



Circulatory System Devices Panel Meeting: Leadless Pacemakers

Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

February 18, 2016

Framework for Today's Discussion

- Please provide your considered opinion on:
 - Acceptable Clinical Event Rates
 - Indications for Use
 - Post Approval Study Questions
- No Safety, Effectiveness or Benefit/Risk votes will be taken
- Please refrain from comparing device performance

Contributions

- Dr. Bram Zuckerman
- Mr. Mitchell Shein
- Ms. Jessica Paulsen
- Ms. Erin Cutts
- Mr. David Pudwill
- Mr. Matthew Hillebrenner
- Dr. Randall Brockman
- Dr. William Maisel
- Ms. Angela Krueger
- Mr. James Swink
- CDR Dimitrus Culbreath
- CDR Sandra Oquendo

FDA Presentation

Section 1: Introduction/Panel Purpose

Section 2: General History

Section 3: Leadless Pacemaker Device Description

Section 4: Comparison of Transvenous and Leadless Pacemakers

Section 5: Pre/Post Market Balance Paradigm

Section 6: Knowledge Base and Knowledge Gaps

Section 7: Final Conclusions

Section 1: Introduction and Panel Purpose

Danielle Dorfman

Biomedical Engineer

Division of Cardiovascular Devices

Office of Device Evaluation, CDRH, USFDA

Introduction

We will discuss:

- General history of pacemaker technology
- Publically available data on clinical trials
- Pre/Post-market balance paradigm
- Knowledge base and gaps

Panel Purpose

FDA is seeking recommendations on:

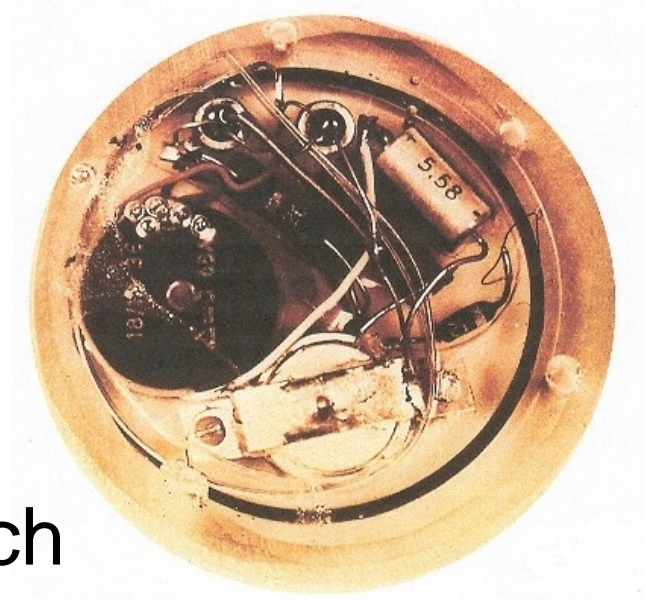
- Acceptable acute adverse event rates
- Indications for use
- Manufacturer-required training
- Elements for post-approval study collection



Section 2: General History

General History: Pacemakers

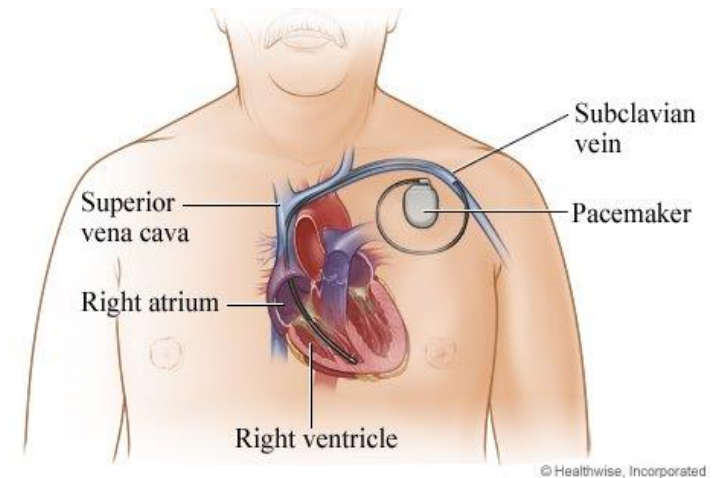
- 1st pacemaker implant → Sweden 1958
- Nearly 1 million people worldwide are implanted with transvenous pacemakers each year



