled subjects in the study may vary from 500 to 900 subjects depending on the number of fractures observed during the study and on the number of implants as specified in the adaptive design. Maximum number of subjects enrolled at each site will be capped at 50 (10% of minimum number of enrollments (500)). Additionally, if the sample size is increased by a certain number of patients based on the adaptive study design, the enrollment cap will increase by 10% of the sample size increase for all sites, e.g., if the sample size increases by 100 implants, the enrollment cap for a given site will increase from 50 to 60 patients. If the sample size increases up to 900 enrollments, the enrollment cap will be 90 enrolled subjects per site. For the cohort of the first 150 implanted subjects, a single site cannot contribute more than 20% of subjects, i.e., the maximum number of subjects implanted at each site will be capped at 30 subjects, to minimize site bias for the stage 1 pre-market report.

This study will be conducted using an electronic data capture system (e.g., Oracle Clinical Remote Data Capture system, or OC RDC). The study will have a Data Monitoring Committee (DMC), Clinical Event Committee (CEC), and Episode Review Committee (ERC). The CEC will adjudicate adverse events and the adjudication data will be collected in the Clinical Adjudication System (CASE). The Episode Review Committee (ERC) containing independent reviewers will be utilized to review and adjudicate device-treated episodes to determine appropriateness of therapy (shocks and ATP) delivered to subjects. Data collection from ERC review will take place in WebEGM.

Inclusion and exclusion criteria are standard criteria for a clinical study, e.g., to ascertain required data collection, and/or are chosen to reduce risk of the defibrillation protocol and of confounding factors for evaluation of the safety of the lead. The inclusion and exclusion criteria can be found in CIP sections 8.3 and 8.4.

5.1 Adaptive Design

The LEADR Clinical Study design is adaptive with regard to both sample size and follow-up duration. The adaptive design is described in detail in CIP section 13.2.

The adaptive design features two decision points based on Next Generation ICD lead fractures observed in the trial. At these decision points only the number of fractures will be assessed. The primary and ancillary objectives will not be evaluated.

The first decision point occurs by the time of 500 subject implant attempts. If no fractures have been observed based on the data snapshot at that time point, enrollment will be halted, and all enrolled subjects will be followed. If instead six or more fractures have been observed, the trial will be halted for safety. If 1 to 5 fractures have been observed, the sample size will be increased accordingly (Table 1). To further account for subjects who enroll in the study but exit prior to an implant attempt, up to 900 subjects may be enrolled.

The second decision point will be when the first 500 subjects with an implant attempt have had the opportunity to have a 6-month visit (i.e., either the close of the 6-month visit window for the 500th subject with an implant attempt if that subject is still enrolled but did not have 6-month visit, or the date of the 6-month visit for the 500th subject with an implant attempt if the subject is still enrolled, or the date when the last still enrolled subject among the first 500 subjects with an implant attempt had their 6 month visit). If based on the data snapshot taken at that time point, no more than one fracture has been observed in the trial, the data will be analyzed when the first 500 subjects with an implant attempt have had the opportunity to be followed for 12 months, and an initial pre-market application report submitted to applicable regulatory agencies for review as needed. If instead more than one fracture has been observed by this time point, the data will be analyzed once the last (e.g., 600th, 700th, 800th) subject with an implant attempt has had the opportunity to reach a 12 month follow-up, and at that point an initial pre-market application report will be submitted to applicable regulatory agencies (see Table 1). Regardless, approximately 6 months later a follow-up report will be submitted with most subjects followed to 18 months.

Table 1 provides the likelihood of these decision point outcomes based on 10,000 simulations of the study under two scenarios. The first scenario is the assumed Next Generation ICD lead true performance, which assumes a fracture-free rate of 99.9% and 99.8% at 12 months and 24 months respectively. In this scenario there is an over 85.7% chance of observing no fractures by the 500th implant attempt, and a 99.2% chance of observing at most 1 fracture by the 500th implant attempt. There is also a 94.3% chance of observing at most one fracture by 6 months following the 500th implant attempt, which would determine the time frame for the initial pre-market report.

The second scenario is that the Next Generation ICD lead true performance is similar to that of the Fidelis lead, with an estimated 6-month fracture-free rate of 99.2% and 12-month fracture-free rate of 98.4%.In this scenario there is an 89.9% chance of observing one or more fractures by the 500th implant attempt, and a 98.6% chance of observing more than 1 fracture by the second decision rule of 6 months after the 500th implant attempt.

R-code for implementing the simulations is found in section 10.1.

Table 1: Adaptive Design Decision Rules & Operating Characteristics

Stage	Time Point	Decision Rule	Chance of Occurrence	
			Next Generation ICD lead	Fidelis-like Lead
Sample Size Assessment	500th Implant Attempt	**0 Fractures Observed**: Halt enrollment	85.7%	10.1%
		1 Fracture Observed: Increase to 600 implant attempts	13.4%	23.4%
		2 Fractures Observed: Increase to 700 implant attempts	0.8%	26.5%
		3-5 Fractures Observed: Increase to 800 implant attempts	0.03%	37.1%
		6+ Fractures Observed: Halt Trial	0.0%	2.9%

Stage	Time Point	Decision Rule	Chance of Occurrence	
			Next Generation ICD lead	Fidelis-like Lead
Follow-up Assessment	6 months after 500th implant Attempt	**≤ 1 Fracture Observed**: Analyze at 12 months post-500th implant attempt	94.3%	1.4%
		> 1 Fracture Observed: Analyze at 12 months post-last implant attempt	5.7%	98.6%

6. Determination of Sample Size

6.1 Primary Objectives

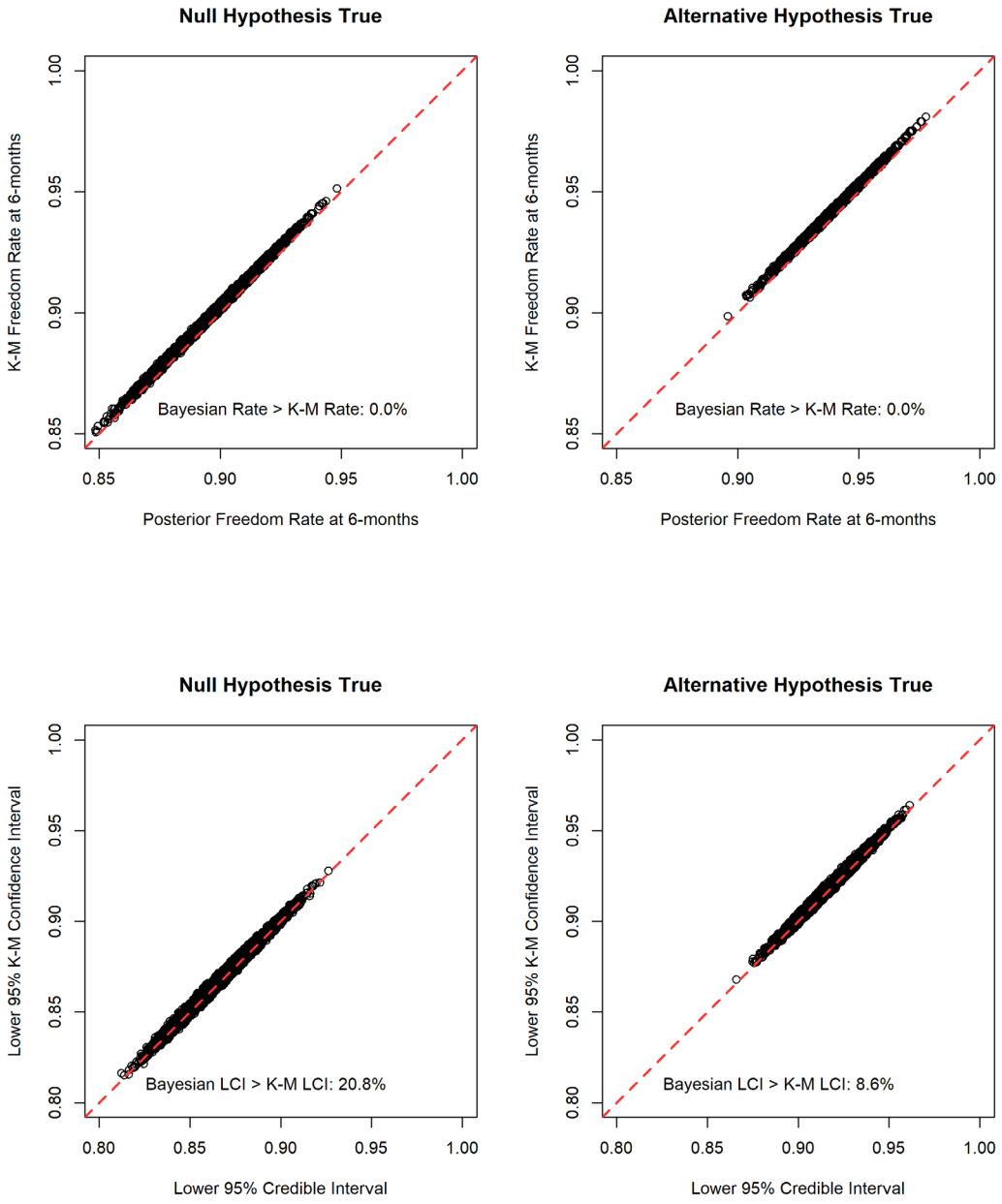
There are two primary objectives (safety and efficacy). The safety primary objective sample size requirement will refer to subjects who undergo an implant attempt of the Next Generation ICD lead, while the efficacy primary objective sample size will be defined as subjects who complete the implant defibrillation testing protocol. Furthermore, as described in section 5.1, the adaptive sample size of the study is based on the observed number of RV lead fractures in the study. Based on the decision rules outlined in section 5.1 the initial sample size is 500 subjects but may be increased to 800 subjects undergoing an implant attempt. To further account for subjects who enroll in the study but exit prior to an implant attempt, up to 900 subjects may be enrolled.

The sample size determination for the primary safety and efficacy objectives as well as the stage 1 safety objective is described in detail below. The overall study sample size of at least 500 subjects with an implant attempt is based on the primary safety objective.

Simulation studies using the statistical programming language R, show that the determined sample sizes for the primary safety (at least 500 subjects with implant attempt) and efficacy objective (at least 95 subjects completing the defibrillation testing protocol) provide at least 90% power to reject the null hypotheses associated with the primary safety and efficacy objectives based on the assumed performance of the Next Generation ICD lead while maintaining a false positive rate of 2.5%. R code for conducting the simulation studies for the primary safety and efficacy objectives are found in sections 10.1 and 10.2 respectively.

For the primary safety objective, frequentist non-parametric Kaplan-Meier estimates were also compared with the planned Bayesian analysis with a prior as described in section 7.9.1.4 during the simulation study. Comparisons between a Kaplan-Meier analysis and the planned Bayesian show that the lower bound of the 95% two-sided confidence interval from the Kaplan-Meier analysis at 6 months exceeded the 95% lower two-sided credible interval bound in the majority of simulations (see Figure 1 below, lower panels). The true rate of freedom from major complication at 6 months was assumed to be either 94.5% (alternative hypothesis, good lead) or 90% (null hypothesis, bad lead). It can further be seen that the Kaplan-Meier rate for freedom from major RV lead related complications at 6 months is similar to the posterior median for the 6-month rate estimated from the Bayesian model (Figure 1, upper panels). Hence, the Bayesian methodology with the selected prior appears robust.

Figure 1: Comparison between Results of Kaplan-Meier Analysis and Bayesian Analysis Methods



6.2 Stage 1 Safety Objective

The goal of the stage 1 safety objective is to provide an estimate of the 3-month RV lead-related major complication-free rate after 150 subjects have at least 3-months (90 days) of post-implant follow-up experience. A 95% credible interval for the 3-month RV lead related major complication free rate will be computed to quantify the level of the uncertainty of the estimate at the time of the stage 1 analysis. Simulations in R show that at the time of the stage 1 pre-market report, the lower credible interval for

the RV lead related major complication freedom rate should be within 5% of its point estimate as described in section 7.9.7.5.

7. Statistical Methods

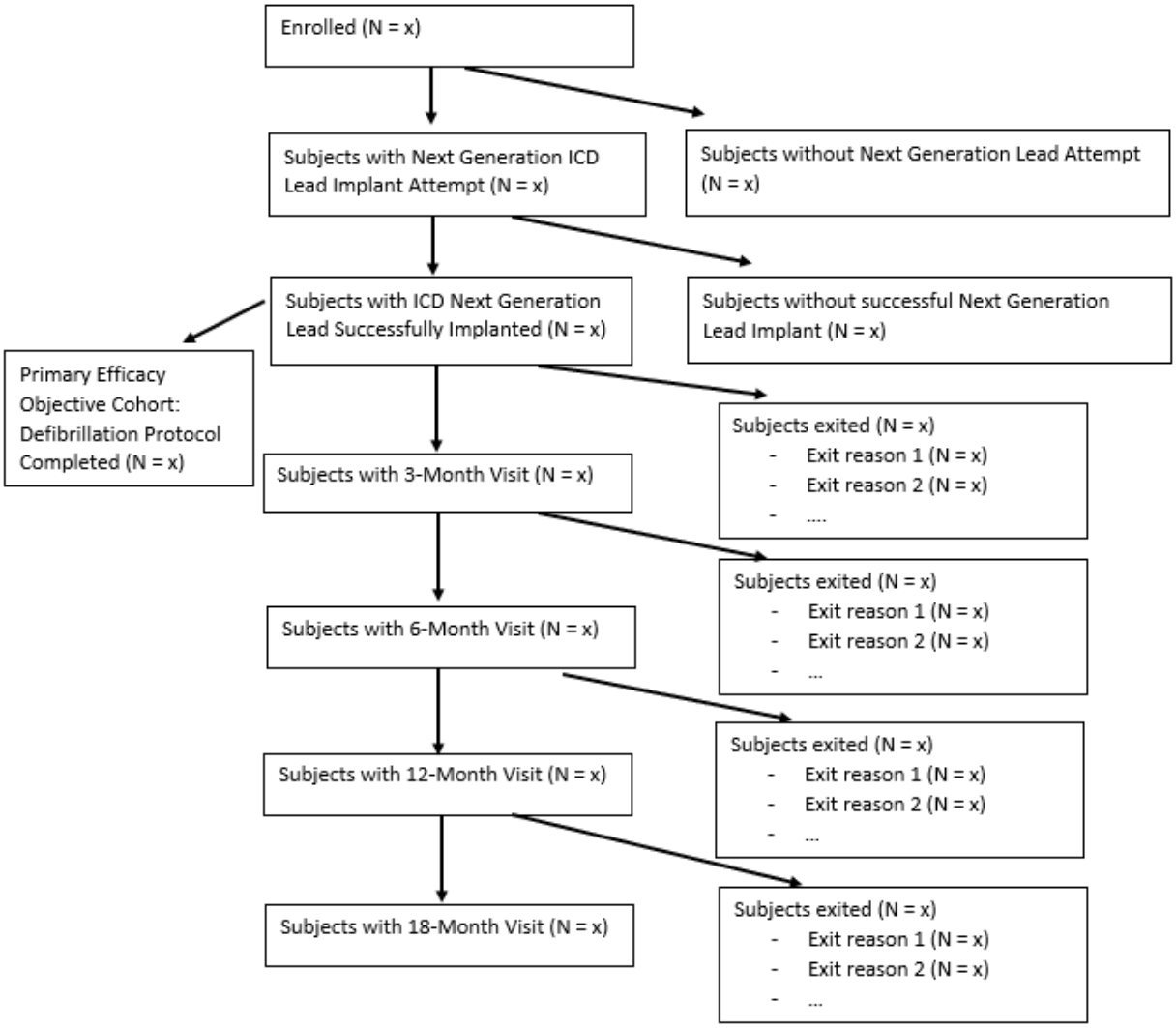
7.1 Study Subjects

7.1.1 Disposition of Subjects

Subjects who meet all the inclusion and none of the exclusion criteria are eligible to be enrolled in this study. When a subject and the principal investigator or authorized designee, as required, have personally signed and dated the informed consent form (ICF), the subject is considered a subject enrolled in the study. After enrollment, subjects will undergo implant of the Next Generation ICD implant and ICD/CRT-D device. Subjects will return for follow-up visits at 3 months, 6 months, and every 6 months thereafter until study closure.

