SCDM Live

Sept. 29 – Oct. 2, 2024 | Boston, MA

Transforming FDA Approaches: The Role of In-silico Data, Multiscale Modeling, and Generative AI in Medical Device Product Development

Session Speakers

Darrell Swenson, PhD

Director of Numerical and Physiology Modeling

Medtronic

Steven Kreuzer, PhD

Senior Managing Engineer

Exponent

Afrah Shafquat, PhD

Senior Data Scientist

Medidata

Heidi Sernoff, MD

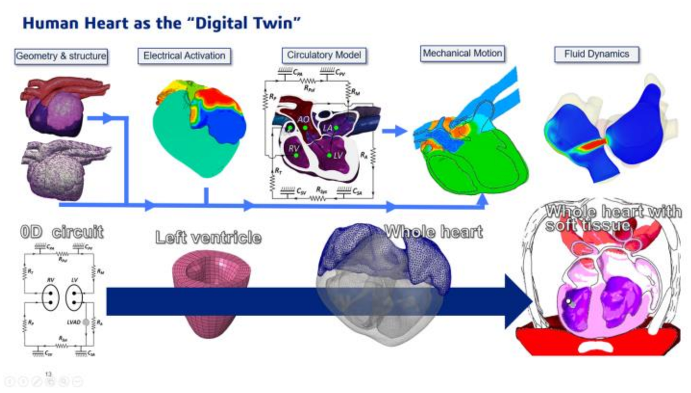
Director

Medidata

Session Format

Focus: The rapidly evolving role of In-Silico Data in Medical Device Product Development

Lessons Learned on the Virtual Patient & Digital Twin Journey

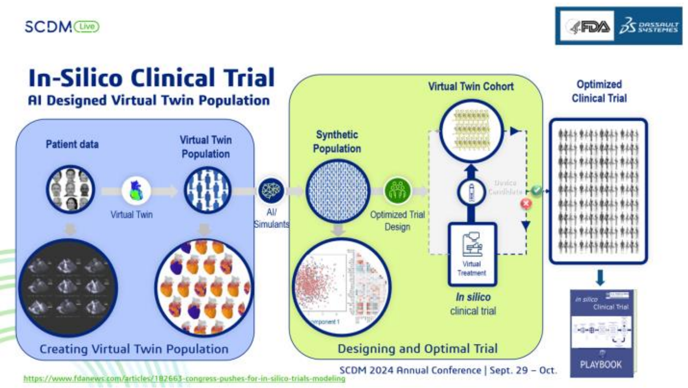


Darrell Swenson
Medtronic

In Silico Clinical Trial Data in Regulatory Decisions

Steven Kreuzer
Exponent

Generative Virtual Twins for Optimized Clinical Trial Design



Afrah Shafquat
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Transforming FDA Approaches: The Role of In-silico Data, Multiscale Modeling, and Generative AI in Medical Device Product Development

