2014VP Virtual Patient Engineering Model

The 2014VP ICD lead is the subject of this Original IDE. The purpose of this document is to discuss the engineering model used to generate virtual patients who are implanted with this lead. The virtual patient model incorporates *in-vitro* test data, *in-vivo* use condition measurements, and a statistical reliability projection methodology, to predict the *in-vivo* survival of the lead, all of which will be discussed below.

Using the virtual patient model, the simulated lower 5% confidence bounds on intracardiac fracture survival for the 2014VP patient population at 5 and 10 years are 99.75% and 99.62%. This compares favorably to the results of the same methodology applied to the predicate product 2005 lead, which had simulated results at 5 and 10 years of 99.68% and 99.58%, and has had acceptable performance in the field.

We propose the following for consideration of a clinical study design: 1) the maximum % of virtual patients would be in the range of 30-50%, and 2) the type I error would be in the range of 0.15-0.20, as supported by the influence, risk, and credibility of the virtual patient model.

A bibliography of relevant published and unpublished literature is also provided in support of this Original IDE application.

Clarifying notes

For the purposes of this mock Original IDE submission, the only sections with detail are those relevant to a fracture survival endpoint, which is specific to fracture inside the heart, i.e., a single failure mode, in a single anatomical zone. If this were an actual submission for a new device, all failure modes in all anatomical zones would be addressed. Additionally, there would be extensive documentation related to many other areas, such as packaging, shelf-life, sterilization, etc. The out of scope areas are indicated in the outline.

The engineering model (referred to as the virtual patient model, or VPM) discussed herein estimates *in-vivo* fatigue fracture survival. This is accomplished by matching potential *in-vivo* loading conditions with data from bench tests performed at a range of stress levels. Thus, the central calculation is based on empirically-derived fatigue strength curves. We note that other techniques such as finite element analysis (FEA) might also be employed to simulate device performance, but were not employed in this case.

We recognize that for the review team to perform a complete evaluation of the proposed ranges for the percentage of virtual patients (potentially replacing 30-50% of the real patients) and type I error (0.15-0.20), it would be necessary to provide additional clinical statistical data and analysis. The sponsor team plans to provide this information in an upcoming pre-submission that focuses on the clinical study. We request that the review team evaluate the current pre-submission information using the aforementioned ranges with the expectation that a detailed statistical analysis is forthcoming in a different pre-submission meeting.

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Out of scope

- Risk Management
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1. Design Overview

The design of the 2014VP lead results in a change in handling characteristics as compared to the predicate product model 2005 lead, which has acceptable field performance since its market release in 2005. Additionally, manufacturing changes that improve fatigue performance[1] of the MP35N[2] conductor material have been implemented. Together, these changes are expected to result in equal or better fatigue performance in the patient population. The 2005 and 2014VP lead cross sections are shown in Figure 1.

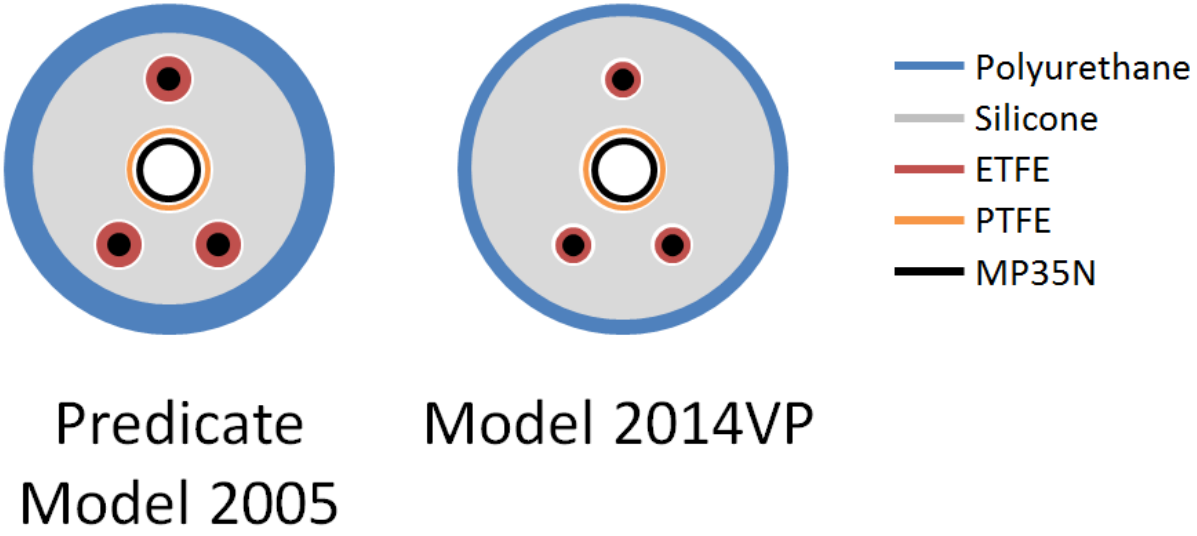

Figure 1: Cross sections of the predicate product model 2005 and 2014VP

Comparisons between the design and performance attributes of the predicate product model 2005 and 2014VP leads are given in Table 1 and 2.

Table 1: Comparison between Product Models 2005 and 2014VP: Design

Component or Dimension	Difference
Implant method, tools, indications	None
Outer diameter, conductor dimensions, electrodes, connector	None
Outer polyurethane insulation	2014VP (thinner)

[1] The manufacturing changes to the MP35N result in a reduced number and size of titanium nitride (TiN) particles. These particles commonly act as fatigue crack initiation sites [5].

[2] MP35N is a trademark of SPS Technologies, Jenkintown, PA, USA

Component or Dimension	Difference
Inner silicone multilumen insulation	Lumen diameters (larger), outer diameter (smaller)
ETFE insulation around cables	2014VP (thicker)
Pacing (inner) coil, sensing and defibrillation cables	Improved manufacturing process for conductor material (see reference [5])

Table 2: Comparison between Product Models 2005 and 2014VP: Performance

Test or Performance Attribute	Difference
Handling	Favorable physician handling measured in animal and bench simulator
Lead body stiffness	2014VP less stiff (section 3.1.2)
Fatigue strength	2014VP improved (section 3.3)

Fracture performance is affected by lead body stiffness and fatigue strength, and therefore will be discussed in section 3. The virtual patient model takes into account both factors.

2. Virtual Patient Model Overview

The expected field performance for fracture survival for the 2014VP lead is estimated by a virtual patient model (VPM). The VPM is an algorithm that predicts the fracture survival for patient cohorts based on distributions of the following input data as depicted on the left in Figure 2:

- lead curvatures measured from imaging,
- activity levels for patients in different age categories, and
- fatigue life (S-N) curves of manufactured leads

Cohorts of virtual patients can be simulated using the VPM algorithm, generating families of survival curves as the output, which are shown on the right side of Figure 2. The VPM algorithm is presented in this section, and is described in greater detail in [1]. As noted above, we are only considering lead fracture inside the heart. In an actual submission for a cardiac lead, all components and all anatomical zones would be accounted for.

The inputs and outputs of the VPM are discussed briefly in this section, and in more detail in section 3. The description of the algorithm is intended to introduce the VPM at a high level. Worked examples and discussion of calculations are given in section 4.