This is a single arm study. A flow-chart similar to Figure 2 will be created to describe patient disposition.

Figure 2: Patient Flowchart LEADR Study



Study exits will be summarized according to exit reasons, e.g., lost-to follow-up, death, study completion, unsuccessful procedure etc. This summary will be valuable for assessing reasons for premature study exits and to assess the impact of premature study exits on study results. Violation of inclusion and exclusion criteria at baseline will be summarized for all enrolled patients.

The following tables will be created to summarize patient disposition:

1. Number (%) of patients per center
2. Number (%) of patients by visit/procedure
3. Visit window compliance
4. Study exit summary

7.1.2 Clinical Investigation Plan (CIP) Deviations

A study deviation is defined as an event within a study that did not occur according to the CIP. Deviations from the clinical investigation plan will be collected as deviations on the Study Deviation electronic Case Report Form (eCRF). Deviations will be summarized in report(s) using descriptive statistics, e.g., in a table by protocol deviation category as chosen by the site on the eCRF. The number of deviations per category, the number and percentage of subjects with a deviation in each category will be reported.

Inclusion/exclusion violations will not result in subjects being excluded from analysis of objectives. If it is discovered that subjects not meeting the inclusion/exclusion criteria underwent an implant attempt and possibly defibrillation testing, additional analyses may be performed with these subjects excluded.

On the deviation eCRF study sites will enter “COVID-19” within the answer to the question “What was the reason for the protocol deviation” for COVID-19 pandemic-related deviations. Sites will be trained and asked to provide sufficient details to clearly describe the situation or the cause of the COVID-19 related deviation.

7.1.3 Analysis Sets

The analysis sets (analysis cohorts) are described in Table 2 and their use is indicated in Table 3. All subjects who sign informed consent will be defined as the ‘All Enrolled’ cohort. The primary safety objective and secondary objective will be analyzed using all enrolled subjects with a Next Generation ICD lead implant attempt.

The primary efficacy objective will be analyzed using the first 95 enrolled subjects who complete defibrillation protocol at implant. Subjects who complete the defibrillation protocol but had study deviations from the defibrillation protocol (e.g., defibrillation protocol was completed after pre-hospital discharge) will be included in the primary efficacy analysis cohort. A per protocol analysis will be completed only considering the subjects within the primary efficacy cohort who completed the defibrillation protocol without any deviations and who had no violations with regard to exclusion criterion 5 (see Table 7 in CIP). Subjects who cannot complete the defibrillation protocol due to an insufficient number of episodes being inducible (e.g., zero induced episodes) will be excluded from the analysis and reported separately. Results from subjects who undergo defibrillation testing only at the physician’s discretion after the sample size requirement has been met for this objective will also be reported separately.

In addition, sensitivity analyses will be performed for the primary safety and primary efficacy objectives to assess the robustness of the results when there is missing data. These analyses are described in detail in section 7.9.1.7 and section 7.9.2.7.

Table 2: Definition of Analysis Sets

Cohort	Definition
All Enrolled	All subjects who signed informed consent (i.e. informed consent date not blank)
Primary Safety	All enrolled subjects with an implant attempt (i.e. implant eCRF indicates that at least one implant attempt completed, that is Question 'Was any 093000 lead attempt done' is answered with yes)
Primary Efficacy	First 95 enrolled subjects who completed the defibrillation protocol at implant
Primary Efficacy – Per Protocol	All subjects within first 95 enrolled subjects who completed the defibrillation protocol at implant without deviations with regard to the defibrillation protocol and no violation of exclusion criterion 5
Successfully Implanted	All enrolled subjects who were successfully implanted
Safety	All subjects who signed informed consent
Stage 1 Safety	All enrolled subjects with an implant attempt (i.e. implant eCRF indicates that at least one implant attempt completed, that is Question 'Was any 093000 lead attempt done' is answered with yes) and enrolled by the time point that 150 subjects complete their 3-month visit

Table 3: Use of Analysis Sets

Analysis Item	Analysis set
Baseline summary	All Enrolled
Attrition and follow up summary	All Enrolled
Primary Safety Objective	Primary Safety
Primary Efficacy Objective	Primary Efficacy, Primary Efficacy – Per Protocol
Secondary Objective	Primary Safety
Ancillary Objective #1	Successfully Implanted*,**
Ancillary Objective #2	Successfully Implanted*,**
Ancillary Objective #3	Successfully Implanted*,**
Stage 1 Safety Objective	Stage 1 Safety
Adverse Event summary	Safety
Device Deficiency summary	Safety
Deviation summary	All Enrolled

*To be included in the analysis for the ancillary objectives, the respective measurements (Pacing capture thresholds, R-wave sensing amplitude, pacing impedance) need to be available for the respective visits.

**If the initially implanted Next Generation ICD lead is not active anymore at the respective visit, the subject will be excluded from analysis.

7.2 General Methodology

Data analysis will be performed by Medtronic statisticians or designees.

Data summaries for categorical data will be summarized as count, e.g., number of patients, and/or number of events, and a percentage relative to the total number of patients/events. The denominator will be explicitly identified when not clear from the context. For continuous variables, standard deviation, median, quartiles, minimum and maximum will be provided as applicable.

The secondary objective will be analyzed using Bayesian methodology making use of virtual patient data from an engineering model that will be incorporated using an informative prior as described in section 7.9.3.4.2. The virtual patients will be discounted if their data does not agree with the data from the clinical study patients (see details in section 7.9.3.4). For consistency, all other objectives will employ Bayesian methodology as their primary analysis methodology. Bayesian credible intervals will be reported as two-sided 95% credible intervals.

Frequentist methods may be used for supportive analyses (e.g. poolability analyses) as described below.

7.3 Center Pooling and Poolability

The study is expected to be conducted at up to approximately 60 study sites. Participating geographies are expected to include but are not limited to Australia, China, Hong Kong, Malaysia, Singapore, Japan, EMEA (Europe, Middle East, and Africa), Canada, Puerto Rico, and the United States. There will be no minimum limit that each investigator must enroll. Maximum number of subjects enrolled at each site will be capped at 50 (10% of minimum number of enrollments (500)). If the sample size is increased by a certain number of patients based on the adaptive study design, the enrollment cap will increase by 10% of the sample size increase for all sites, e.g., if the sample size increases by 100 implants, the enrollment cap for a given site will increase from 50 to 60 patients.

Poolability assessments for gender and geographic region (US vs non-US) will be assessed for both primary objectives using frequentist methodology.

In each case a significance level of 0.15 will be utilized to evaluate whether the endpoint(s) differ by values of the covariate. In the case of the primary safety objective, a Cox proportional hazards model will be fit with gender and geographic region included.

SAS code similar to the code below can be used for region or gender:



Additionally, hazard rates for the primary safety endpoint will be compared using a Cox model with a frailty term for investigational sites. Sites will be included if they have at least five subjects with an implant attempt. SAS code similar to the code below can be used:



In the case of the primary efficacy objective, the effect of gender and region on defibrillation efficacy will be evaluated separately using Fisher's exact tests.

SAS code similar to the code below can be used:



If these tests indicate that heterogeneity of study results across sites, regions or gender may be a concern, further analyses may be performed to investigate the source of heterogeneity.

Other pre-specified subgroups for which poolability may be assessed include subgroups based on BMI, younger (≤20 years) versus older adult subjects (>20 years) and race and/or ethnicity as applicable by geography given a sufficient number of subjects (≥10) are available within each group.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

All available data will be included in the data listings and tabulations. Subject attrition will be summarized and reasons for study exits, in particular premature exits will be summarized (see section 7.1.1).

With regard to the primary safety objective, data from subjects who exit the study prior to experiencing a major RV lead related complication will be included up until the date of their last exposure to the Next Generation ICD lead at which point they will be censored. As a sensitivity analysis to assess the robustness of results to data missingness, a tipping point analysis will be performed including subjects who do not complete 6 month-follow-up due to being lost to follow-up or due to an unsuccessful implant. Details regarding this analysis are provided in section 7.9.1.7.

For the primary efficacy objective, only subjects who complete the defibrillation protocol at implant will be included in the primary analysis that determines if the primary efficacy objective is met. Subjects who begin the defibrillation testing at implant but do not complete the defibrillation testing protocol will be included in a sensitivity analysis. Specifically, a tipping point analysis will be performed based on all subjects undergoing defibrillation testing at implant to determine the robustness of results to the missing data. Further details are given in section 7.9.2.7.

For the ancillary objectives involving device electrical data, missing data from visits can be replaced by data from a device interrogation within the visit window, if applicable.

7.5 Adjustments for Multiple Comparisons

No adjustments for multiple comparisons or multiplicity are planned. The primary objectives will be both evaluated at a significance level of 0.025. However, for the study to be considered successful overall, the null hypotheses for both the primary safety and efficacy objectives must be rejected.

The primary efficacy objective will be performed once all required subjects have completed defibrillation testing, and provided in the stage 1 report (see section 7.8.3). The stage 1 safety objective will be evaluated once 150 subjects undergoing implant of the Next Generation Lead have completed their 3-month follow-up visit. Depending on the study's enrollment rate it is projected that several hundred subjects will have a Next Generation ICD lead implant attempt at the time the stage 1 safety objective is evaluated. The study's primary safety objective will be evaluated once with a timing dictated by the study's adaptive design (see SAP section 5.1 and CIP section 13.2 for details). While the same endpoint, and a similar parametric approach will be employed for both the analysis of the stage 1 safety objective and the primary safety objective, there will not be an adjustment for multiplicity as the former analysis is not compared against a pre-specified performance goal and the Bayesian paradigm allows for refinement of the posterior distribution of the hazard rate parameters as additional data is compiled.

7.6 Demographic and Other Baseline Characteristics

Descriptive statistics will be used to summarize baseline and demographic characteristics. In particular, cardiovascular medical history and surgical history will be summarized.

BMI will be calculated as weight in kg/(height in m)^2. Age in years will be calculated by the following formula: date of enrollment, i.e., informed consent date, – date of birth, if date of birth is available. If not, the age in years as indicated on the baseline eCRF will be used.

7.7 Treatment Characteristics

Descriptive statistics will be used to summarize implant procedure information collected, including:

- Procedure details from eCRF attempt1 (093000 Lead Implant Attempt 1) and attempt2 (093000 Lead Implant Attempt 2 if more than one 093000 lead implant attempted)
- RV lead procedure time (minutes) for successful implants:
    - If successful implant, (time 093000 lead successfully implanted – time the RV catheter is inserted into the patient) in minutes
- Lead and catheter handling assessment

Furthermore, procedure details from eCRF attempt1 and eCRF attempt2, lead and catheter handling assessments completed at system modifications, if applicable, i.e., if the 093000 lead was replaced, will be summarized using descriptive statistics.

Medications will be collected at implant. The start date and dosage of the following medications will be collected at implant:

- Sotalol
- Amiodarone
- Propafenone
- Flecainide

- Mexiletine
- Dofetilide
- Dronedarone

A table will be created summarizing the number of subjects taking each medication specified above.

7.8 Interim Analyses

There are several pre-specified time points for reports while the study data collection is ongoing. Details of these reporting time points and reports are specified in the sections below.

No interim analysis of the study's primary objectives is planned. However, the number of Next Generation lead fractures observed after 500 implant attempts and after 500 subjects have the opportunity to complete their 6-month post-implant visit will be used to determine the final number of enrolled subjects and follow-up period respectively per the adaptive study design described in section 5.1.

7.8.1 Annual Reporting

It is anticipated that some regulatory authorities will require annual reporting of study progress. These reports will include summaries of subject enrollment, baseline and medical history, study deviations, and adverse events.

7.8.2 DMC Reporting

A Data Monitoring Committee (DMC) will be formed for this study. The details on DMC responsibilities and process will be available in the DMC Charter. DMC reports will be developed at a frequency requested by the DMC. Reporting to the DMC will include an open report available to the steering committee and study team. The open report will include content similar to that provided for annual regulatory reporting. In addition, a closed report may be developed that will include summaries of primary safety and efficacy endpoints if requested by the DMC. The closed report will be treated as confidential and only available to members of the DMC and those preparing the closed report.

7.8.3 Stage 1 Pre-Market Reporting

A stage 1 pre-market report will be developed once the requirements for analyzing the study's primary efficacy (section 7.9.2) and stage 1 safety objective (section 7.9.7) have been satisfied (i.e. when 150 subjects with a Next Generation ICD Lead complete the 3-month visit). The stage 1 pre-market report will be used to support marketing applications in countries outside the US where applicable. Frozen datasets used to develop the stage 1 pre-market report will be stored by Medtronic in a secure network location.

This report will include evaluation of the study's primary efficacy objective, stage 1 safety objective, and ancillary objectives and include all data from subjects enrolled at the time of the database freeze for this report.

7.8.4 Initial US Pre-Market Application Report

An initial pre-market application (PMA) report will be developed once the requirements for analyzing the study's primary safety objective has been satisfied as determined by the adaptive study design described in section 5.1. This report will include evaluation of the study's primary efficacy (section

7.9.2) and safety objective (section 7.9.1), secondary objective (section 7.9.3), and ancillary objectives and include all data from subjects enrolled at the time of the database freeze for this report. The initial US PMA report will be used to support a marketing application in the US.

7.8.5 Updated US Pre-Market Application Report

An updated PMA report will be developed approximately 6-months following submission of the initial US PMA report. This report will include updated information regarding the performance of the Next Generation ICD lead with respect to the secondary objective (lead fractures). At the time of the database freeze for this report it is anticipated that most subjects will have had the opportunity to complete their 18-month follow-up visit. This report will provide the US FDA updated information on the performance of the Next Generation ICD lead and provide updated information on lead performance for other geographies requiring Clinical Evidence Reports.

7.8.6 Final Report

A final report will be developed after all subjects have exited the study.

7.8.7 Other Reports

Other reports may be generated at the request of international regulatory bodies if applicable.

7.9 Evaluation of Objectives

7.9.1 Primary Safety Objective

The primary objective is to demonstrate that the freedom from major complications related to the Next Generation ICD lead at 6 months post-implant exceeds a pre-specified threshold of 90%. The endpoint is defined as a subject's first occurrence of a major complication related to the Next Generation ICD lead, as determined by an independent Clinical Events Committee, that occurs on or prior to 6 months (182 days) post implant.

For an adverse event to meet the endpoint, the event must have occurred within 182 days (inclusive) of the Next Generation ICD lead implant and be adjudicated by the CEC as being a major complication related (causal relationship) to the Next Generation ICD lead. Major complications are those complications resulting in:

- Death
- Lead Fracture
- Hospitalization (in-patient)
- Prolongation of an existing hospitalization by at least 48 hours
- System Revision (reposition, replacement, explant)

7.9.1.1 Hypothesis

The hypotheses for this objective are as follows, with π_6 denoting the 6-month freedom from major RV lead related complications:

$H_O: \pi_6 \leq 0.90$

$H_A: \pi_6 > 0.90$

7.9.1.2 Performance Requirements

The two-sided 95% lower credible bound for the 6-month RV lead-related major complication-free rate must exceed a pre-specified threshold of 90%.