Lessons Learned on the Virtual Patient and Digital Twin Journey




Darrell Swenson, PhD

Medtronic

Director of
Numerical and
Physiology Modeling

Kevin Sack, PhD

Medtronic

Technical Lead

Physiology Modeling

Sofia Monaci, PhD

Medtronic

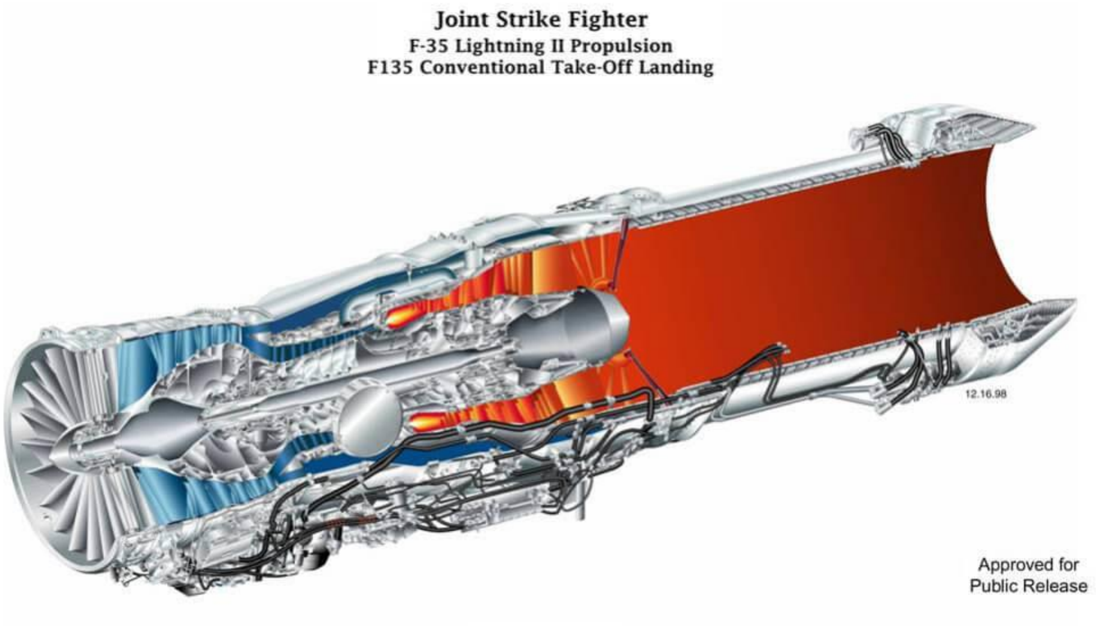
Physiology Modeling

Nya Perry

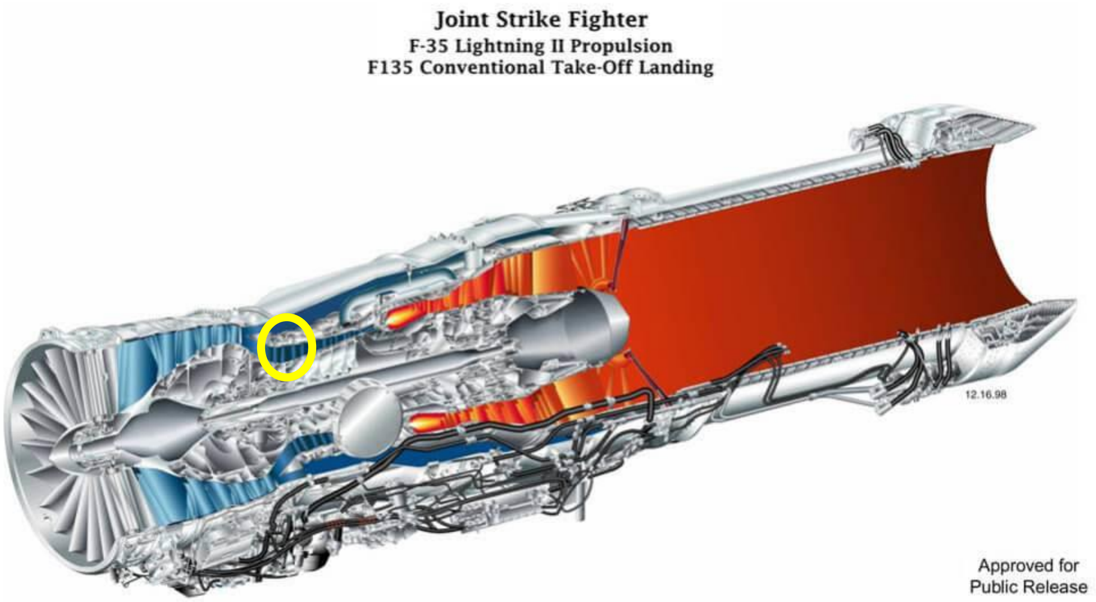
Medtronic

Physiology Modeling

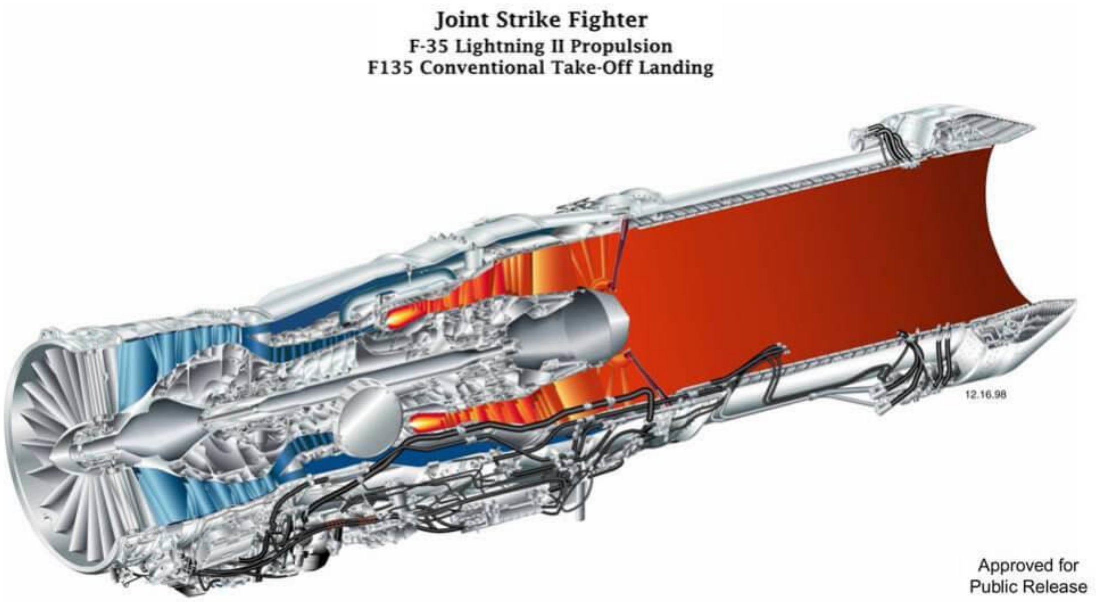
Introduction to the Digital Twin



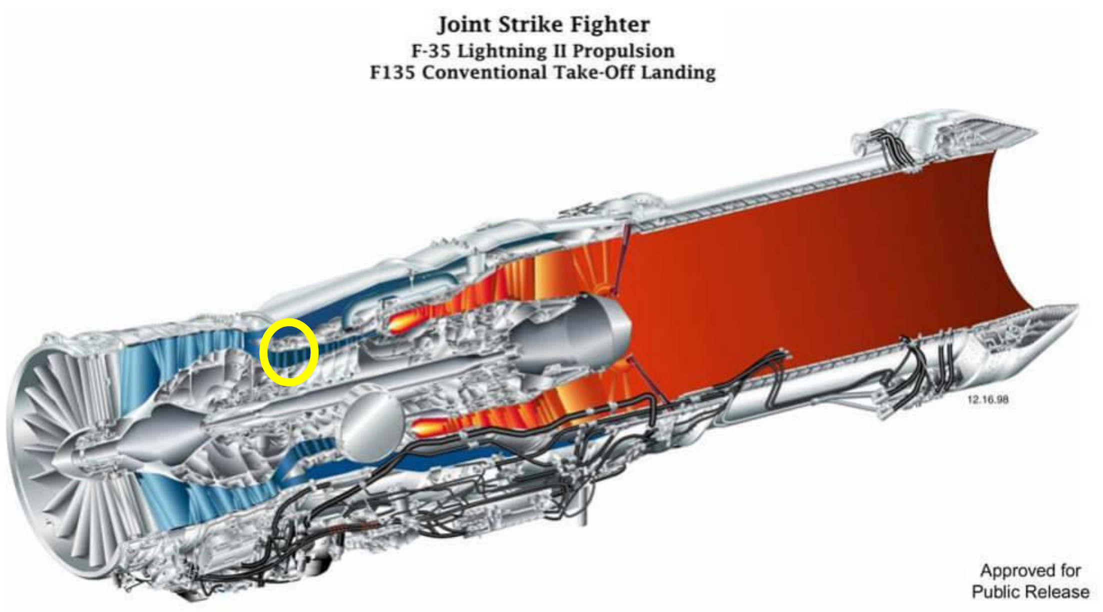
Introduction to the Digital Twin

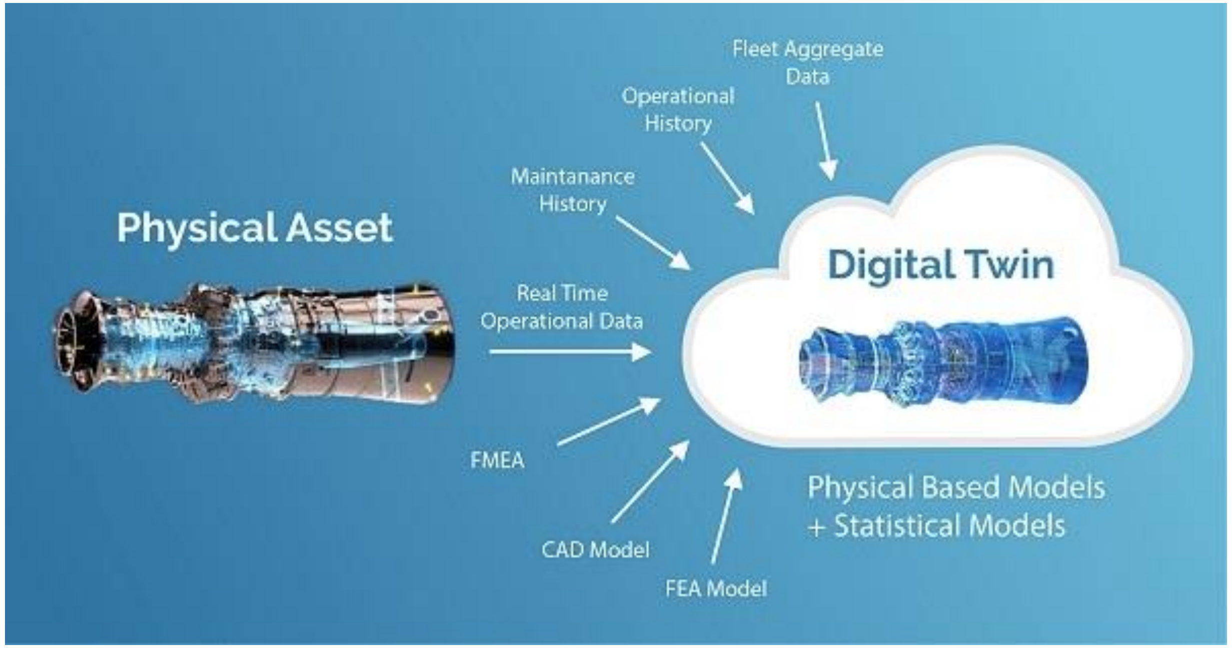


Introduction to the Digital Twin



Introduction to the Digital Twin





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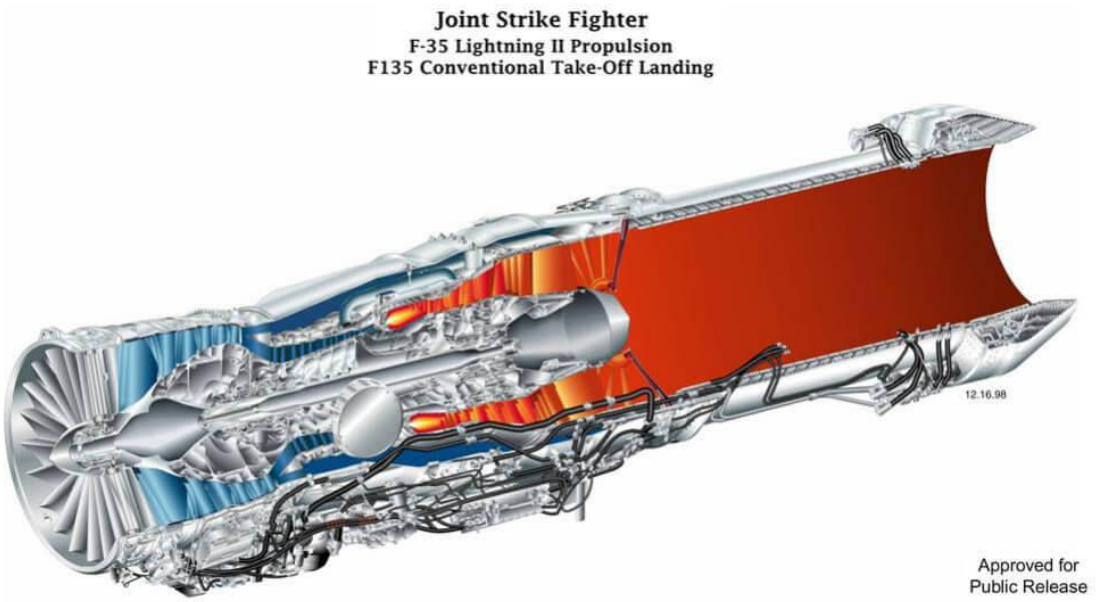
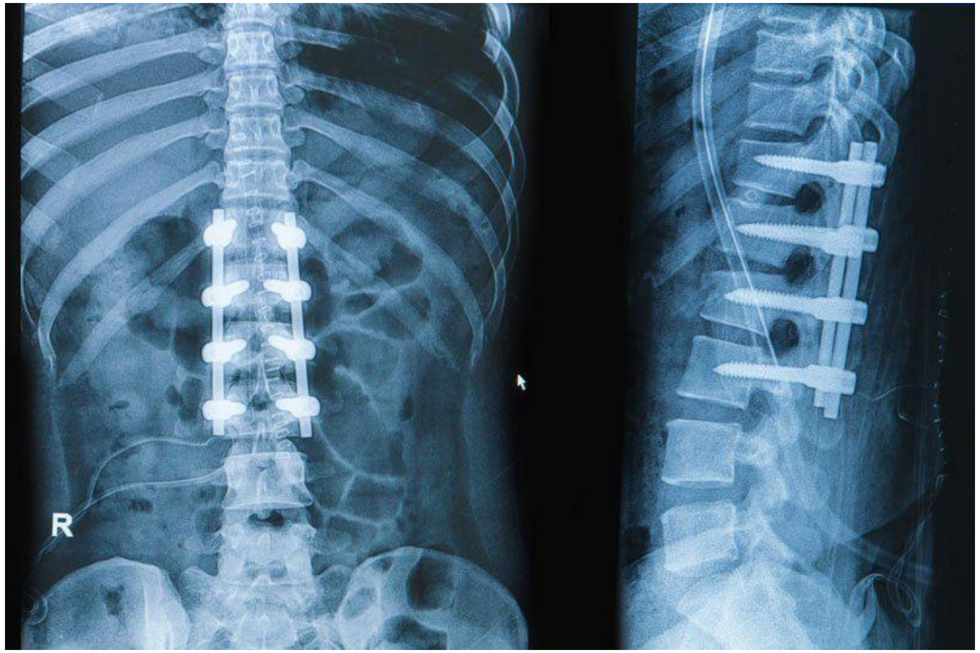
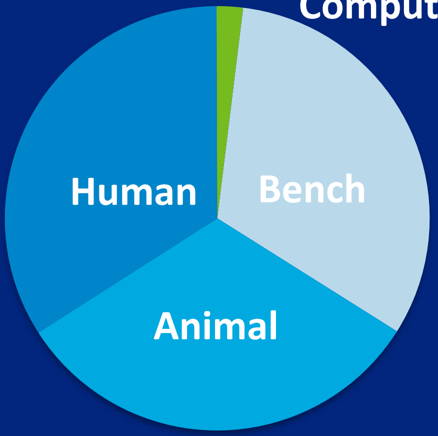




Regulatory Evidence

* Adapted from Bill Murray (CEO, MDIC), "21st Century Cores: Modernizing Clinical Trials, Testimony to Congress 7/2014

Current state



Phase 1

Credibility & Methods
Therapy feasibility & refinement
Reduce animal trial size

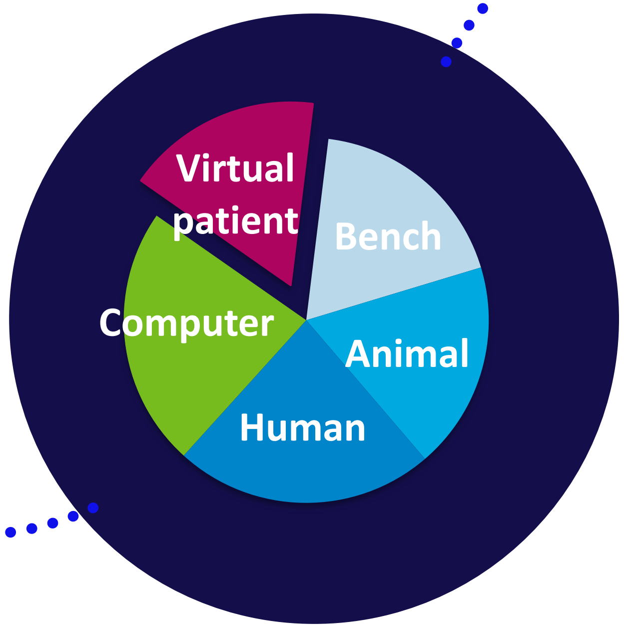
Phase 2

Infrastructure & excellence
Replace animal trials & optimize human clinical trials

Phase 3

Widescale impact
Improve clinical trial success rates

Future state



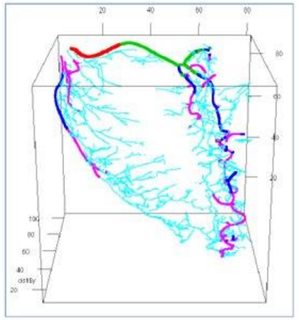
Obstacles
- Understanding clinical study complexity
- Asking the right questions

Modeling and Simulation to Generate Regulatory Evidence

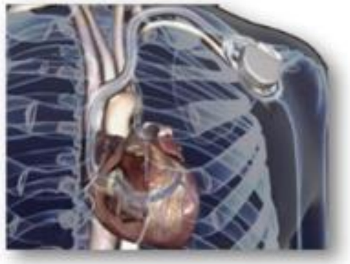
Reduce Clinical Endpoints

Augment Clinical Trials

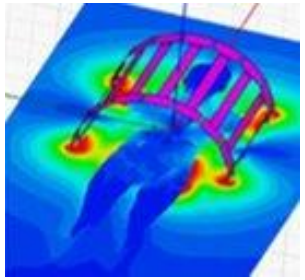
Avoid Clinical Trials



Leadless Pacemaker Fixation

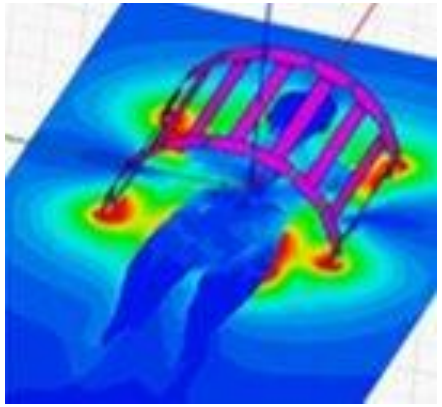


LEADER Study – Lead Fracture Model



MRI Safety Labeling

How are we impacting clinical studies



MRI modeling as Safety Evidence
Standard across most Regulatory Bodies

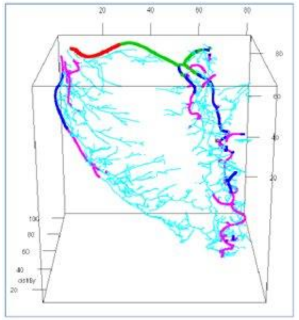
- Provide Evidence where Clinical studies are not practical
  - Very rare events
  - Underrepresented Populations
  - Too dangerous
  - Branching decision trees