First Pacemaker Implant*

Transvenous Pacemaker (PM) Description

- Implantable
- Power supply and electronics
- Substitute for the heart's intrinsic pacing system
- Correct cardiac rhythm disorders
- Pocket and leads required



Regulatory Classification

- Life-sustaining or life-supporting = Class III
- A premarket approval application (PMA) is required to demonstrate reasonable assurance of safety and effectiveness

Elements of PMA Review

- Bench and Animal Data
 - Biocompatibility
 - Sterilization
 - Steroid
- Manufacturing and Quality System
- Clinical Data
- Device Labeling
- Post-Approval Study Design



Section 3: Leadless Pacemaker Device Description

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Leadless Pacemakers (LPs)

- Same inherent functionality as transvenous, single-chamber pacemakers
- No leads or pocket required
- Currently being studied for VVIR pacing

LP Device Description

- Self-contained in a hermetically sealed capsule
- Fixation mechanism (helix or tines)
- Monolithic controlled release device (MCRD)
- Rate-responsive functionality
- Estimated device longevity: 7-12 years

Medtronic Micra



Micra Leadless Pacemaker*

- Length: 25.9 mm
- Introducer: 23-French via the femoral vein into the right ventricle
- Fixation: 4 electrically inactive nitinol tines
- Rate-responsive: Accelerometer

Medtronic Micra

CE Mark: April 14, 2015 based on results from 60 patients over 3 months in the Medtronic Micra TPS Global Clinical Trial, which evaluated:

- Serious adverse events
- 24 hour ambulatory electrocardiograms
- Device function
- Electrical variables

St. Jude Medical Nanostim



Nanostim Leadless Pacemaker*

- Length: 40 mm
- Introducer: 18-French via the femoral vein into the right ventricle
- Fixation: Helix
- Rate-responsive: Temperature sensor

St. Jude Medical Nanostim

CE Mark: August 5, 2013 based on results from 33 patients over 3 months in the LEADLESS study which evaluated:

- Serious adverse events
- Device function
- Electrical variables



Section 4: Comparison of Transvenous and Leadless Pacemakers

Comparison

Similarities	Novel Leadless Design
<ul style="list-style-type: none"> • Similar functionality • Paces the RV endocardium • Steroid at electrode-tissue interface 	<ul style="list-style-type: none"> • No pocket • No lead • Battery longevity • Fixation mechanism • Implantation procedure • Device retrieval • Device replacement procedure

Acute Complications

	Transvenous	Leadless
Lead Related	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Pocket Related	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Pneumothorax	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Groin Access	<input type="checkbox"/>	<input checked="" type="checkbox"/>
Cardiac Injury	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>

Chronic Complications and Performance

- Transvenous Pacemakers
 - Decline in battery life
 - Lead-related complications
- Leadless Pacemakers
 - Unknown

Section 5: Pre/Post Market Balance Paradigm Development Strategy for Leadless Pacemakers