Formally, the null hypothesis will be rejected in favor of the alternative if there is greater than 97.5% posterior probability that π_6 exceed 0.90 (the performance goal). Specifically,

$$P(\pi_6 > 0.9 \mid \lambda_1, \lambda_2, X_i) > 97.5\%,$$

where λ_1 and λ_2 are the priors for the rate of RV lead related major complications as described below and the X_i are the X_i are the time to RV lead related major complication or censoring time for the i subjects.

7.9.1.3 Rationale for Performance Criteria

A detailed rationale based on the review of previous Medtronic ICD and CRT-D studies as well as of the Investigational Device Exemption (IDE) study for the SelectSecure Model 3830 pacing lead is provided in the CIP section 13.5.3.

7.9.1.4 Analysis Methods

Survival analysis methods were chosen to allow inclusion of data from subjects in the analysis who might exit or die prior to the 6-month time. Survival analysis methods have been used effectively to assess safety in several previous Medtronic pre-market studies, i.e., EV ICD Pivotal (ongoing, ClinicalTrials.gov Identifier: NCT04060680), Attain Stability Quad (PMA submission 2019) (Jackson, et al., 2020), Micra Transcatheter Pacing System (PMA submission 2015) (Reynolds, et al., 2016), and Model 3830 lead IDE study (Gammage, et al., 2006). In addition to that survival analysis is also utilized for post market surveillance of existing Medtronic products.

Sensitivity analyses will be performed to assess the robustness of results to the primary analysis method and modelling assumptions. A Bayesian analysis approach with a piecewise exponential model (see details of methods below), which is the primary analysis method for the primary safety objective in the LEADR study, has been previously applied for the BLOCK HF study (Curtis, et al., 2013).

A subject's survival time will be computed as each subject's time to first Next Generation ICD lead - related major complication or time to last exposure to the Next Generation ICD lead if a subject does not have a major complication, in which case the subject will be censored. Last exposure to the Next Generation ICD lead will be defined as the date of their last follow-up visit, study exit date (if exited for reason other than lost-to-follow-up), or date of death, whichever is last. Additionally, if a subject has an explant of the Next Generation ICD lead, that is not related to a Next Generation ICD lead major complication, the subject will have their last exposure date set to their explant date. All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis.

For inferential analyses (primary analysis method), a piecewise exponential model will be assumed with two intervals of interest: 0-1-month post-implant, and 1 month and beyond post-implant, as it is possible the rate of lead-related major complications may differ in the acute (first 30 days) compared to more chronic time points. This assumption is based on the historical data from previous Medtronic studies (see CIP section 13.5.3).

Let λ_1 denote the hazard rate for 0-1 month post-implant attempt, and let λ_2 denote the hazard rate for 1 month post-implant attempt and beyond. The survival function (S(t)), will have the equation

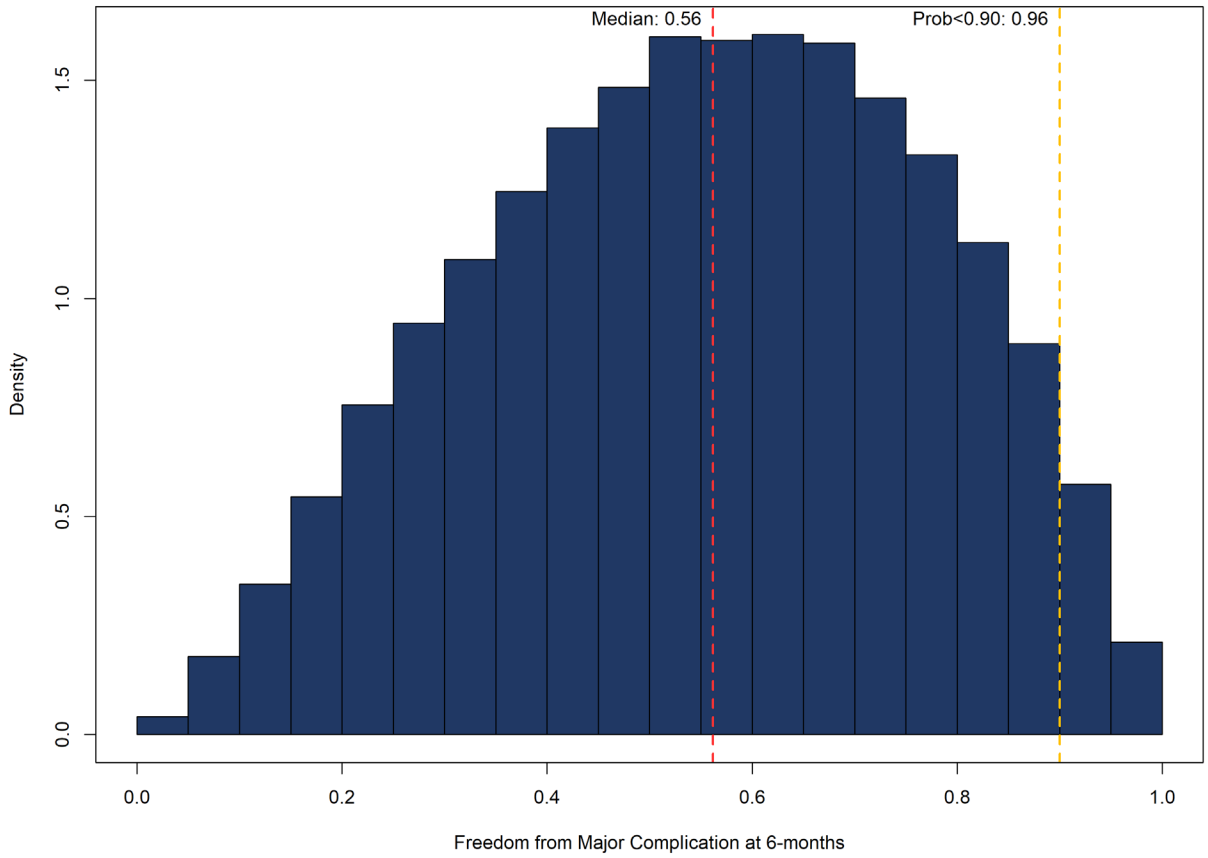
$$S(t) = \begin{cases} exp(-\lambda_1 t), & t \in [0,1) \\ exp(-\lambda_1)exp\big(-\lambda_2(t-1)\big) & t \in [1,\infty) \end{cases}$$

Using the shape and rate parameterization of the Gamma distribution, the following prior distributions are assumed for λ_1 and λ_2:

λ_1 ~ Gamma (1, 3.48), λ_2 ~ Gamma (1, 12.33)

This results in a skeptical prior distribution for the 6-month endpoint free rate that has a median of 56.2%, with 96.1% of the prior distribution for S(6) less than the performance goal of 90%. The prior distribution for the 6-month endpoint free rate is shown in Figure 3. The red dashed vertical line displays the median of the prior distribution and the yellow dashed vertical line corresponds to the performance goal of 0.90 on the probability scale (i.e. 90%). As described in section 7.9.1.5 these priors ensure the false positive rate is <2.5%.

Figure 3: Prior Distribution for 6-month Complication Free Rate



These prior distributions will be combined with the prospective event/follow-up data to generate posterior distributions for each event rate, which will be as follows:

λ_1~ Gamma (1 + # of first endpoints within 1 month, 3.48 + Total Survival Months through 1 month),

λ_2 ~ Gamma (1 + # of first endpoints between 1 & 6 months, 12.33 + Total Survival Months between 1 and 6 months)

These posteriors will be utilized to determine the posterior distribution for the 6-month freedom from Next Generation ICD lead-related major complication rate. From this distribution a posterior median and 95% two-sided credible interval will be generated. If the 6-month lower bound of the credible interval exceeds 90%, the objective will be met.

The results from the inferential analysis for the primary safety objective will be displayed in a table similar to Table 4.

Table 4: RV Lead Related Major Complication Free Rate at 6 Months

	Number of Subjects	Number of Subjects with Event	Major Complication Free Rate at 6 Months (Posterior Median)	95% Credible Interval	Posterior Probability Major Complication Free Rate > 90%
RV lead related major complication free rate	XXX	XXX	XX.X%	(XX.X%, XX.X%)	XX.X%

The number of RV lead related major complications and the number and percentage of subjects with an event will be summarized per Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) term in a table similar to Table 5.

Table 5: RV Lead Related Major Complications by MedDRA Preferred Term

Adverse Event (MedDRA PT term)	RV Lead Related Major Complications	
	Number of Events	Number of Subjects, % of Subjects
Lead dislodgment	…	…
…		
Total		

Since the primary safety objective of major complications related to the RV lead is a composite endpoint (i.e., death, lead fracture, hospitalization, prolongation of hospitalization, and system revision), each component of the primary safety endpoint will be reported separately in a table similar to Table 6.

Table 6: RV Lead Related Major Complications by Endpoint Component

Endpoint Component	RV Lead Related Major Complications	
	Number of Events	Number of Subjects, % of Subjects
Death	…	…
Lead fracture		
…		
Total		

A Kaplan-Meier curve will be extended through at least 12 months for longer term safety evaluation. Additionally, the accuracy of the piecewise exponential assumption will be assessed graphically by superimposing the freedom from RV related major complications and its 95% credible interval through

6-months based on the Bayesian piecewise exponential model on the Kaplan-Meier estimates for the freedom rate and its 95% confidence interval. The Kaplan-Meier estimator through 6-months and its 95% two-sided confidence interval will also be provided as a sensitivity analysis.

SAS code similar to the code below can be used to generate the Kaplan-Meier estimates for the Next Generation ICD lead-related major complication freedom rate:

[redacted]

R code similar to the following may also be used to generate the Kaplan-Meier estimates:

[redacted]

7.9.1.5 Power and Frequentist Type I Error Control

A simulation study was performed to determine the power and type I error control (i.e., the chance that the lower 95% bound exceeds 90% when the true complication rate is 90%) of the Bayesian methodology under the alternative and null hypothesis. The simulation study incorporated the adaptive nature of the study allowing the sample size to adapt based on the number of lead fractures observed as described in Table 1.

The simulation study included scenarios under the null hypothesis where the functional form of the piecewise exponential model was mis-specified (see section 10.3). For each scenario 10,000 simulations of the study were simulated. The simulation program for conducting the simulations is included in section 10.1. In all scenarios, the study attrition rate is assumed independent of the major complication rate and is assumed to follow a Weibull distribution with 4% of subjects exiting the study by 30-days and 10% at 1-year. Subjects were enrolled at a rate of up to 4 subjects per center per month with a most likely value of 1 with a total of 47 centers activating over a period of 13 months.

Table 7 shows that under the planned alternative hypothesis where the assumed freedom from RV related major complications is 95.5% at 1-month post-implant and 94.5% at 6-months post-implant the power of the study is 94.4%. Under all null hypothesis scenarios studied, the type I error rate was <2.5% indicating that the type I error rate is well controlled.

Table 7: Power and Frequentist Type I Error Control for the Primary Safety Objective

Scenario	Assumptions	Probability of Rejecting Null Hypothesis
Planned alternative hypothesis	Major complication free rate of 95.5% at 1-month post-implant and 94.5% at 6-months post-implant	0.944
Next Generation lead performs worse than expected, but better than null scenario	Major complication free rate of 95.5% at 1-month post-implant and 92.0% at 6-months post-implant	0.255
Null hypothesis scenario #1	Major complication free rate of 95.5% at 1-month post-implant and 90% at 6-months post-implant	0.017
Null hypothesis scenario #2	Major complication free rate of 91.0% at 15-days post-implant and 90% at 6-months post-implant	0.013
Null hypothesis scenario #3	Major complication free rate of 90.5% at 5-months post-implant and 90% at 6-months post-implant	0.015

7.9.1.6 Determination of Subjects/Data for Analysis

The primary safety analysis dataset (Table 3) will be used for this objective. Specifically, all subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Model Next Generation ICD lead implant procedure. If the subject experiences a safety endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a safety endpoint but does not have any successful implant the survival time will be set to time 0.

7.9.1.7 Missing Data

For subjects who do not complete follow-up through 6 months due to being lost to follow-up or unsuccessful implant, a tipping point analysis will be performed including these subjects to assess robustness of the result to incomplete follow-up. Subjects who exit the trial prior to 6 months for other reasons that may plausibly be assumed independent of lead performance (e.g. geographic relocation of subject) will not be included in the tipping point analysis. Firstly, subjects having an unsuccessful implant (without major RV lead related complication) will be considered one-by-one as observed events. Secondly, subjects being lost-to follow-up as indicated on the exit CRF and without a major RV lead related complication before being lost to follow-up, will be considered one-by-one as observed events in the order in which they were exited. For example, a subject who was lost to follow-up 60 days post-

implant will be considered in the analysis to have met the endpoint prior to a subject that was lost to follow-up 90 days post-implant.

To aid in interpretation of the tipping point, stochastic methods may be employed. For example, suppose there are 15 subjects with missing data and the inference flips from rejecting the null hypothesis to failing to reject the null hypothesis if 9 of the 15 subjects are assumed to meet the primary safety endpoint. To determine the plausibility of the tipping point being reached (i.e. ≥9 subjects have an event), the probability of the tipping point being met (or exceeded) will be computed under two scenarios. The first where the event rate hazard for subjects with a missing endpoint is based on the posterior distributions of λ_1 and λ_2 and one where event rate hazard for subjects with missing data is twice the posterior rate based on the observed data (i.e. $2\times \lambda_1$ and $2\times \lambda_2$).

7.9.2 Primary Efficacy Objective

Demonstrate the percentage of subjects successfully defibrillated at implant with the Next Generation ICD lead exceeds a pre-specified threshold of 88%.

7.9.2.1 Hypothesis

The hypotheses for this objective are as follows, with π denoting the implant defibrillation success rate expressed as probability:

$H_O: \pi \leq 0.88$

$H_A: \pi > 0.88$

7.9.2.2 Performance Requirements

Performance Requirements for this objective define both the endpoint and the performance goal. The endpoint, defibrillation testing success, is defined as:

- One induced sustained shockable ventricular arrythmia (SSVA) episode successfully terminated with a 18J shock, or
- 2 consecutive SSVA episodes successfully terminated with 25J shocks

Notes:

- In one of the two consecutive SSVA episodes, up to two 25J shocks are permitted.
- To achieve final system configuration, changing the position of the ICD generator and/or the lead or changing shock polarity is permitted.
- Subjects can return for testing on another day if testing is not fully completed on the day of implant.

The 95% lower credible bound for the percentage of subjects successfully defibrillated will be compared against a pre-specified threshold of 88%.

Formally, the null hypothesis will be rejected in favor of the alternative if there is greater than 97.5% posterior probability that the defibrillation success rate π exceed 0.88 (the performance goal).

Specifically,

$P(\pi > 0.88 \mid \alpha, \beta, X_i) > 97.5\%$,

where α and β are the parameters for the Beta prior Beta(α,β) for the defibrillation success rate as described below and the X_i are defibrillation successes or failures for the *i* subjects included in the primary efficacy objective cohort.

7.9.2.3 Rationale for Performance Criteria

A rationale for the performance goal is provided in the CIP section 13.6.3.

7.9.2.4 Analysis Methods

Descriptive statistics will be used to summarize the results of the defibrillation testing at implant. The defibrillation testing at implant is collected on the ELEC eCRF.

