Clinical Trials Augmented by Simulation and Bench Testing

Mock Submission Informational Meeting

MDIC

MEDICAL DEVICE INNOVATION CONSORTIUM

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Outline

Background of MDIC and working group

Virtual patients – what are they?

Statistical framework – how can we integrate virtual patients into a human clinical trial?

Augmenting clinical trials with virtual patients is a paradigm shift that can provide faster access to new therapies for patients while increasing rigor in the development process.

MDIC Highlights and Overview

Founded 2012 | 43 Members | 5 Projects

- Congressional testimony on modernizing clinical trials
- White House-FDA roundtable on patient data donation
- $500K funding from FDA for Patient Centered B-R project
- $650K funding from FDA for Quality Engagement Forum

A 501(c)3 - Public-Private Partnership collaborating on Regulatory Science to make patient access to new medical device technologies faster, safer, and more cost-efficient

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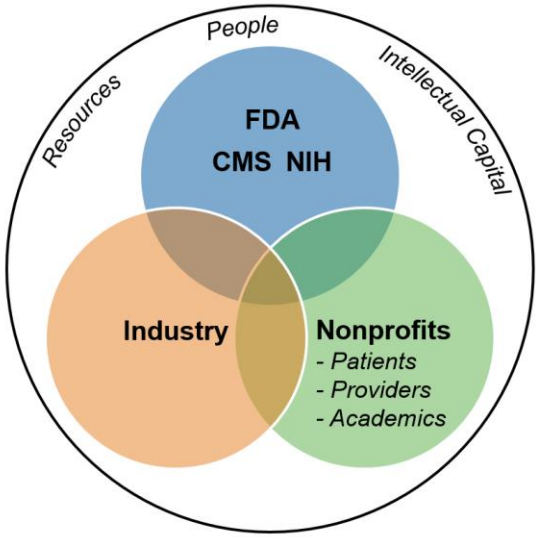


Align Resources

Accelerate Progress

Achieve Results

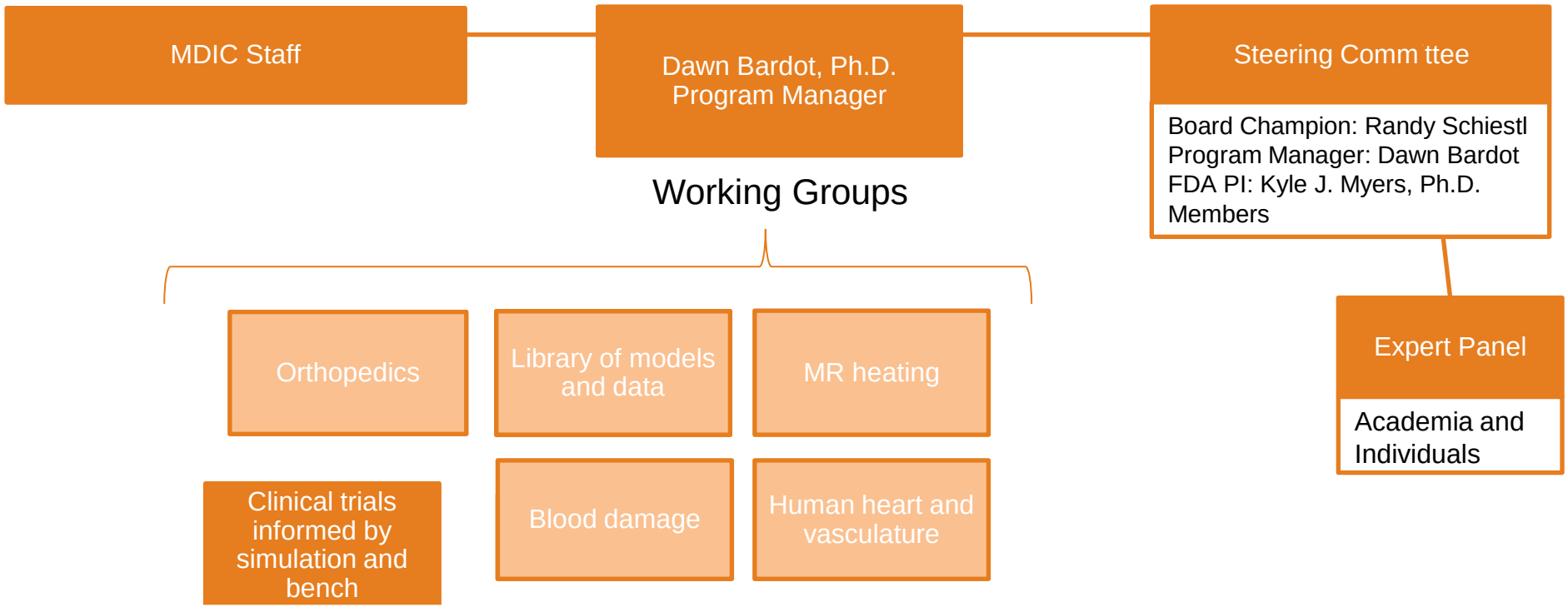
WORKING COOPERATIVELY
with FDA to re-engineer pre-competitive technology innovation

