Development, Testing, Trialing And Approval Of New Leads

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MY CONFLICTS OF INTEREST ARE

Physicians Advisory Board: Medtronic

Research: MDT, BSci, SJM, BioControl, Biosense, Admittance Technologies

Physician Training Programs SJM, Spectranetics

Design of a Product

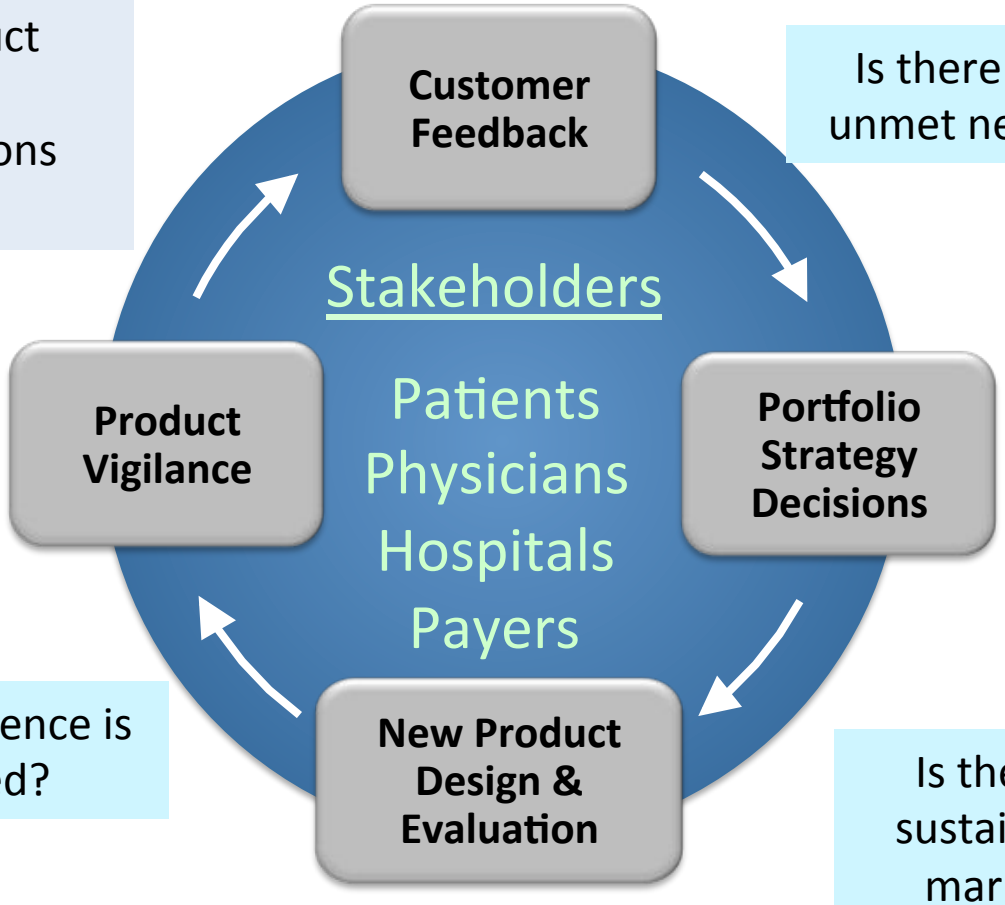
Things to consider

- Voice of the customer- what are the unmet needs
- Reliably-what is the expectation of the product?
- Manufacturability- can the product be manufactured with a high degree of consistency, lowest cost and highest quality

Product Development Cycle

Product Development Cycle

How is the product performing? What complications are occurring?



Is there an unmet need?

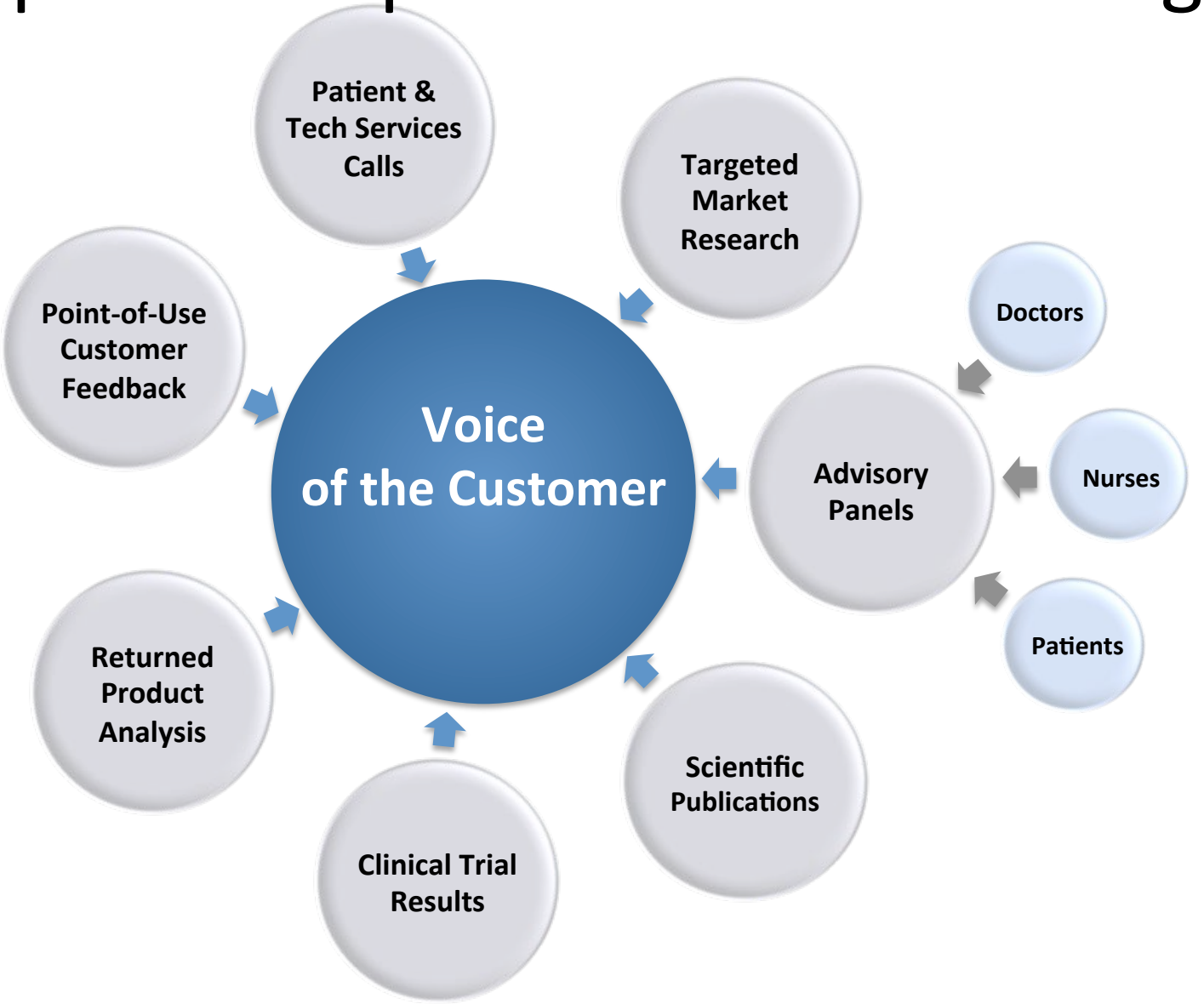
What will be the new technology advancements?