Modeling and Simulation to Generate Regulatory Evidence

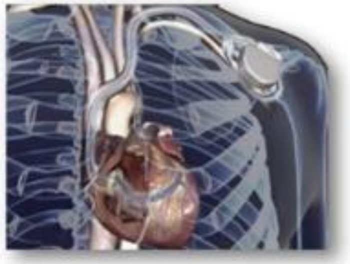
Reduce Clinical Endpoints

Augment Clinical Trials

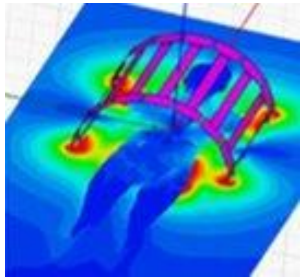
Avoid Clinical Trials



Leadless Pacemaker Fixation



LEADER Study – Lead Fracture Model

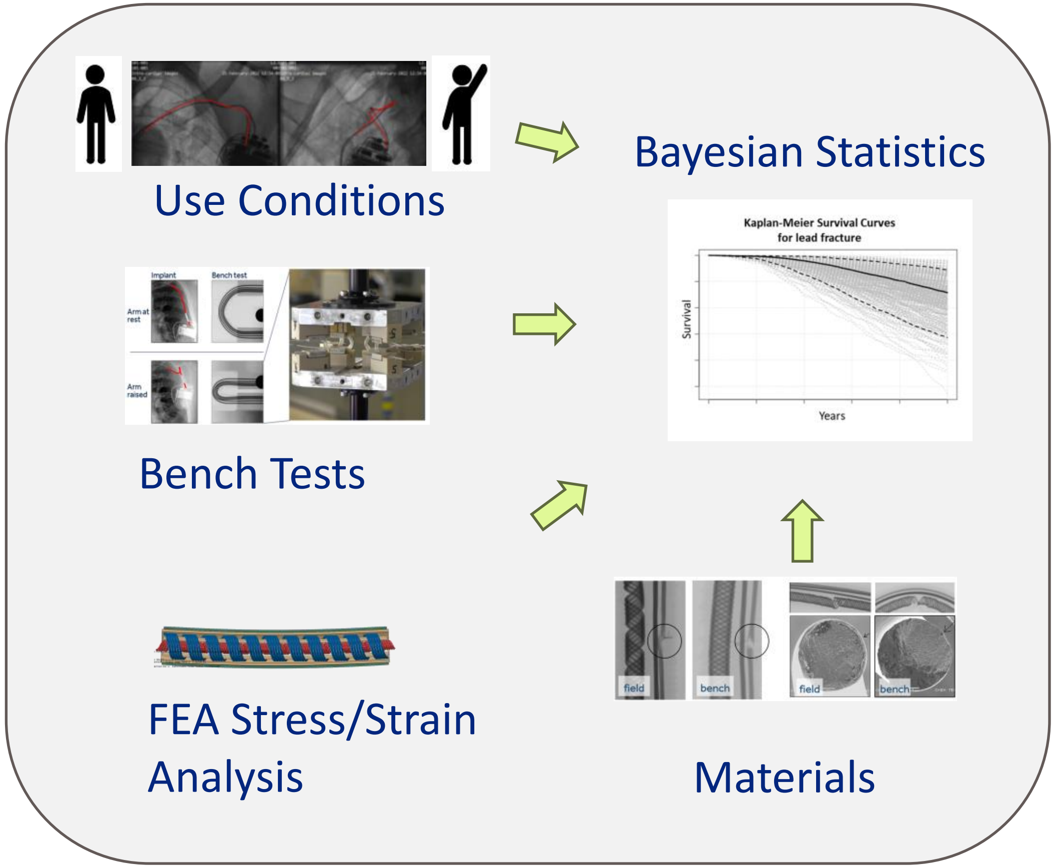


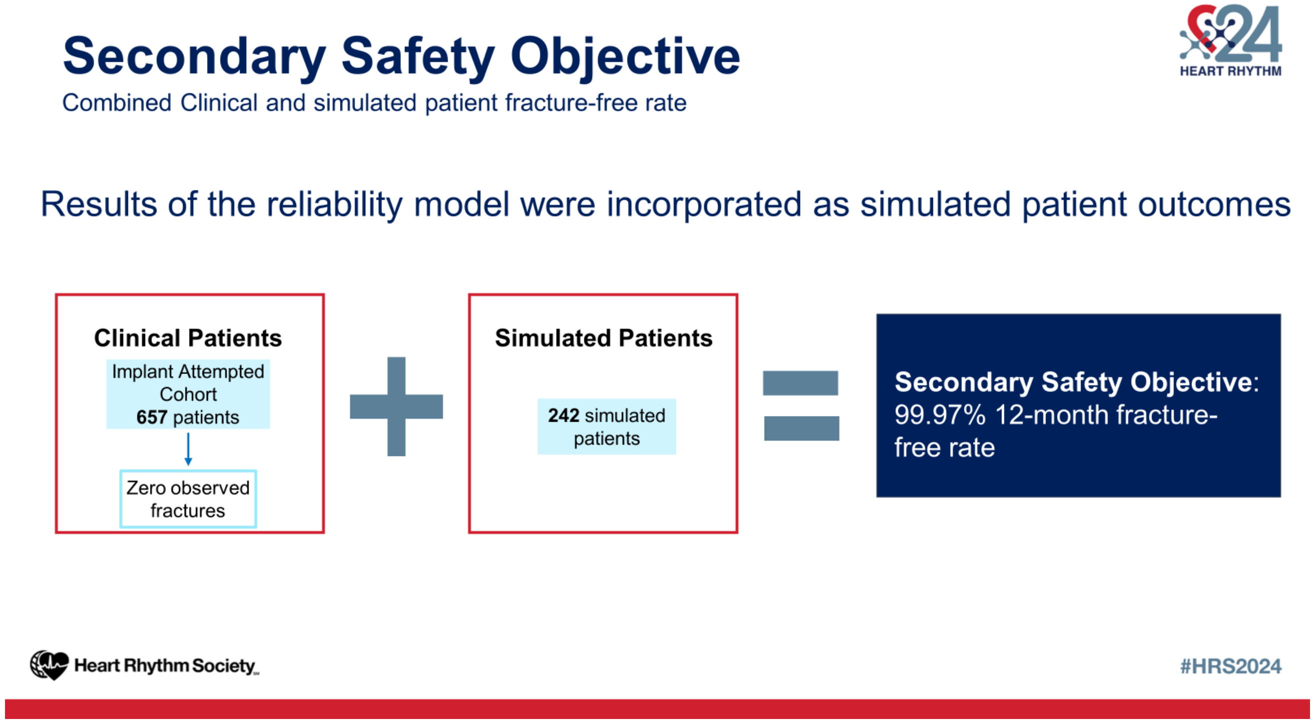
MRI Safety Labeling

Predictive Engineering Augments Clinical Findings

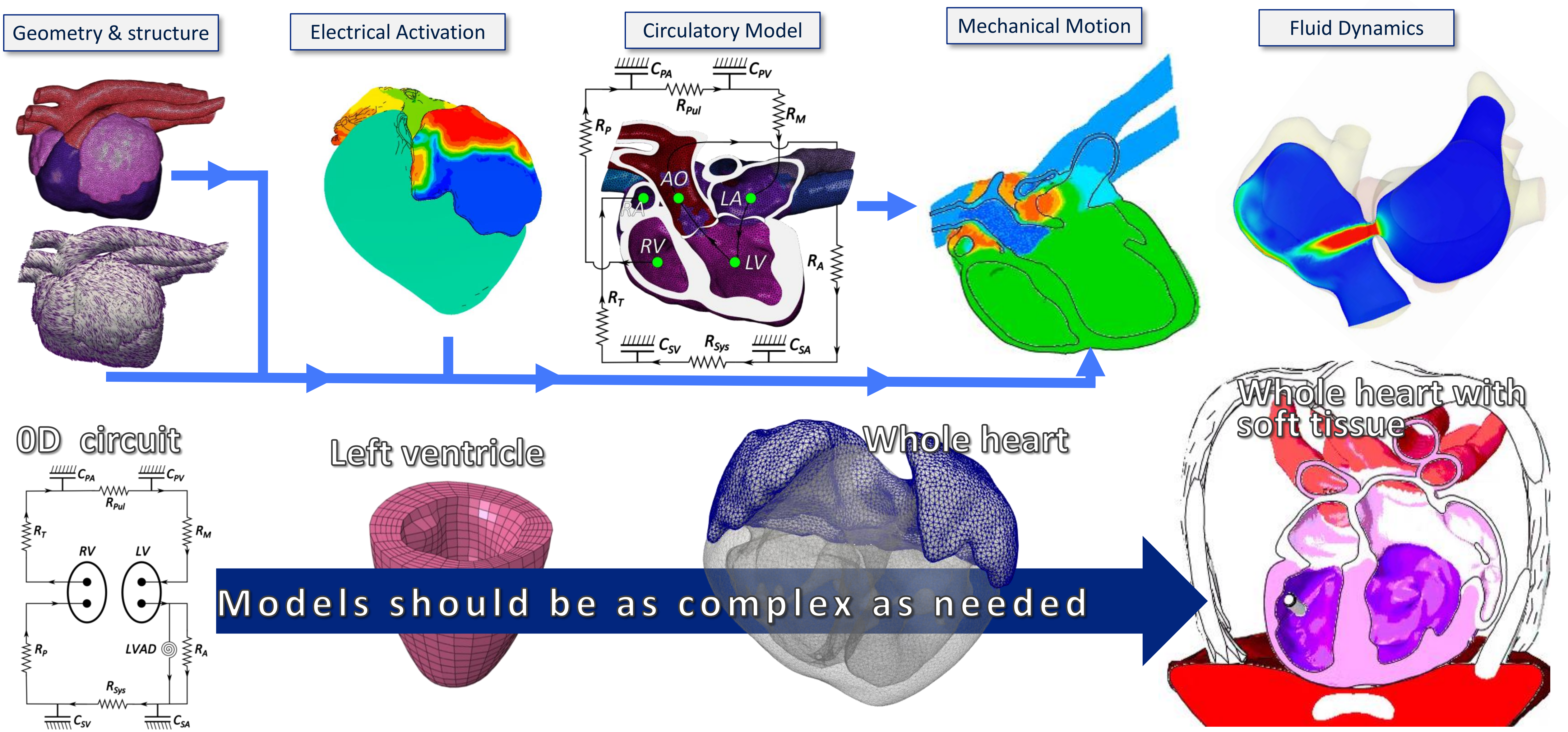
LEADER STUDY

Predictive Engineering Model of Lead Fracture

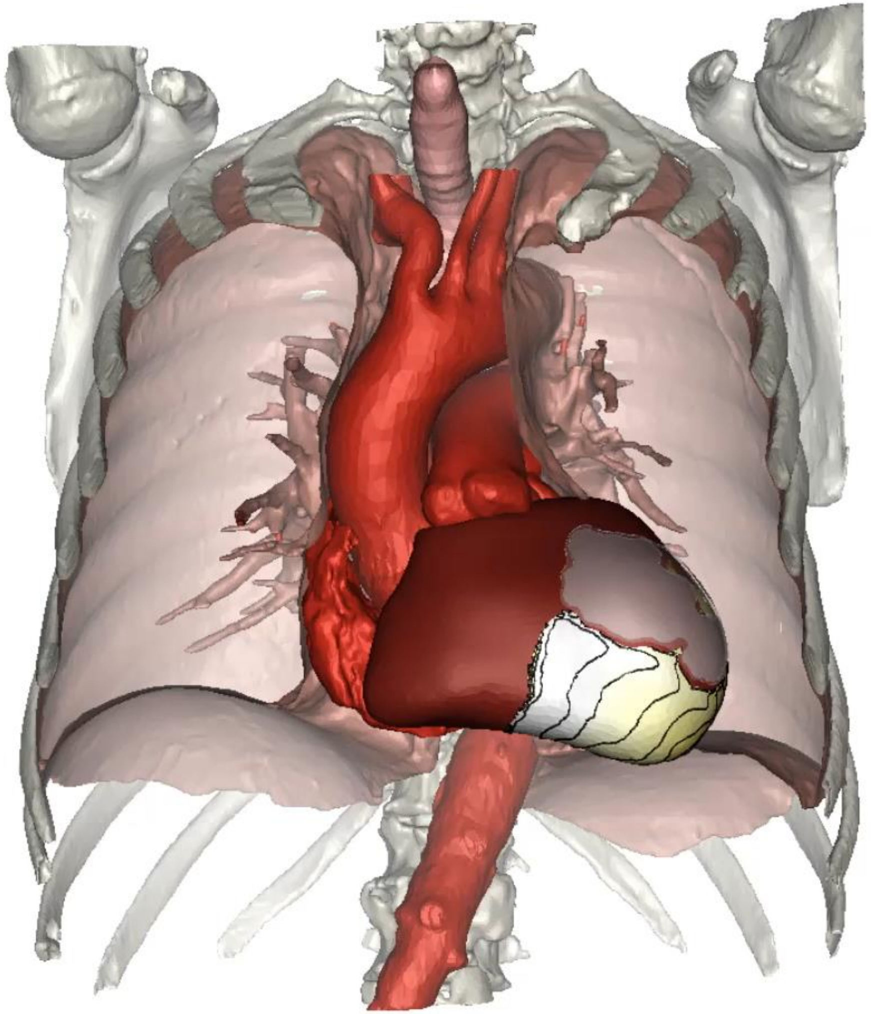




Human Heart as the "Digital Twin"

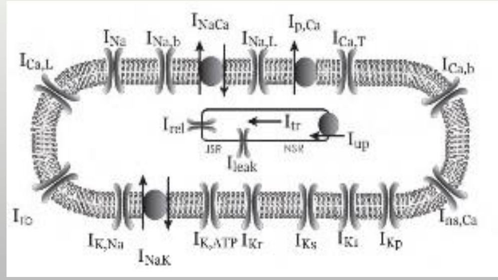


Multi-Scale Computational Electrophysiology

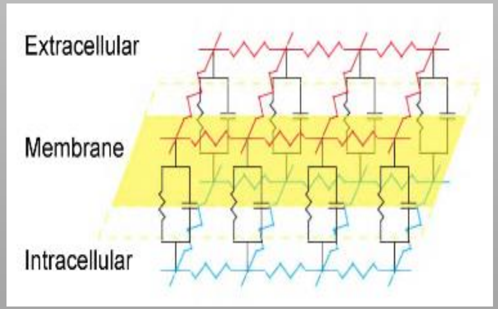


Reaction Diffusion Bidomain
Ten Tuscher Cell model

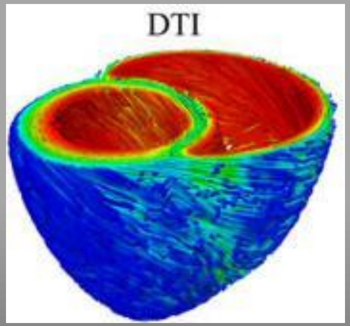
Cellular

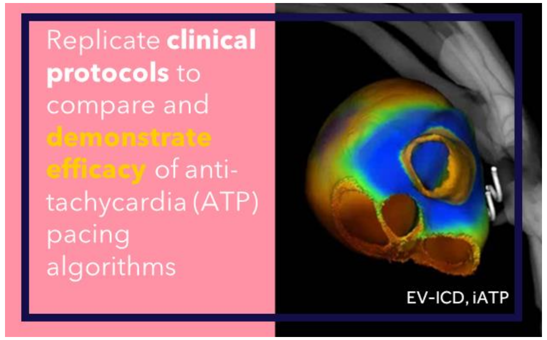


Tissue



Organ





Case Study 1: Investigation into intrinsic-ATP efficacy

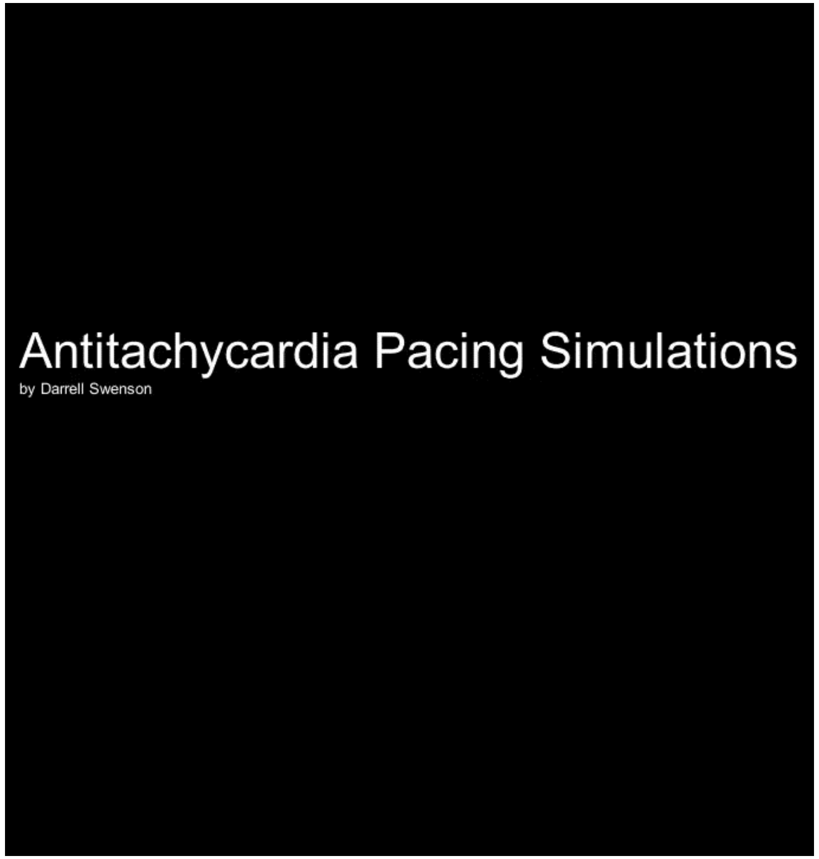
Problem:

Low ATP success rates.