REDUCING TIME
and resources needed for new technology development, assessment, and review

HELPING PATIENTS
gain access to new medical technologies sooner

Precompetitive space: Standards, data and processes that are common across the industry

Computer Modeling & Simulation Project Team Structure

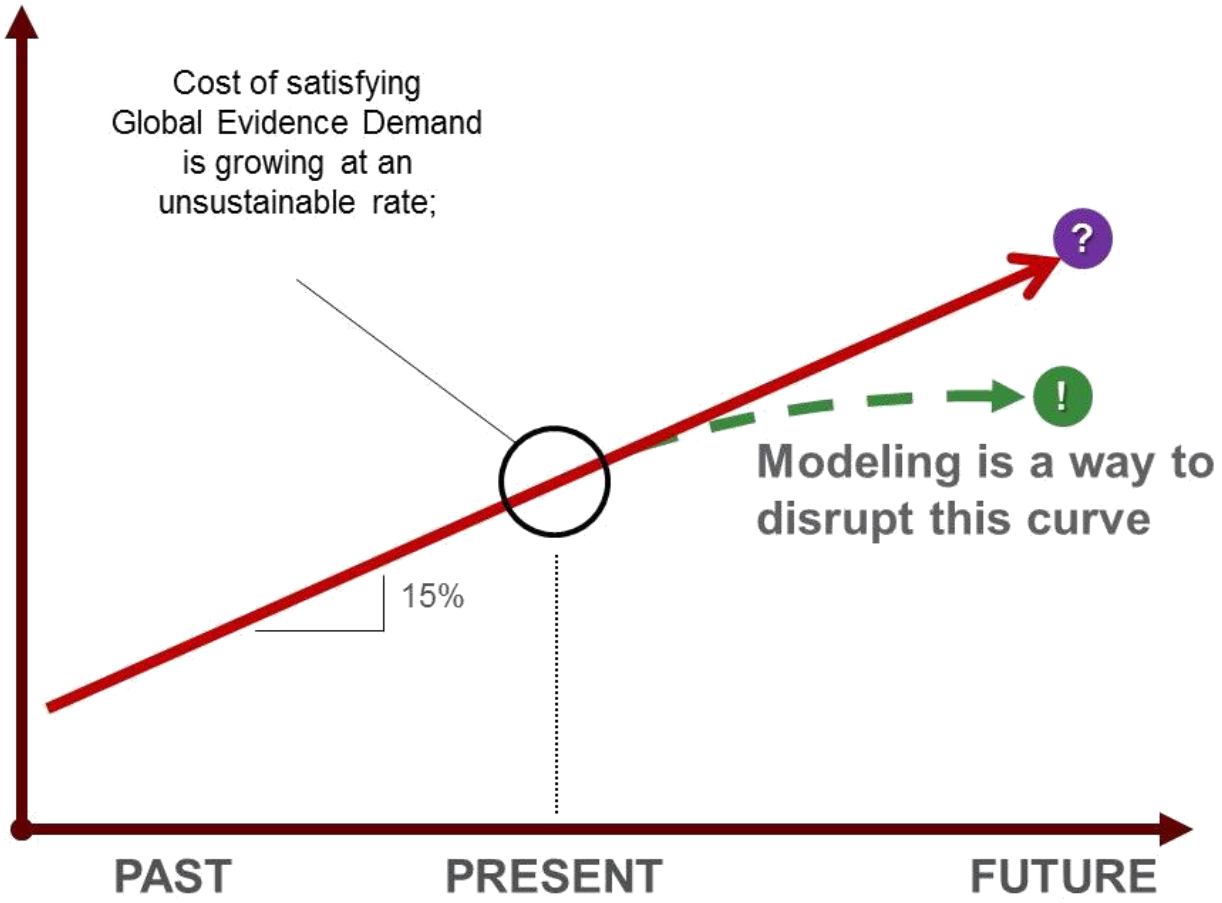


- Chair: Tarek Haddad, Medtronic
- Diverse collection of skill sets and organizations
- Mock submission team is a subset
    - FDA, MDIC, ANSYS, BD, St. Jude Medical, Medtronic