Is there a sustainable market?

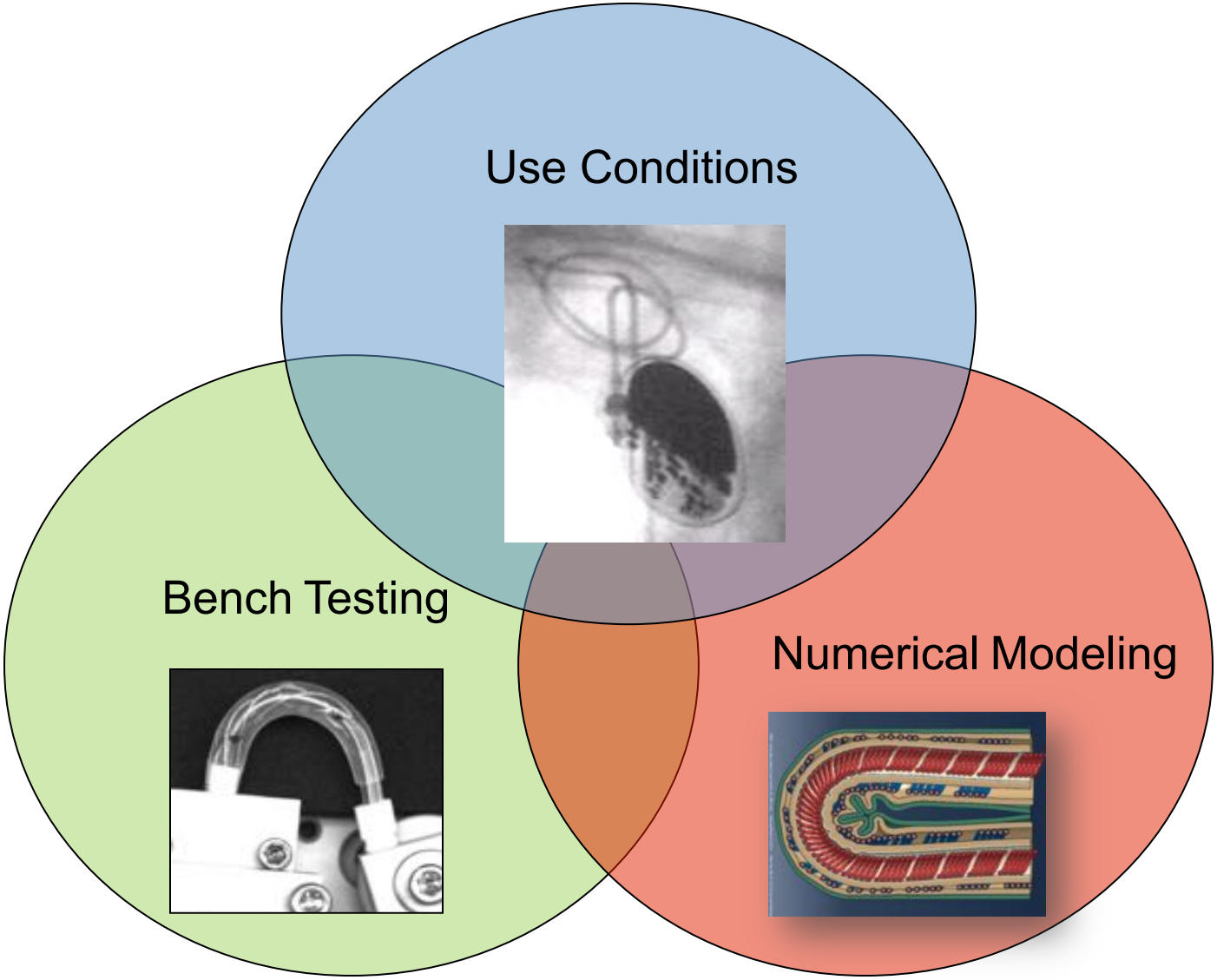
What is the design intent of the product?

What evidence is needed?