For an induced episode to be considered successfully terminated by the system the shock result recorded on the ELEC eCRF must be either "ICD/CRT-D Shock Successful" or "Manual ICD/CRT-D Shock Successful" or successful termination should be confirmed by the episode review committee.

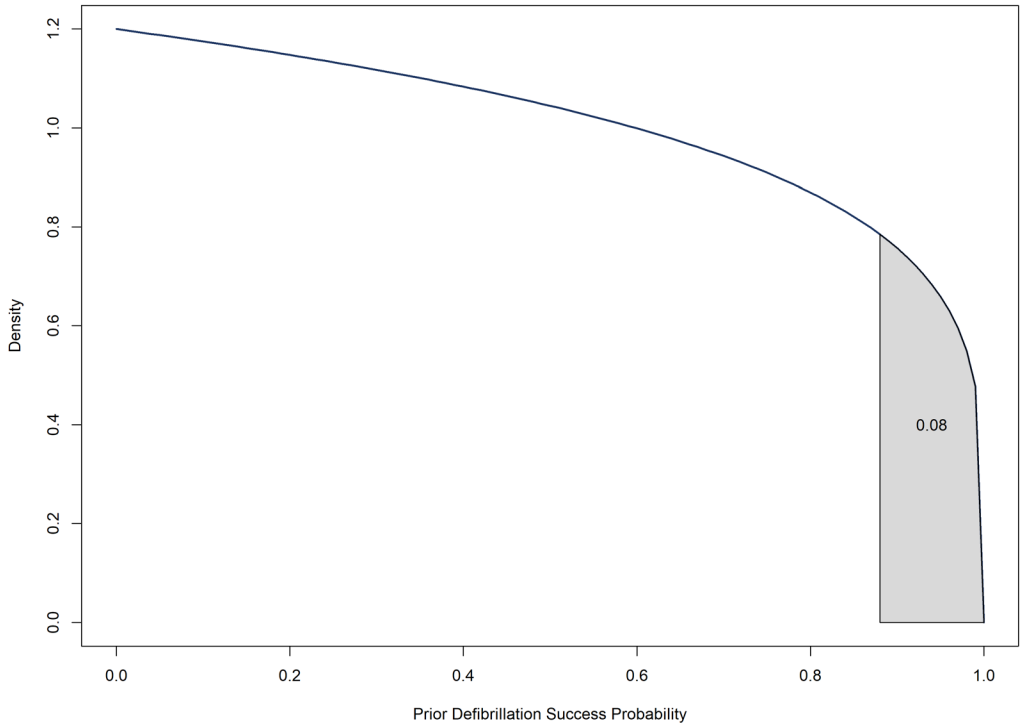
A table or histogram will be generated to show the distribution of subjects successful with a single successful defibrillation attempt at ≤18J, successful with two successive episodes terminated by ≤25J, etc. The defibrillation protocol specifies that the subject has a successful defibrillation if the first episode is successfully terminated by a single shock of 18J. However, for the statistical analysis, if the first episode is successfully terminated by a single shock of less than 18J, this will also be considered a successful defibrillation. Similarly, if two successive episodes are terminated by ≤ 25J, this will also be considered a successful defibrillation.

For inferential analysis, Bayesian methodology will be employed. Specifically, the following Beta prior distribution is used for π, the proportion of subjects who would pass the defibrillation protocol for this study:

$\pi \sim Beta(1.0, 1.2)$.

Compared to the performance goal of 0.88, this is a skeptical prior since it has an expected value of 1.0/(1.0+1.2) = 0.45 and 50th percentile of 0.44 with only 8% of the distribution exceeding the performance goal of 0.88 on probability scale (88% on percentage scale) as shown in the shaded region of Figure 4 below.

Figure 4: Prior Distribution for Defibrillation Success



The resulting Beta posterior distribution for π will be Beta(1.0 + # of successes, 1.2 + # of failures). From this Beta posterior distribution, a posterior mean and 95% two-sided credible interval for the proportion of subjects who successfully pass the defibrillation protocol will be generated. The objective will be met if the lower 95% credible bound exceeds 88%. Subjects who cannot complete the defibrillation protocol due to an insufficient number of episodes being inducible (e.g. zero induced episodes) will be excluded from the analysis and reported separately. Results from subjects who undergo defibrillation testing only at the physician's discretion after the sample size requirement has been met for this objective will also be reported separately.

Results for the primary efficacy objective will be summarized in a table similar to Table 8 below:

Table 8: Defibrillation Protocol – Analysis Results

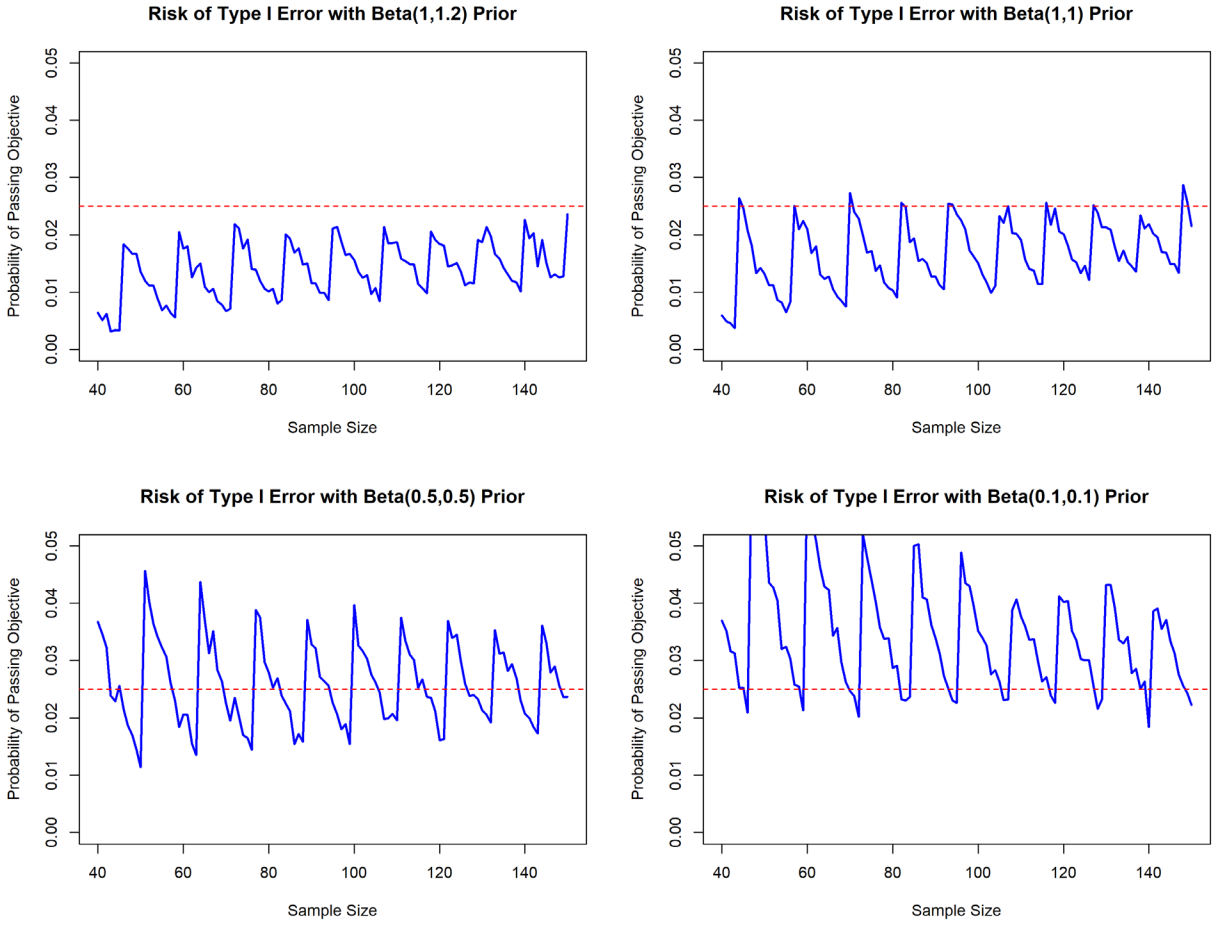
	Number of Subjects	Defibrillation Success Rate	95% Credible Interval	Posterior Probability Defibrillation Success Rate > 88%
Defibrillation Success Rate	XXX	XX.X%	XX.X% - XX.X%	XX.X%

7.9.2.5 Power and Frequentist Type I Error Control

The prior Beta(1,1.2) was chosen based on simulations showing that this prior is more conservative than other priors and that the type 1 error is well controlled across a range of sample sizes. Figure 5 shows

the relationship between sample size and chance of passing the objective (blue line) under the Null Hypothesis scenario (true defibrillation efficacy = 88%) using four different priors (the proposed prior Beta(1.0,1.2), a uniform flat prior Beta(1.0,1.0), Jeffrey's prior Beta(0.5,0.5) and a non-informative prior Beta(0.1,0.1)). The dashed red line shows the type 1 error Medtronic wants to maintain (0.025, i.e. 2.5%). The proposed prior of Beta(1,1.2) maintains an acceptable false positive rate (i.e., chance the lower 95% bound exceeds 88% when the true defibrillation rate is 88%), namely at or below 2.5% across a range of sample sizes, while the other priors are less conservative. An R-program computing the type I error rate for the primary efficacy objective is provided in section 10.2.

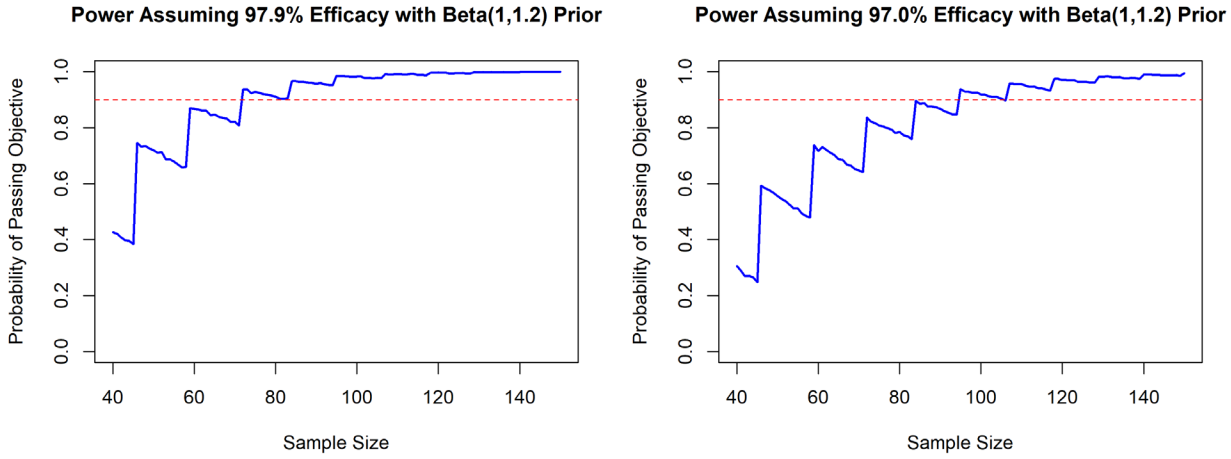
Figure 5: Risk of Type 1 Error with Different Beta Priors



Notes: Horizontal dashed redline is 0.025.

Figure 6 indicates that the power to pass the primary efficacy objective under the Beta(1,1.2) prior is at least 90% if the sample size is ≥95 subjects and the true Next Generation RV lead defibrillation efficacy is 97.0% or higher.

Figure 6: Study Power with a Beta(1,1.2) Prior



Notes: Horizontal dashed line is 0.90 corresponding to 90% power.

7.9.2.6 Determination of Subjects/Data for Analysis

The primary efficacy analysis dataset (Table 3) will be used for the analysis of this objective. Specifically, only a subset (≥95) of enrolled subjects undergoing implant of the Next Generation ICD lead are required to undergo defibrillation testing so as to reduce risk and burden to the subject. All subjects who complete the defibrillation protocol within this subset of required patients will be included in the analysis. Subjects who complete the defibrillation protocol but had study deviations from the defibrillation protocol (e.g., defibrillation protocol was completed after pre-hospital discharge) will be included in the primary efficacy analysis cohort. A per protocol analysis will be completed only considering the subjects within the primary efficacy cohort who completed the defibrillation protocol without any deviations and who had no violations with regard to exclusion criterion 5 (see Table 7 in CIP). Subjects who cannot complete the defibrillation protocol for reasons such as an insufficient number of episodes being inducible will be excluded from the analysis and reported separately. However, these subjects will be included in a tipping point analysis as described below.

Results from subjects who undergo defibrillation testing only at the physician's discretion after the sample size requirement has been met for this objective will also be reported separately.

Figure 6 in the CIP outlines the steps of defibrillation testing at implant. Subjects who complete the defibrillation protocol are those who ended with a checkmark (denoting 'Implant criteria met') or a cross sign (denoting 'Implant Criteria not met') in their defibrillation testing based on this diagram.

7.9.2.7 Missing Data

A tipping point analysis will be performed to assess the robustness of the result to missing data. Subjects, who attempted defibrillation testing (i.e. had at least one induced episode) prior to the closure of defibrillation testing as announced by Medtronic but did not complete defibrillation testing, will be included in the tipping point analysis.

Let $n_{missing}$ be the number of subjects who are not included in the primary analysis described above. Starting at 0 and ending at $n_{missing}$, the number of failures is changed by adding 1 failure at a time and

a two-sided 95% credible interval will be produced each time. If at any point the lower credible limit is less than or equal to 88%, then this number of failures within the missing subjects that results in the study failing to reject the null hypothesis of this objective is the tipping point.

To aid in interpretation of the tipping point, stochastic methods may be employed. For example, suppose there are 10 subjects with missing data and the inference flips from rejecting the null hypothesis to failing to reject the null hypothesis if 7 of the 10 subjects with missing data are defibrillation testing failures. To determine the plausibility of the tipping point being reached (i.e. ≥7 subjects with missing data fail defibrillation testing), the probability of the tipping point being met (or exceeded) will be computed under two scenarios. Both scenarios will utilize the posterior distribution for defibrillation success. The first scenario will assume that subjects with missing data have the same posterior probability for defibrillation success as the subjects where the outcome was observed. The second scenario will assume that subjects with missing data have half the odds of defibrillation success compared to subjects where the outcome was observed.

7.9.3 Secondary Objective

The secondary objective (safety) is to estimate the fracture-free rate of the Next Generation ICD lead throughout the study duration.

7.9.3.1 Hypothesis

There are no hypotheses for this objective. Rather the goal is to estimate the lead fracture free survival rate and its uncertainty during the study follow-up period.

7.9.3.2 Performance Requirements

At each desired time point (6, 12, 18, and 24 months), two-sided 95% credible intervals for the Next Generation ICD lead fracture-free rates will be generated using a combination of prospective and virtual patient data derived from engineering models.

Long-term fracture survival of the Next Generation ICD lead will be evaluated utilizing:

- Pre-market Original IDE study with 12+ months (initial US PMA report) and 18-month follow-up (updated US PMA report).
- Virtual patient model, combining rigorous bench testing to failure with in-vivo use condition data. Virtual patients will be combined with data from study subjects using the methodology developed by industry and FDA statisticians through the Medical Device Innovation Consortium's Computing Modeling and Simulation Working Group (Haddad, et al., 2017) as described in section 7.9.3.4.2.

7.9.3.3 Rationale for Performance Criteria

A rationale is provided in the CIP section 13.7.3.