Expense and difficulty in conducting clinical trials to compare ATP algorithms

Proposal:

Utilize **patient-derived models** to compare burst ATP and novel iATP algorithms under real-world scenarios, **and understanding why ATP fails**

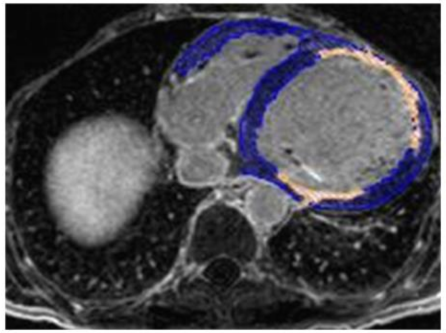


Swenson et al. "Direct comparison of a novel anti-tachycardia pacing algorithm against present methods using virtual patient modeling." Heart Rhythm 17, no 9 (2020): 1602-1608

Patient Derived Models

Clinical Data

LGE MRI



EP Data

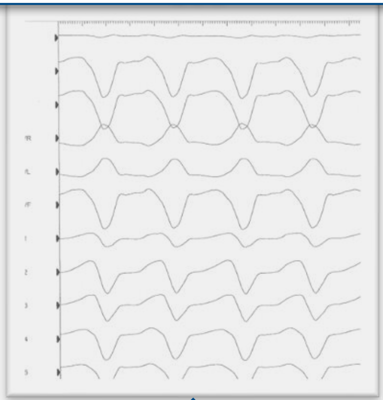
	ERP 1	ERP 2
Med 1	600/290	400/260
Med 2	500/270	350/240
Med 3	600/270	350/220
Med 4	600/260	400/230
Med 5	600/290	350/240
Med 6	600/300	300/240
Med 7	600/270	350/240
Med 8	600/290	350/250
Med 9	600/280	350/240
Med 10	600/280	NA
Med 11	600/280	350/240
Med 12	600/280	350/250

Induction Protocol

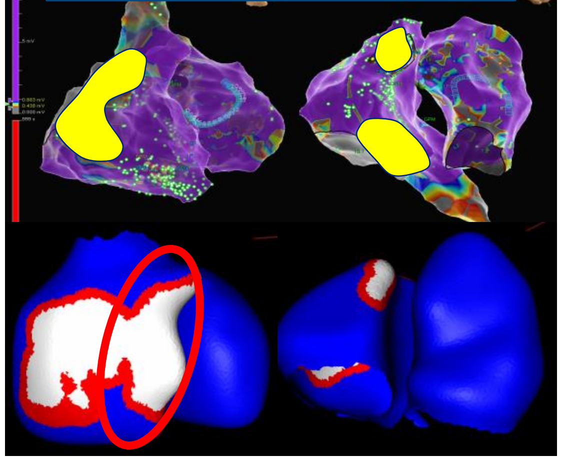
VT1	VT2
600/310/220/200	400/290/220
500/280/210	350/250/200
350/210/200/200	NA
600/250/250	400/240/210
NA	NA
NA	NA
NA	NA
600/320/240/210	350/280/220/200
600/290/220/200	350/280/200/200
600/300/230	NA
600/250/200/200	350/240/200/200
600/280/200/200	350/280/230

Physician Adjudication

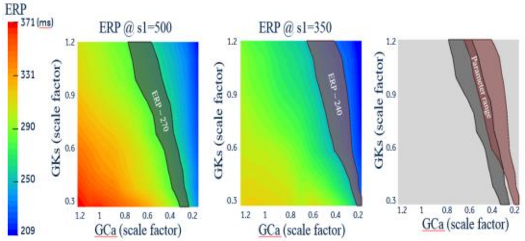
ECG



Scar Definition

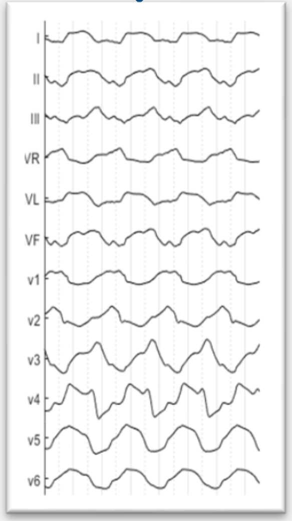


Machine Learning



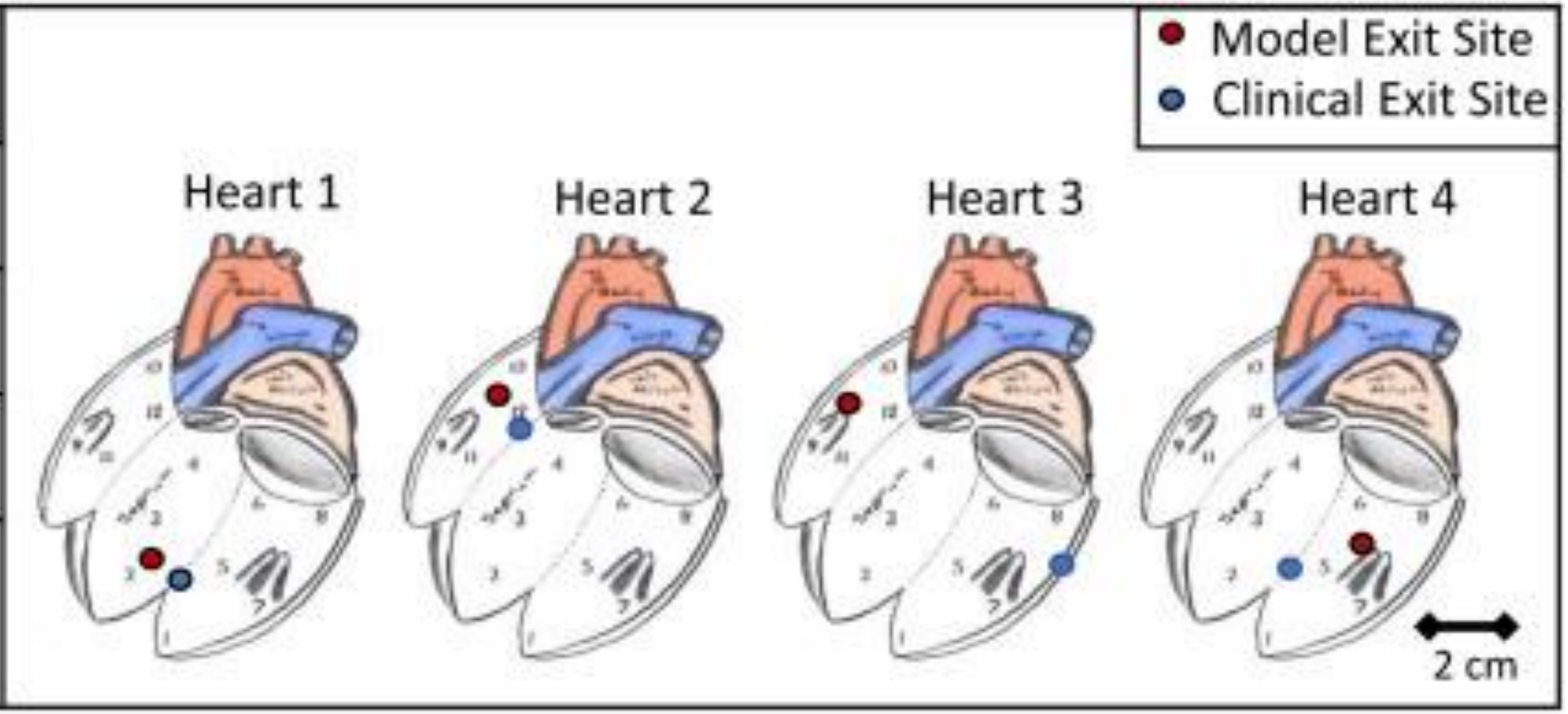
Cell Model Parameter Fitting

Induced VT



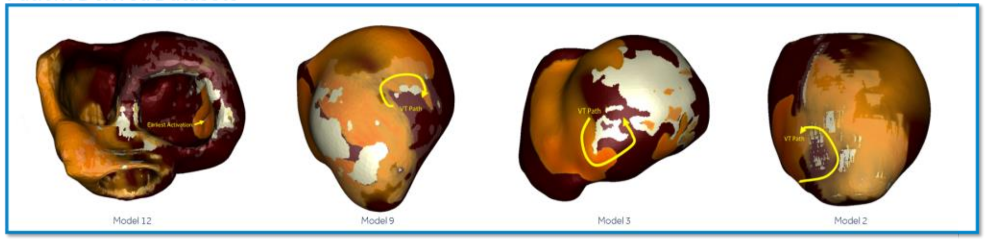
Adjudication

Heart	VTCL	Exit Site Match
Heart 1	345	< 2 cm
Heart 2	350	< 2 cm
Heart 3	370	< 2 cm
Heart 4	330	2-3 cm

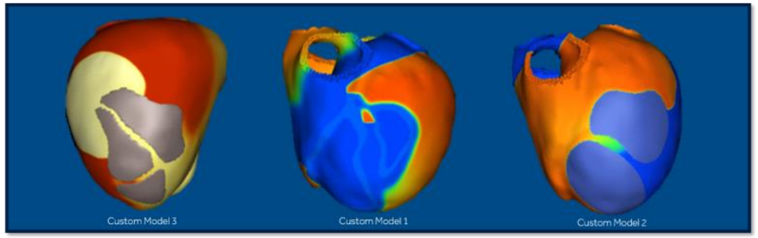


Virtual Human VT Modeling Cohort

Patient Derived Datasets

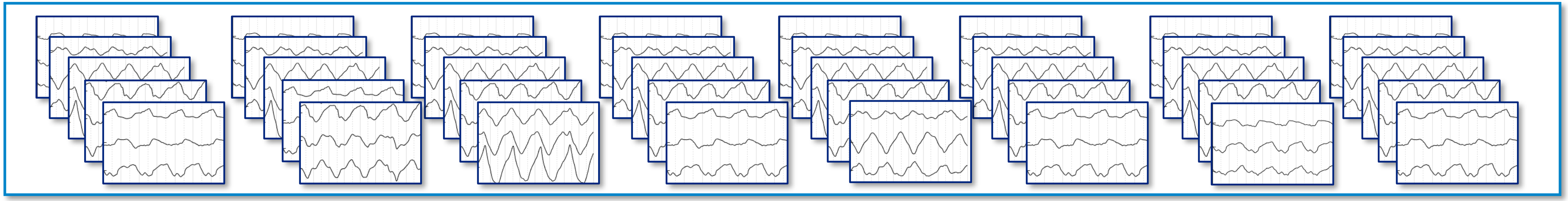


Custom Scar Datasets



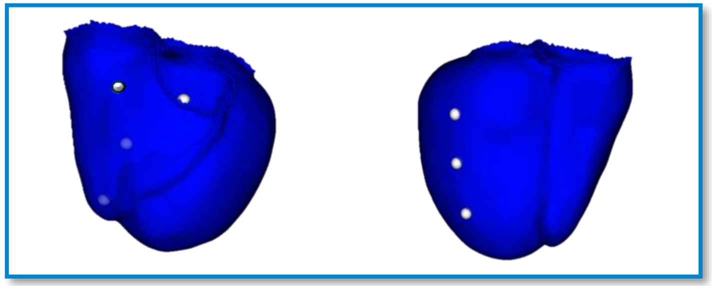
X **5** **EP STATES**

Measured in Clinic + Small changes to EP parameters
E.g. Ischemia, Medication, Dehydration, …