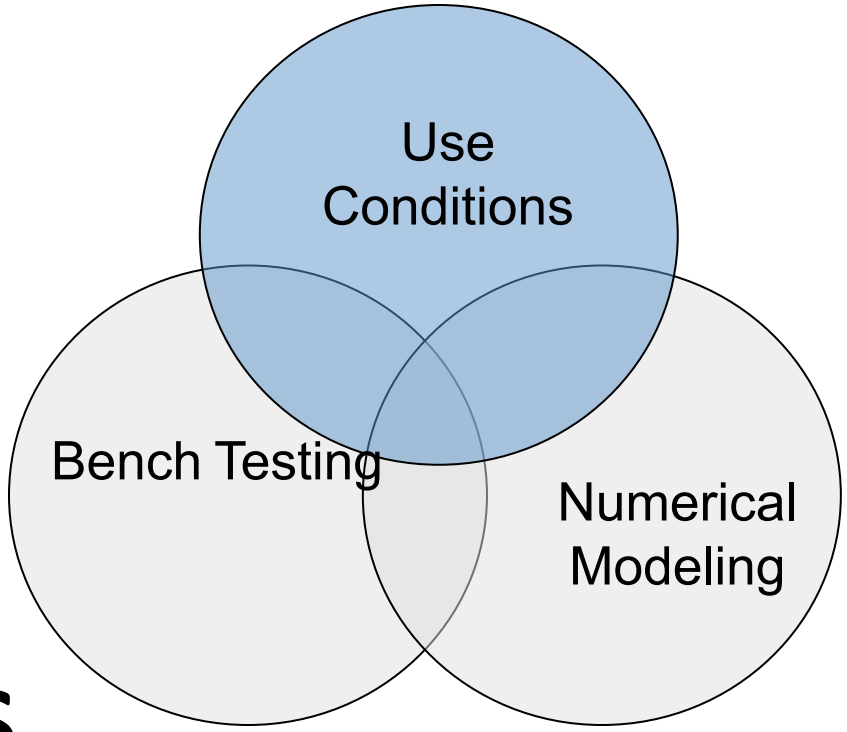
Important input into Product Design



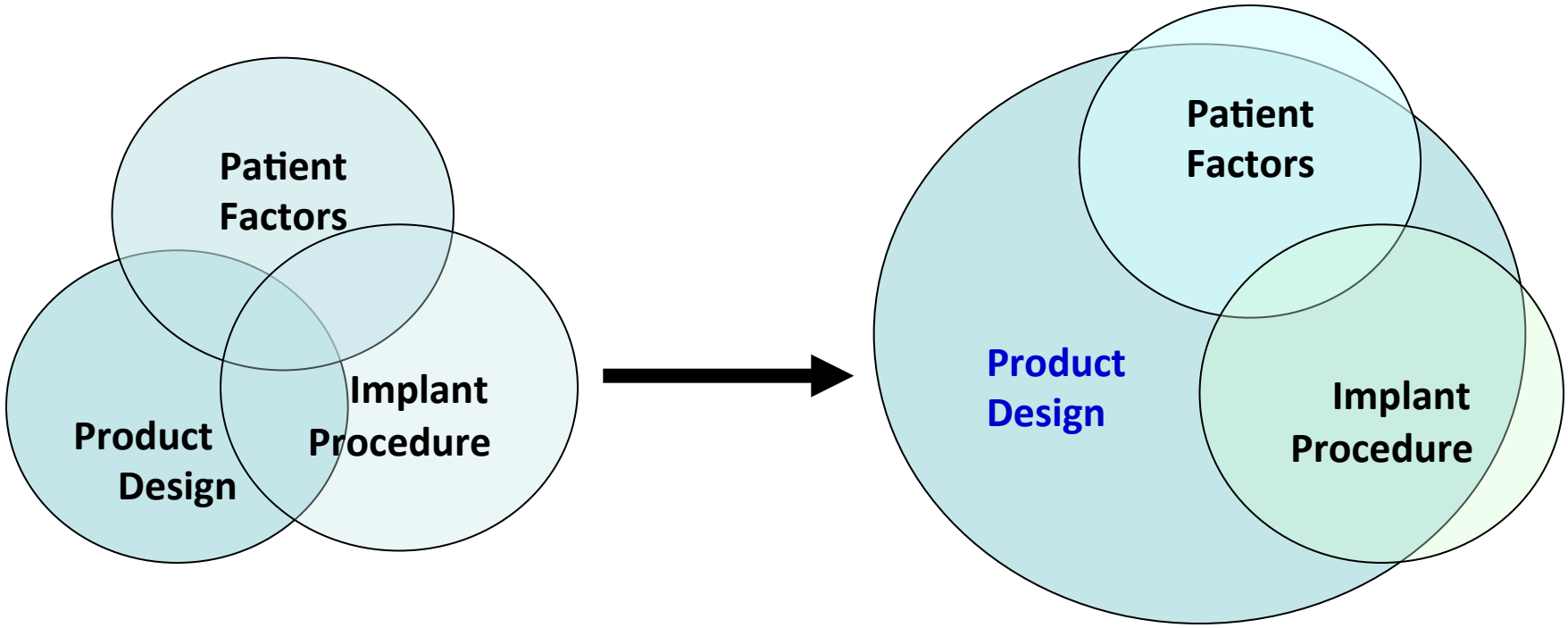
Three Fundamentals For Developing And Testing Reliable Product