7.9.3.4 Analysis Methods

For descriptive purposes, a Kaplan-Meier curve will be generated using each subject's time to first Next Generation ICD lead fracture or time to last exposure to the Next Generation ICD lead if the subject does

not experience a lead fracture, in which case the subject will be censored. Last exposure to the Next Generation ICD lead will be defined as the date of their last follow-up visit, study exit date (if exited for reason other than lost-to-follow-up), or date of death, whichever is last. Additionally, if a subject has an explant of the Next Generation ICD lead that is not related to a lead fracture, the subject will have their last exposure date set to their explant date. All subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis.

Fracture free performance of the Next Generation Lead will be estimated using Bayesian analysis methods. Specifically, the Bayesian analyses will be performed using a piecewise exponential model with two intervals of interest: 0-12 months post-implant, and 12 months and beyond post-implant, as it is possible the rate of fractures may vary between the first and second 12-month periods. The Bayesian analyses will be performed using two different prior distributions for the fracture rate as follows:

1. An analysis based only on data collected from subjects during the clinical study. This analysis will utilize a non-informative prior.
2. An analysis based on data collected from subjects during the clinical study when combined with virtual patient data developed from a fatigue survival engineering model. The virtual patient data are combined with data from subjects enrolled in the clinical study by using an informative prior with parameters developed from the engineering model.

Both Bayesian analyses are described in detail below.

7.9.3.4.1 Analysis Based on Non-Informative Prior

The piecewise exponential mode for RV lead failure is defined as follows. Let λ_1 denote the fracture hazard rate for 0-12 month post-implant attempt, and let λ_2 denote the fracture hazard rate for 12 months post-implant attempt and beyond. The survival function (S(t)), will have the equation

$$S(t) = \begin{cases} exp(-\lambda_1 t), & t \in [0, 12) \\ exp(-12\lambda_1)exp\left(-\lambda_2(t-12)\right) & t \in [12, \infty) \end{cases}$$

When *n* subjects have had an implant attempt, let X_i be the time until fracture (or censoring if no event is yet observed) for subject *i*, and d_i is an indicator of an event (thus d=0 implies subject *i*'s fracture time is censored). Let X_{ij} be the "time spent" by subject *i* in interval *j*. Let d_{ij} be the indicator of an event for subject *i* in interval *j*. The likelihood function is

$L(\lambda_1, \lambda_2 | \text{data}) = \prod_{j=1,2}(\lambda_i)^{dij}\exp(-\lambda_i x_{ij})$

Using the shape and rate parameterization of the Gamma distribution, the following prior distributions are assumed for λ_1 and λ_2: λ_1~Gamma(0.1,0.1) and λ_2~Gamma(0.1,0.1).

The posterior distribution for λ_i, i=1,2 would then be $\lambda_j | \text{data} \sim \text{Gamma}(0.1 + \sum_{i=1 \text{ to } n} d_{ij}, 0.1 + \sum_{i=1 \text{ to } n} x_{ij})$.

7.9.3.4.2 Virtual Patient Data Incorporation

Virtual patient data will be incorporated into the analysis using informative priors for λ_1 and λ_2. The informative priors for λ_1 and λ_2 will be determined based on the lead fracture survival engineering model which incorporates *in-vivo* stress conditions (i.e. *in-vivo* curvature), fatigue testing, and patient activity levels (i.e. cyclic use conditions).

Obtaining Virtual Data Prior Values Based on Engineering Model

Briefly, images collected from a biplane imaging sub-study will be analyzed to determine *in-vivo* bending curvature conditions, i.e., parameters for the distribution of in-vivo bending curvature will be determined. The distribution parameters will take into account uncertainty based on the sample size. The biplane imaging study is a sub-study of the LEADR study. The information about curvature will be combined with fatigue testing and patient activity levels to simulate a distribution for fracture free survival. A detailed description of the lead fracture survival engineering model is provided in the document entitled "LEADR Study Virtual Patient Model Overview". The final output from the engineering model based on data from the biplane imaging sub-study will be available prior to the analysis of the LEADR study's primary safety and secondary objectives.

The biplane imaging sub-study will enroll approximately 60 subjects and collect imaging data in patients with a least 3 months of follow-up. The final engineering model results and report from which the virtual patient data will be computed based on the imaging sub-study is expected to be completed prior to the analysis of the LEADR study's primary safety and secondary objective.

The virtual data will be incorporated in the form of an informative prior Gamma (α_{v1},β_{v1}) distribution for λ_1 and an informative prior Gamma (α_{v2},β_{v2}) distribution for λ_2.

The actual values of α_{v1}, β_{v1}, α_{v2} and β_{v2} will be determined based on the lead fracture survival engineering model which incorporates *in-vivo* stress conditions (i.e. *in-vivo* curvature), fatigue testing, and patient activity levels as described above. The output of this model will be fracture free survival along with its uncertainty. Medtronic will use the output of this engineering model to identify the hazard rate (and its uncertainty) for lead fracture between implant and 1-year and after 1-year (i.e. λ_{v1} and λ_{v2}). The Gamma parameters α_{v1}, β_{v1}, α_{v2} and β_{v2} will be set such that E(λ_{v1}) and E(λ_{v2}) equal the λ_{v1} and λ_{v2} values observed from the engineering model, but reflect the uncertainty (i.e. variance) observed in the engineering model associated during each yearly interval. However, β_{v1} and β_{v2} will be capped at 500 patient years (i.e. 6000 patient months) if the final engineering model has an uncertainty level that would be analogous to more than 500 patient years. Additionally, the value for β_{v1} and β_{v2} together with the parameter δ (proportion of clinical follow-up years actually observed during each interval vs the maximum possible follow-up of 500 patient years with the minimum sample size of 500 implant attempts) will ensure that the virtual patients cannot contribute more than the actual clinical patients. The final fracture survival engineering model will be completed following the completion of the LEADR biplane fluoroscopy imaging sub-study which is being used to assess *in-vivo* curvature of the Model 093000 lead (Next Generation ICD Lead) during clinical use. A grid search will be used to identify the α_{vi} and β_{vi} that minimize the sum of the squared differences in the expected survival based on the virtual prior and the projected fracture free survival from the final engineering model, lower 2.5% of the survival rate based on the virtual prior and the lower 2.5% credible boundary of the engineering model, and the 97.5% of the survival rate based on the virtual prior and the upper 97.5% credible boundary of the engineering model. If there is more than one unique solution to the α_{vi} and β_{vi} that minimize the sum of the squared differences, the most parsimonious solution will be used (e.g., a solution where $\beta_{v1} = \beta_{v2}$ and/or $\alpha_{v1} = \alpha_{v2}$).

The R program in section 10.4 demonstrates how the virtual patient priors for λ_1 and λ_2 can be determined from the engineering model.

Discounting the Virtual Patient Prior

The informative priors for λ_1 and λ_2 will be discounted (i.e. down weighted) so that the "virtual patients" cannot contribute more than the observed clinical data. In statistical terms, the informative priors for λ_1 and λ_2 will be down weighted using a discounting approach. Specifically, the priors for λ_1 and λ_2 will be down weighted by two factors:

1. ρ_i=degree of agreement between the Gamma(α_{vi},β_{vi}) distribution and the posterior for λ_i using the non-informative Gamma(0.1,0.1) prior, and
2. δ_i= proportion of clinical follow-up data obtained relative to the minimum planned sample size of 500 subjects with an implant attempt (i.e., total patient years in that interval divided by total of 500 subjects undergoing an implant attempt). δ_i will not exceed 1 in the case more than 500 years of clinical follow-up are accrued during an interval.

Both parameters make use of the prospective data to determine the influence of the virtual data on the overall results. In the case of ρ_i, for example, the difference between the posterior for λ_i based on the non-informative Gamma(0.1,0.1) prior and the virtual data Gamma(α_{vi},β_{vi}) distribution will be assessed by generating 10,000 values from each distribution and taking the difference between the 10,000 generated paired values; the 10,000 differences would then be assessed to see how often they were smaller or larger than 0.

ρ_i = 2 × (1-max(proportion of differences > 0, proportion of differences < 0))

For example, if 80% of the paired differences are positive, then ρ_i = 2 × (1-0.8) = 0.4. The minimum value of ρ_i would be 0 if all differences were positive or all differences were negative. The maximum value of ρ_i would be 1 if all 50% of the differences were positive and thus 50% of the differences also were negative.

In the case of δ_i, for example, if among 500 subjects with an implanted attempt the total amount of follow-up data in the interval 0-12 month post-implant period equals 475 years, then the prior for that interval would be multiplied by a factor of δ=475/500 = 0.95 to down weight the influence of the prior by 5%. A similar approach is employed for the 12-24 month interval.

Prior to Posterior Calculation Incorporating Virtual Patients

The final posterior distributions for λ_i, i=1,2 would be

$\lambda_j | \text{data} \sim \text{Gamma}(\rho_i\delta_i\alpha_{vi} + 0.1 + \sum_{i=1 \text{ to } n} d_{ij},\ \rho_i\delta_i\beta_{vi} + 0.1 + \sum_{i=1 \text{ to } n} x_{ij})$.

The final posterior distribution for λ_1 will be used to generate corresponding posterior distributions and 95% credible intervals for the fracture-free rate at 6 and 12 months using the formulas exp(-6λ_1) and exp(-12λ_1), respectively. The posterior distributions for λ_1 and λ_2 will be used to generate corresponding posterior distributions and 95% credible intervals for the fracture-free rates at 18 and 24 months using the formulas exp(-12λ_1)exp(-6λ_2) and exp(-12λ_1)exp(-12λ_2), respectively.

The posterior distributions using only clinical data (i.e. excluding virtual data) will be used to generate 95% two-sided credible intervals for the fracture-free rate at 6, 12, 18, and 24 months to assess the robustness of the result excluding virtual data.

The R program in section 10.1 demonstrates how these calculations can be performed in practice.

7.9.3.4.3 Influence of Virtual Patient Data

To demonstrate the influence of the virtual patient data, two scenarios were investigated in a simulation study. In the first, the Next Generation ICD lead is assumed to have its anticipated performance with a fracture rate of 99.9% at 12-months post-implant and 99.8% at 24-months post-implant. In the second scenario, the lead is assumed to have poor Fidelis-like performance with a fracture free survival rate of 99.2% at 12-months and 98.4% at 24-months post-implant. In both cases, the informative prior based on the engineering model (i.e. virtual patient data) was assumed to be Gamma(0.9,6000) (i.e. an expected failure rate of 0.9 per 6000 patient follow-up months) for both the 0-12 month interval and beyond 12-month intervals. Note that the actual informative prior based on the engineering model will be determined as described in section 7.9.3.4.3.

Notably, as shown in Figure 7, the 95% credible intervals for a well performing lead and a poor performing lead with a Fidelis-like fracture rate do not overlap by the time of the initial PMA-analysis (Figure 7 blue lines versus yellow lines). Additionally, while the incorporation of the virtual patient data using the informative prior does increase the precision for a lead with excellent performance (compare solid and dashed blue and gray lines) it does little to increase the precision of a lead with poor performance (compare solid and dashed yellow and red lines) due to the discounting of the virtual prior as described above. The simulation study showed that at the 24-month timepoint the 95% credible interval will shrink on average by 10.1% for an excellent performing lead while it will shrink by only 1.2% compared to using a non-informative prior for a lead with poor Fidelis-like performance (Table 9). The R code in section 10.1 performs the simulations.

Figure 7: Estimated 95% Credible Intervals for Fracture-free Rates by Reporting Period



Table 9: Estimated 95% Credible Intervals for Fracture-free Rates by Reporting Period

Analysis	Time Point	Fracture-free Rate Time Point	Data Cohort	Estimated 95% Credible Intervals	
				Next Generation ICD lead	Fidelis-like Lead
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]

*Virtual data refers to data generated by the engineering model
Note for example at 24-months the 95% credible interval width shrinks by [redacted] when the virtual data is added relative to its width based only on clinical data for a lead with the assumed performance of the Next Generation ICD lead while it only shrinks by [redacted]% when the virtual data are used for a lead with Fidelis-like failure rates.

7.9.3.5 Determination of Subjects/Data for Analysis

The primary safety analysis dataset (Table 3) will be used for the analysis of this objective. Specifically, all subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Model Next Generation ICD lead implant procedure. If the subject experiences a fracture endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a fracture endpoint but does not have any successful implant, the survival time will be set to set to time 0.

7.9.4 Ancillary Objective #1

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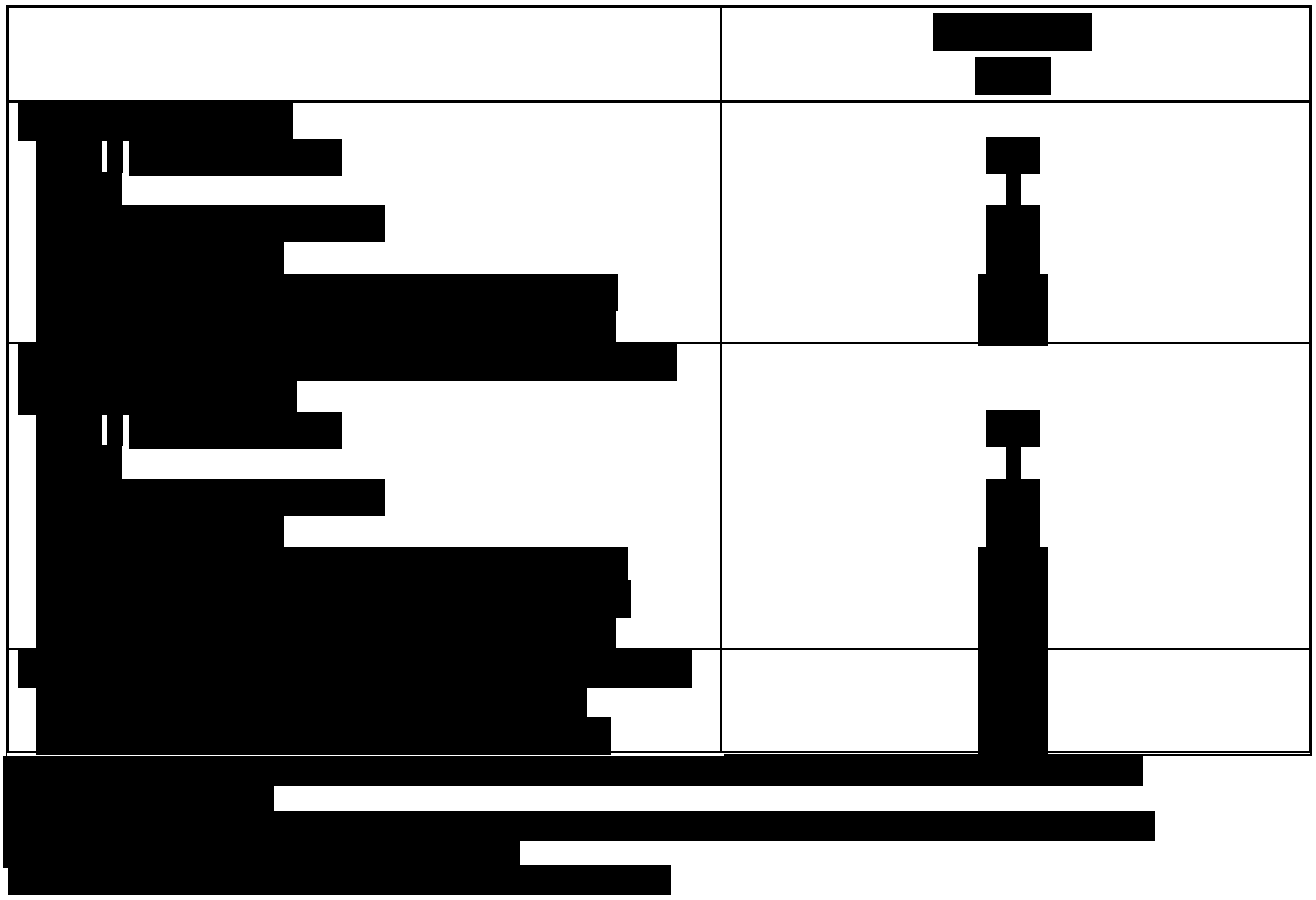
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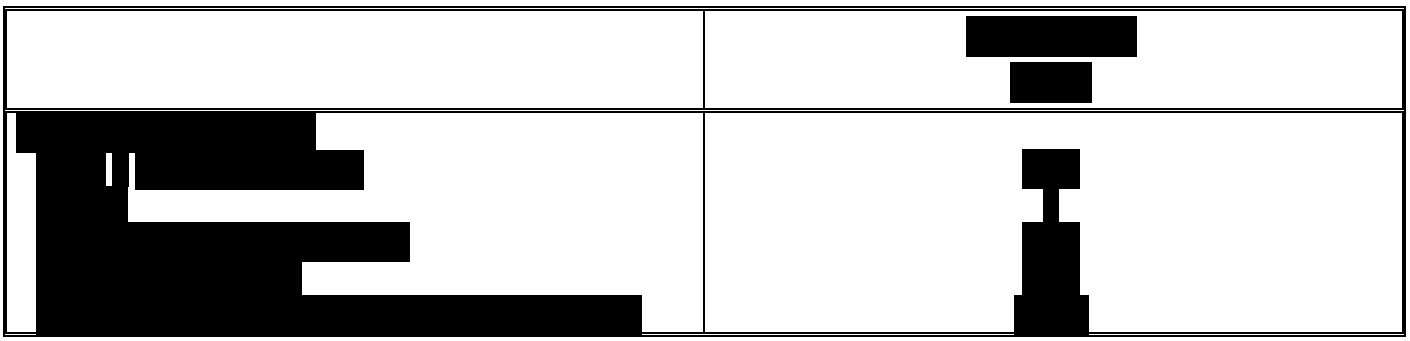
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7.9.7 Stage 1 Safety Objective

The stage 1 safety objective is to estimate the 3-month RV lead-related major complication-free rate.