Trends Transforming Clinical Research

Demands:
↑ Evidence
↑ Stakeholders
↑ Geographies
↑ Value

Rapid rise in costs due to:
↑ Complexity
↑ Number of outcome variables
↑ Follow-up time
↑ Post-market data



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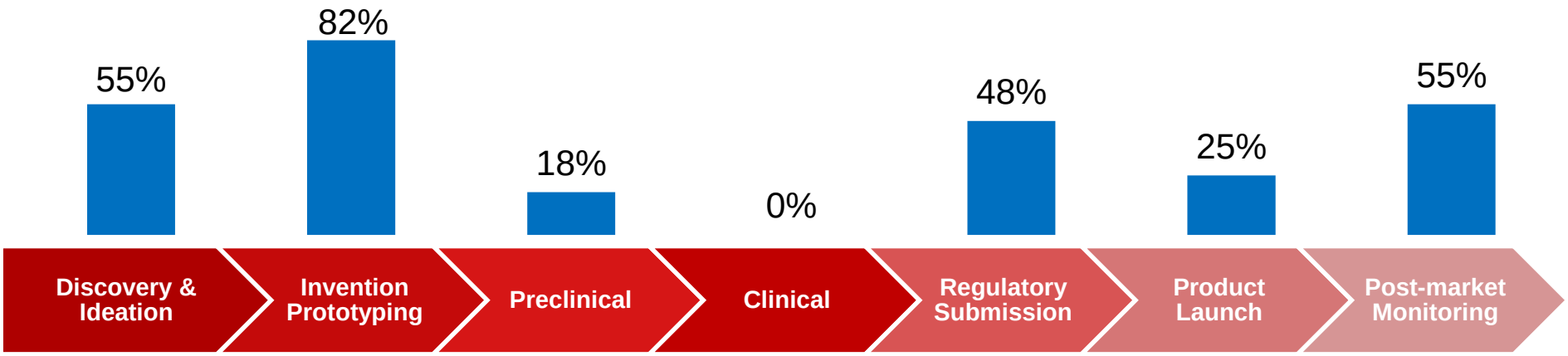
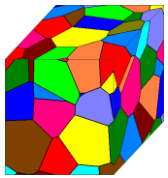
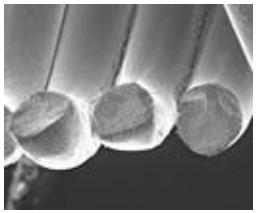
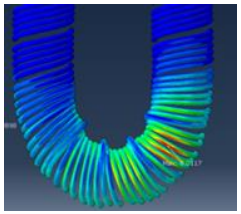
*Adapted from Kuntz, “Insights on Global Healthcare Trends”, 2/13/2013.

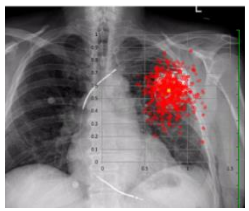
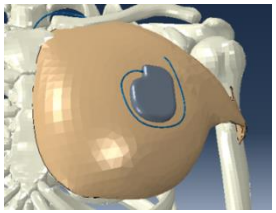
Use of Modeling across Lifecycle



- Animal studies
- Use conditions
- Virtual prototyping
- Material characterization

- Device structure & function
- Systems interaction
- Design optimization
- Failure analysis