USE CONDITIONS



Understanding Use Conditions



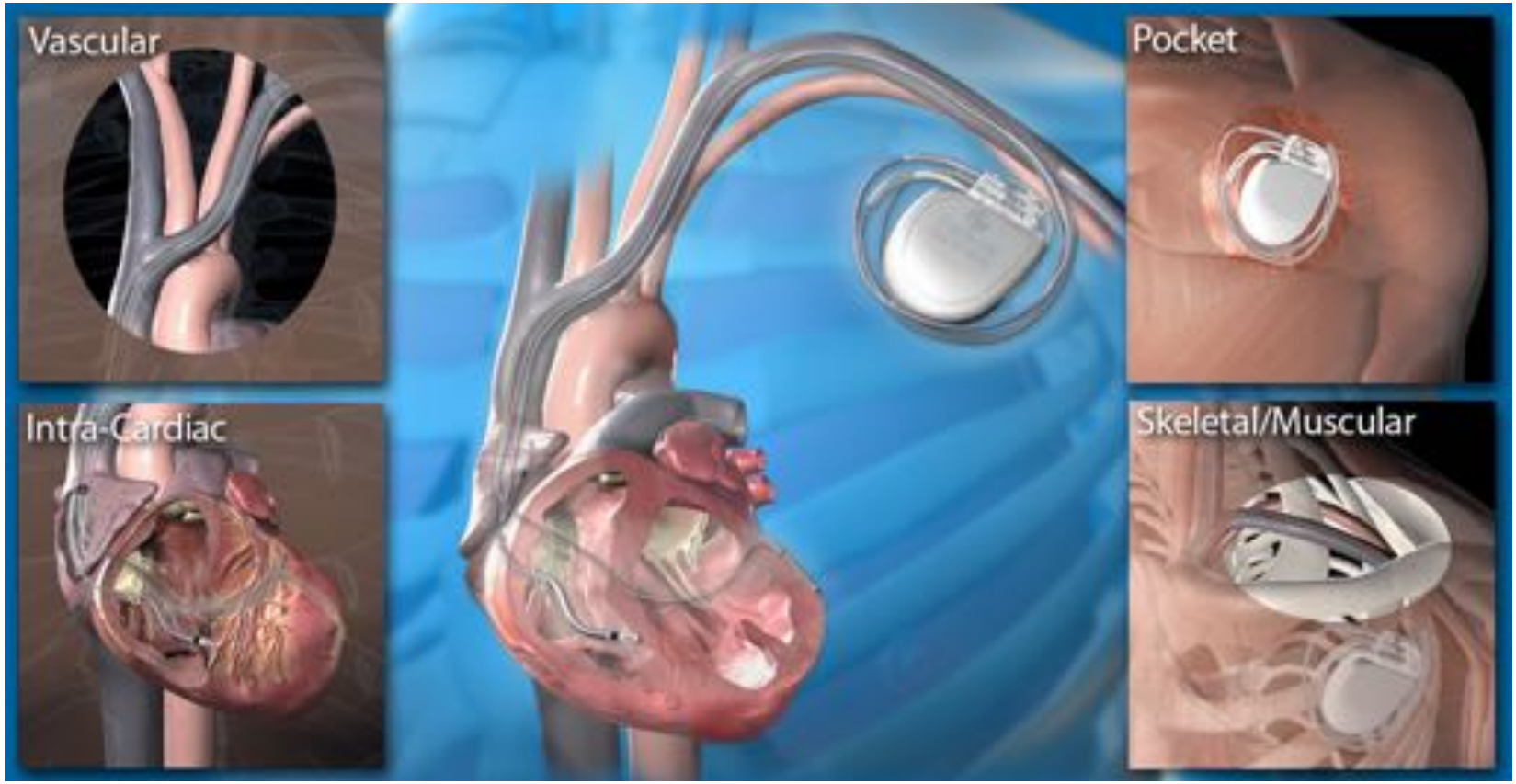
Wilkoff, "Lead failures: Dealing with even less perfect" Journal of the Heart Rhythm Society July 2007

"There are three contributing factors to lead failures: lead construction, implantation technique and patient factors".

Use Conditions :
Different Zones, Different Loads

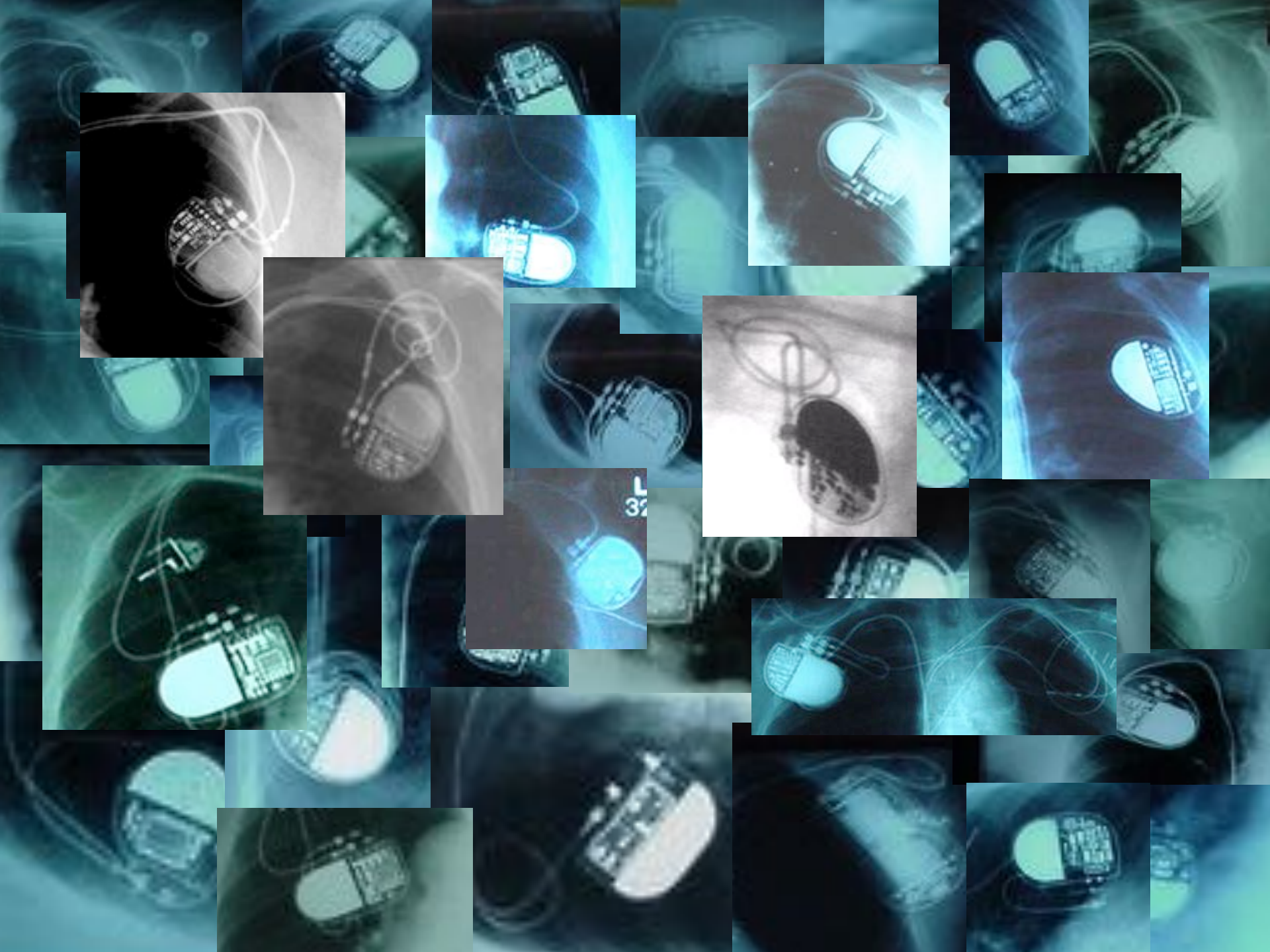
Lead shape changes with respiration, ~10's of millions of cycles, relatively low stress