The endpoint for the stage 1 safety objective is the same as for the primary safety objective with the exception that the event must occur within 90 days (inclusive) of the Next Generation ICD lead implant attempt. This objective will be evaluated once 150 subjects complete their 3-month visit and include all subjects that have had a Next Generation ICD lead implant attempt at the time of the visit cutoff for analysis.

7.9.7.1 Hypothesis

There is no hypothesis for this objective since it is descriptive in nature. The goal is to estimate the freedom from RV lead related major complications and its 95% credible interval through 3-months post-implant.

7.9.7.2 Performance Requirements

There are no prespecified performance requirements for this objective. However, the 95% credible interval will provide the range of plausible values for the freedom from major RV lead related complications at 3-months post-implant based on the data at the time of the stage 1 pre-market report.

7.9.7.3 Rationale for Performance Criteria

A rationale is provided in the CIP section 13.11.3.

7.9.7.4 Analysis Methods

As described in CIP section 13.1.1 and SAP section 7.8.3 the stage 1 safety objective will be evaluated when 150 subjects complete their 3-month follow-up visit. The analysis of this objective will include all subjects with a Next Generation ICD lead implant attempt at the time of the database freeze for the evaluation of this objective. Depending on the study's enrollment rate it is projected that several hundred subjects will have an implant attempt by the time this objective is evaluated.

For descriptive purposes, a Kaplan-Meier curve will be generated using each subject's time to first Next Generation ICD lead related major complication or time to last exposure as defined in section 7.9.1.4, in which case the subject will be censored.

Additionally, a two-sided 95% credible interval will be computed from the piecewise exponential survival model described in CIP section 13.5.4 with the exception that the posterior distribution for λ_2 will be computed as follows:

λ_2 ~ Gamma (1 + # of first endpoints between 1 & 3 months, 12.33 + Total Survival Months between 1 and 3 months)

The posteriors for λ_1 and λ_2 will be used to determine the posterior distribution for the 3-month freedom from Next Generation ICD lead-related major complication rate and its two-sided 95% credible interval.

7.9.7.5 Credible Interval Width

Based on the simulation study described in section 7.9.1.5 the number of subjects with an implant attempt, estimated 3-month major complication freedom rate and its estimated lower 95% credible interval were computed under 3 different scenarios. Table 15 shows that at the time of the analysis for the stage 1 pre-market report, the lower credible interval for the RV lead related major complication free rate should be within 5% of its point estimate.

Table 15: Precision of 3-Month RV Lead Related Major Complication Free Rate at the Stage 1 Safety Analysis Timepoint

Subjects with Implant Attempt (95% Monte Carlo Interval)	Scenario	Estimated 3-month Freedom Rate[1]	Estimated Lower 95% Credible Interval[1]	Probability Distance Between Point Estimate and Lower Credible Interval within 5.0%[2]
362 (334 – 391)	Planned (6-month freedom rate is 94.5%)	94.5%	91.6%	>99.9%
	6-month freedom rate is 92%	93.6%	90.3%	>99.9%
	Null Hypothesis (6-month freedom rate is 90%)	92.8%	89.3%	>99.9%

[1]Median estimate across 10,000 simulations.
[2]Proportion of simulations where distance between the 3-month freedom rate and its lower two-sided 95% credible interval was ≤ 5.0%.

7.9.7.6 Determination of Subjects/Data for Analysis

The stage 1 safety analysis dataset (Table 3) will be used for the analysis of this objective. Specifically, all subjects undergoing an implant attempt of the Next Generation ICD lead will be included in the analysis. If a subject has multiple Next Generation ICD lead implant procedures during the study, time 0 for the subject will be set to the date of the subject's first successful Next Generation ICD lead implant procedure. If the subject experiences a safety endpoint prior to their first successful implant (e.g. at an unsuccessful implant attempt) or experiences a safety endpoint but does not have any successful implant the time of their endpoint will be set to time 0.

7.10 Safety Evaluation

All adverse events will be collected throughout the study duration, starting at the time of signing the ICF. For purposes of reporting, events shall be captured on an AE eCRF.

An independent CEC will review and adjudicate, at a minimum, all events classified by the investigator or Medtronic as procedure or system related to determine relatedness and complication (major, minor) or observation classifications. Specifically, for an adverse event to classify for CEC review, the event needs to have causal, probable, possible, or unlikely indicated as relatedness. Additionally, the CEC will classify all lead and system alerts as well as all potential LSEs identified by the clinician in the absence of a device alert as RV lead system events (RV LSE), Non-RV lead system events (Non-RV LSE), or other events based on the definitions in CIP section Table 12. Additionally, the CEC will provide an adjudication for all reported deaths, including system/procedure relatedness and cardiac relatedness.

If available, the CEC adjudication will be used for reporting. If the CEC adjudication is not available (e.g. interim reports), the investigator classification will be used. If there is a disagreement between the CEC

and the investigator, this disagreement will be reported in terms of AE listings/death listings, however the CEC's classification will be used for analysis purposes.

Results will be summarized using descriptive statistics. Number of events, number and percentages of subjects experiencing system and/or procedure-related adverse events will be reported, as well as, in the case of system-related events, the specific component of the system to which the event was related to describe adverse device effects. The seriousness of adverse events and type of event (complication/observation) will also be summarized as well as whether events were unanticipated adverse device effects or unanticipated serious adverse device effects. Details of individual adverse events including MedDRA key term, actions, outcome, relatedness and seriousness will be listed.

The prevalence of adverse events will further be summarized by MedDRA (Medical Dictionary for Regulatory Activities) key term. The Preferred Term (PT) term will be used. The number of events and the number of subjects and the percentage of subjects with an event will be summarized per each PT Term.

A listing of deaths will be provided with cardiac relatedness (cardiac death, sudden cardiac-death, etc). All subject deaths must be reported by the investigator to Medtronic on an AE eCRF (AE with fatal outcome).

Additionally, any device deficiencies related to the Next Generation ICD lead or accessories will be collected. Device deficiency information will be collected throughout the study and reported to Medtronic. An eCRF should be completed for each device deficiency that did not lead to an Adverse Event. The term and center description of individual device deficiencies and whether they could have led to a serious adverse device effect will be reported in a listing.

Adverse events, deaths, and device deficiencies will be summarized for the 'Safety' cohort.

7.11 Health Outcomes Analyses

No pre-specified health outcomes analyses are planned for the LEADR study.

7.12 Changes to Planned Analysis

This Statistical Analysis Plan does not deviate from the planned statistical analysis in the CIP. Any change to the data analysis methods described in the Clinical Investigational Plan will require an amendment only if it changes an objective of the Clinical Investigational Plan. Any other change to the data analysis methods described in the Clinical Investigational Plan and this Statistical Analysis Plan, and the justification for making the change, will be described in an updated version of the Statistical Analysis Plan or the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

8. Validation Requirements

To ensure the quality and correctness of the statistical results and datasets created for the study, the following validation requirements will be implemented.

Level I validation (independent programming) will be performed on programs related to inferential analyses regarding the primary objectives, while level II validation (peer review) will be performed for other programs related to the primary objectives and to all other objectives, as well as for programs

summarizing non-objective related information such as baseline demographics, study deviations, follow-up compliance, and study exits. Level III validation (self-validation) will be acceptable for programs, which were previously validated level I or II and which have only minor changes from the validated version.

Independent programming means that an internal Medtronic statistician will write code independently of the original analysis code and results from the two programs will be compared to confirm matching results.

9. References

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Jackson, K. P. et al., 2020. Performance of a novel active fixation quadripolar left ventricular lead for cardiac resynchronization therapy: Attain Stability Quad Clinical Study Results. *Journal of Cardiovascular Electrophysiology,* pp. 1147-1154.

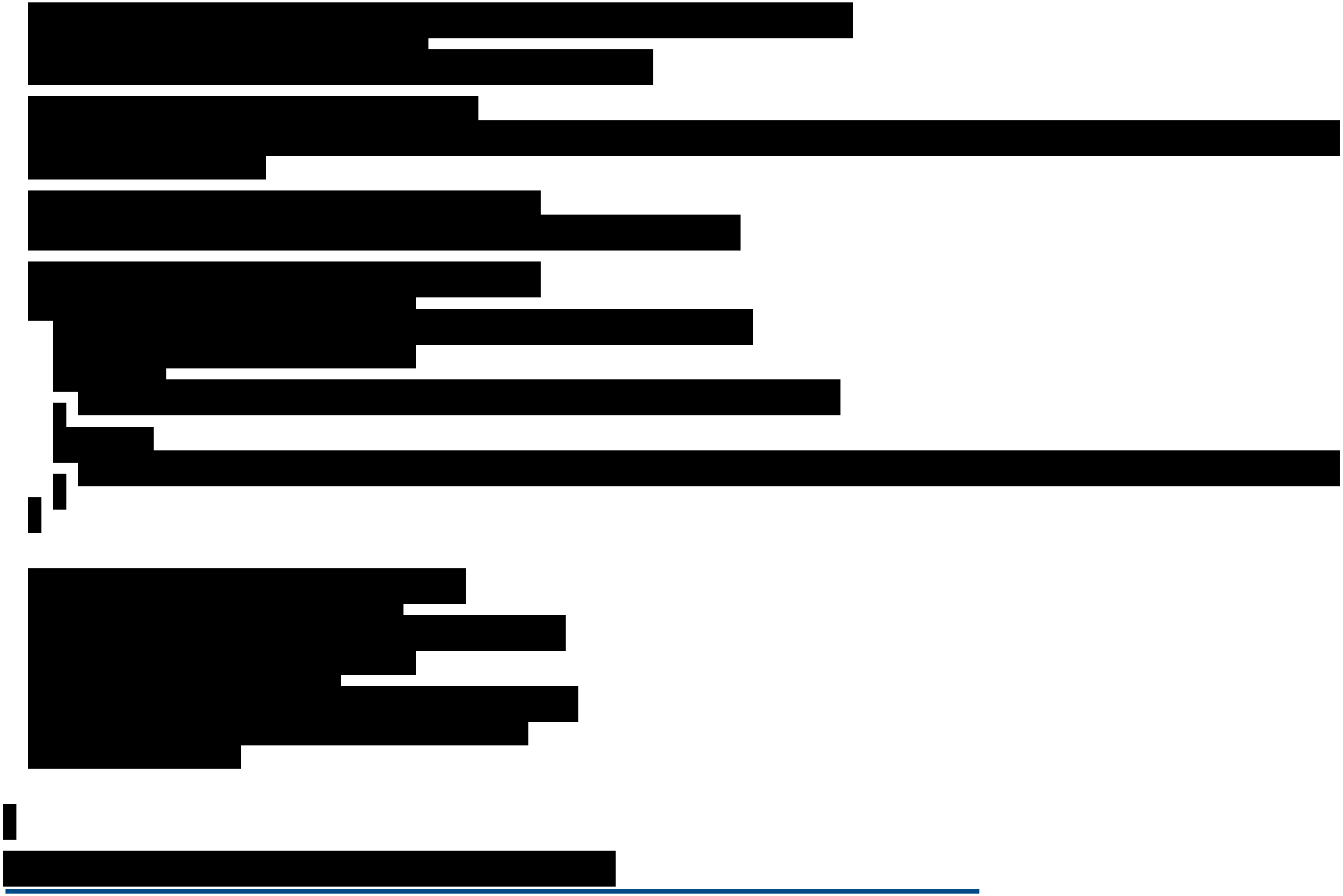
Reynolds, D. et al., 2016. A Leadless Intracardiac Transcatether Pacing system. *The New England Journal of Medicine,* pp. 533-541.