X **8-10** **PACING LOCATIONS**

Each location has a unique interaction with the VT



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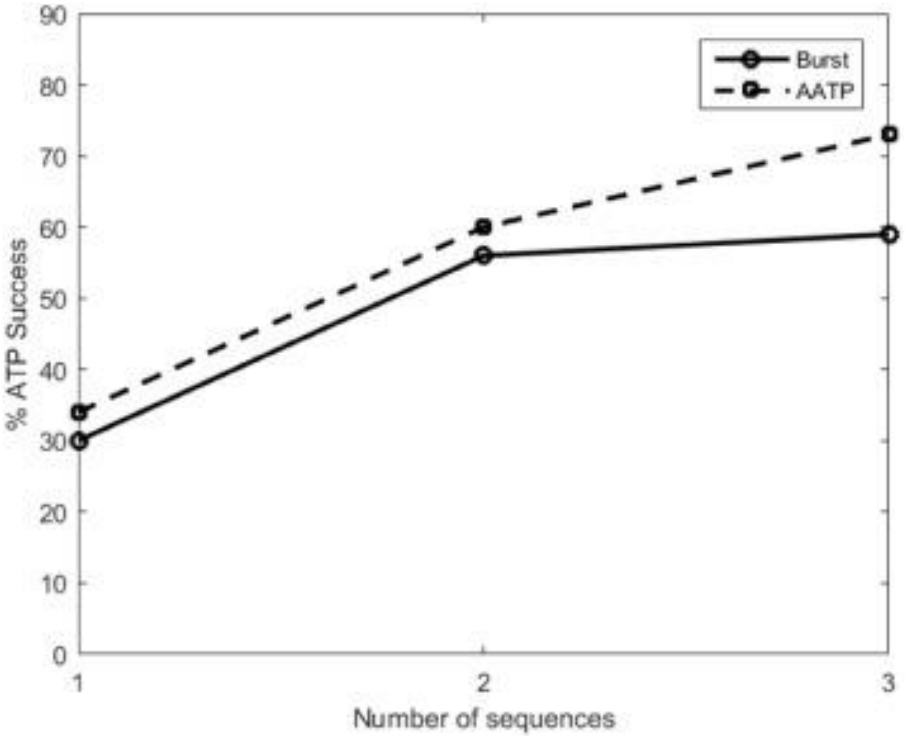
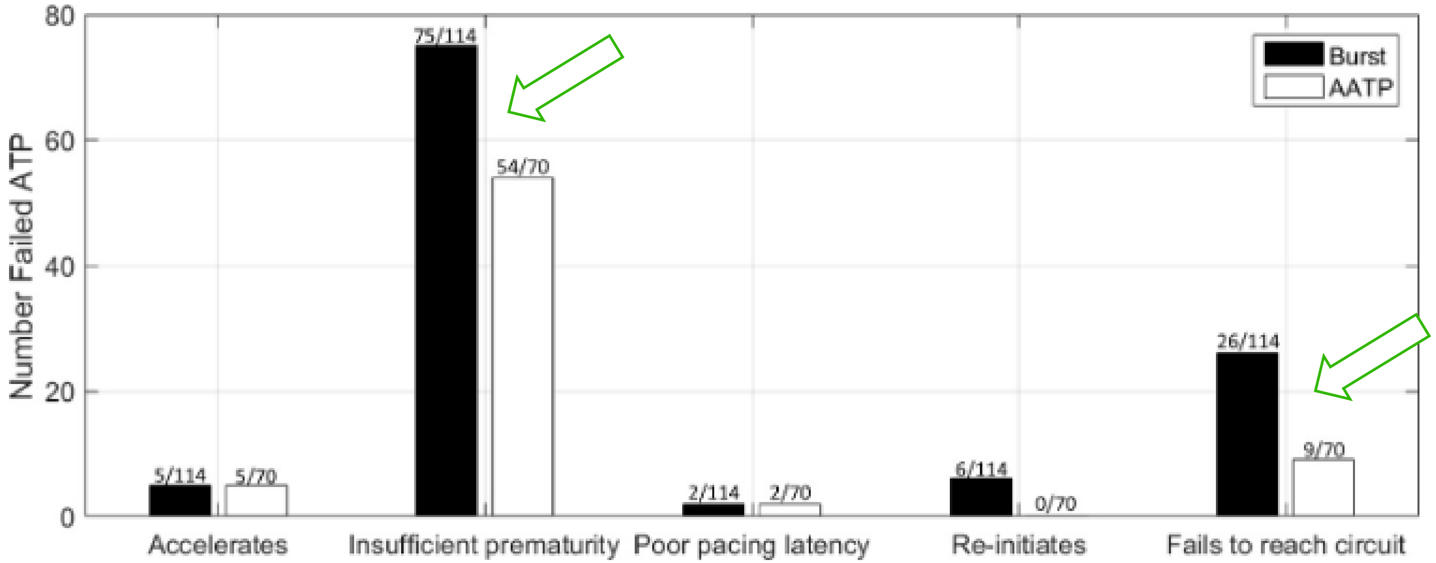
259 **VIRTUAL PATIENTS**

iATP efficacy is 17% greater than conventional ATP

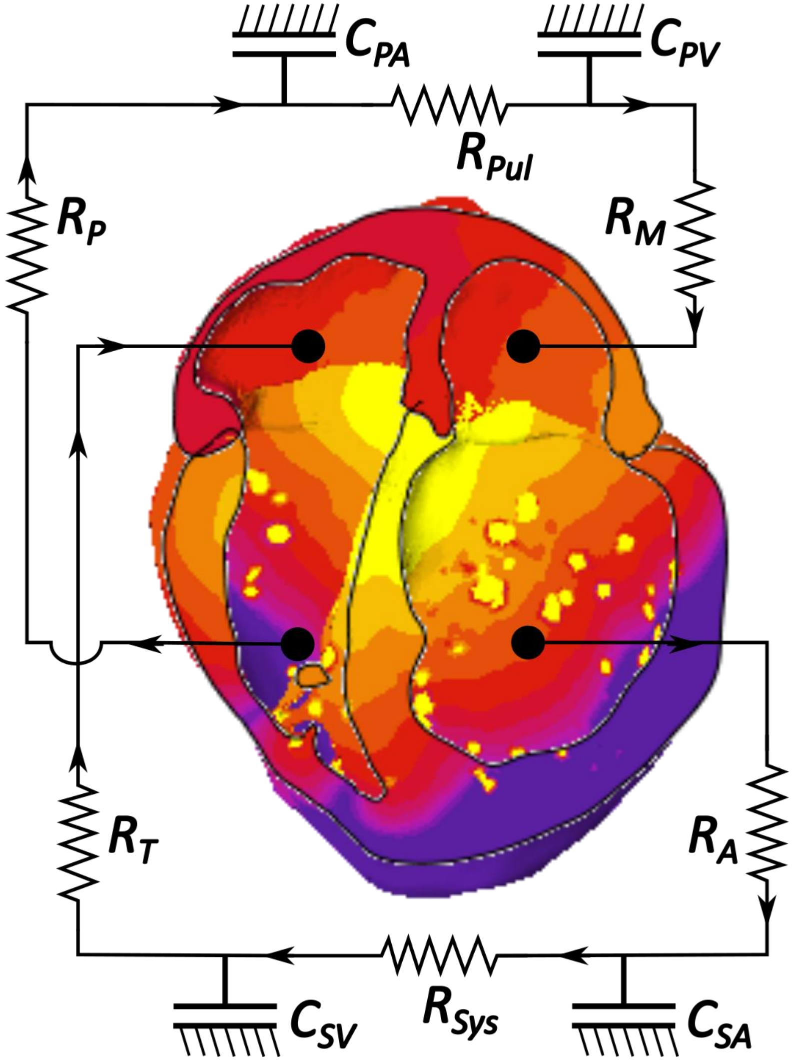
- iATP continues to learn



- iATP adapts to common mechanisms of failures without increase in accelerations



Case Study 2: Effects of high-rate pacing in HF-pEF patients



Problem:

Limited effective therapy for patients with HF-pEF

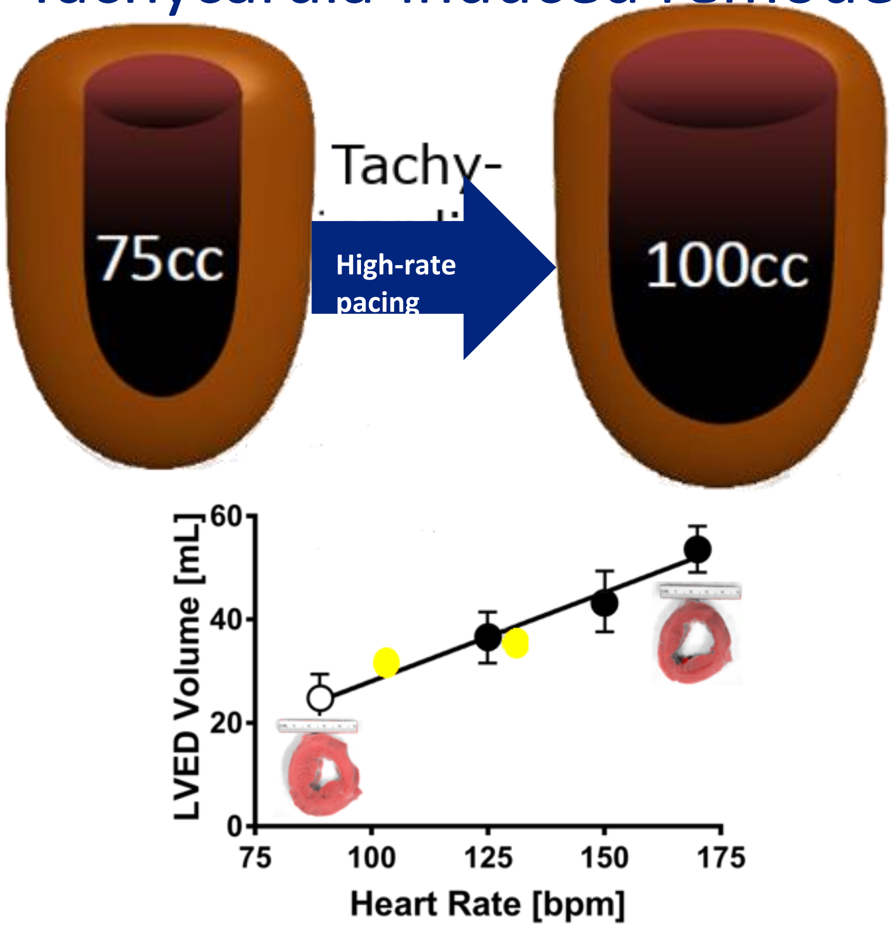
Necessity of designing a clinical trial to probe tachycardia remodeling as HF-pEF therapy

Proposal:

Utilize **whole-heart model** to investigate impact of **higher rate pacing** and help improve **safety and success of clinical study design**

Modeling New Therapies for HFpEF

- Tachycardia-induced remodeling

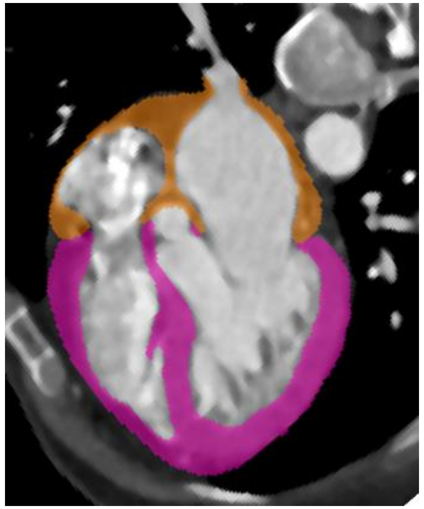


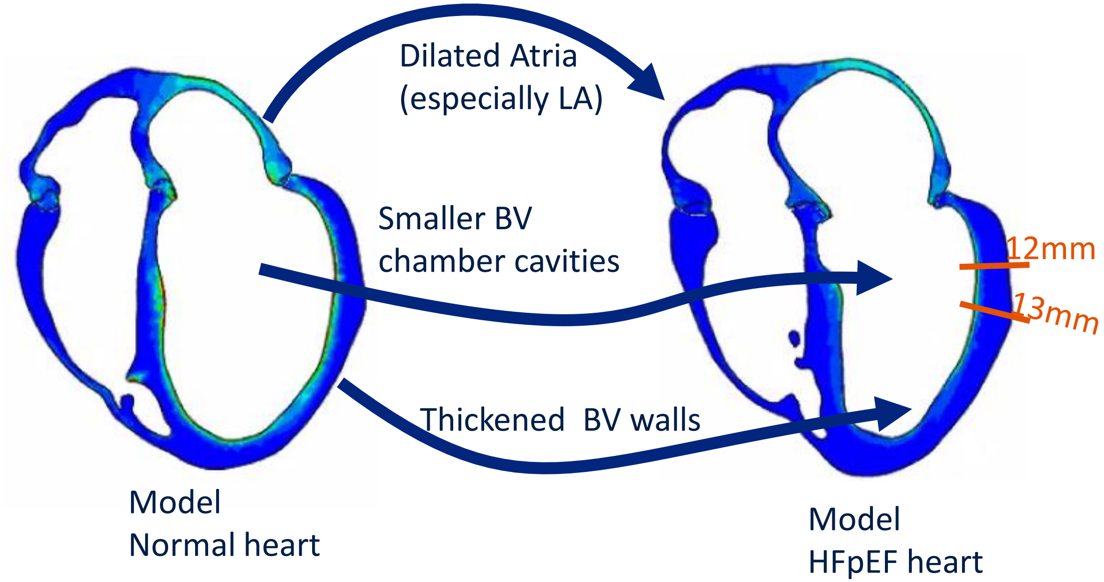
- This is a new concept that utilizes a standard pacemaker to elevate heart rates (100+ bpm) for sustained periods of time.

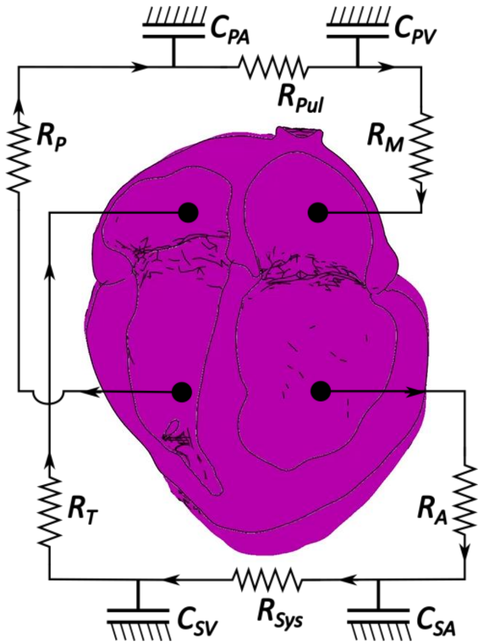
- After two small human studies, **key questions remained:**

1. **What pacing sites to use?**
2. **What is necessary for remodeling to occur?**
3. **what is a safe rate range?**
4. **should AV-intervals be set?**

Overview of the 4chamber HFpEF model







	Normal	HF25	HF50	HF75	HF100
Myocardial stiffness [1-4]	baseline	150%	200%	250%	300%
Peak tension capacity (kPa) [7]	baseline	80%	80%	80%	80%
Lusitropic capacity [1-3,5,6]	baseline	79%	53%	26%	0%
Contractility reserve [7,8]	baseline	75%	50%	25%	0%
LV EDP (mmHg) [2-4]	9.3	17.3	21.7	27.5	30.7
mLAP (mmHg) [4,12]	6	12	16	22	27
MAP (mmHg) [1,4,9,10]	93	93	96	99	103

[1] R. Wachter *et al.*, "Blunted frequency-dependent upregulation of cardiac output is related to impaired relaxation in diastolic heart failure," *Eur. Heart J.*, vol. 30, no. 24, pp. 3027–3036, 2009.