**CAPT Brian Lewis, MD,
US Public Health Service
Arrhythmia Cardiologist**

**Division of Cardiovascular Devices
Office of Device Evaluation, CDRH, USFDA**

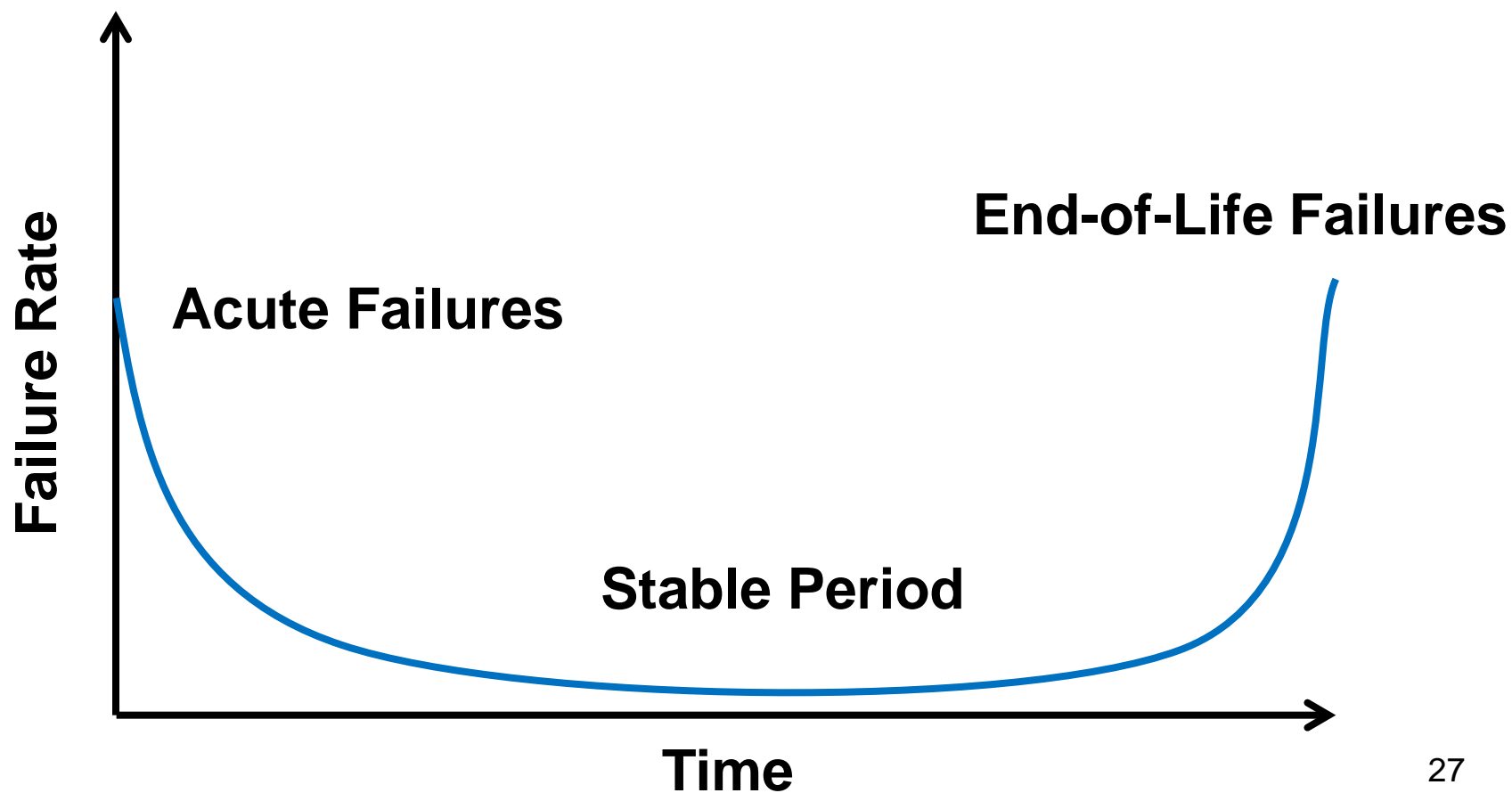
Overview

- Data Requirements for Transvenous PMs
- Data Requirements for LPs
 - Pre-Market
 - Post-Market

FDA Data Expectations: Transvenous VVIR Pacemaker Systems

- Mature technology, extensive market experience
- Similarities across models
- Bench testing experience
- Implant, fixation, electrical data well understood
- New lead designs → reliability concerns
- Post Approval Studies (5 year, resolution: 0-1.5%)

Time Course of Lead Failures



Post Approval Studies Needed

- To Characterize:
 - “Real world” outcomes
 - Key subgroup outcomes
 - Late chronic adverse events

Pre/Post Market Balance

- CDRH Strategic Priorities
- Pre-Market: reasonable assurance
- Post-Market:
 - Where to draw the line on the bathtub curve?
 - Novel battery, managing device expiration
 - Study size (ability to precisely estimate rates)
 - Study duration (capture key chronic events)