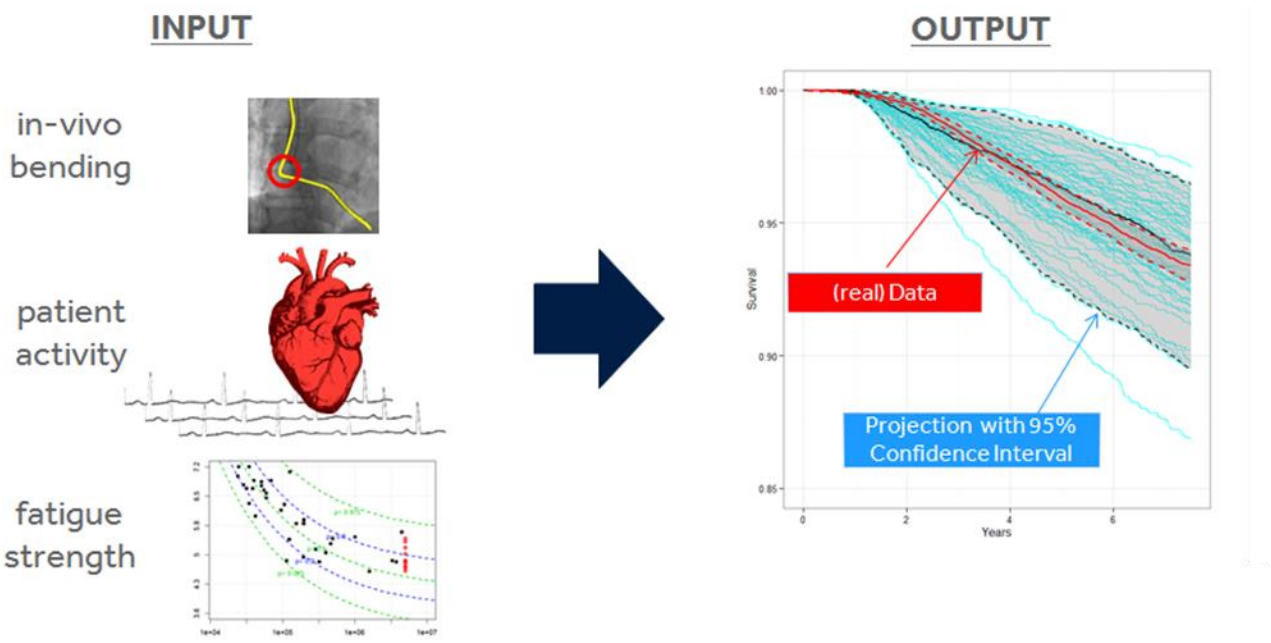

Figure 2: Illustration of the virtual patient model. Note that patient activity is represented by heart beats in the example presented here for fatigue fracture inside the heart.

2.1 VPM Algorithm

The VPM simulates lead fracture rate in many cohorts of patients, as discussed in [1,3][3]. Each individual patient cohort is the result of a Monte Carlo simulation expressing variability due to patient anatomy, physician implant factors, material properties and manufacturing tolerances, captured by the VPM inputs. However, because the variability is not known exactly (e.g., the mean and standard deviation for fatigue strength are estimates from the available data), we simulate multiple patient cohorts with different possible levels of variability, i.e., uncertainty for each input. This can be thought of as a Monte Carlo simulation of Monte Carlo simulations.

A high level version of the algorithm to generate a single virtual patient is as follows:

a. Generate random patient (age), based on patient demographics from predicate device registry, to capture mortality for competing risk calculation. Note that age may also be used as a surrogate for activity level in many other cases. We are assuming a constant heart rate of 79 beats per minute for all patients, regardless of age.

b. Generate random implant curvature (i.e., bending) (see section 2.2 and 3.1) to represent how the lead was implanted during the surgery and the patient's anatomy.

[3] The algorithms in references [1] and [3] have slight differences. The approach discussed in [3] had the intent of matching field performance with modeled results, and contained analysis elements such as healing time, and load ratio effects that improved the quantitative projection ability. The algorithm in [1] has been simplified, with the sole goal of distinguishing the field performance of leads with good field performance from those that do not have good field performance. This objective does not require the output to match absolute field performance, but rather to preserve the relative ranking between products.

c. Generate random fatigue strength using curvature from steps a & b as inputs. (see section 2.3 and 3.3)

d. Convert cycles to years assuming 79 beats per minute.

e. Based on patient age and time to fracture, determine whether the lead will fracture during the life of the patient.

This process is repeated many (e.g. 500) times to simulate an entire cohort of virtual patients, using a Monte Carlo simulation.

In order to generate multiple patient cohorts, we generate new values for the parameters (e.g., location parameter, scale parameter, mean, standard deviation) of the statistical distributions for curvature and fatigue strength and repeat the process. The reason there is variability in these parameters is because the original data sets have a finite sample size, resulting in uncertainty. Examples are given in section 4. Note that some parameters (e.g. patient age, mortality and heart rate) may have negligible uncertainty due to the large sample size for input data, or if the virtual patient model is relatively insensitive to variation in that parameter.

The distribution of simulated implant survival for the multiple patient cohorts at particular time points will be the output of interest that is compared to clinical trial results. Additional discussion will be given in the Clinical Investigation section.

2.2 Assumptions

There are a number of simplifying assumptions for the VPM. These assumptions are specific to the single failure mode being discussed, namely fracture of the cardiac lead that occurs inside the heart. Engineering models for other devices, failure modes, and anatomical locations will have their own unique assumptions. Additionally, we have made some assumptions specifically for this mock submission that would not be expected for the evaluation of a real product. The assumptions with brief justification are listed below in Tables 3 and 4.

Table 3: Assumptions specific to the engineering model (but could apply to a real product)

Assumption	Justification
Loading conditions can be simplified to pure bending, i.e. any torsion or axial loads present *in-vivo* do not significantly impact lead fracture.	Analytical and numerical calculations of stress and strain that result from cardiac torsion and axial loading are significantly smaller than stress and strain that result from cardiac bending.
In-vivo curvature oscillates between single maximum and minimum values. In other words, each cardiac contraction causes the same cyclic curvature to occur, with one cycle per heartbeat.	Confirmed by analysis of curvature vs. time during heart beat from previous imaging studies.

Assumption	Justification
Every patient exhibits an average of 79 heart beats per minute over their lifetime	Heart rate measurement in a population similar to the targeted implant demographic found a mean of 79 and standard deviation of 13 beats per minute [2]. Additionally, the particular failure mode discussed here is relatively insensitive to this level of variability in cycle count.
The curvature achieved in a bench test is sufficient to replicate the loading produced by that same curvature measured *in-vivo.* The lead path away from the location of maximum curvature will not affect the results.	Because the axial length change is minimal in a cardiac lead (~less than 1%), coil and cable loading has been shown[4] to rely almost entirely on local curvature for the 2014VP lead.
Fracture detected on the bench via DC resistance increase is analogous to a clinical event such as a lead impedance alert, inappropriate therapy, or failure to deliver therapy.	Clinically significant increase in DC resistance is typically on the order of 100's of ohms for the pace/sense circuit. Bench test resistance measurement is capable of more precision.
Fatigue strength measured on as-manufactured test samples sufficiently represents the fatigue strength of a lead that has been implanted in the body for any duration.	MP35N mechanical properties are stable in storage, shipping, and implant conditions. The temperature exposure under these conditions is well below the melting and processing temperatures required to cause a significant change in mechanical properties.
Use conditions (curvature) are stationary with time. In other words, the curvature that is applied on the first day of implant is the same curvature that is applied after 10 years of implant.	Although longitudinal *in-vivo* imaging data from the same patient was not used in this analysis, the data that was used to develop the VPM was obtained from a range of implant durations, therefore the variability present in the data set is assumed to incorporate change in curvature over time.
The statistical distribution for curvature is lognormal.	Statistical distribution analysis of measurements.
The statistical distribution for fatigue cycles to fracture at a particular stress level is lognormal.	Statistical distribution analysis of measurements.
Bending orientation is random	Handling studies show uniform distribution of implant orientation.[5]
The lead will not be removed from service for	Conservative assumption, primarily ignores

[4] Hypothetical analysis, not discussed further in this document

[5] Hypothetical data, not discussed further in this document.

Assumption	Justification
any reason other than fracture or patient death, for use in calculating fracture survival rate.	explants due to infection.

Table 4: Assumptions related to this mock submission (not applicable for an actual product)

Assumption
Test methods for bending stiffness and fatigue strength, as discussed in sections 3.1 and 3.3, are based on AAMI standards that are currently in draft form. We refer to the versions that are current as of 14 August 2015 and also assume hypothetical data generated using these tests.
The AAMI Lead Imaging Study discussed in section 3.1 is still in the planning stages. For this document, we assume completion of the study and also will assume hypothetical study results.
Field performance data for the hypothetical predicate lead model 2005 is assumed, and is based on a composite of currently marketed ICD leads.
Hypothetical verification and validation activities for the VPM are described in section 6, however actual data is not presented.

2.3 Model inputs

Model inputs consist of the following, as illustrated above in Figure 2. Each item is discussed in detail below.