Lead shape changes with arm movement. Millions of cycles, potentially high stress

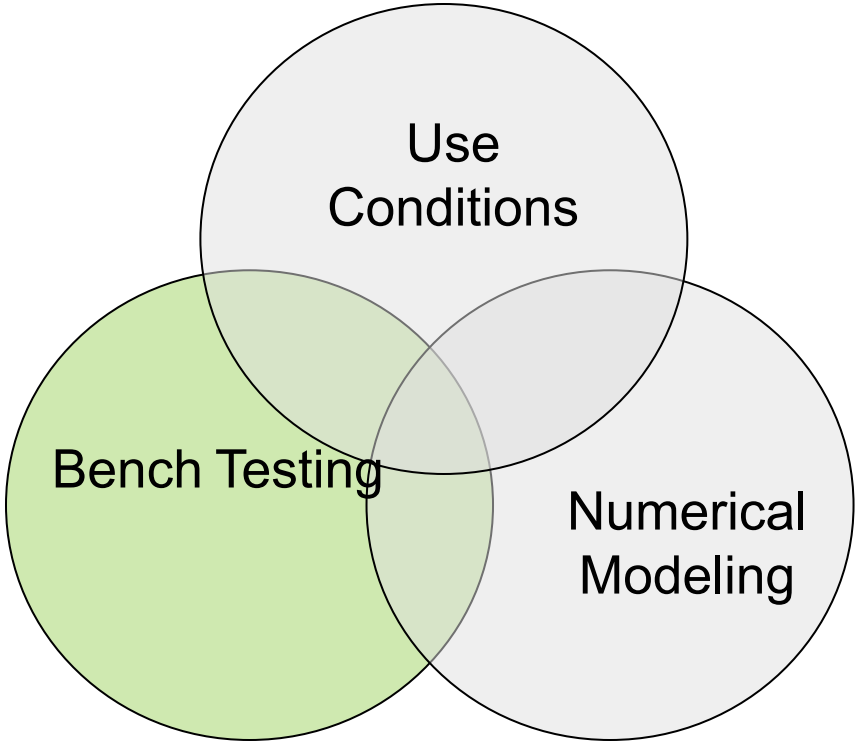


Lead shape changes with every heart beat. ~100's of million of cycles, relatively low stress

Lead shape changes with arm movement. Millions of cycles, potentially high stress



BENCH TESTING



Bench Testing for Leads

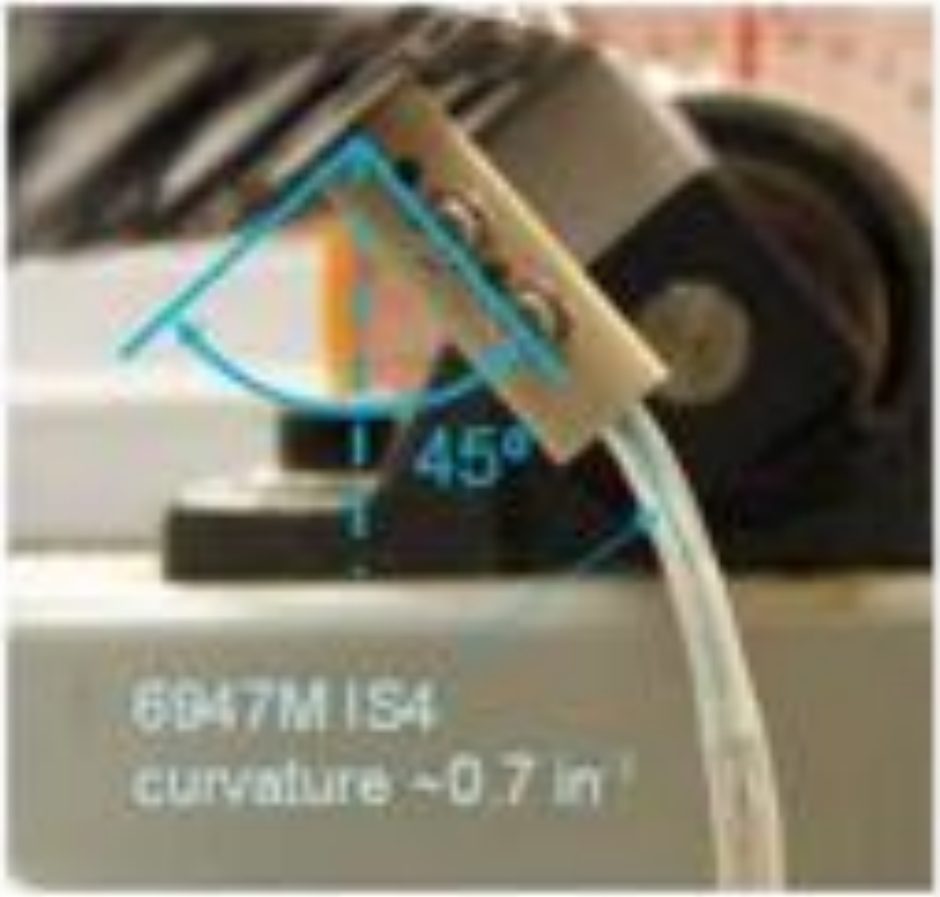
- Electrical checks (before & after tests)
  - Resistance, Impedance, Insulation Integrity
- Preconditioning
  - Sterilization, temp cycles, temp shock, shipping simulation
- Distal tip, body, and connector flex tests
  - Up to 400 million cycles, multiple orientations for asymmetrical leads
- Tip stiffness testing
  - Buckling test against hard surface, pressure vs. tip area
- Junction & overall tensile testing
- Connector insertion/extraction
- Stylet & guidewire compatibility tests
- Suture sleeve tests (slippage)

Focus for Improvements?

Making testing predictive of field clinical performance.