Section 6: Knowledge Gained and Remaining Knowledge Gaps for Leadless Pacemakers

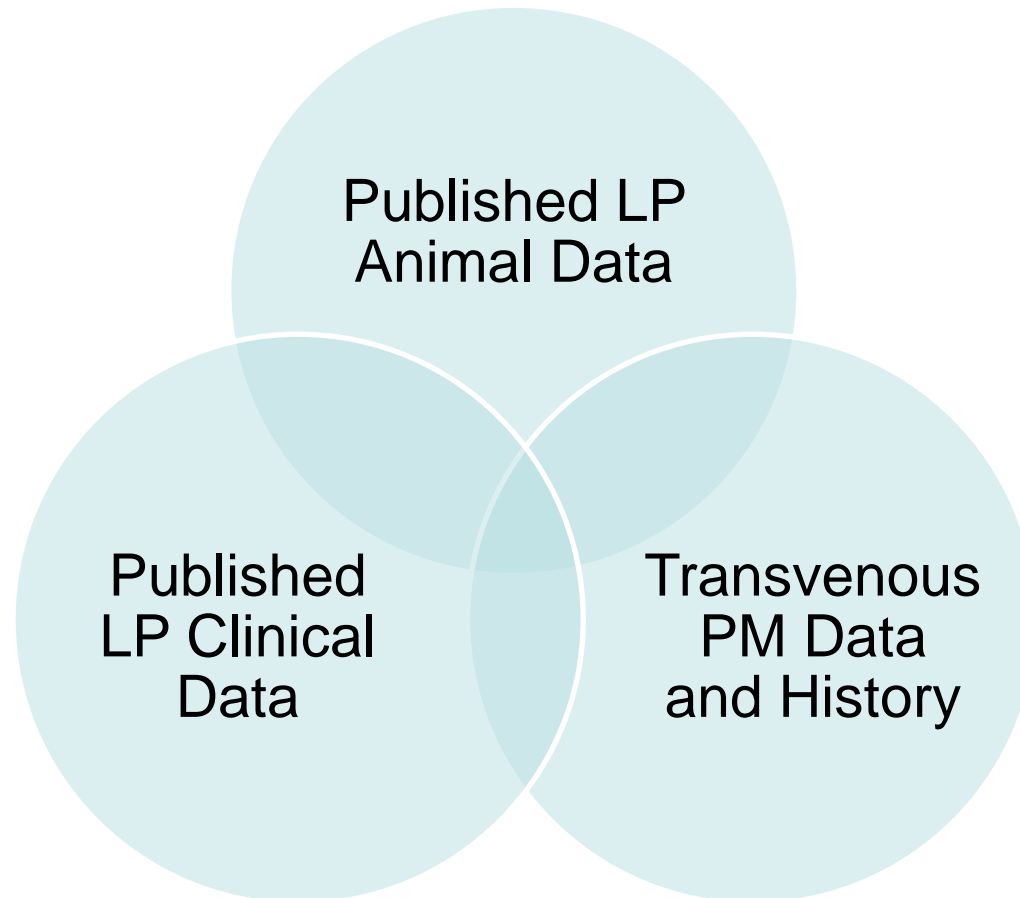
Kimberly Selzman, MD, MPH

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Knowledge Gained and Remaining Knowledge Gaps for LPs



Leveraging Transvenous PM Experience

Similarities

- Similar functionality
- Paces the RV endocardium
- Steroid at electrode-tissue interface

Differences

- No pocket
- No lead
- Battery longevity
- Fixation mechanism
- Implantation procedure
- Device retrieval
- Device replacement

Leveraging Transvenous PM Experience

- **CAN LIKELY LEVERAGE:**
 - Pacing Capture Threshold (PCT)
 - Sensing
 - Steroid Elution
- **CANNOT LIKELY LEVERAGE:**
 - Dislodgements
 - Procedural complications
 - Device-related complications