- *In-vivo* curvature, also referred to as applied stress (section 3.1)
    - Bending stiffness and *in-vivo* curvature have been measured for predicate lead models and a statistical relationship has been created[6].
    - Bending stiffness has been measured on the bench for the 2014VP lead model
    - A statistical projection of expected *in-vivo* curvature has been created for the 2014VP lead model
- Patient activity, also referred to as cycle count (section 3.2)
    - The relevant patient activity for fracture inside the heart is heartbeats. For simplicity, we assume 79 beats per minute [2] for all patients. Note that fatigue in other regions of the anatomy would incorporate other measures of activity, for example arm movements for fatigue in the shoulder region.
- Fatigue strength (section 3.3)
    - *In-vitro* fatigue testing has been conducted on a finite number of parts to measure fatigue strength over a range of curvature (applied stress) conditions.

[6] This refers to the AAMI Lead Imaging Study, which is still in the planning stages. See section 3.1 for additional discussion.

The stress-to-cycle (S-N) curve was created for the 2014VP and 2005 lead models.

- A statistical model has been fit to the data to allow for generating random fatigue strength curves for virtual patients [1,3]

2.4 Model output

The VPM simulates the time to lead fracture in multiple cohorts of virtual patients. Fracture occurs when the accumulated bending cycles due to patient movement (heart beats in this case) are sufficiently high both in count and amplitude to cause a crack to propagate through all of the wires in a conductor, interrupting the electrical circuit.

Fracture is detected on the bench via DC resistance monitoring during a fatigue test. Fracture is measured clinically by a combination of impedance monitoring with the implantable defibrillator, clinical observation of events such as inappropriate therapy or failure to deliver therapy, and analysis of products returned to the manufacturer. Comparison of fractures generated in bench tests with fractures found in returned product has shown that the two detection methods are sufficiently equivalent for the VPM being discussed here.

For the purposes of incorporating virtual patients into a clinical study, the individual values of time to fracture within a cohort are analyzed to find a fracture rate for that cohort at a particular time point, for example 1% at 5 years. The rates for the combined set of cohorts then form a distribution of fracture rates. This distribution will be used in the statistical analysis of the clinical study.

Complete results and discussion are given in section 5.

3. Discussion of Model Inputs

This section provides additional detail about the two primary inputs to the VPM, which are applied stress and cycle count. We represent the applied stress by curvature, in units of inverse centimeters (cm^{-1}). The lead bends between maximum and minimum amounts of curvature with each heartbeat, discussed in section 3.1 below. One fatigue cycle accumulates with each heartbeat, so we can use heart rate to convert cycle count to time.

3.1 *In-vivo* curvature

We require knowledge of *in-vivo* curvature of predicate leads for two reasons: 1) We need to replicate the mode of deformation on the bench, and 2) statistics from the *in-vivo* data are used to generate the applied stress in the VPM. This section describes how these data were obtained.

Fatigue fracture can occur when a lead cycles between two curvatures. Lead centerline curvature is a practical *in-vivo* measurement that has been shown to be a good surrogate for stress and strain and is therefore useful to evaluate fracture reliability. Curvature is the reciprocal of radius and is expressed in units of 1/length. Curvature amplitude is defined as (maximum curvature - minimum curvature)/2. Mean curvature is the average of the maximum and minimum curvatures. By specifying the max and min curvature, or the mean curvature and amplitude, the

loading conditions for a fatigue test are fully defined. Figure 3 illustrates maximum and minimum curvature conditions for a lead coil.

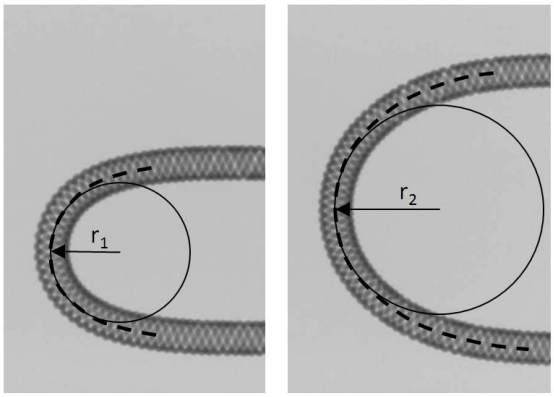

Figure 3: Bending radius on a coil at a maximum curvature (left) and minimum curvature (right) position. Dashed lines indicate the centerline and solid circles indicate the bending radius. The tightest bending radius is indicated with an arrow. Curvature is 1/radius.

The path of an implanted lead is a function of patient anatomy, implanter technique and lead body stiffness[7]. Assuming these three factors are the same, we would expect the degree of lead curvature to be the same for two different implants. Anatomy and implant technique are essentially independent of the lead design and are statistically similar for large cohorts of patients. Stiffness can be measured on the bench. We discuss prior measurements of *in-vivo* curvature in section 3.1.1, lead body stiffness in 3.1.2, and the expected *in-vivo* curvature of the 2014VP lead in 3.1.3.

The expected distribution of *in-vivo* curvature will be calculated following the approach detailed in AAMI PC WG1 N169, Annex B, Rev E [1][8].

3.1.1 *In-vivo* Curvature measured in clinical studies

Lead body curvature inside the heart has been measured for a set of products currently on the market with known stiffness in the AAMI Lead Imaging Study[7]. Biplane fluoroscopy was used to acquire images throughout one complete cardiac cycle, and 3D lead paths were reconstructed at each time point. Peak curvature along the lead path was then measured for a cardiac cycle,

[7] The correlation between *in-vivo* curvature inside the heart and lead body stiffness is planned to be assessed with a clinical imaging study sponsored by the AAMI PC WG1 Transvenous Leads Working Group. This study will incorporate multiple lead models with a range of stiffness. As of August 2015, this study is still in the planning stage. In the analysis presented here, we assume the study has been completed and a correlation between stiffness and curvature has been established.

[8] The analysis method detailed in AAMI PC WG1 N169, Rev E is currently a draft standard and is not in final form. The method for determining *in-vivo* use conditions based on bending stiffness has not been detailed as of Revision E. For this document, we assume the method to be developed and the standard to be finalized.

yielding a curvature mean and amplitude for each point along the lead path. Figure 4 shows two simultaneous fluoroscopic views of a lead, along with the resulting 3D reconstruction.

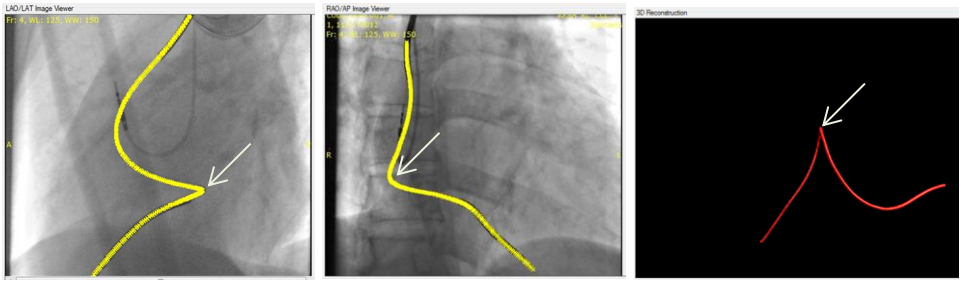

Figure 4: Sample images of lead deformation *in-vivo*. Left anterior oblique and right anterior oblique views are shown in the left and center images. The resulting 3D reconstruction is shown on the right. The location of peak curvature is indicated with an arrow.

Figure 5 shows several examples of lead path shapes illustrating the presence of variability in implanted curvature.

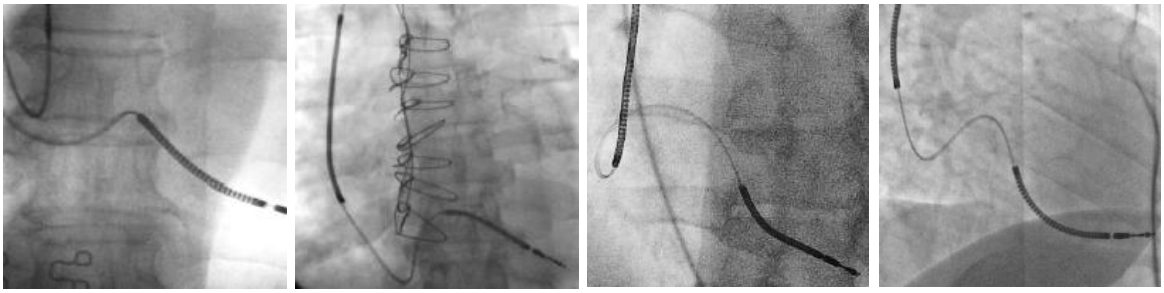

Figure 5: Variability of intracardiac lead curvature

The intracardiac curvature amplitude from the AAMI Lead Imaging Study was found to be distributed lognormal, with the location parameter correlated with lead stiffness[9]. The scale parameter was independent of stiffness. Study results showing intracardiac curvature vs. stiffness are shown in Figure 6.