10. Statistical Appendices

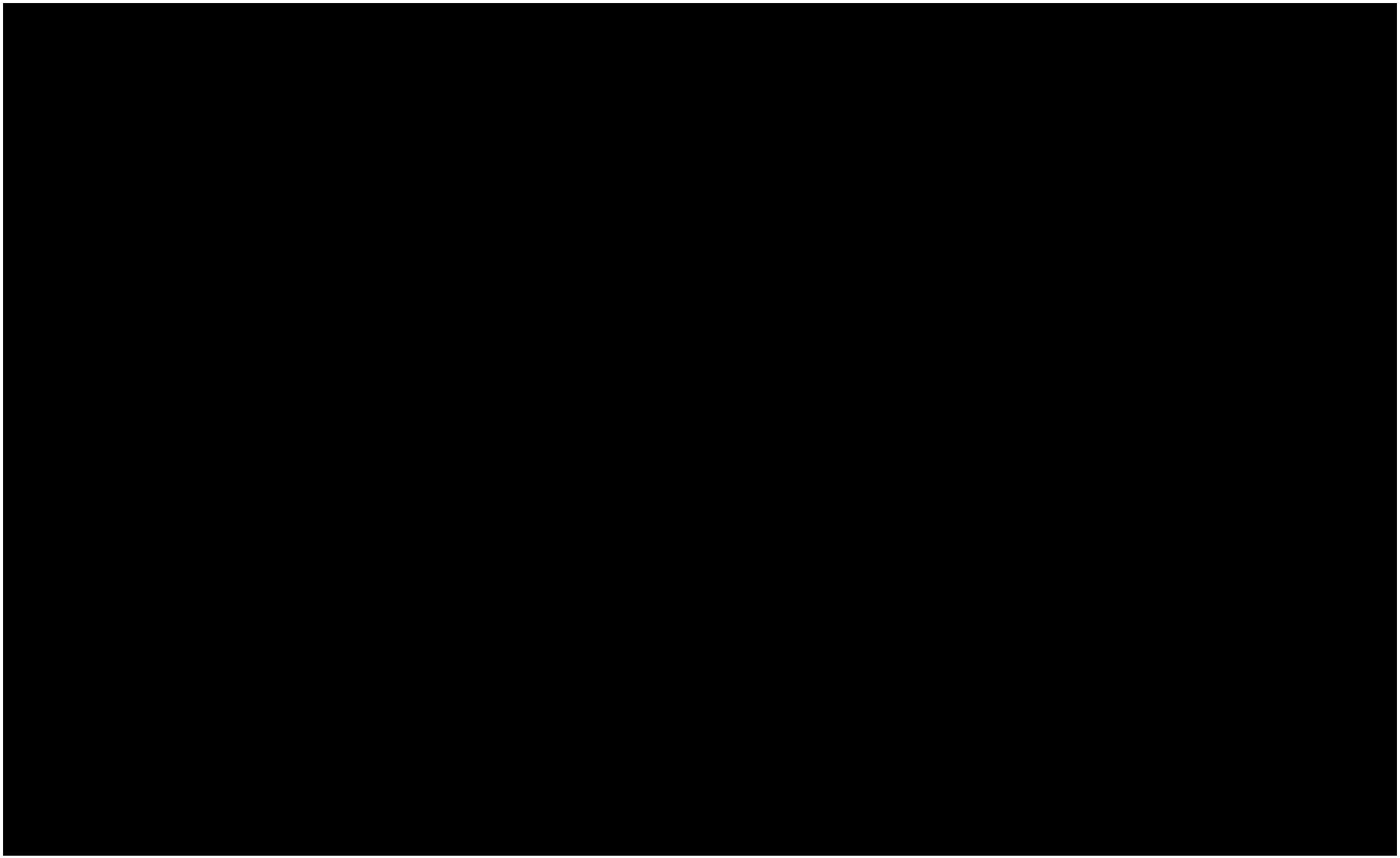


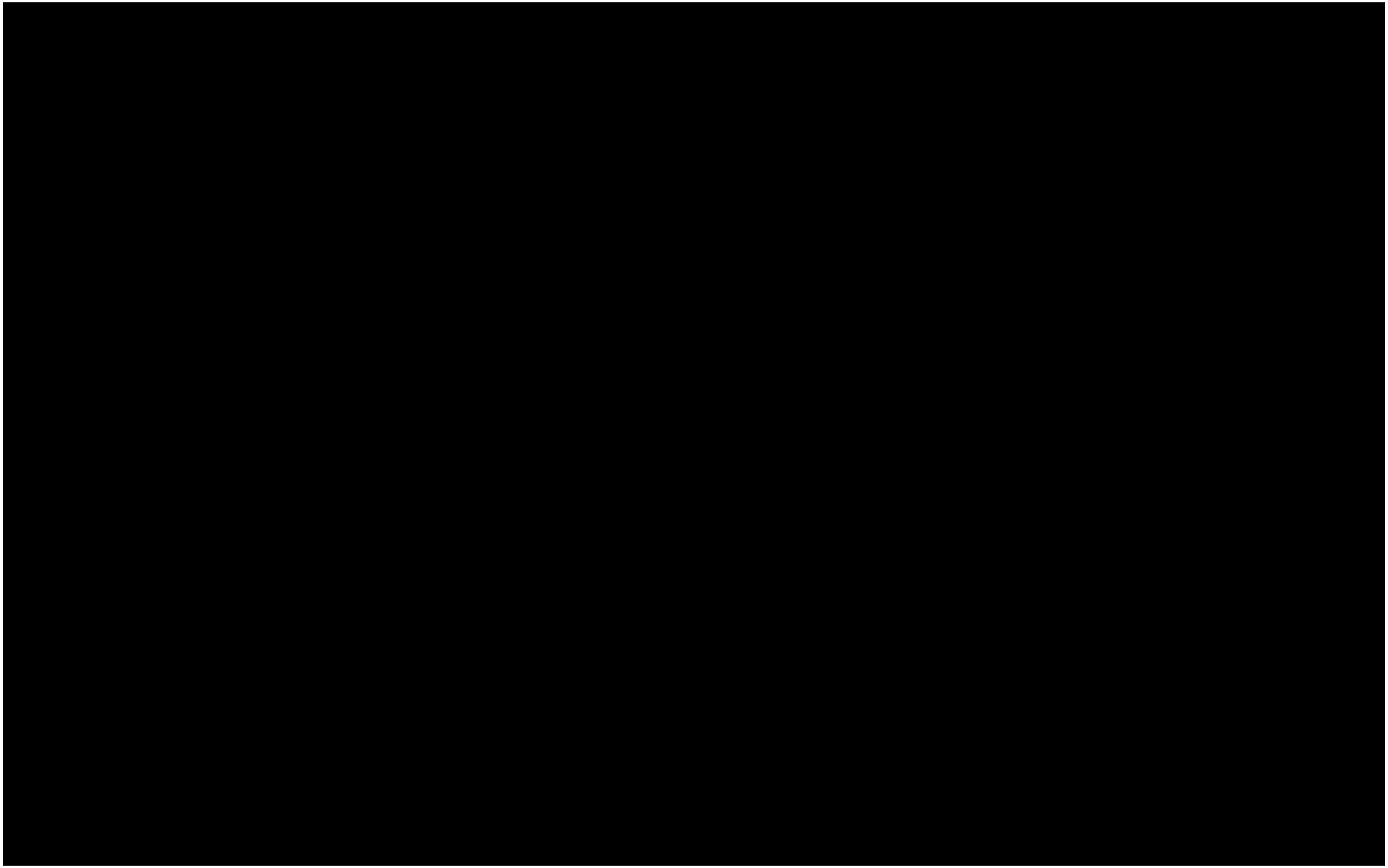
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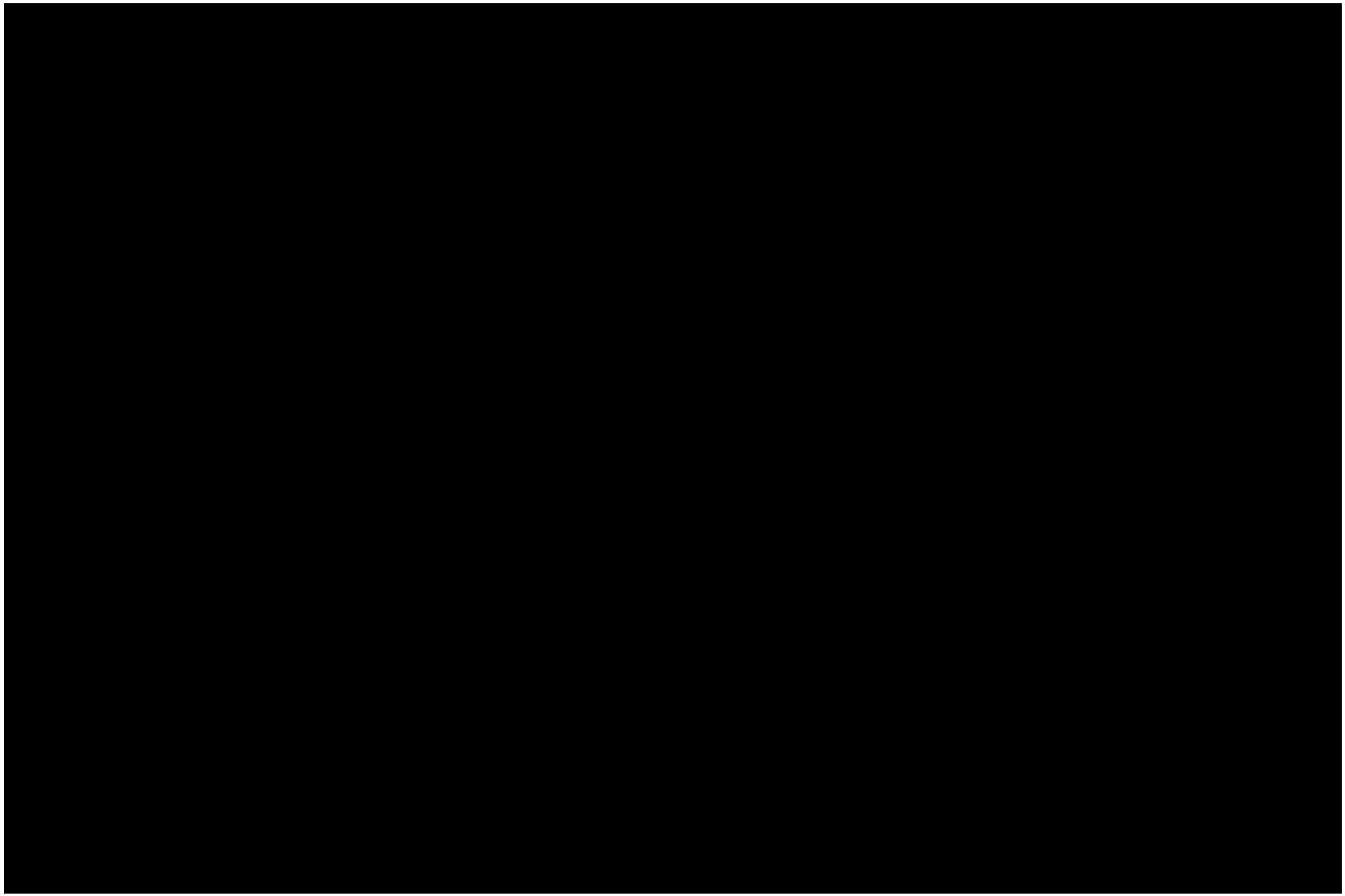
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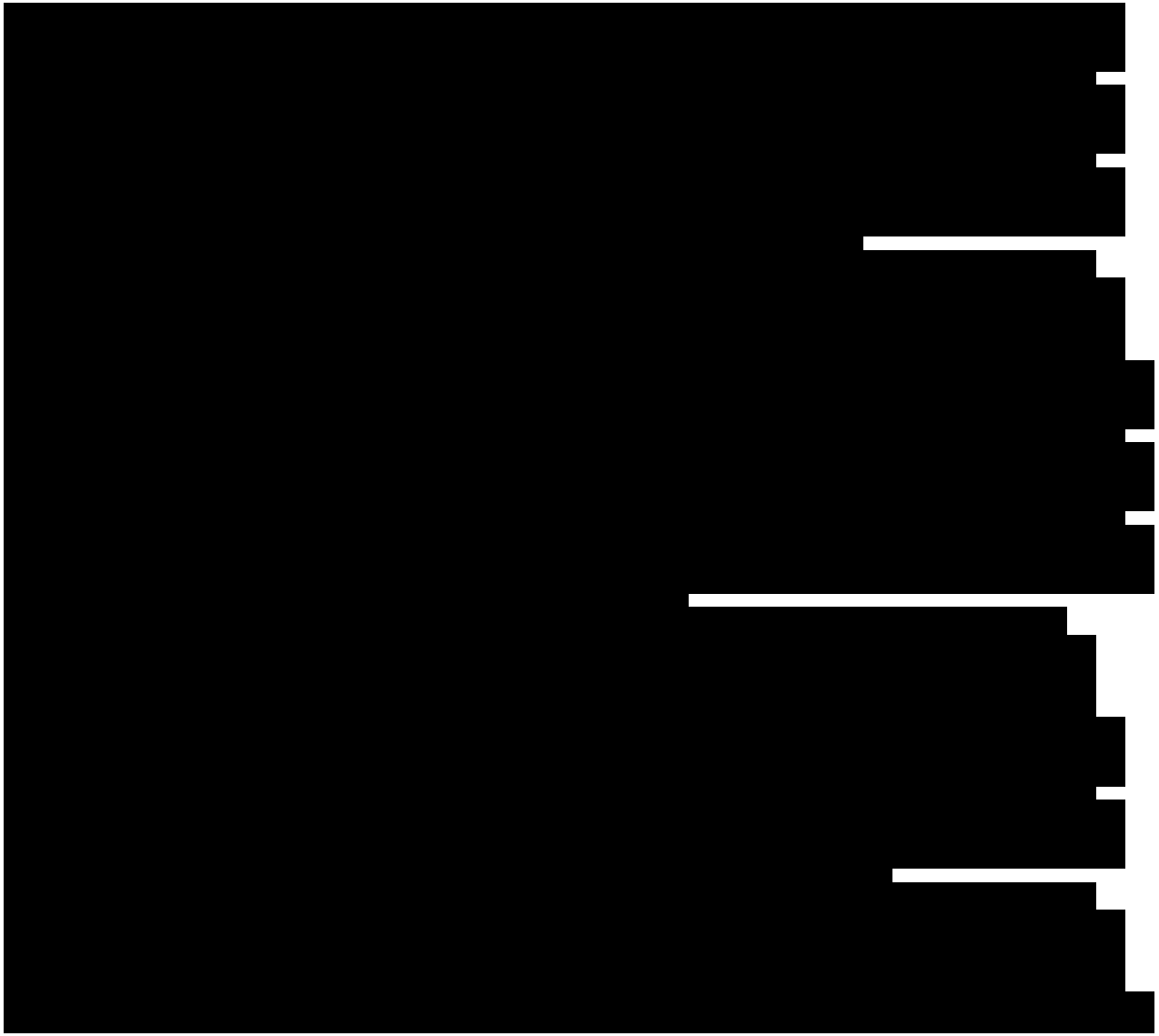
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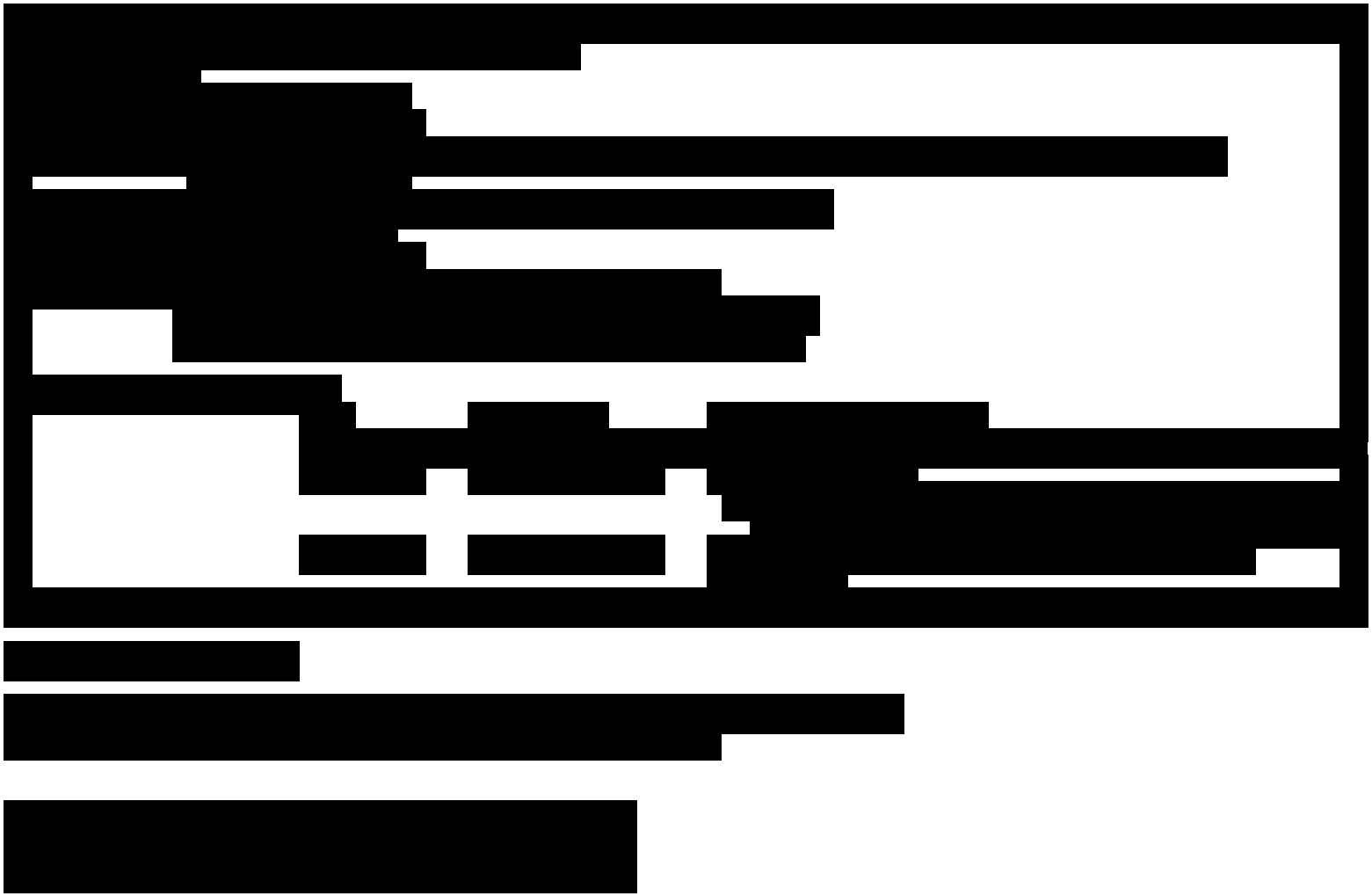
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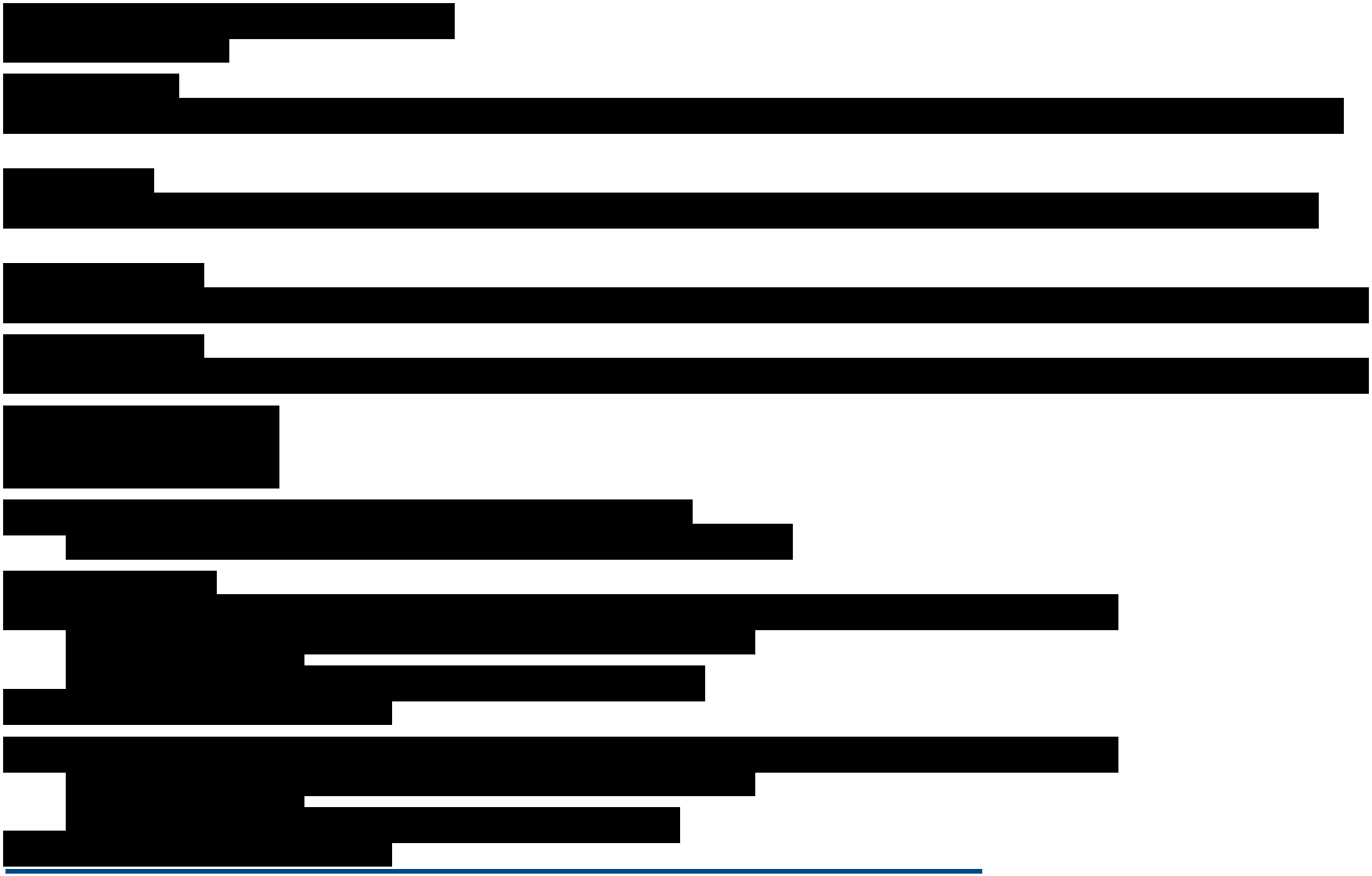
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10.2 R-program to Compute Primary Efficacy Objective Type 1 Error