Knowledge Gained So Far LP Experience to Date

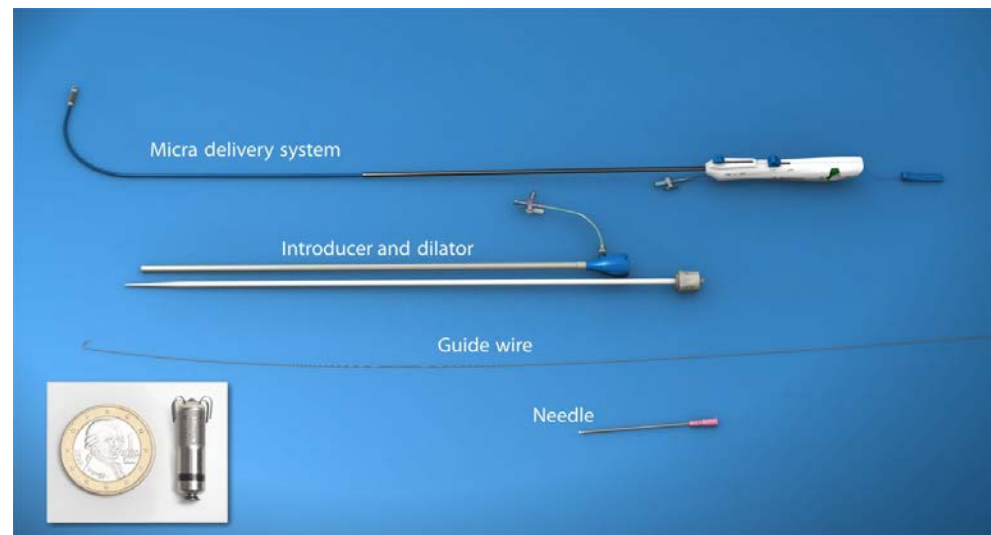
- Acute implant adverse events
- Acute sensing and PCT
- Short-term (30 day) sensing and PCT
- Mid-term (6-12 month) sensing and PCT

Implanting the LP

- Groin access via the femoral vein
- Groin sheaths are 18-23 French
- Navigate catheter over a longer distance from IVC to RV
- Device deployment



St Jude Nanostim delivery catheter*



Medtronic Micra delivery catheter**

*Mountfort et al. European Society of Cardiology Congress 2013

**Ritter et al. European Heart Journal. 2015.

Implant AEs: LP (n=1251)

Major Device-related Complications	4.0-6.5%
Acute Cardiac Perforations <ul style="list-style-type: none"> any cardiac injury pericardiocentesis cardiac surgical repair 	1.5-1.6% <ul style="list-style-type: none"> 1.5-1.8% 1.0%-1.1% 0.3%
Embolizations + Dislodgements	0-1.1%
Problem requiring reoperation	0.3-0.8%
AV fistulas, Pseudoaneurysms	0.6-0.7%
Serious Access Site Bleeding	0.4%
Pneumothorax	N/A
Procedure-related Deaths	0.24%

Implant AEs:

LP

TV PM

Major Device-related Complications	4.0-6.5%	4-5.8% [∞]
Acute Cardiac Perforations <ul style="list-style-type: none"> any cardiac injury pericardiocentesis cardiac surgical repair 	1.5-1.6% <ul style="list-style-type: none"> 1.5-1.8% 1.0%-1.1% 0.3% 	0.4%* <ul style="list-style-type: none"> 0.4% 0.3% 0%
Embolizations + Dislodgements	0-1.1%	1.8%*
Problem requiring reoperation	0.3-0.8%	2.4% [∞]
AV fistulas, Pseudoaneurysms	0.6-0.7%	N/A
Serious Access Site Bleeding	0.4%	0.26*
Pneumothorax	N/A	0.7-2.2%* ^{^∞}
Procedure-related Deaths	0.24%	0.01% [^]

*Udo et al Followpace Heart Rhythm 2012 ^Kirkfeldt et al Heart Rhythm 2011[∞] Kirkfeldt Eur H J 2014

Implanting the LP: Learning Curve

- Often seen with any new device or new technology
- Experience tends to result in decreased procedural complications
- St. Jude conducted an analysis of operator experience*

Implanting the LP: Safety Profile in 600 Subjects

Age	76 years
CAD	28-40%
COPD	12%
DM	27-29%
Heart Failure	16-17%
AF	73-76%

Mid-term Safety (6-12 months)

- Almost all device related AEs occurred in first 2 weeks
- Loss of device function 0.1%
- System Revision 0.4%
- Device repositioning for sensing/threshold issues roughly 1% over 1 month
- No reported device infections

Mid-term Effectiveness (6-12 months)

Sensing: R wave >5 mV	93-98%
Mean R wave at 6 months:	9-15 mV
PCT: < 2V @ 0.24-0.4ms	93-98%
Mean PCT at 6 months:	0.5-0.6V