[9] The curvature data presented here is partially based on intracardiac curvature measured on a market released lead. Because the AAMI Lead Imaging Study is not complete, the relationship with stiffness is an assumption for demonstration purposes and not meant to imply any existing relationship. The full data set would include a mean curvature along with curvature amplitude. Here we assume a constant load ratio of 0.7, which relates mean and amplitude, so by specifying curvature amplitude and load ratio, the loading conditions are fully determined.

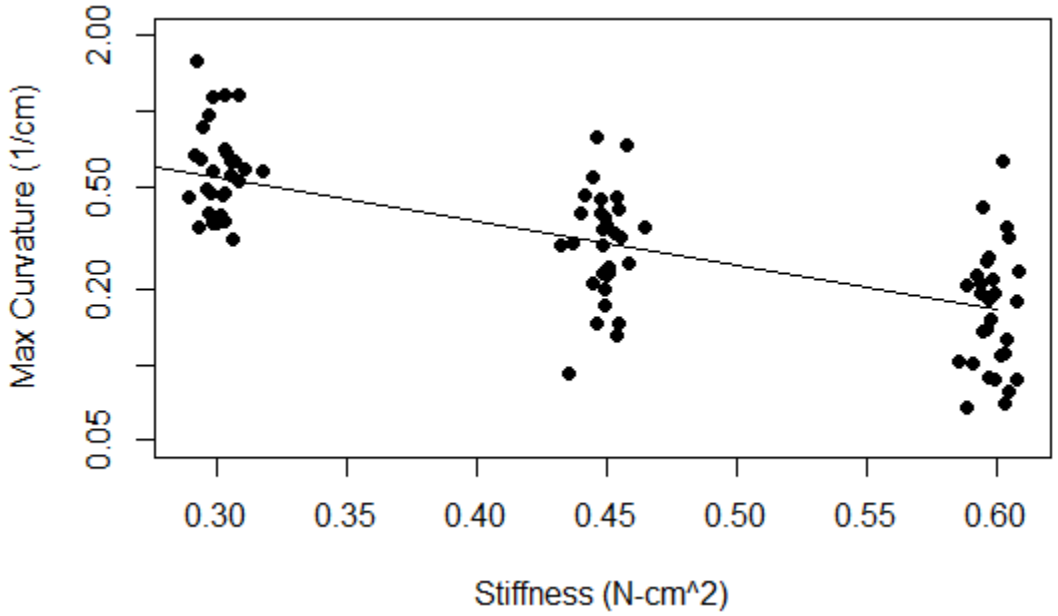

Figure 6: Intracardiac curvature amplitude vs. lead stiffness from the AAMI Lead Imaging Study

The projected *in-vivo* curvature distribution for the 2014VP lead will be simulated using the stiffness relationship and variability found in the AAMI Lead Imaging study according to the following relationship:

$$max\ curvature(cm^{-1}) = lognormal(0.6 - 4K, 0.44) \quad (1)$$

Where K is the average bending stiffness of the 2014VP lead at a centerline curvature of 1 cm^{-1}.

3.1.2 Bending stiffness

As reported earlier, the 2014VP lead is less stiff than the predicate 2005 lead due to the decreased outer insulation thickness. Therefore, we expect the distribution of *in-vivo* curvature for the 2014VP to be higher than predicate product 2005. Bending stiffness of the two leads was determined according to the measurement method described in Annex E of AAMI PC WG1 N169. A sample test image is shown in Figure 7, and the test data is tabulated in Table 5[10].

[10] The test data in table 1 is based on data reported in AAMI PC WG1 N290, Revision I, Figure 24. Bending stiffness is calculated by dividing the bending moment (N-cm) by the curvature (cm^{-1}).

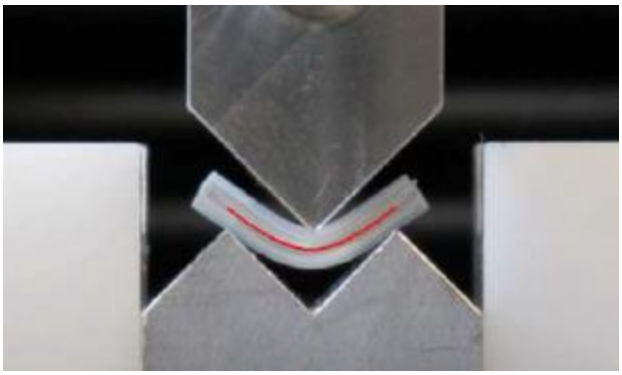

Figure 7: Sample image of deformation in bending stiffness test

Table 5: Bending stiffness at a curvature of 1 cm^{-1} for lead product models 2005, 2014VP

	Product Model 2005	Product Model 2014VP
mean ($N\text{-}cm^2$)	0.5	0.4
std. deviation ($N\text{-}cm^2$)	0.02	0.02
sample size	20	20

Note about FEA: For scope purposes, we only discuss experimental measurement of bending stiffness in this document. In many cases, determination of bending stiffness via finite element analysis is a straightforward process. It is plausible that a manufacturer might provide bending stiffness data in this step from a suitably validated finite element model.

3.1.3 Expected *in-vivo* curvature of 2014VP lead

Based on equation (1) and the data in table 5, the expected distribution parameters for the 2005 and 2014VP leads are given in Table 6. Sample data from the expected *in-vivo* distributions of maximum curvature for the 2005 and 2014VP leads are shown in Figure 8.

Table 6: Lognormal distribution parameters and equivalent means and standard deviations

all parameters in cm^{-1}	Product Model 2005	Product Model 2014VP
location	-1.4	-1
scale	0.44	0.44
mean	0.27	0.41
standard deviation	0.13	0.19

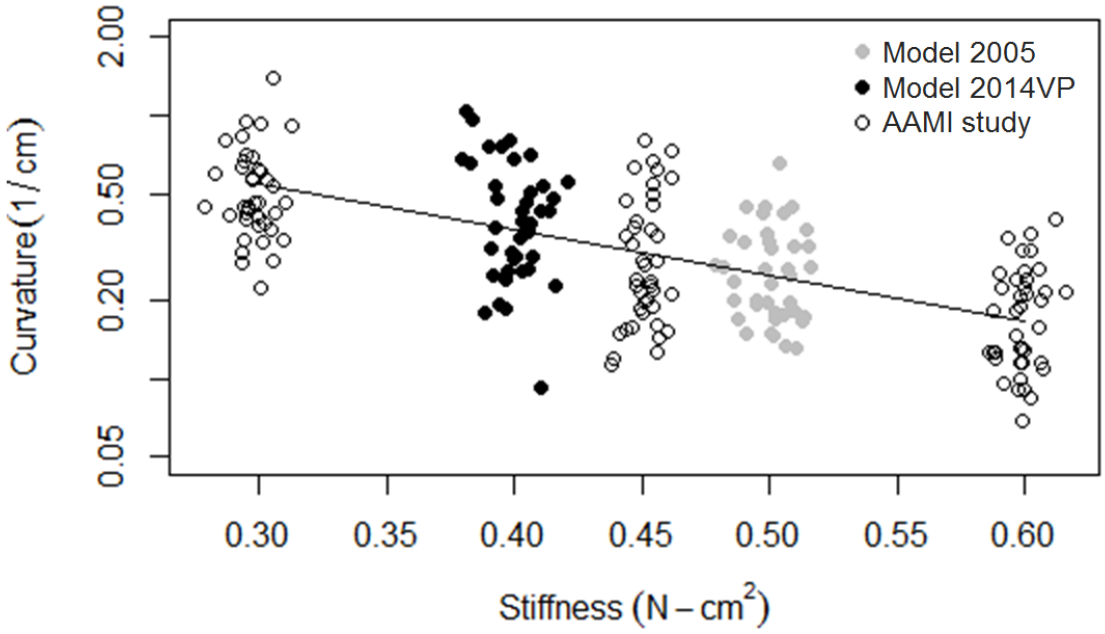

Figure 8: Expected *in-vivo* curvature amplitude distribution for product model 2005 (filled grey dots) and product model 2014VP (filled black dots). Data from AAMI Lead Imaging Study, reproduced from Figure 6 are shown for clarity. Jitter was added to the x-axis (stiffness) values for clarity.