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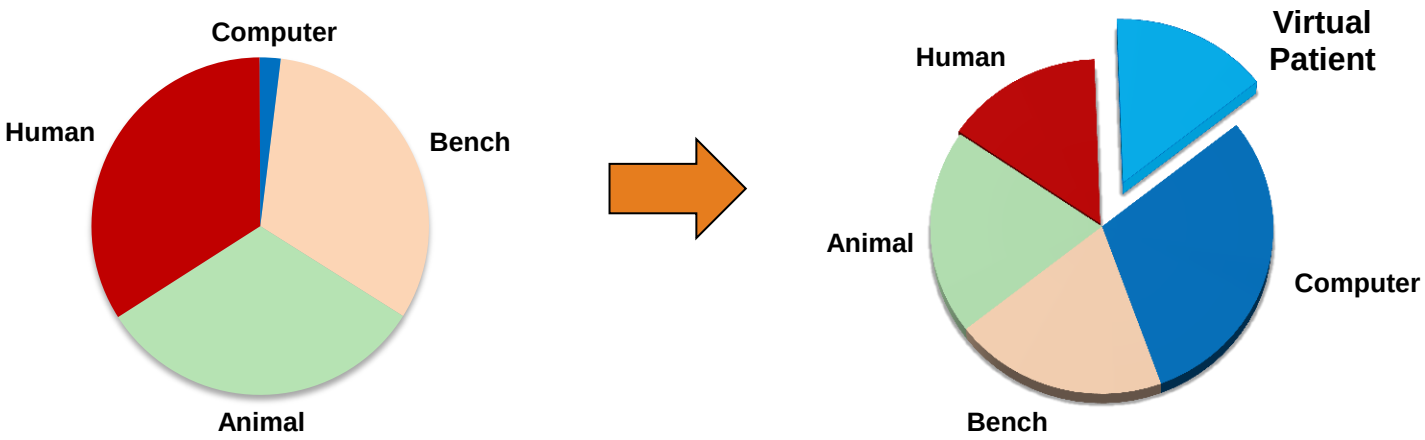
* Results from 2014 MDIC survey of 35 participating medical device companies

Disrupting Clinical Trial Design with Virtual Patients

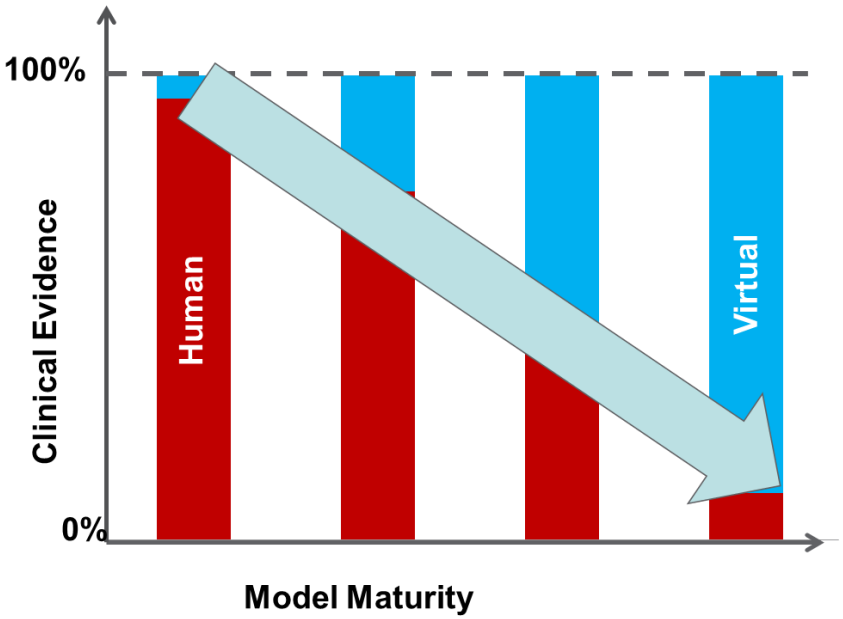
Sources of Evidence



- Combine physical and probabilistic models to simulate clinically relevant outcomes in virtual patients
- Use Bayesian methods to integrate virtual patients into clinical trial
- Maintain clinical endpoints with reduced sample size