Connector Bench Testing ISO Standard

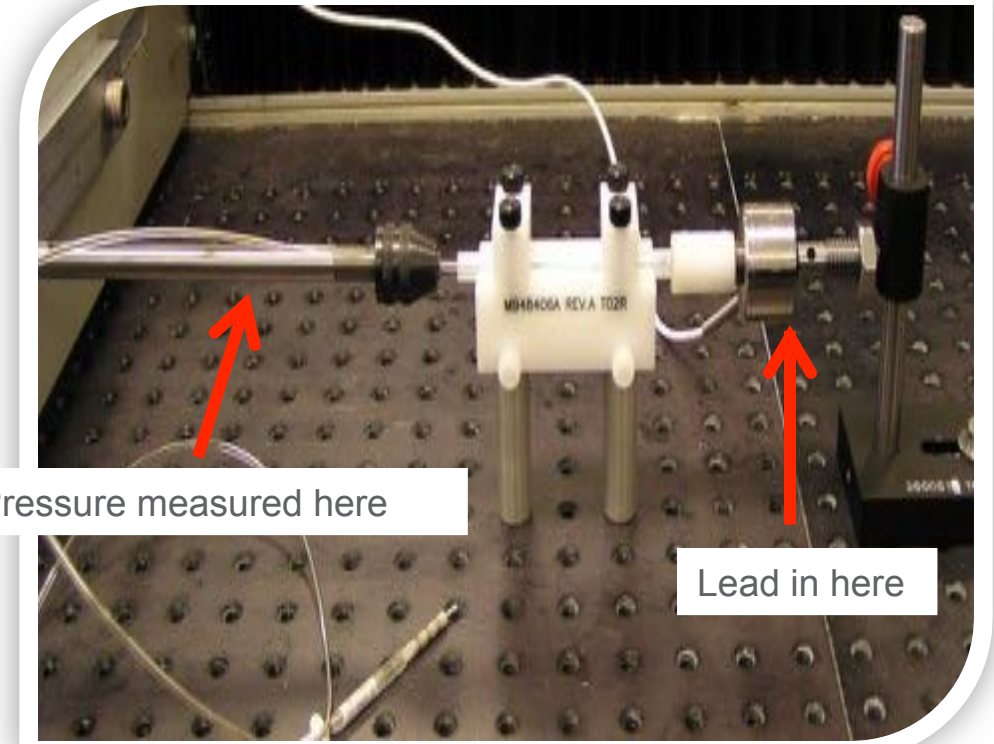
±45° connector test



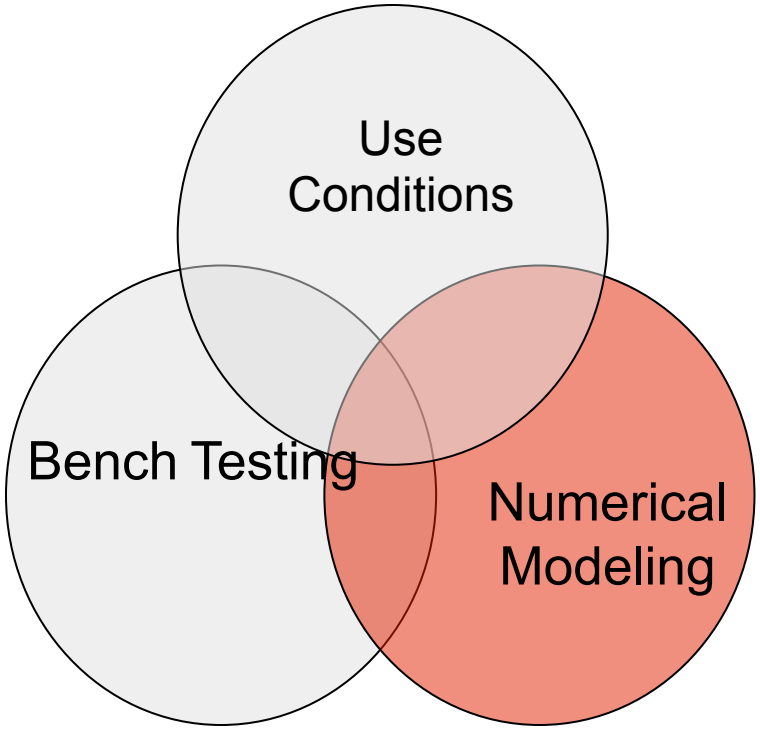
Moving beyond standards to predict reliability.

Example of lead stiffness tests adjusted for the leads application.