3.2 Patient activity

Lead curvature needs to be paired with a cycle count in order to serve as an input for fracture prediction. For lead fracture inside the heart, a cycle is one heartbeat. Therefore, cycles will be converted to time using a population average value for the heart rate [2]. Per the list in section 2.1, we assume that there is no other motion other than cardiac contraction.

3.3 Fatigue Strength

Given a set of use conditions (curvature amplitude and cycle counts), the fracture survival depends on the fatigue strength of the implanted lead. Although it is not possible to know the exact strength of any particular device, the statistical distribution of fatigue strength over a range of curvature amplitudes can be estimated from bench testing.

Key assumptions related to the fatigue testing from the list in section 2.1 are:

- The localized curvature measured *in-vivo* can be replicated in a bench test by applying that same degree of curvature.
- Fracture detected on the bench via DC resistance increase is analogous to a clinical event such as a lead impedance alert, inappropriate therapy, or failure to deliver therapy.
- Fatigue strength measured on as-manufactured test samples sufficiently represents the fatigue strength of a lead that has been implanted in the body for any duration.

- The statistical distribution for cycles to fracture at a given stress level is lognormal.

Also from the list of assumptions in section 2.1, we assume hypothetical test data and final forms of several test methods that are currently in draft form (AAMI PC WG1 N169).

3.3.1 Bench test measurement of fatigue strength

Fatigue strength testing was conducted per AAMI PC WG1 N169 Annex F, Rev E [1], with typical test deformations illustrated below in Figure 9. Note that the test deformations reproduce the loading mode for the *in-vivo* curvature as discussed in section 3.1[11].

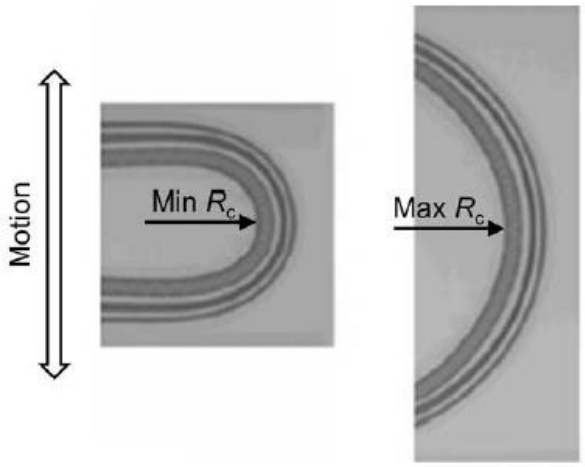

Figure 9: X-ray images showing deformation of the 2014VP lead at maximum (left) and minimum curvature (right) positions. The bench test cycles the lead between these two positions.

The fatigue data is modeled using equation B.1 from AAMI PC WG1 N169:

$$\ln(cycles) = \beta_0 + \beta_1 S^{-\beta_2} + e$$

where β_0, β_1, and β_2, are the fatigue curve coefficients and e is an error term, assumed to be normally distributed.

Fatigue test curvature amplitudes were selected to provide test-to-failure data at levels that are sufficient to generate fractures and also allow prediction of reliability given the expected use condition distribution. Note that the curvature amplitude (i.e., applied stress) required to generate fracture is generally greater than what was measured *in-vivo*. If this were not the case, the expected fracture rate in the field would be very high.

A typical fatigue strength data set comparing the 2005 and 2014VP leads, along with curve fits showing the median fatigue strength, is shown in Figure 10[12]. Fracture data represents the first

[11] Note that results from the AAMI Lead Imaging Study have been assumed.

[12] The data shown in Figure 10, which will also be used for the virtual patient model, is hypothetical, but was generated based on the positive control fatigue data in AAMI PC WG1 N142 Revision C [4].

component to fail in each sample[13]. In the figure it is evident that fracture may occur at different cycles given a particular applied stress. This variability can be due to manufacturing tolerances, surface imperfections, or intrinsic material property variation. Note that the improved fatigue life of the 2014VP lead is more pronounced at lower stress levels, due to the improved material manufacturing process for MP35N, reducing the number of hard titanium nitride inclusions as discussed in [5]. These inclusions are frequently the initiation locations for fatigue cracks.

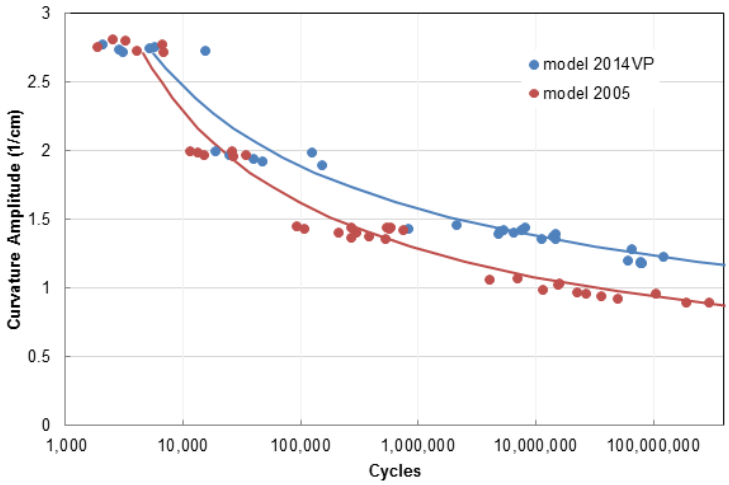

Figure 10: Typical fatigue strength data for the conductors of the 2005 and 2014VP leads, with curve fit to the median.

Because the 2014VP lead is not axially symmetric, fatigue testing was conducted at multiple orientations, illustrated in Figure 11. This allows for projection of fatigue reliability with orientation as a random input. The addition of random orientation increases the variability in the fatigue data at any given *in-vivo* curvature amplitude.

Note about FEA: For scope purposes, we only discuss experimental measurement of fatigue strength in this document. In many situations, it is practical to use finite element analysis (FEA) along with experiments in fatigue analysis. Assessment of orientation sensitivity is one such area. It is likely that an actual product evaluation would utilize FEA to determine stress and strain as a function of orientation, and then calibrate a fatigue strength model with a smaller number of experiments.

[13] There are a total of four conductors that could fail in the 2005 and 2014VP lead bodies: two defibrillation cables, a cable for sensing, and the coil for pacing.

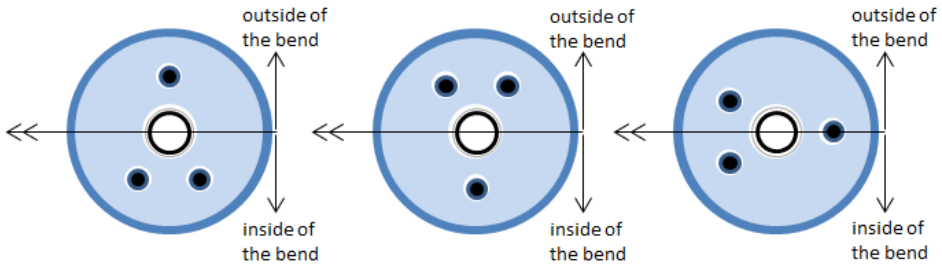

Figure 11: Illustration of fatigue test orientations.

4. Examples

The basic VPM algorithm was given in section 2.1 and will be illustrated in more detail below with examples. The first two examples show how clinical lead performance for fracture survival depends on both the *in-vivo* use condition and fatigue strength. Note that patient activity in these examples is simply represented as 79 heart beats per minute and applications in other anatomical regions would incorporate other measures of activity.

Example 1: individual patient with 2014VP lead

a. Patient: male, 81 years, expected additional lifetime of 6 years[14]
b. Implant curvature amplitude: 1.23 cm^{-1}
c. Fatigue life at amplitude of 1.23 cm^{-1}: 120,740,119 cycles
d. 120,740,119 ÷ 79 ÷ 60 ÷ 24 ÷ 365 = 2.9 years
e. 2.9 (lead lifetime) < 6 (patient lifetime), counts as a fracture

Example 2: individual patient with 2014VP lead

a. Patient: female, 71 years, expected additional lifetime of 15 years
b. Implant curvature amplitude: 1.13 cm^{-1}
c. Fatigue life at amplitude of 1.13 cm^{-1} = 752,325,272 cycles
d. 752,325,272 ÷ 79 ÷ 60 ÷ 24 ÷ 365 = 18 years
e. 18 (lead lifetime) > 15 (patient lifetime), counts as censored

As stated in section 2.1, the distribution parameters for *in-vivo* curvature and fatigue strength are simulated multiple times, reflecting the uncertainty due to finite sample size in the input data. The next two examples show the effect of use condition and fatigue strength source data sample size on the estimation for the simulation.