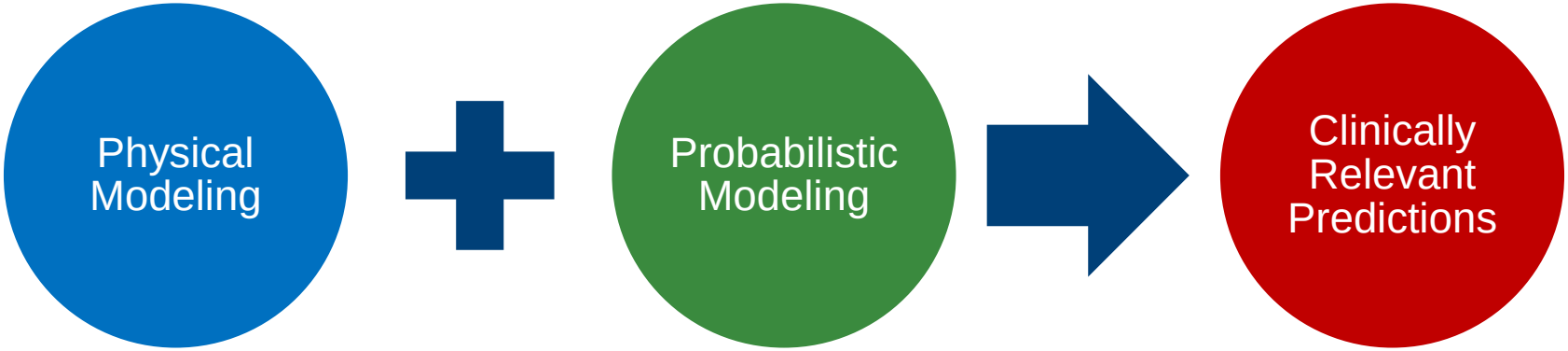
Not all models are created equal

- Model maturity dictates number of virtual patients
- Early phase models still add benefit



Human evidence replaced by virtual patients

What Makes a Virtual Patient?



Well Characterized Physics:
- Mechanical
- Electrical
- Heat
- Diffusion

Knowledge of Physiology:
- Local device ↔ tissue interactions
- Failure modes
- Tissue remodeling

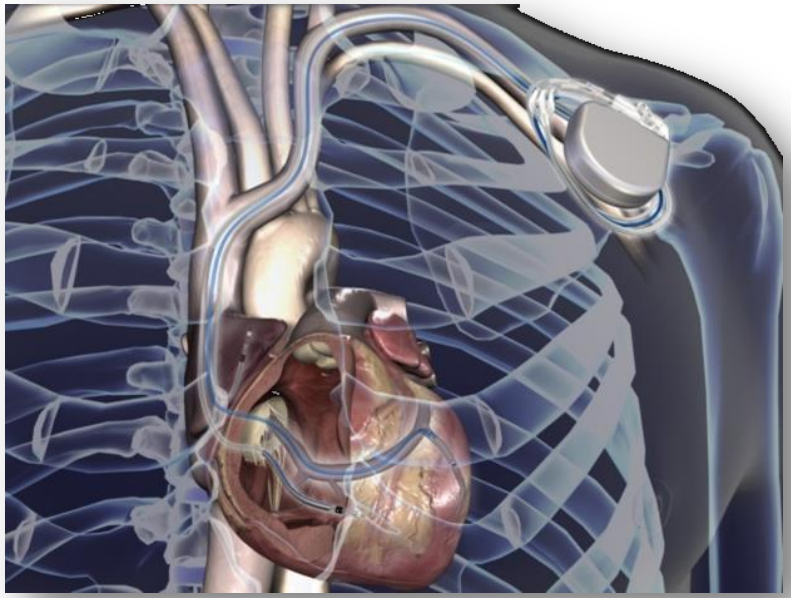
Variability:
- Age
- Gender
- Activity level
- Implant factors
- Physical tolerances

Uncertainty:
- Sample size
- Measurement error/bias
- Model bias

Safety & Reliability Related End Points:
- Nitinol frame failure
- Cardiac lead failure
- Pacemaker housing cracks
- Response to MRI
- Cardiac rhythm detection
- Orthopedic implant fracture

Case Study: Bayesian Lead Fracture Prediction

- ICD lead pacing coil fracture
- Many applicable models, lead fracture is a good example

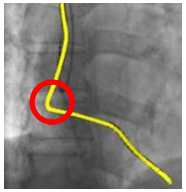


Haddad, Himes, Campbell, *Reliability Engineering and System Safety*, 123 (2014)

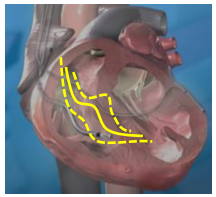
Case Study: Bayesian Lead Fracture Prediction