RIGHT HEART TIP STIFFNESS TEST



LEFT HEART TIP STIFFNESS TEST



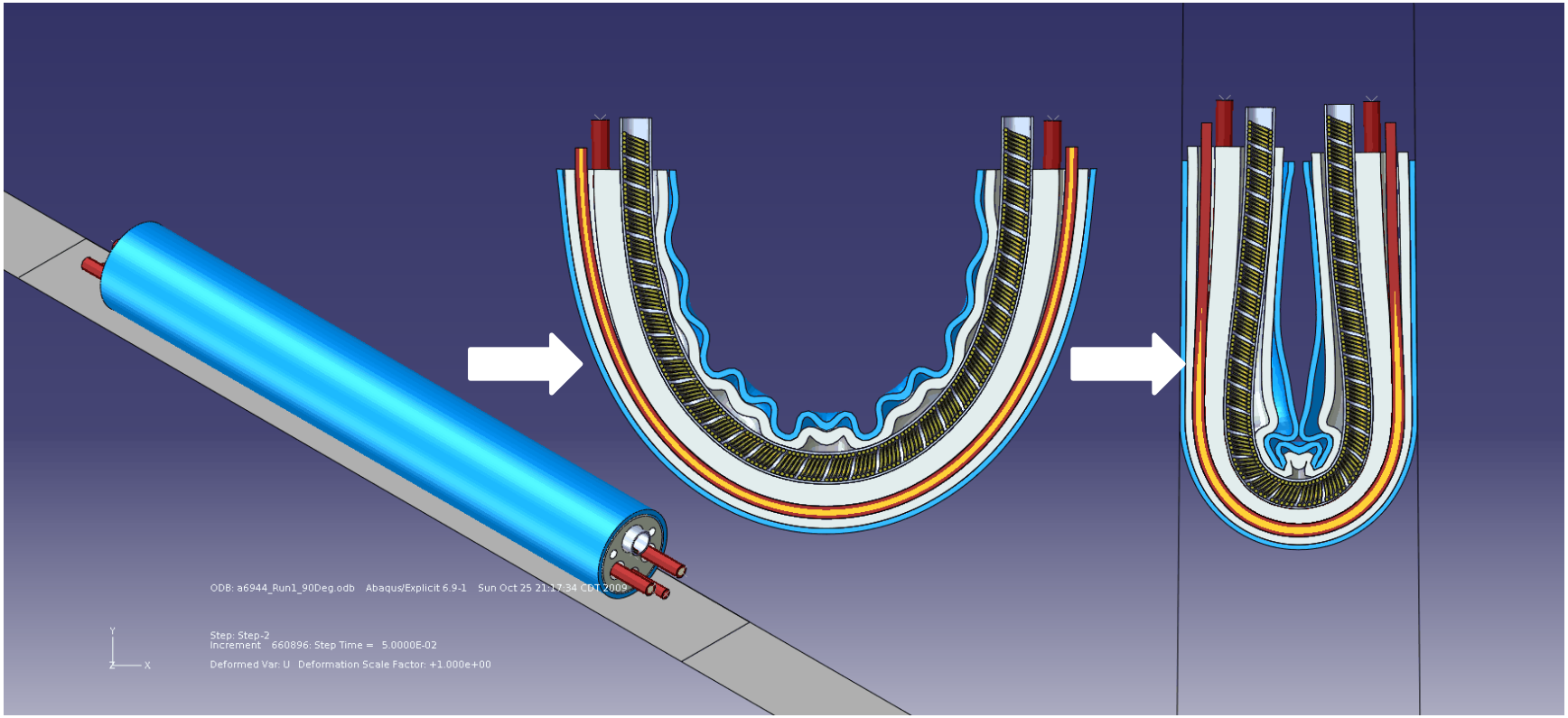
NUMERICAL MODELING

Mechanical Integrity (clavicle/ first rib)

Tubing without compression lumens: under severe pressure, stress concentrated between conductor lumens

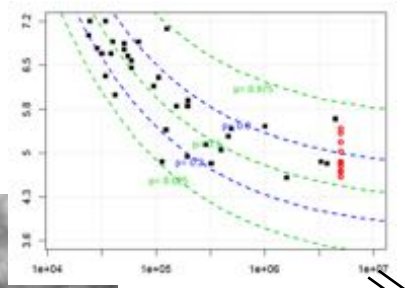
Tubing with wonder lumens: under severe pressure, stress concentrated between conductor lumen and wonder lumen

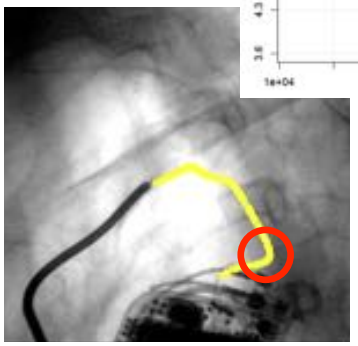
Numerical Simulation Of Lead Bending



- Loading based on in-vivo use conditions
- Model outputs will be stress / strain (for structures)

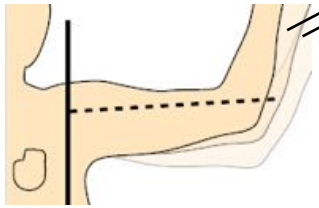
Putting it all together to understand survivability