[2] M. Kawaguchi, I. Hay, B. Fetics, and D. A. Kass, "Combined ventricular systolic and arterial stiffening in patients with heart failure and preserved ejection fraction: Implications for systolic and diastolic reserve limitations," *Circulation*, vol. 107, no. 5, pp. 714–720, 2003.

[3] D. Westermann *et al.*, "Role of left ventricular stiffness in heart failure with normal ejection fraction," *Circulation*, vol. 117, no. 16, pp. 2051–2060, 2008.

[4] M. R. Zile *et al.*, "Myocardial stiffness in patients with heart failure and a preserved ejection fraction contributions of collagen and titin," *Circulation*, vol. 131, no. 14, pp. 1247–1259, 2015.

[5] M. R. Zile, C. F. Baicu, and W. H. Gaasch, "Diastolic Heart Failure - Abnormalities in Active Relaxation and Passive Stiffness of the Left Ventricle," *N. Engl. J. Med.*, vol. 350, no. 19, pp. 1953-1959+2018, May 2004.

[6] K. E. Runte *et al.*, "Relaxation and the Role of Calcium in Isolated Contracting Myocardium from Patients with Hypertensive Heart Disease and Heart Failure with Preserved Ejection Fraction," *Circ. Hear. Fail.*, vol. 10, no. 8, pp. 1–15, 2017.

[7] B. A. Borlaug, C. S. P. Lam, V. L. Roger, R. J. Rodeheffer, and M. M. Redfield, "Contractility and Ventricular Systolic Stiffening in Hypertensive Heart Disease. Insights Into the Pathogenesis of Heart Failure With Preserved Ejection Fraction," *J. Am. Coll. Cardiol.*, vol. 54, no. 5, pp. 410–418, 2009.

[8] B. A. Borlaug *et al.*, "Global cardiovascular reserve dysfunction in heart failure with preserved ejection fraction," *J. Am. Coll. Cardiol.*, vol. 56, no. 11, pp. 845–854, 2010.

[9] A. M. Shah *et al.*, "Cardiac structure and function and prognosis in heart failure with preserved ejection fraction," *Circ. Hear. Fail.*, vol. 7, no. 5, pp. 740–751, 2014.

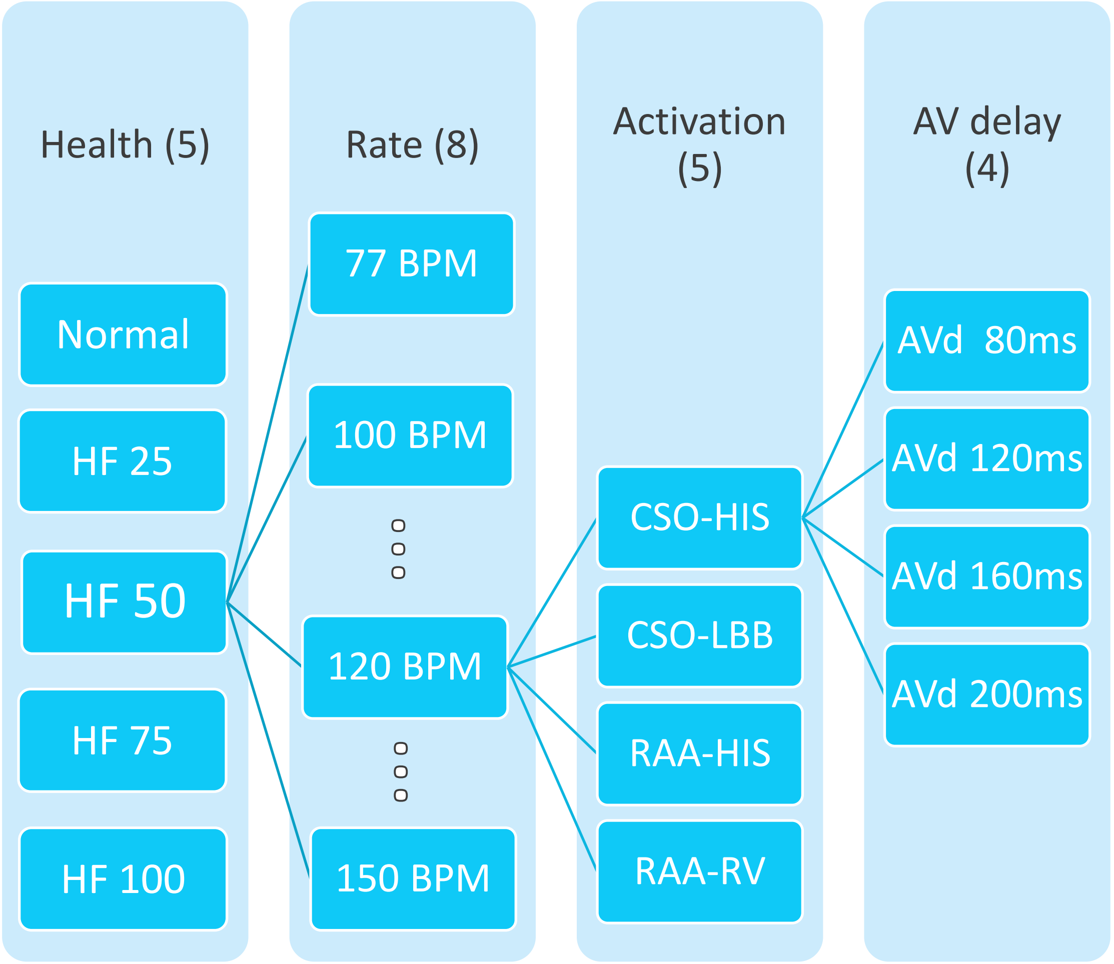
[10] M. R. Zile *et al.*, "Prevalence and significance of alterations in cardiac structure and function in patients with heart failure and a preserved ejection fraction," *Circulation*, vol. 124, no. 23, pp. 2491–2501, 2011.

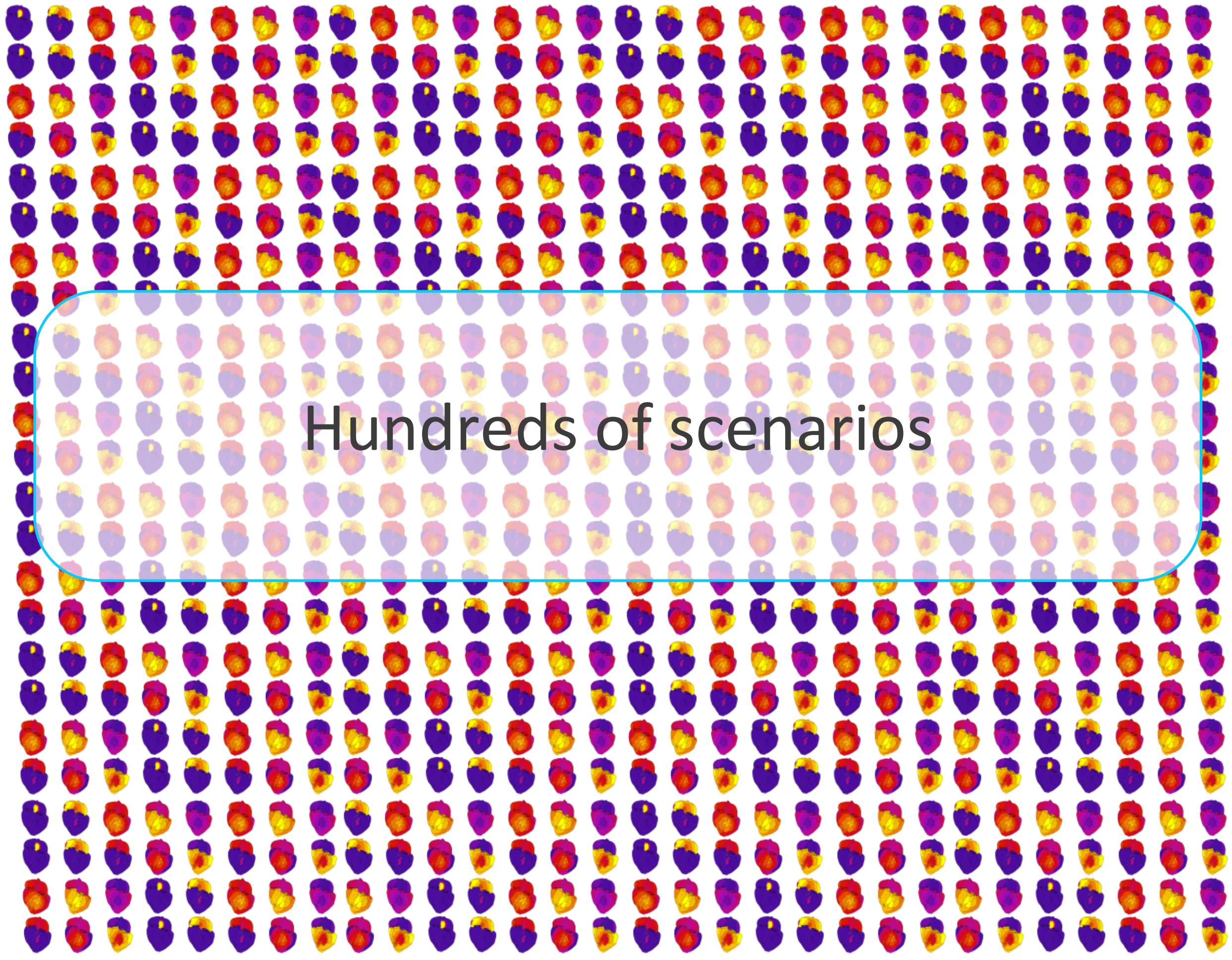
[11] A. M. Shah *et al.*, "Prognostic importance of impaired systolic function in heart failure with preserved ejection fraction and the impact of spironolactone," *Circulation*, vol. 132, no. 5, pp. 402–414, 2015.

[12] E. Wolsk *et al.*, "Central and Peripheral Determinants of Exercise Capacity in Heart Failure Patients With Preserved Ejection Fraction," *JACC Hear. Fail.*, vol. 7, no. 4, pp. 321–332, 2019.