INPUT

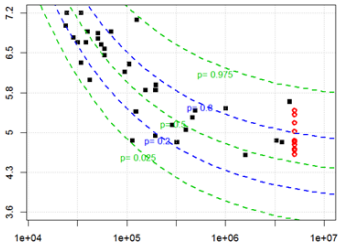
in-vivo bending



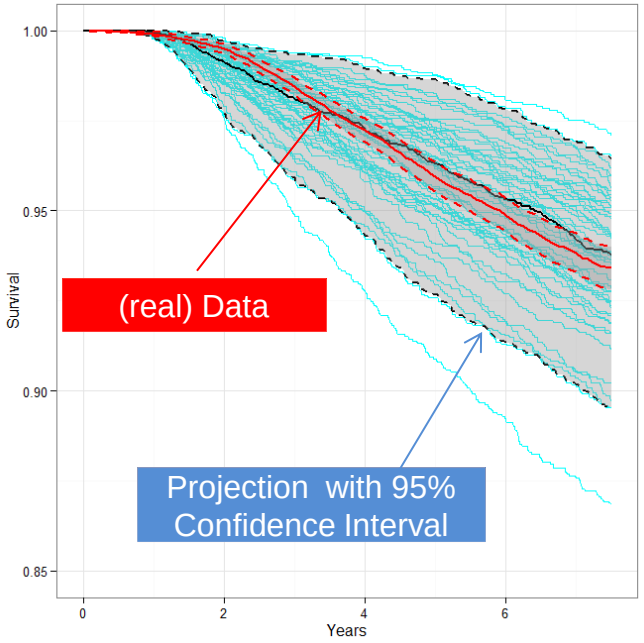
patient activity



fatigue strength



OUTPUT



- Simulate many combinations of virtual patients & clinical trial
- Propagate variability and uncertainty to predict survival with confidence bounds

Model Validation Example: Intracardiac Fatigue Fracture

Inputs:

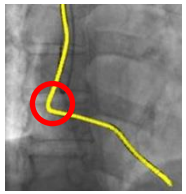
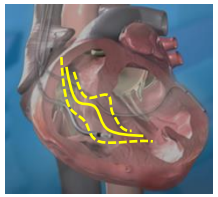
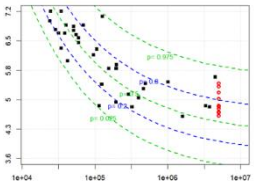
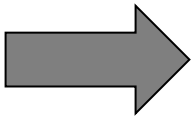
- In-vivo lead bending: measuring the quantity of interest, utilize AAMI clinical study
- Bench testing: applying the proper deformation on the bench, utilize AAMI test

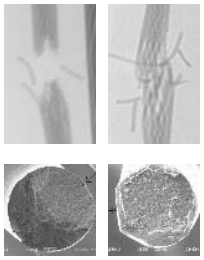
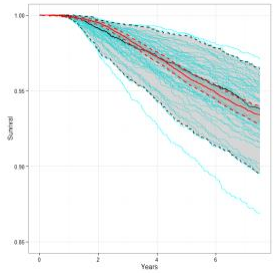
Model:

- Capture sample size uncertainty, bias due to gage R&R, etc.
- Follow software tool validation methods

Outputs:

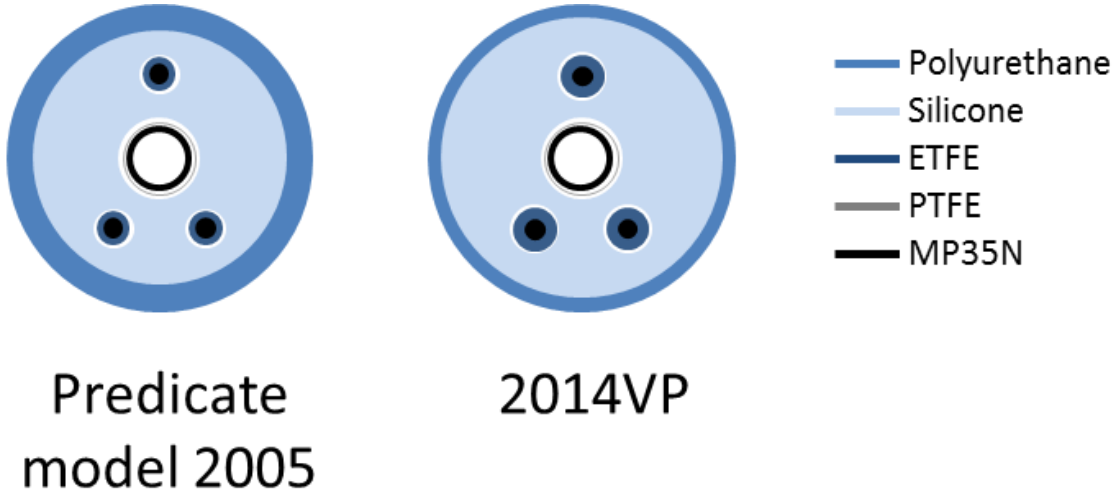
- Use market released products to show that prediction matches field performance
- Morphology of bench failures matches field returns

Each predictive model will be evaluated case by case due to differences in inputs, outputs, failure modes, etc.