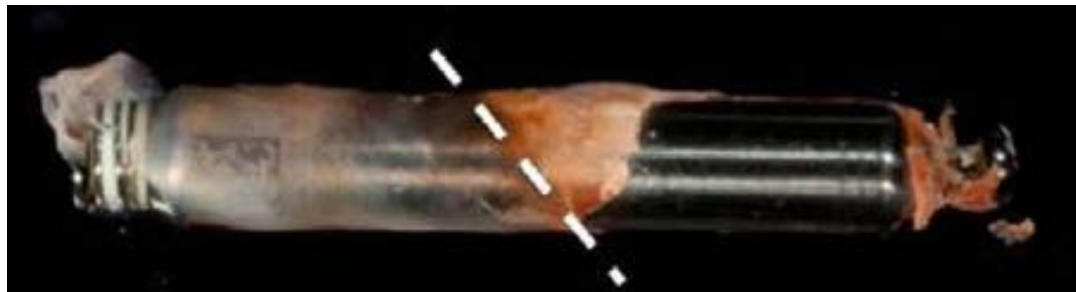
Remaining Gaps in Knowledge

- Real world safety and effectiveness
- Long-Term (>5 year) Reliability
- Long-Term (>5 year) Safety
- Battery Longevity
- Device Retrieval
- Best Practices at Device EOL
- Device-Device interaction

Knowledge Gap: Device Retrieval

Minimal data is currently available on encapsulation

- Case Report: significant encapsulation and adhered to papillary muscle at 1 year
- Case Report: fibrous capsule at 19 months



Kypta, Blessberger, Lichtenauer. Clin Res Cardiol Oct 2015.

Tjong, Stam, van der Wal, et al. Circ Arrhythm Electrophysiol Oct 2015.

Bonner, et al. Extraction of the Micra Transcatheter Pacemaker System. HRS poster 2014.

Bongiorni, et al. Retrieval of a Transcatheter Pacemaker in Sheep after a Mid Term Implantation Time. HRS 2015.

Sperzel, et al. Feasibility Efficacy and Safety of Percutaneous Retrieval of a LP. JAFIB Oct 2015.

Knowledge Gap: Device Replacement

- Best practice is not known
- Different options exist:
 - Remove LP and place new LP or TV PM
 - Turn LP off and place new LP or TV PM
- Device-Device interactions not well understood

Knowledge Gap: Co-Implantation Concerns

- Electrical Concerns:
 - Cross talk?
 - Mechanical interference?
 - Electrical short?
- Mechanical Concerns:
 - Limit on LPs in the RV?
 - Affect RV function?
 - Thrombogenicity?



Section 7: Final Conclusions

Conclusions: Knowledge Gained

- *Implant procedure has >95% success rate*
- *Safety of device and implant procedure*
- *Effectiveness, measured by sensing and pacing thresholds, are in accepted range and remain fairly stable over at least 6-12 months*

Conclusions: Knowledge Gaps

- *AE in real world, particularly procedural AE*
- *Long term safety and incidence of late device failures*
- *Long term effectiveness*
- *Battery longevity*
- *Device Retrieval*
- *How best to handle devices at device EOL*
- *Device-Device interactions*

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- http://conference-cast.com/hrs/SP22_player/mbrplayer/player.aspx?conferenceFolder=HRS2013AM&SessionFolder=SP22&LectureID=11233&configFile=config_prod.xml



Thank You

Questions?



FDA Questions to Panel

- 1) Ms. Patel
- 2) Dr. Lewis
- 3) Ms. Dorfman
- 4) Dr. Selzman

Question 1A

Please discuss the clinical significance and any concerns you might have for the rate of occurrence of each of the following adverse events observed to occur at implant with leadless pacemaker devices as compared to traditional pacemakers.

- Cardiac Perforation
- Pericardial Effusion
- Dislodgement
- Embolization (i.e. acute migration during implant necessitating retrieval)
- Serious groin complications necessitating repair or transfusions

Question 1B

There were certain subgroups that were reported in the published studies as having a possible increased risk of a cardiac perforation during the implant procedure i.e. female patients and patients with a low BMI.