[14] Additional lifetime for patients in examples 4.1 and 4.2 determined based on U.S. Social Security Actuarial Life Table: http://www.ssa.gov/OACT/STATS/table4c6.html

Example 3: effect of *in-vivo* sample size on uncertainty in modeled use condition distribution

To demonstrate the effect of sample size in the input data for *in-vivo* curvature, we assume an underlying lognormal distribution with location and scale parameters of -1 and 0.44 cm^{-1}. *In-vivo* data is sampled from this distribution. The sampled data is used to estimate potential use condition distributions for the virtual patients. Using Bayesian statistical methods, variability in these estimated distributions is introduced based on the number of samples. Figure 12 below shows simulated virtual patient *in-vivo* curvature distributions for different numbers of samples. Uncertainty due to finite sample size is reflected by increased variability in the simulated distributions[15]. Note that the upper percentile of the simulated distribution increases as the sample size used to estimate the distribution decreases.

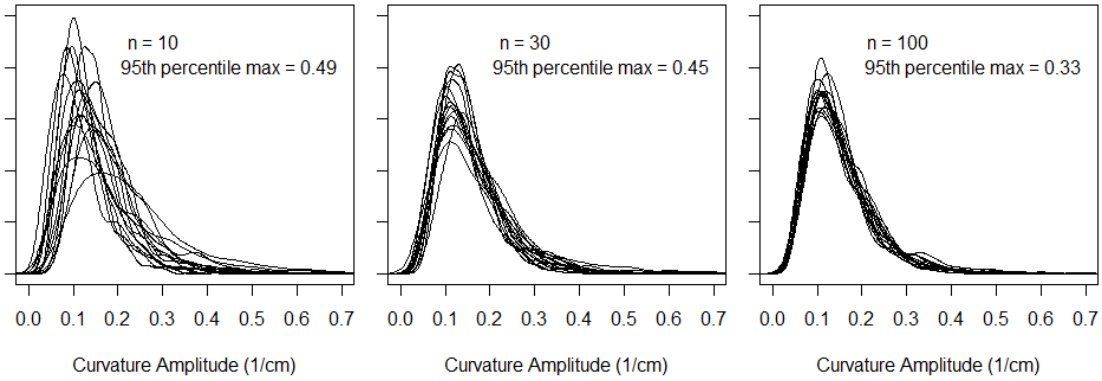

Figure 12: Simulated distributions of *in-vivo* curvature, all generated by sampling from a lognormal distribution with location and scale parameters of -1 and 0.44. Samples sizes used to estimate the distributions were 10 (left), 30 (center), and 100 (right).

Increased variability in the simulated use condition distributions will lead to larger confidence bounds in the final simulations of virtual patient survival. This creates a natural incentive to maximize the sample size for input data.

Example 4: effect of bench test sample size on uncertainty in fatigue strength estimation

To demonstrate the effect of sample size on the fatigue strength confidence bounds, we begin with a simulated data set, based on the data shown in Figure 10. Using the same curve fit parameters, we generate 10, 30, and 100 fatigue test data points, and then perform statistical analysis to fit the data and generate confidence bounds. The results are shown in Figure 13 below. Note that the width of the confidence bounds increases by over an order of magnitude of cycles as sample size decreases from 100 to 10.

[15] A good example for the effect of sample size on distribution uncertainty is the standard error of a sample mean, which is equal to the standard deviation of the sample divided by the square root of the number of samples. In this example, the precision of the estimate for the population mean is proportional to the inverse of the square root of the sample size.

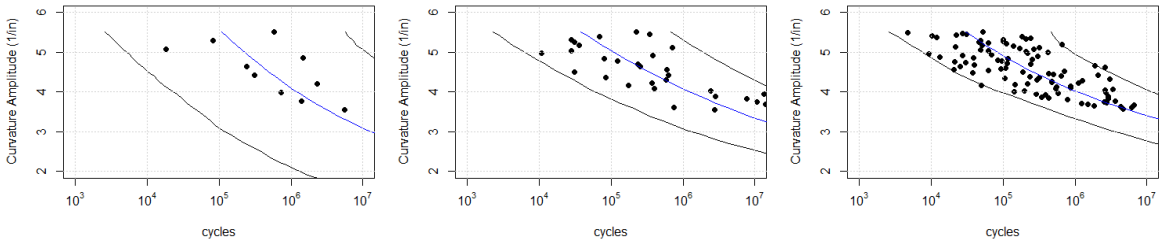

Figure 13: Fatigue strength data shown with median fit (blue) and confidence bounds (black lines) for sample sizes of 10, 30, and 100. Confidence bounds represent lower and upper 95% confidence for the 5th and 95th percentile of the distribution.

5. Results

Figure 13 shows the simulated fracture survival for the patient population virtually implanted with the 2014VP lead. The heavy line is the median result, and the lighter lines show the family of simulated outcomes. The lower 5% confidence bound is a dashed line.

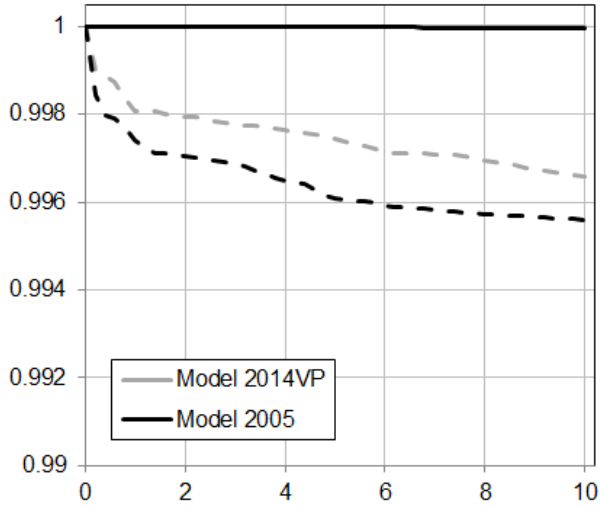

Figure 13: Simulated fracture performance of the 2014VP lead compared with simulated performance of predicate product model 2005 lead. Lower 5% confidence bound on fracture survival rate at 10 years is shown with a dashed line and is 99.66% for the 2014VP lead and 99.56% for the 2005 lead.

6. Model verification and validation

To determine the appropriate level of verification and validation (V&V) needed to support the use of the VPM, we will leverage the risk-informed credibility assessment method developed by the ASME V&V40 Subcommittee on Computational Modeling for Medical Devices [ref].

The risk-informed credibility assessment method is a framework for establishing and assessing the ***credibility***, defined as the trust, through the collection of evidence, in the predictive

capability of a computational model (or approach) for a ***context of use*** (COU). The COU is the specific role and scope of a computational model used to inform a decision. We use ***model risk*** – the possibility that a computational model may lead to a false/incorrect conclusion that might result in patient harm – to establish the sufficiency of the V&V activities for the computational model for the COU.

The V&V process begins with the identification of the COU for the computational model. In this case, the role of the computational model is to determine the survival rate of the model 2014VP lead. The goal is to use survival data from the VPM to augment the actual survival data collected from a pivotal study, to establish a combined survival rate for the model 2014VP lead.

Model risk is a combination of the VPM influence and the decision consequence. The influence is the relative contribution of the VPM to the decision as compared to other available evidence. In this IDE, the influence of the VPM is balanced with clinical data from a pivotal study. Moreover, there is a weight/error associated with the VPM. If the VPM predictions do not align with the clinical predictions, then less data from the VPM will be used. Therefore, the influence is moderate.

The decision consequence is defined as the significance of a poor or misinformed decision. Therefore, the patient consequence of a cardiac lead failure is decreased quality of life or increased patient mortality due to inappropriate or ineffective electrical shocks or improper arrhythmia detection. Thus, the decision consequence is high. Therefore, the model risk is moderate-to-high.