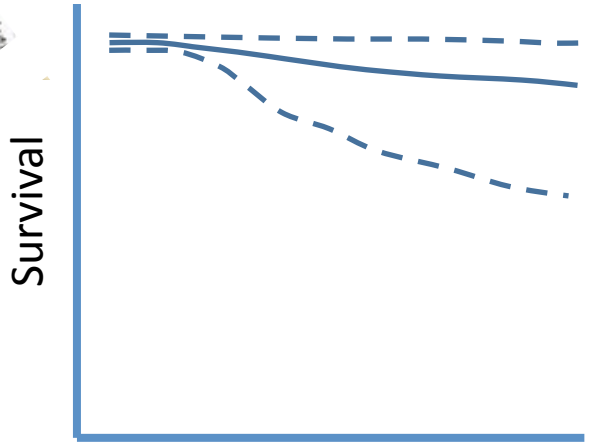
fatigue strength

in-vivo bending



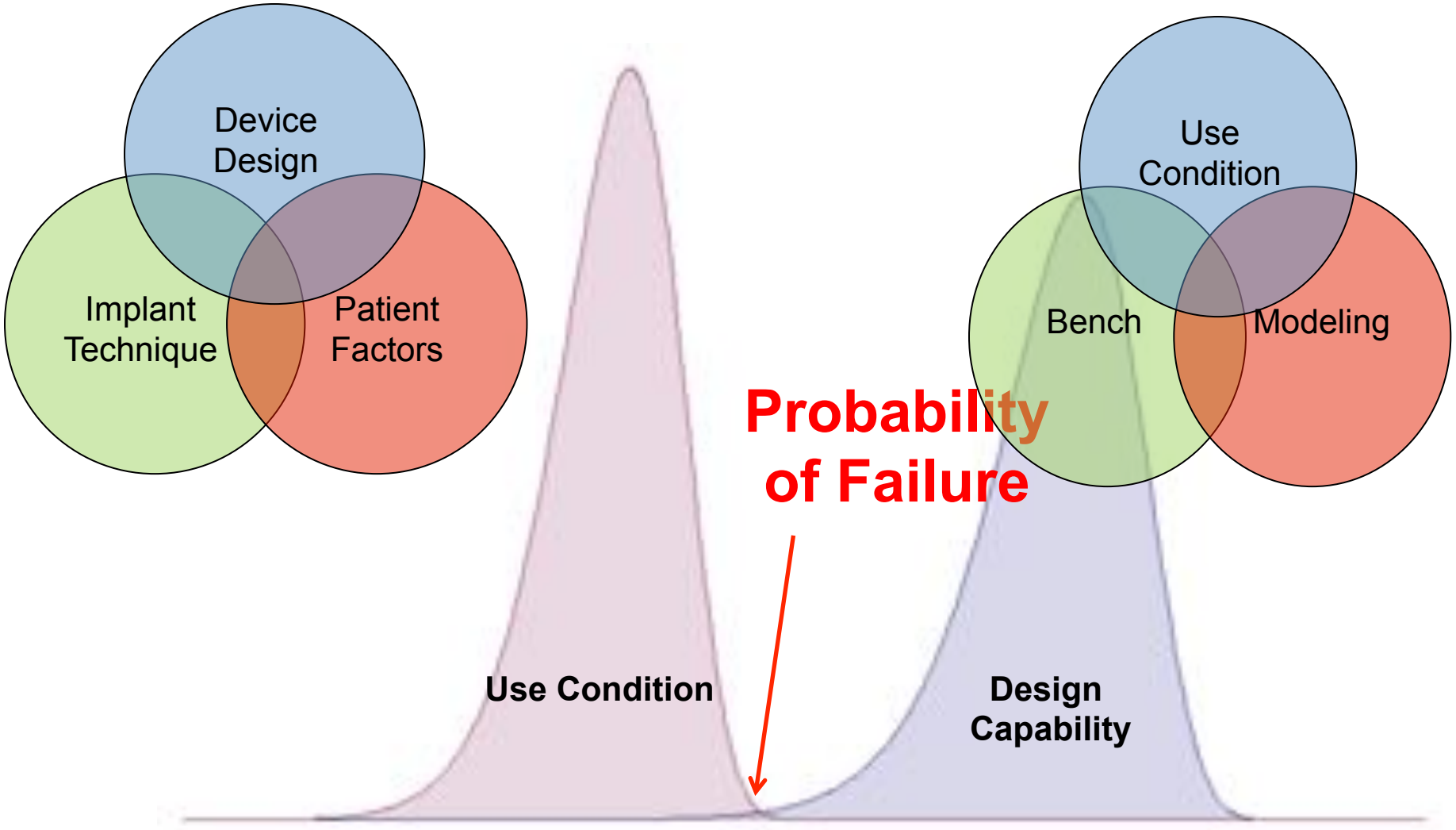
patient activity

Survival Curve



Simulate many combinations, propagate variability and uncertainty to predict survival with confidence bounds

Importance of In-vivo Use Conditions in Development



Safety

"There is reasonable assurance that

a device is safe when it can be determined based on valid scientific evidence that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh the probable risks."

21 CFR 860.7

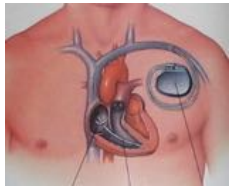
Effectiveness

"There is reasonable assurance that a device is effective when it can be determined, based upon **valid scientific evidence**, that in a significant portion of the target population**,** the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide **clinically** significant results**."**

21 CFR 860.7

Approval

Premarket Data Types



	Pros	Cons
Bench Testing	• Simulate long/severe usage • Large sample sizes • Diversity of mech/elec tests • Consistent repeat tests	• In vivo loads often not well defined or modeled • Tests hard to validate with actual performance data
Animal Studies	• In vivo data • Handling data • Biostability data	• Not perfect representation of human anatomy
Human Clinical Studies	• The real deal for implant data and acute performance	• Usually only acute data • Small sample sizes • Time / cost
Similar Device Information	• For minor changes, old device performance can support new device data	• Not sure of quality of post-market data

Understand the Agencies: Regulatory Agency Mission

Goal: Protect and promote the public health. Get safe and effective medical devices to market as quickly as possible while ensuring that medical devices currently on the market remain safe and effective

Method: Looks for compliance with Standards and Quality System Requirements which are verified during submission reviews and FDA Audits

Philosophy: **FDA,** then physicians and professional guidelines assess effectiveness

Goal: Get safe medical devices to market as quickly as possible while instituting a post-market surveillance system to ensure patient safety

Method: Looks for compliance with Standards and Quality System Requirements which are verified during submission reviews and Notified body Audits

Philosophy: **Physicians** and professional guidelines assess effectiveness

Risk Based Device Classification

Based on degree and severity of risk, and the benefit of the device.

* Class I: Low Risk [Exempt or 510(k)]
* Class II: Moderate Risk [510(k)]
* Class III: High Risk [PMA/PMA-S approval required]

Classes based on principles of classification:

- Length of time in continuous use
- Degree of invasiveness
- Active or not
- Part of body with which the device is in contact (e.g., heart, CNS)
- Special rules for tissues and drugs

* Class I: Low Risk [Technical File]
* Class IIa: Medium Risk [Technical File]
* Class IIb: Medium-high Risk [Technical File]
* Class III: High Risk [Design Dossier]

Europe: CE Marking

CE marking symbolizes the fact that the natural or legal person having affixed the marking has verified

- that the product conforms to all EU provisions for harmonization which apply to that product
- has subjected the product to the appropriate conformity evaluation procedures

Contents of Technical File/Design Dossier
Similar to US Requirements

- Description of the apparatus, usually accompanied by block diagram
- Wiring and circuit diagrams
- General Arrangement drawing
- List of standards applied (Essential requirement checklist)
- Records of risk assessments and assessments to standards
- Description of control philosophy/logic
- Datasheets for critical sub-assemblies
- Part list
- Copies of any markings and labels
- Copy of instructions (user, maintenance, installation)
- Clinical Evaluation Report (CER)
- Packaging Description/Validation
- Biocompatibility
- Design Verification Data
- Quality control & commissioning procedures
- Declaration of Conformity

Perspectives & Solutions

Post-approval studies for new designs and major design changes can be used to validate bench testing and can provide data on the true performance of pacemaker and ICD leads

- FDA requires post approval studies for new leads with substantive changes from other market approved leads. Design elements include:
  - ✓ 5 year studies
  - ✓ 1000+ subjects (0.4% event rate, 1.0% upper confidence bound)
  - ✓ Full enrollment in first year
  - ✓ 95% freedom from adverse events endpoint @ 5 yrs
  - ✓ Trend analyses & frequent reporting

Summary

- Design
  - Unmet needs and expectations
- Testing
  - Use conditions, Bench, Modelling
- Trials
  - In vivo/ human trials
- Approval
  - Premarket safety and effectiveness, post-market