FINITE ELEMENT MODELING – STUDY DESIGN

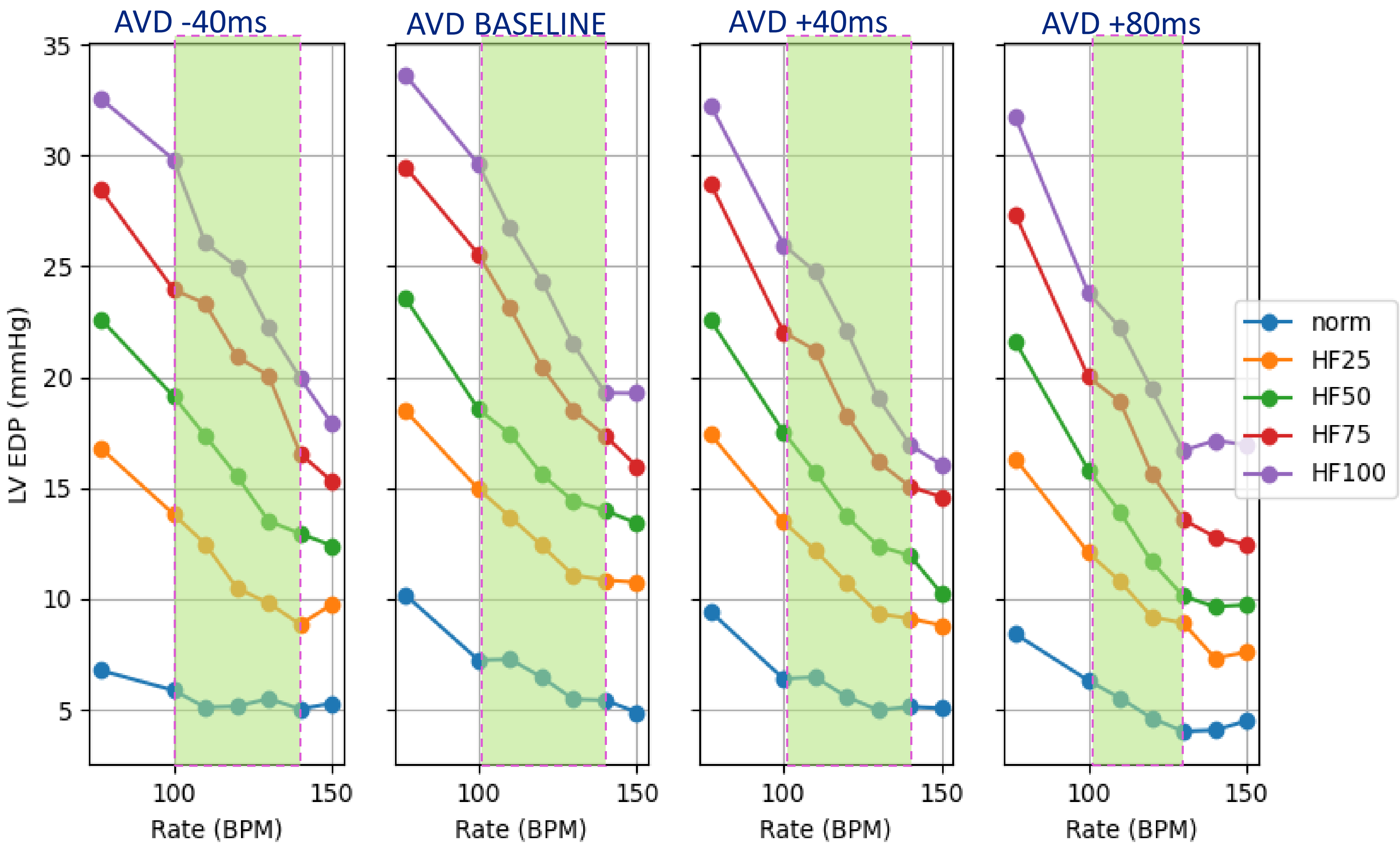
EFFICIENT AND MECHANICALLY MEANINGFUL





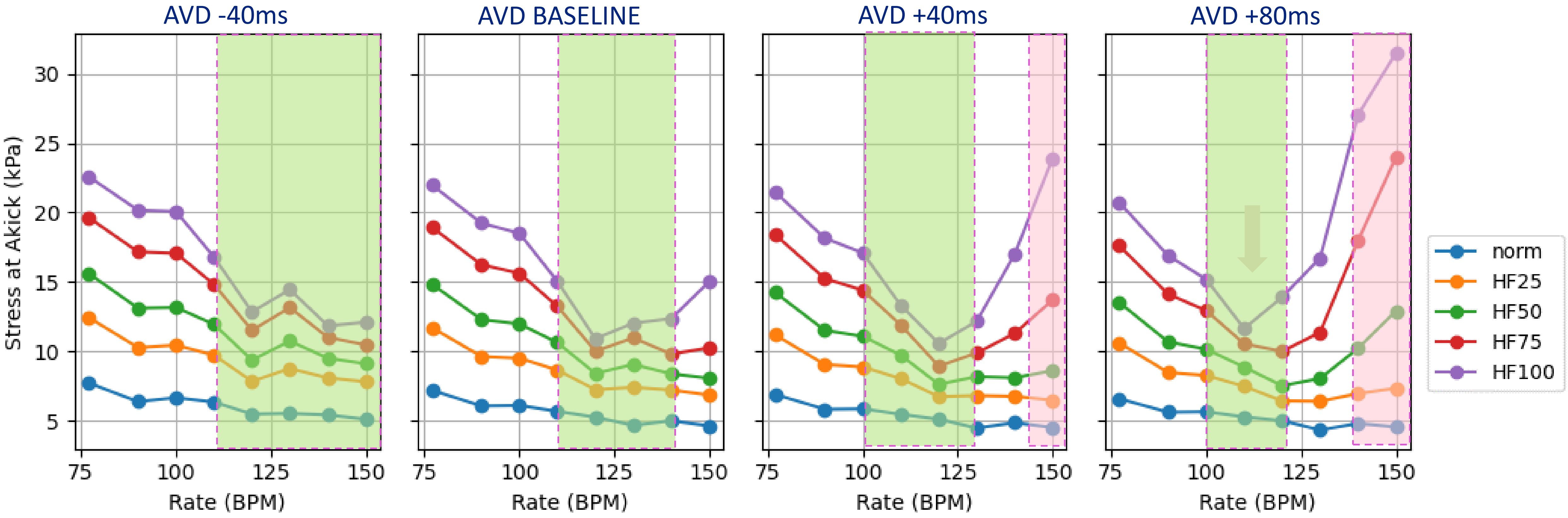
Potential Efficacy: LV EDP reduces with rate, could drive favorable remodeling

IMPROVEMENTS AT ALMOST EVERY RATE AND AVD



Modeling allows new insights: Left atrial stress even more effected by AVD

LONG AV DELAYS INTRODUCE ADVERSE STRESS EARLIER

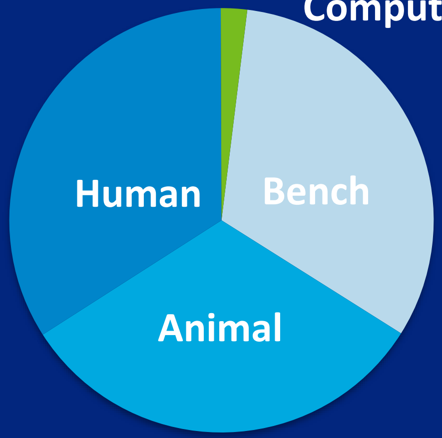


- Increased wall stress means increased tissue damage, working against therapy
- This was also observed in the hypertrophic ventricular endocardium when non-CSP pacing sites were simulated

Regulatory Evidence

* Adapted from Bill Murray (CEO, MDIC), “21st Century Cores: Modernizing Clinical Trials, Testimony to Congress 7/2014

Current state



Credibility & Methods
Therapy feasibility & refinement
Reduce animal trial size

Phase 1

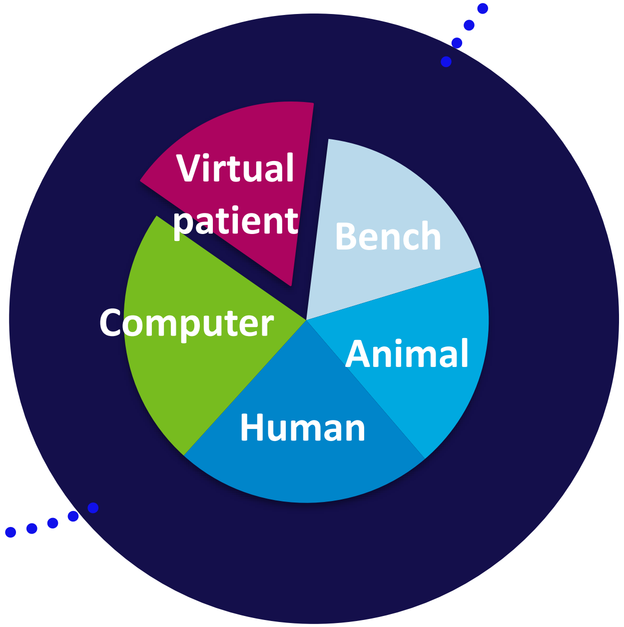
Phase 2

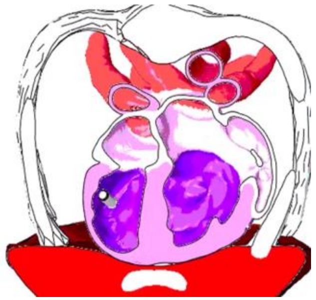
Infrastructure & excellence
Replace animal trials & optimize human clinical trials

Widescale impact
Improve clinical trial success rates

Phase 3

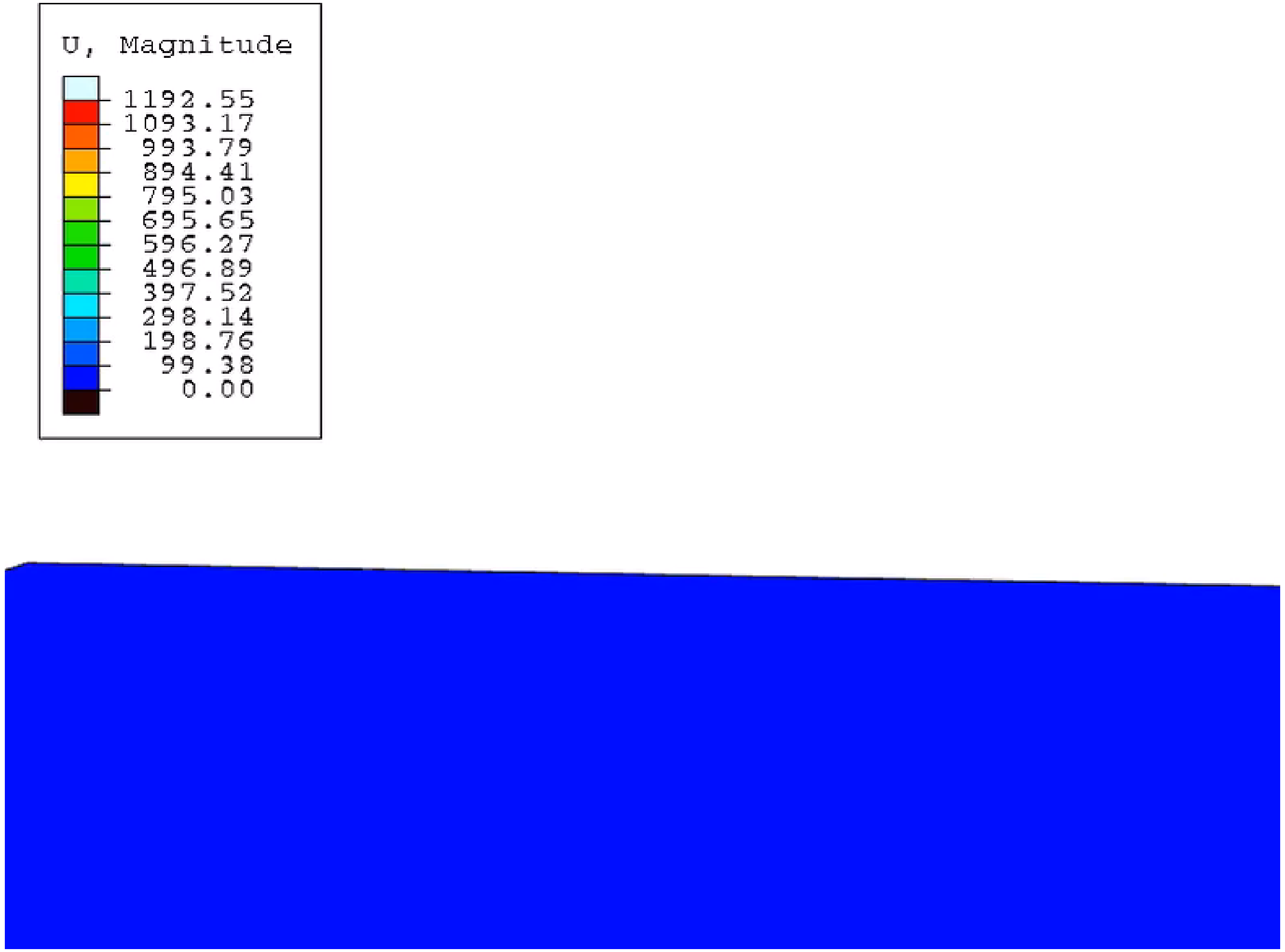
Future state





Opportunity
- Sustentative Progress… in the right way
- Continue to partner to ask the right questions

Thanks!


U, Magnitude
1192.55
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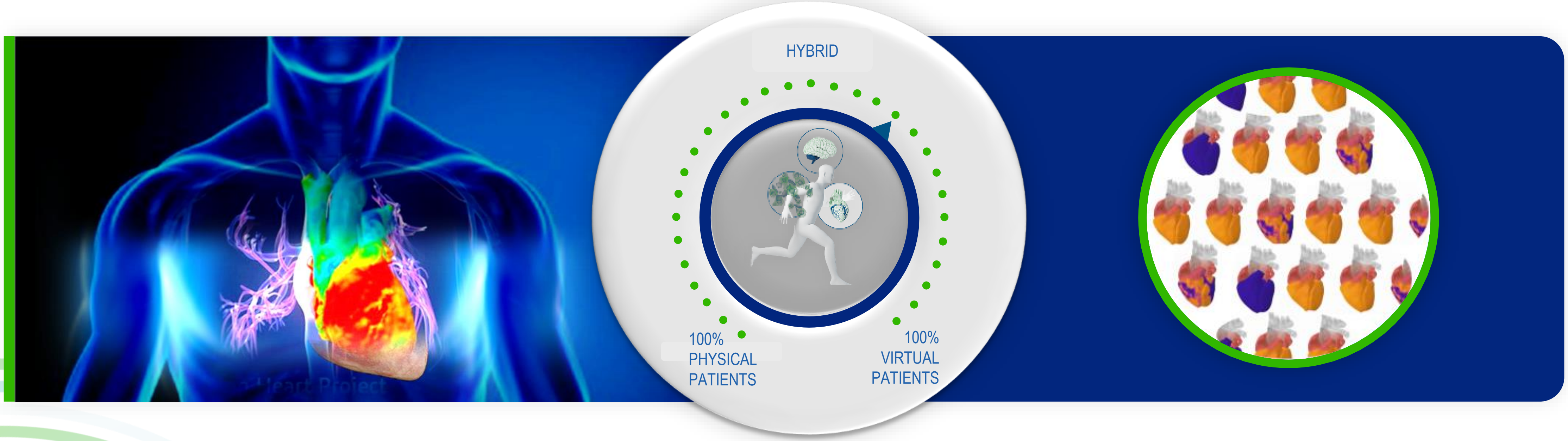
SCDM Live

Sept. 29 – Oct. 2, 2024 | Boston, MA

Transforming FDA Approaches: The Role of In-silico Data, Multiscale Modeling, and Generative AI in Medical Device Product Development

In Silico Clinical Trial Data in Regulatory Decisions



Steve Kreuzer, Ph.D., P.E.
Senior Managing Engineer
Exponent Inc.

It takes too long…

"The way we do business today, how we go about designing, testing, developing, evaluating manufacturing, distributing, and ultimately thereafter accessing technology is not really fit for purpose*.

It's kind of is out of date. It's time to change."

"It's time to change the world."

Dr. Jeff Shuren | FDA Director | Center for Devices and Radiological Health
ENRICHMENT Project Kickoff – Feb 2020

*Less than ½ new Class I Medical Devices every make it to market—Patients suffer & cost gets passed onto those that do.