The components of the VPM that drive the prediction are the model inputs. Therefore, the approach for validating the VPM will be based on the reliability of the inputs and how they are linked in the Monte Carlo simulations that comprise the VPM algorithm. Additionally, the output of the VPM will be compared to field performance of the predicate lead model 2005.

6.1 VPM inputs

The primary VPM inputs are *in-vivo* curvature, patient activity and fatigue strength. The inputs from industry standards include data from four manufacturers who manufacture over 90% of currently marketed leads. The inputs for patient age and mortality come from relatively large device registry and actuarial tables, and are

- *In-vivo* curvature (section 3.1)
    - Bending stiffness and *in-vivo* curvature have been measured for predicate lead models and a statistical relationship has been created, based on the AAMI Lead Imaging Study. The AAMI imaging study incorporated imaging data from 120 patients, which was demonstrated[16] to be a sufficient sample size to distinguish meaningful differences in *in-vivo* curvature distributions.
    - Bending stiffness has been measured on the bench for the 2014VP lead, utilizing methods described in the AAMI draft standard from [1].

[16] Currently documented in AAMI working group document AAMI PC WG1 N239, revision B

- A statistical projection of expected *in-vivo* curvature has been created for the 2014VP lead, following the methods in the AAMI draft standard [1][17]
- Because these inputs are derived from data or methods based on an industry standard, they are considered to be credible.

- Patient activity, also referred to as cycle count (section 3.2)
  - The relevant patient activity for fracture inside the heart is heartbeats. For simplicity, we assume 79 beats per minute [2].
  - Because this input is based on a well-documented physical characteristic of the expected implant population, it is considered credible.
- Fatigue strength (section 3.3)
  - *In-vitro* testing has been completed on a finite number of parts to measure fatigue strength over a range of curvature conditions. Testing followed the methodology of the AAMI draft standard in [1].
  - A statistical model has been fit to the data to allow for generating random fatigue strength for virtual patients [1,3]
  - Because this input is derived from an industry standard it is considered highly credible.

As listed above, the inputs to the VPM consist of industry standard methods and well-documented public health data. Therefore they are considered highly credible.

6.2 VPM algorithm verification

There are a series of calculations performed in the VPM algorithm. When these calculations are performed correctly, the VPM algorithm can be considered sufficiently verified. The calculation steps to be verified are listed below[18].

1. Input data for use conditions and fatigue strength are read into the computational code.
2. Bayesian estimation is used to generate statistical distribution parameters for Monte Carlo simulations.
3. Random patients are generated from the input data distributions.
4. Implant fatigue life is calculated based on *in-vivo* curvature, patient activity (heart beats) and fatigue strength.
5. Fracture or censor is determined based on fatigue life and competing risk due to patient death.

Finally, the underlying computational engine has been shown to be highly credible, for the following reasons. All calculations in the VPM described here are performed using the R

[17] The functional relationship between stiffness and expected *in-vivo* curvature has not yet been documented in the AAMI draft standard, however there is a section for the method to do this.

[18] As mentioned in the list of assumptions, results of the specific verification activity are not presented here, however it is anticipated that those activities would be documented for an actual submission.

programming language and environment (referred to as "R"). Functions utilized in the model are contained in the R base package and recommended packages. These portions of R have been extensively documented and verified by a suite of test protocols. Additionally, there is rigorous version control of the source code for approved releases. Specific details and links are documented by The R Foundation for Statistical Computing at: https://www.r-project.org/doc/R-FDA.pdf [5].

6.3 VPM output

To establish that the output is credible, the VPM was applied to the model 2005 lead in a retrospective manner to demonstrate the predictive capability of the algorithm. Based on clinical data, we know that the 2005 predicate device has had acceptable performance. Figure 14 below shows the simulated field performance (same as in Figure 13), along with the actual field fracture survival, with good agreement between simulated and actual performance. Because of the similarity of the intended use of the two leads, the same level of agreement between simulated and real data is expected for the 2014VP lead.

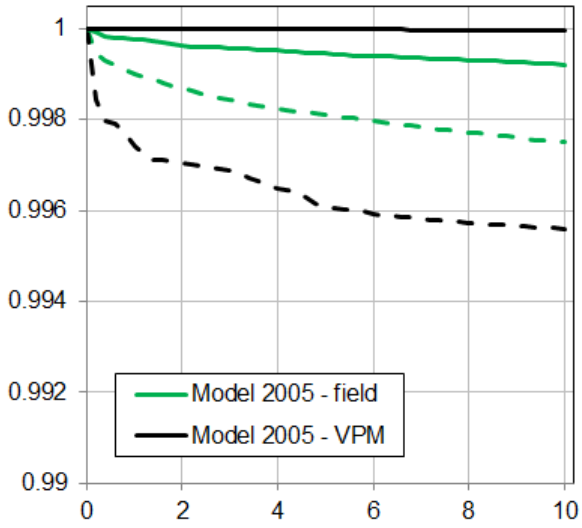

Figure 14: Simulated (black) and field (green) fracture survival for the predicate 2005 lead. Solid lines are point estimates and dashed lines are lower 5% confidence bounds.

Additionally, it is important that the nature of the fracture that is induced on the bench match the nature of the fractures observed clinically. This provides reliability in the assumption that bending of the cardiac lead induced the fracture and not some other mechanism. Therefore, fracture morphology was studied for explanted leads. As illustrated in Figure 15, the observed fracture surfaces are consistent with bending fatigue. Therefore, in addition to the agreement between the simulated and actual fracture survival for the 2005 lead, there is also agreement between the observed fracture morphology observed clinically and on the bench.

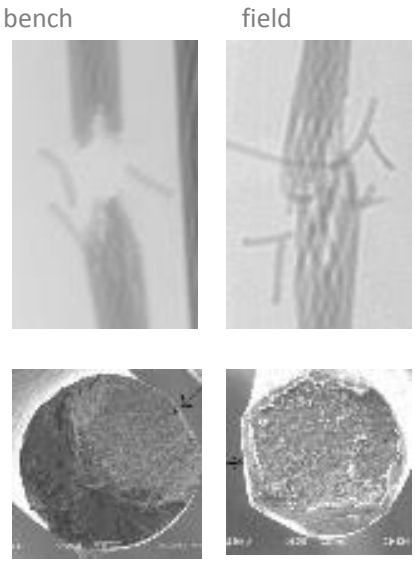

Figure 15: Fracture morphology for bench test (left) and field fractures (right) for cables (top) and coils (bottom).

6.4 VPM Credibility Determination

Because the retrospective failure rate of the 2005 lead is accurately predicted by the VPM, and because the failure mode is accurately replicated based on qualitative comparison of fractures from bench testing and field returns, the VPM is considered to be a credible model for use in projecting virtual patient outcomes to augment a clinical study.

7. Summary

Clinical performance of the model 2014VP ICD lead has been simulated using a Virtual Patient Model (VPM). The VPM incorporates *in-vitro* test data, *in-vivo* use condition measurements, and a statistical reliability projection methodology, to predict the survival of the lead. The context of use for the VPM is to generate data that could be used along with human data in a clinical study. The model input data and algorithm have been shown to be credible for this intended use.

The simulated lower 5% confidence bounds on intracardiac fracture survival for the 2014VP patient population at 5 and 10 years are 99.75% and 99.62%. This compares favorably to the results of the same methodology applied to the predicate product model 2005 lead, which had simulated results at 5 and 10 years of 99.68% and 99.58%, and has had acceptable performance in the field.

From the information provided, we have demonstrated that the VPM is sufficient for use along with actual clinical data to support the safety and effectiveness of the proposed changes for the 2014VP ICD lead.

We propose the following for consideration of a clinical study design: 1) the maximum % of virtual patients would be in the range of 30-50%, and 2) the type I error would be in the range of 0.15-0.20, as supported by the influence, risk, and credibility of the virtual patient model.

8. Bibliography

[1] AAMI_PC_WG1_N169_E, "Outline of Requirements for Fatigue Performance of Cardiac Rhythm Management Leads"

[2] Aronow, Wilbert S., et al. "Association of average heart rate on 24-hour ambulatory electrocardiograms with incidence of new coronary events at 48-month follow-up in 1,311 patients (mean age 81 years) with heart disease and sinus rhythm." The American journal of cardiology 78.10 (1996): 1175-1176.

[3] Haddad, Himes, Campbell, "Fracture prediction of cardiac lead medical devices using Bayesian networks", Reliability Engineering and System Safety, 123(2014); 145-157.