Based on the adverse event rates associated with leadless pacemaker devices, is there any subgroup you would exclude from receiving this device or that you would specify in the labeling?

Question 1C

Please discuss what measures you would recommend to ensure that implanting physicians are adequately trained/informed regarding adverse events and appropriate device and patient selection.

Question 2

Post Approval Study (PAS):

- acute 30 day performance
- long term performance
- device issues at end-of-life (EOL)
- device issues when placed next to an abandoned transvenous pacemaker (TV PM) lead

Question 2Ai

The adverse events most likely to occur within 24 hours include groin complications, hematoma, vascular issues, and perforations.

The events most likely to occur between 24 hours and 30 days include dislodgements and threshold increases.

Please indicate which acute performance issues you believe should be captured through collection of post approval data.

Question 2Aii

FDA would expect sample sizes large enough to provide estimates of adverse events to a specific resolution with confidence intervals. **Please indicate which sample size is appropriate based on the table below.**

ODE Assumed Complication Rate	Target CI Width	Minimum Sample Size Needed	Upper Limit of 95% CI
1%	+/- 0.5%	1741	1.6%
1%	+/- 1.0%	497	2.3%
1%	+/- 1.5%	251	3.2%

Question 2Bi

FDA acknowledges that the long-term performance of leadless pacemakers is not well understood at this time. The estimated longevity for these devices is predicted to be anywhere from 6 to 12 years.

Please comment on the types of late device failures you would expect to be important to capture, given the design of leadless pacemakers.

Question 2Bii

Based on the current paradigm for post-approval studies for leads, a complication-free rate is used as the endpoint for long-term performance.

Please comment on the appropriateness of this endpoint for leadless pacemakers or suggest an alternative endpoint to evaluate the long term performance of these devices.

Question 2Biii

Please provide recommendations for ways to ensure the completion of a long-term post approval study considering:

- a. the difficulty in implementing such a study
- b. patients lost to follow-up over the course of a long study
- c. the ability to characterize end of life device failures
- d. the ability to accurately collect device disposition when a new device is placed

Question 2Biv

Please comment on the ideal duration of follow-up time to assess long term performance of leadless pacemakers.

Question 2Bv

When considering long term performance and potential complications that may occur, does this change the appropriate sample size determined from Part A?

ODE Assumed Complication Rate	Target CI Width	Minimum Sample Size Needed	Upper Limit of 95% CI
1%	+/- 0.5%	1741	1.6%
1%	+/- 1.0%	497	2.3%
1%	+/- 1.5%	251	3.2%

Question 2C

FDA foresees four (4) likely scenarios for device EOL:

Explant Leadless Pacemaker and implant

- another LP
- a transvenous device

Turn OFF the existing LP and implant

- an adjacent LP
- an adjacent transvenous device

Question 2Ci

Please discuss the value of collecting data on how clinicians manage LP devices when they reach EOL.

Is collecting this EOL data necessary?

Question 2Cii-iv

- ii. Given the observational nature of the PAS, what criteria should be used to determine the sample size i.e. acceptable rates of occurrence and precision of rates?
- iii. Regarding the scenarios outlined above, what is an appropriate follow-up time to assess for new device interactions with the previously implanted device?
- iv. Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?

Question 2D

A physician may choose to implant a leadless pacemaker to replace a transvenous VVIR pacemaker system when a patient has a faulty or non-functional lead.

Please discuss if the post-approval study design should incorporate data collection for patients who receive a LP as a replacement for a transvenous system and what type of data should be collected.

Question 3

In the absence of data on long term performance and end-of-life options for leadless pacemakers, please comment on content and points to address for appropriate labeling regarding extractions, replacements, and best practices at this time.

Question 4

Please discuss your views on the clinical role of this technology in patients currently indicated for conventional transvenous single chamber (VVI) pacemakers.

Question 4 Continued

In your discussion, please specifically address the following clinical subgroups:

- Patients in sinus rhythm with symptomatic paroxysmal or permanent second or third degree AV block
- Patients with paroxysmal or transient sinus node dysfunction
- Patients with tachycardia-bradycardia syndrome
- Patients with pacemaker syndrome
- Patients in sinus rhythm and frequent pacing is not expected
- Patients with carotid sinus syndrome



Thank You