The following R program was used to study the type 1 error under different priors.



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10.3 Performance of Bayesian Model when Piecewise Exponential Model Misspecified



Figure 8: Scenarios Where the Piecewise Exponential Model was Misspecified





Figure 9: Comparison between Results of Kaplan-Meier Analysis and Bayesian Analysis Methods when Piecewise Exponential Model Misspecified



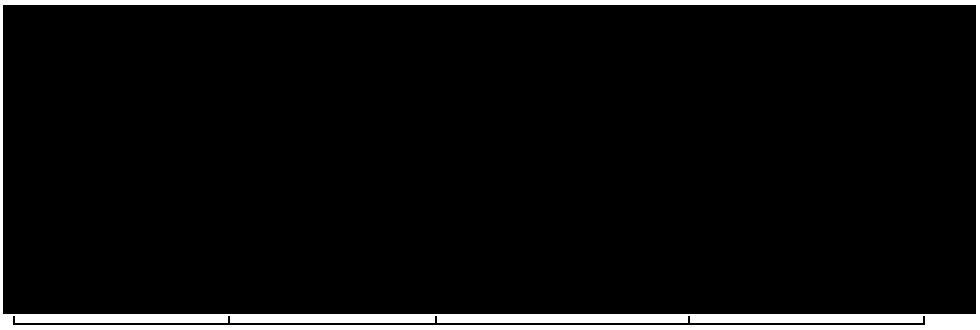


10.4 Determining Virtual Patient Priors from Engineering Model

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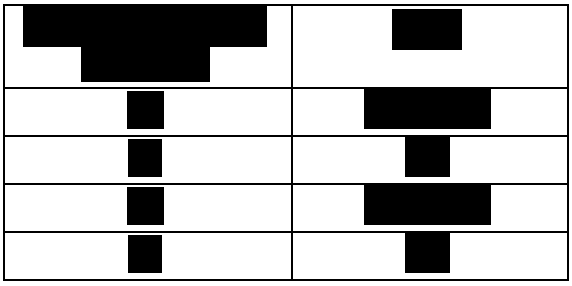
Table 16 displays the numerical engineering model output.

Table 16: Projected Lead Fracture Free Rate from Engineering Model Based on 3830 Select Secure Pacing Lead











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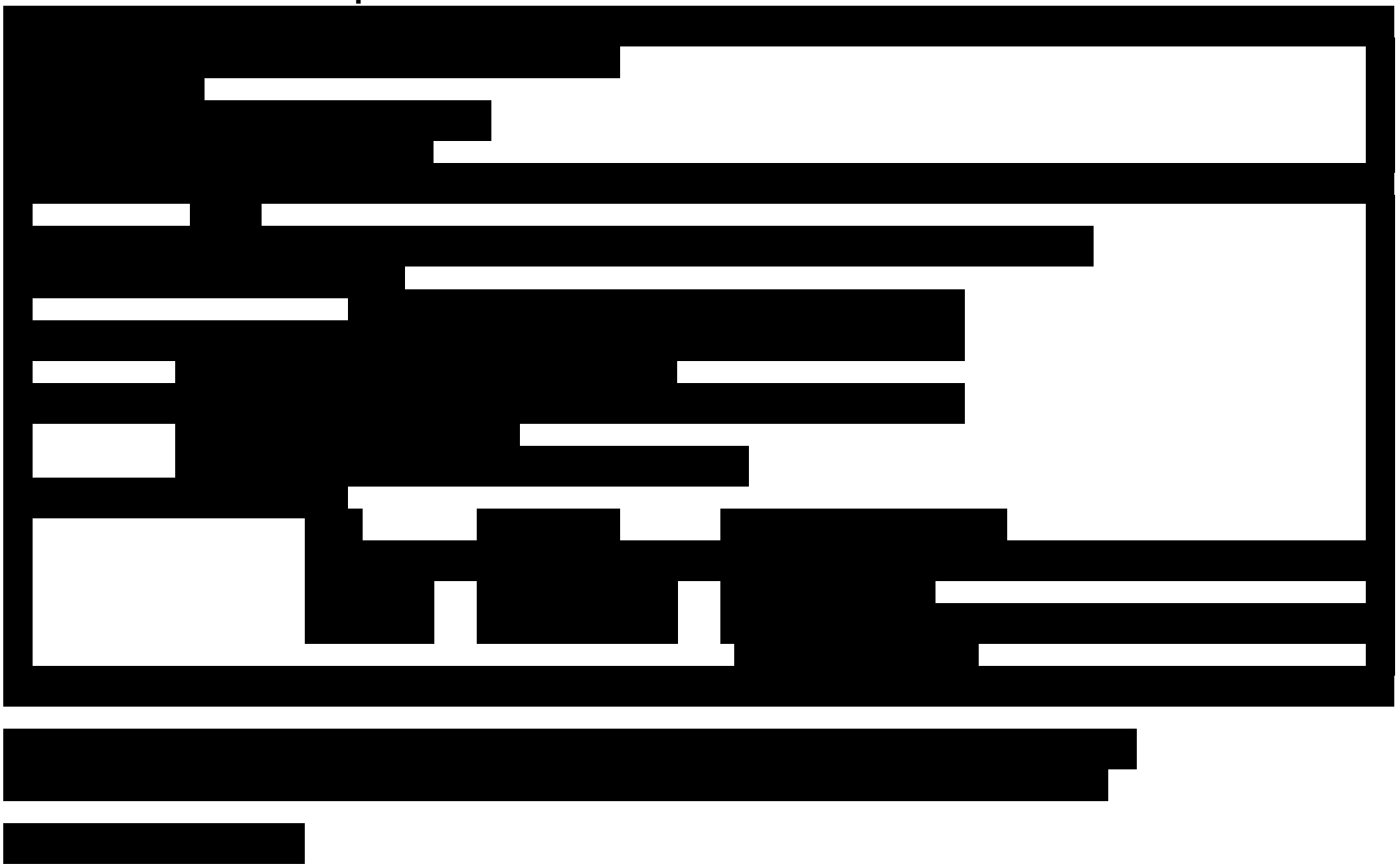
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Figure 11: Comparison of Parametric Fracture Free Survival Based on Virtual Prior Compared to Output from Engineering Model Based on the 3830 Select Secure Pacing Lead

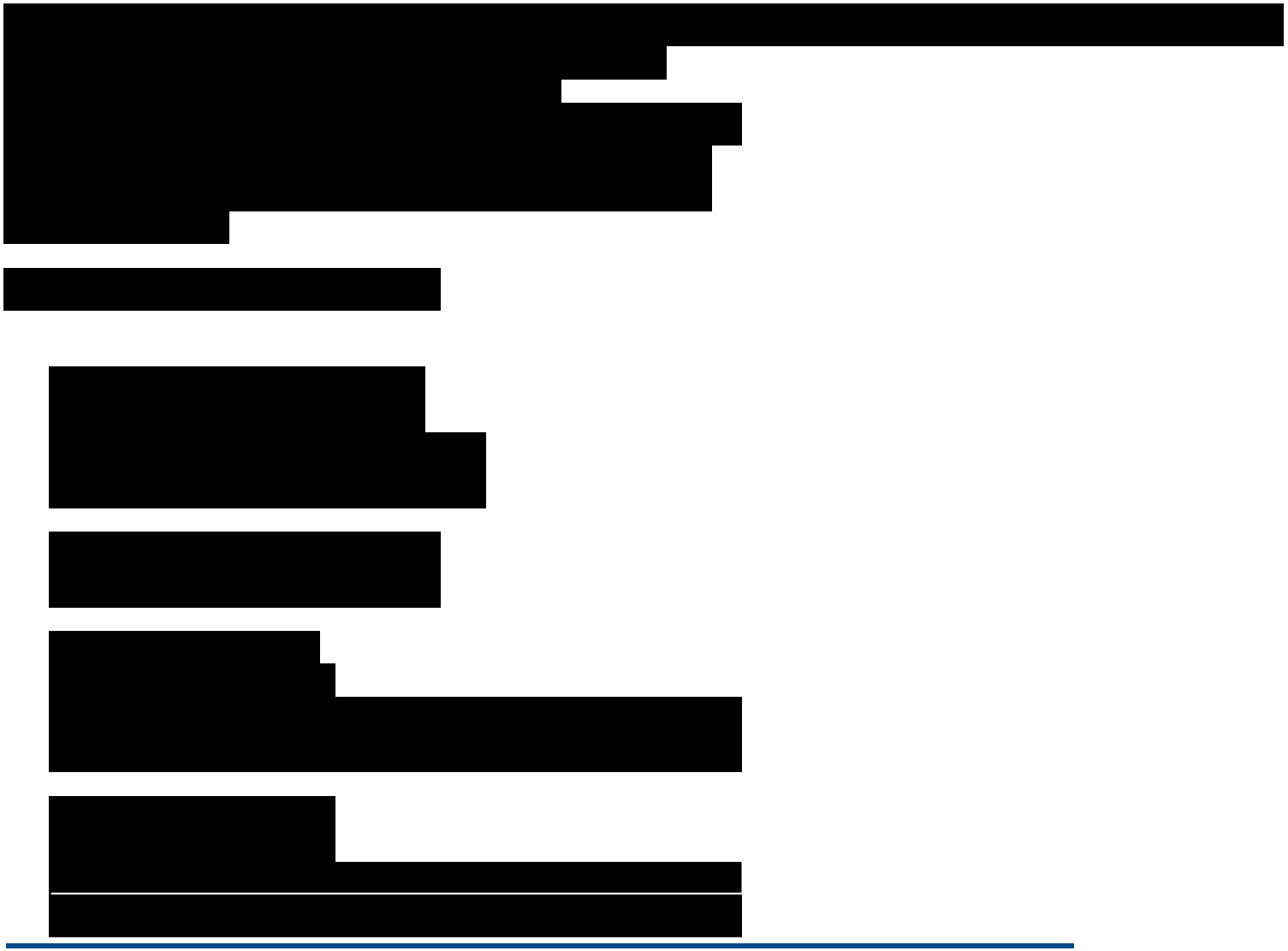


10.4.2 R-code to Compute Virtual Patient Prior



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