[4] AAMI_PC_WG1_N142_C, "Input Data Sets for UUUUU"

[5] Schaffer, Jeremy E., A Hierarchical Initiation Mechanism Approach to Modeling Fatigue Life Variability in 35CO-35NI-20CR-10MO Alloy. Dissertation. Purdue University West Lafayette, 2007. (http://www.fwmetals.com/default/assets/File/fatigue_study.pdf), accessed 17 August 2015

[6] " R: Regulatory Compliance and Validation Issues A Guidance Document for the Use of R in Regulated Clinical Trial Environments ", https://www.r-project.org/doc/R-FDA.pdf, accessed 8 October 2015.

APPENDIX A: Feedback and Questions prior to Informational Meeting Q150804

Question	Where addressed
Extensive clinical trial requirements have been formulated and made available for new lead manufacturers. Please discuss the familiarity of the working group concerning the general requirements for clinical trials investigating new/modified leads and consult our group to learn more about these requirements as needed.	Informational meeting Q150804
During your presentation, please make clear the following: (1) your proposed context of use for demonstration purposes; (2) your proposed context of use for the mock submission; and (3) which elements of your proposal will be based on real or simulated data versus mock data.	Informational meeting Q150804, current pre-submission
Specific lead modifications can lead to expected or known changes in the performance characteristics of the modified lead. For the proposed lead, please discuss the modifications as compared to the predicate lead and how those would be expected to affect the relevant performance characteristics of the proposed lead.	Informational meeting Q150804, current pre-submission
When considering a wholly new lead versus a lead incorporating modifications to an existing lead, please comment on when the virtual patient approach would be appropriate. More specifically, would this approach be applicable without a predicate lead with known clinical experience?	The lack of a predicate would have to be accounted for in model validation activities. This scenario was out of the scope of the current work.
FDA understands that you will incorporate virtual patient data into the clinical study data and the Type I error is likely to be inflated. Please discuss how you will control for Type I error.	forthcoming pre-submission
FDA understands that lead mechanical failure/fatigue fracture is time dependent and for that reason may consider premarket and post market studies to fully address characterizing performance over 5 years. Please discuss with FDA how you will incorporate this important factor into your proposed study. Please include the expected impact of virtual patients on a premarket vs post market clinical trial.	forthcoming pre-submission
You have presented a virtual patient model that appears to perform real-time validation of the model as the clinical trial progresses. FDA believes this is both interesting and concerning. Please discuss generally the risks and the underlying assumptions associated with this approach. In addition, please also discuss example cases where this approach may not be adequate and/or situations where traditional clinical trials will still be required.	forthcoming pre-submission

Question	Where addressed
FDA can envision various scenarios of trial success and failure manifest from the proposed use of virtual patients in clinical trials. Two scenarios that are of interest/concern to FDA are listed below. Please discuss if multiple scenarios could be incorporated into the mock submission.	forthcoming pre-submission
The virtual patients provide a poor fit to the clinical performance of the lead. Please demonstrate a successful discounting of the virtual patients in the clinical trial. Can you estimate how much more time such a scenario would add to the clinical trial?	forthcoming pre-submission
The virtual patients provide a good fit to the clinical performance of the lead. Please demonstrate when and by how many the clinical trial can be reduced.	forthcoming pre-submission
FDA understands that lead mechanical failure occurs at low rates and can be very challenging to clinical trial design. Please comment on how your approach handles low observed relevant rates, locations of failure, and how small but potentially important changes in the observed rates (for instance, 1 additional fracture) could affect the use of virtual patients?	forthcoming pre-submission
FDA understands that a variety of lead mechanical failure modes can pertain to any new design but that your study will focus on only one, fatigue fracture. This issue could be important to your project since a marketing application might need data to address every key performance concern, not just selected concerns. Please discuss whether other endpoints considered in a clinical trial would influence the discount of virtual patients.	forthcoming pre-submission
FDA wishes to mention that gaps are likely to remain in the data required to adequately support a PMA using your approach since you have understandably and intentionally focused on just one safety aspect of lead performance. Please be aware of this when describing the scope of this mock submission.	current pre-submission, forthcoming pre-submission
FDA understands that the virtual patient model will be used to simulate the expected fatigue performance of the new lead. Please discuss whether you plan to include engineering data for the purposes of the mock submission, and identify the source of the engineering data.	current pre-submission

Question	Where addressed
FDA understands that fatigue performance of the hypothetical ICD lead will be modeled by incorporating bench fatigue strength with in-vivo use conditions based on predicate leads. Are the data for the predicate leads real data or mock data? In your submission, you refer to the work of the AAMI PC/CRMD WG01, in particular, the fatigue testing in AAMI document N169_E and the human use data being collected by the clinicians in the working group. It is unclear if this AAMI data will be used for the mock submission. Please discuss this in more detail.	current pre-submission
Please discuss the criteria for deciding when to make the comparison between clinical data and virtual patient data, i.e., how do you determine the sample size used for making the comparison described in scenarios a and b above? Also, please make clear how the criteria for acceptable lead performance from the simulations are derived and how does it compare with those observed in previously conducted clinical trials.	forthcoming pre-submission

APPENDIX B: Minutes from Informational Meeting Q150804

The meeting was held at 10:30, July 14 2015, in room G264 of building 66 at the FDA White Oak Campus.

Attendees were:

FDA Review Team
Mitchell Shein –Acting Deputy Director DCD
Erin Cutts – Acting Branch Chief IEDB
Robert Kazmierski – Lead Reviewer
Brian Lewis – Clinical Reviewer
Patrick Jones – Mechanical Reviewer
Nandini Duraiswamy – Mechanical/OSEL
Donna Walsh – Mechanical/OSEL
Xuefeng Li – Statistics Reviewer
(Jack) Jie Zhou – Statistics Reviewer

MDIC
Tarek Haddad – Medtronic
Adam Himes - Medtronic
Rajesh Nair – FDA
Laura Thompson – FDA
Telba Irony – FDA
Valentin Parvu – BD
Marc Horner – ANSYS
Dawn Bardot – MDIC
Russ Klehn – St Jude

Other FDA Attendees
Danielle Dorfman
Jessica Paulsen
Hetal Patel
(Laura) Hong Lu

The outline of the presentation was:

Introduction (Tarek Haddad, Medtronic)

Virtual patient overview (Marc Horner, ANSYS)

Virtual patient example, mock submission lead (Adam Himes, Medtronic)

Clinical trial design (Rajesh Nair, FDA)

Statistical methods (Laura Thompson, FDA)

Summary and conclusion (Tarek Haddad, Medtronic)

The sponsor team expects to apply for two pre-submission meetings, one to discuss the engineering model and one to discuss the statistical framework. In the notes below, references to one or the other of these future activities was noted where appropriate.

The following feedback and / or discussion was noted:

- On slide 2 and 32 of the presentation, the second to last bullet should be corrected to read "If virtual patients have higher than or equal to the failure rate of the real patients, n_0 gets bigger.
- It would be useful to show modeled fracture rate of predicate leads as well as for the new lead. This should be discussed in the engineering model pre-submission.
- Although the clinical trial endpoint is at 2 years, the engineering model is capable of predicting beyond that (e.g. 10 years). These extended predictions would be informative and should be presented. These would also be useful in a post-market surveillance setting. This should be discussed in the engineering model pre-submission.
- Model assumptions and simplifications should be clearly stated. An example was posed by the review team, where progressing disease state or body development may alter the use conditions over time (e.g. cardiac hypertrophy, change in activity level). A more sophisticated model might incorporate time-dependent use conditions, although a sponsor might choose to assume a stationary use condition distribution (e.g. activity level does not change over time). This should be discussed in the engineering model pre-submission.
- There is a need for clarifying examples of the discounting process for virtual patients. For example, if n_0 is 100, how many simulated patients might be incorporated into the effective weight of 100? This should be discussed in the statistical framework pre-submission.
- There is a need for clarifying examples of the use condition data collection at an interim look. In particular, there are questions about how this would affect the output of the engineering model, as well as the performance of the clinical trial. For example, if the activity level of the clinical trial cohort is much higher than originally assumed, what would happen? This should be discussed in the statistical framework pre-submission.
- There were multiple questions about the method for simulating type I error with this method. Examples should be given in the statistical framework pre-submission.