Test Vehicle for Mock Submission



Hypothetical new ICD lead

- Similar to predicate lead
- Design changes to improve handling
- Evaluate impact on clinical fatigue fracture performance

Statistical Framework: How to Combine Virtual Patients with Clinical Data

Bayesian methods

- Use virtual patients as a prior
- Similar to the way we use historical data
- Engineering models truly are the prior

Power Prior

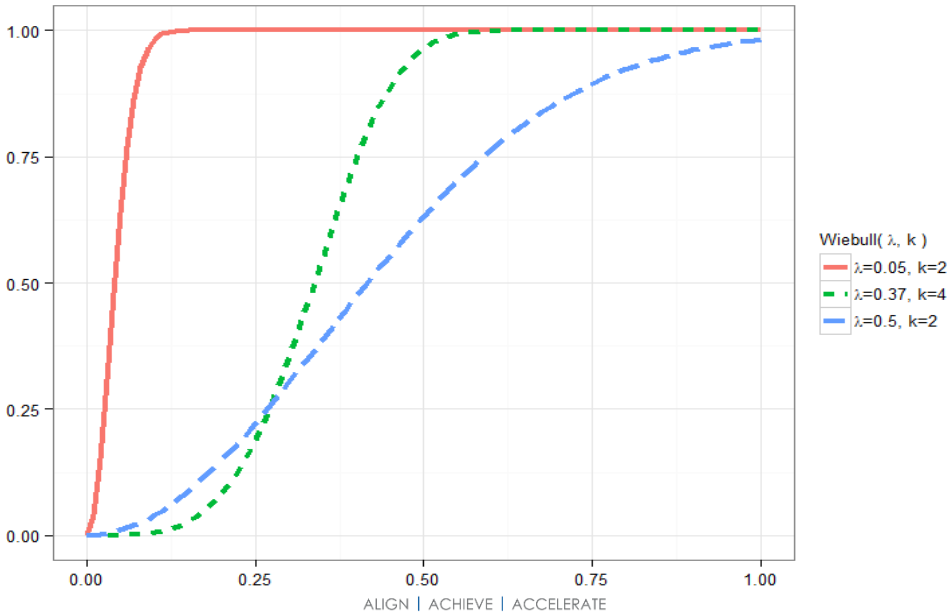
- Currently used to down weight historical data
- Unlike a historical clinical data set, there are unlimited virtual patients
- Reformulate Power Prior
- Can get effect sample size of virtual patients (n_0)

Combination incorporates

- Uncertainty in the virtual patients & current data
- Weighting virtual patients to the effective prior sample size of n_0

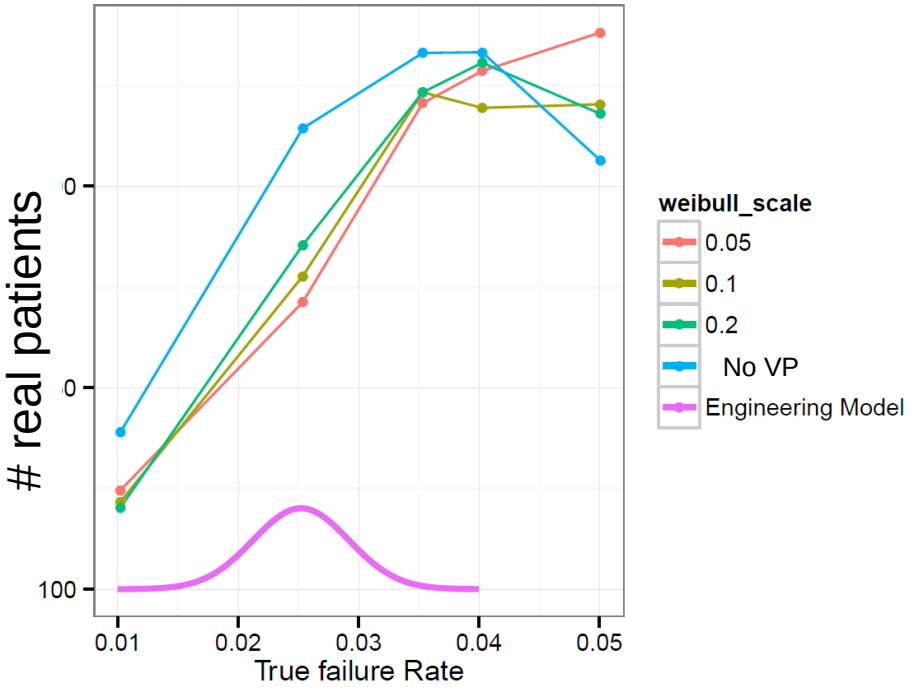
Virtual patient sample size (n_0)

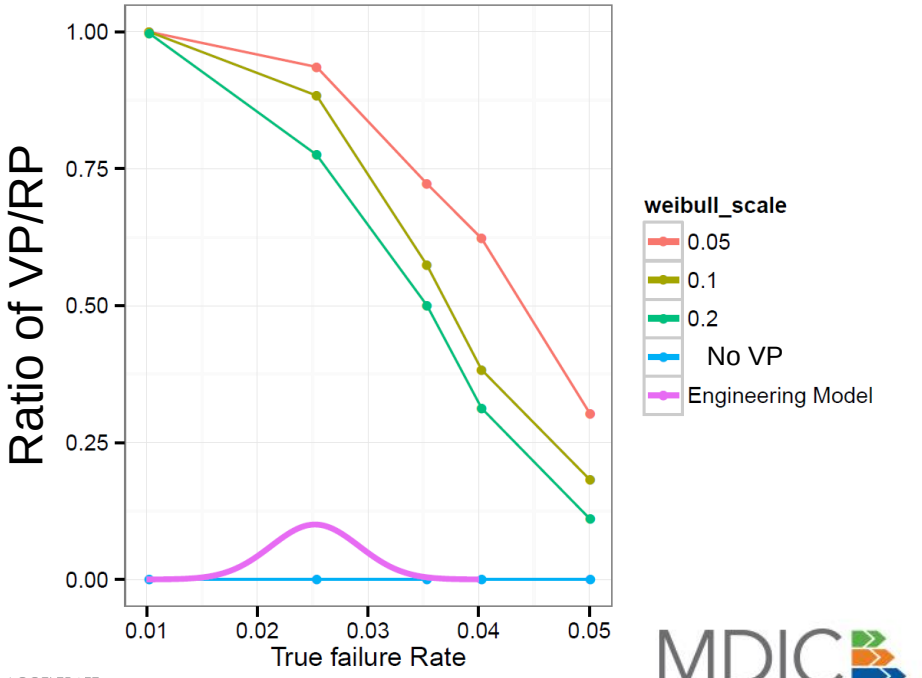
- Big enough → more efficient study
- Small enough → real data governs the trial outcome
- Use loss function to determine optimal n_0
  - If virtual patients ≠ real patients, then n_0 is small
  - If virtual patients = real patients, then n_0 is big, up to some n_{max}



Adaptive Bayesian design

- Take sequential looks at data as trial progress
- Adaptive sample size
- Compare real to virtual patients, apply loss function
- As real ≠ virtual then virtual→0, need to enroll more real patients
- Converts to traditional adaptive design





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Patient and Business Impact

Patient

- Fewer patients exposed to clinical trials
- Extend understanding
  - Pediatrics, gender bias, elderly
- Latent / rare failures
- Less uncertainty about product performance

Business

- Reduced trial size
- Shorter trial time
- Less uncertainty of product performance

Additional Features

Use condition collection

- Staged clinical trial
- First proportion of patients to collect additional use condition data
- Update virtual patients with collected use conditions
- Re-assess viability of clinical trial

Post market surveillance

- Same methodology works well in a surveillance setting
- Model gives context for post-market performance

Model present in total lifecycle!

Activities

- **Disruptive trend in regulatory science: virtual patients**
- **FDA / industry collaboration**
- **Peer review**
  - **Published by FDA (2010):** guidelines for Bayesian statistics in clinical trials. Establishes suitability of Bayesian methods for clinical trials
  - **Complete:** MDIC clinical trial augmentation working group formed in May 2014
  - **In progress:** Publication of combined Bayesian Network with clinical trial/surveillance paper, journal submission **Q2 2015**
  - **In progress:** Mock submission activities with FDA / MDIC (lead fracture endpoint), pre-sub informational meeting **Q2 2015**, targeting **FDA workshop Q4 2015**

Summary

Augmenting clinical trials with virtual patients is a paradigm shift that can provide faster access to new therapies for patients while increasing rigor in the development process.

MDIC working group

- FDA / Industry collaboration
- Diverse collection of skill sets and organizations

Virtual patients

- Using bench tests and simulation to model clinical outcomes
- Incorporate input variability and uncertainty
- Case by case validation

Statistical framework

- Modify existing power prior methods
- Number of virtual patients controlled by loss function
- Validated model at the end of the trial