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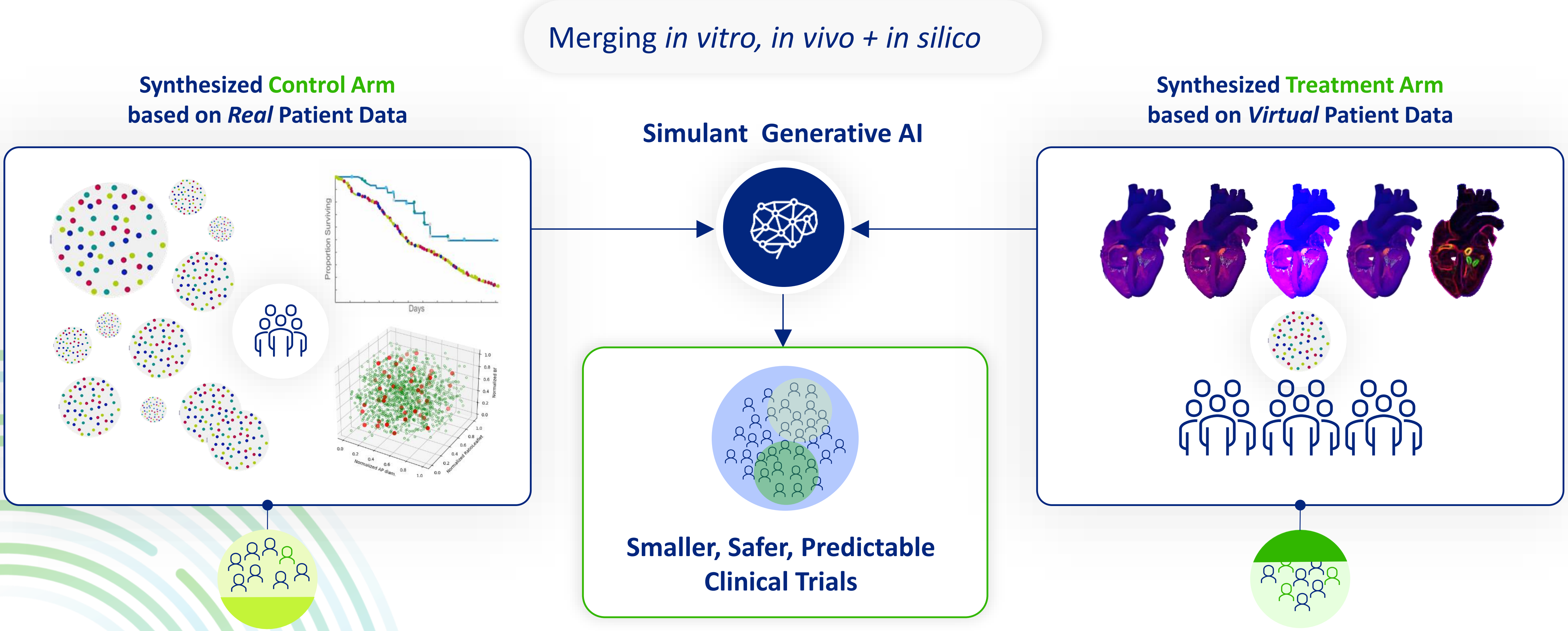
Virtual Patients: A New Era of Digital Evidence



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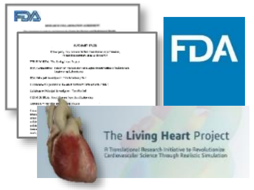
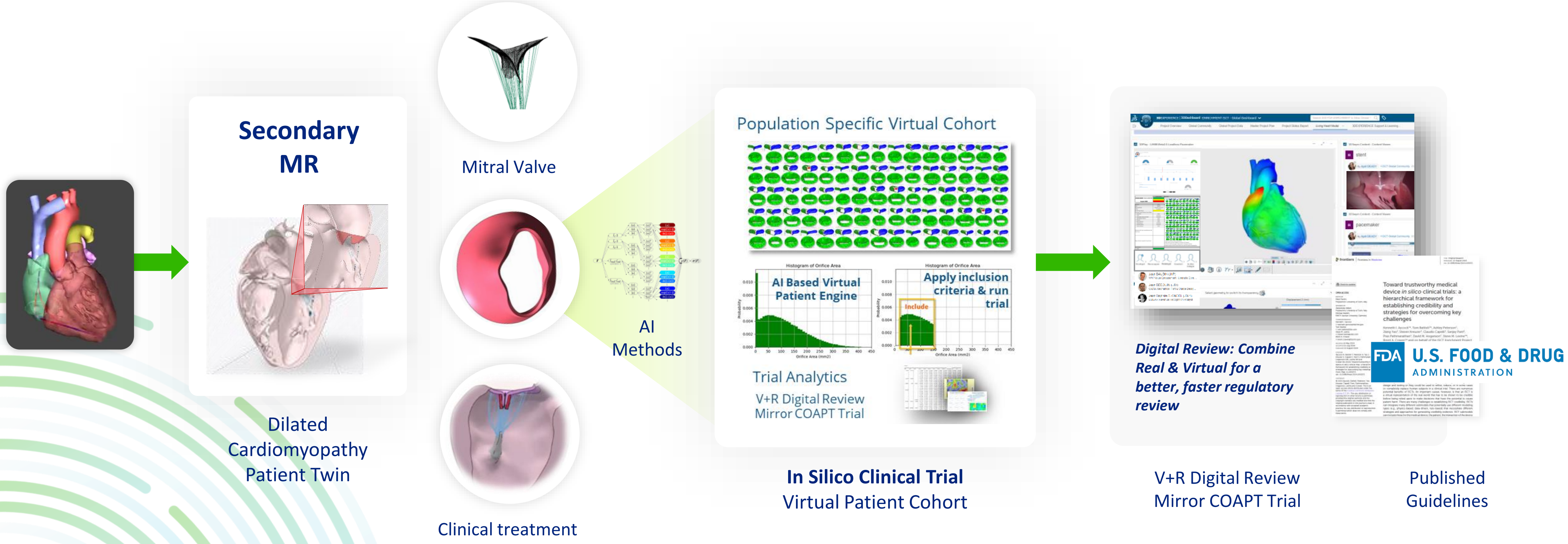
The Living Heart Project

Virtual Twin of a Human Heart

ENRICHMENT *in silico* Clinical Trial
with Living Heart as a Virtual Patient Population



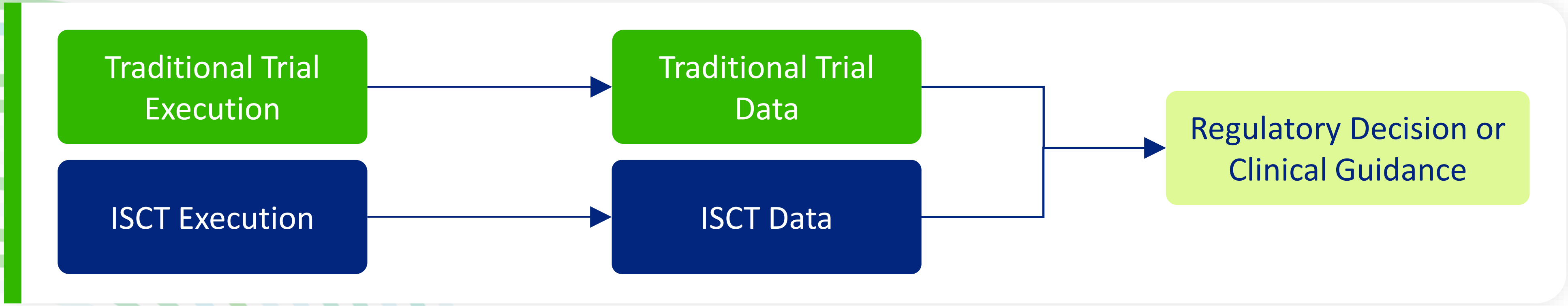


Use of ISCT Data in Clinical Trial Decision Making

Enrichment via Prospective Trial Design & Execution

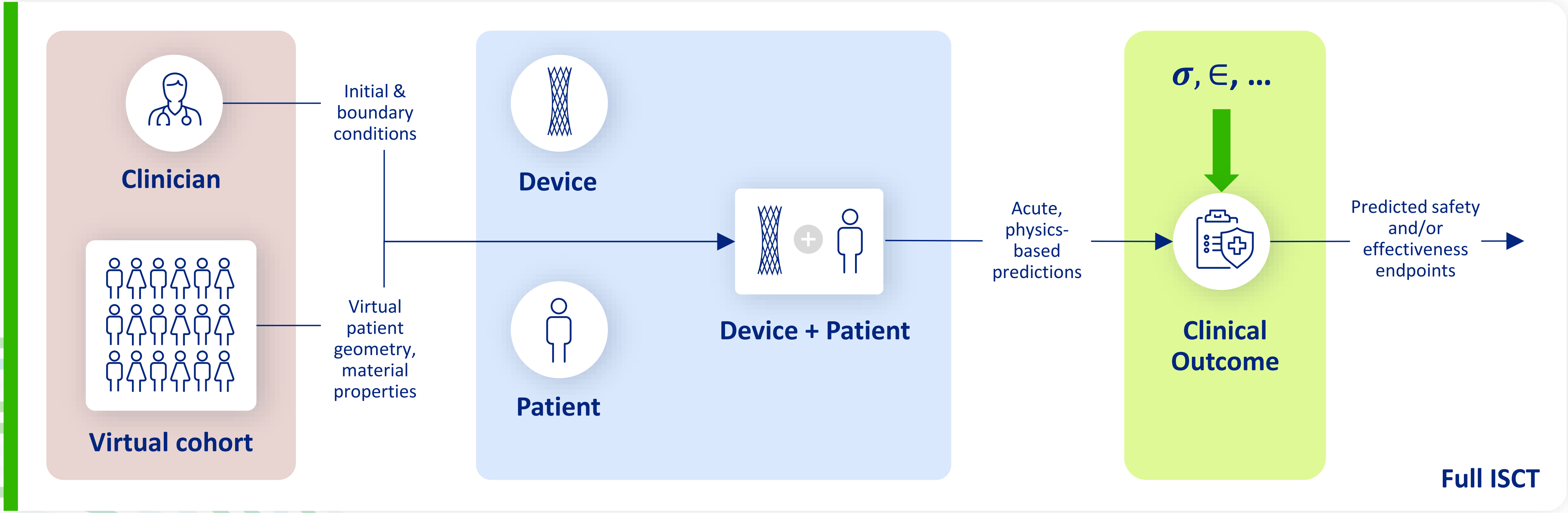
- Lower Risk
- Better Outcomes
- Faster Decisions

Enrichment via Data Incorporation



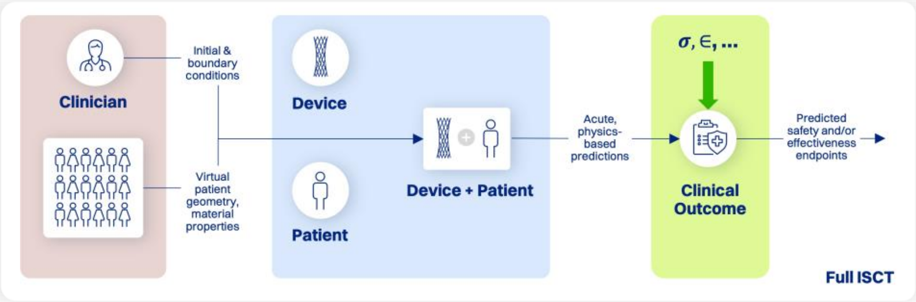
- Smaller Cohorts
- Lower Costs
- Broader Diversity

In Silico Clinical Trials



Clinical experience + data → target population
Computer model of new medical treatment
Clinical outcome predictions

In Silico Clinical Trials – Data Types



Statistics of Patient Populations

- Anatomy
- Tissue Characteristics
- Systemic Physiology
- Activity Levels

Device + Individual Patients

- Anatomy
- Tissue Characteristics
- Systemic Physiology
- Activity Levels
- Device Interaction

Clinical Outcome

- Traditional clinical endpoints
- Measurable digital health
- Inferred / non-measurable

Data required for ISCT

Data used for trial analysis

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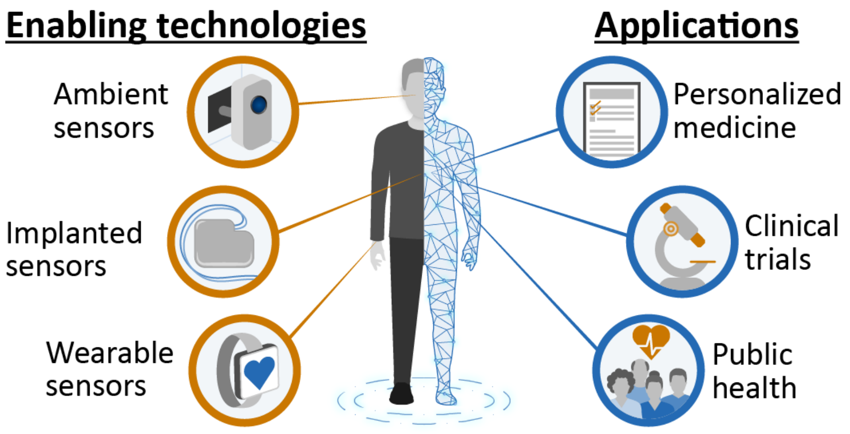
Needed: Improved Diagnostic & Interventional Data

More complete procedural data to calibrate ISCTs	CT, echo, robotic procedure data, etc.	
Higher fidelity understanding of procedure success	Useful for high fidelity predictions of interventions.	
Pharma & biotech applications (absence of a device)	**Clinical Delivery** Infusion rates, physiological data, etc.	**Patient Delivered** Compliance rates, longitudinal physiological data, including at times of injections, etc.

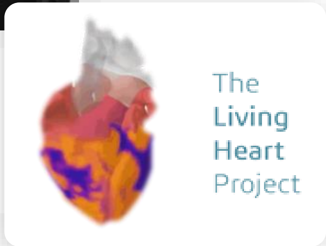
U.S. Government Accountability Office (GAO)
Feb, 2023

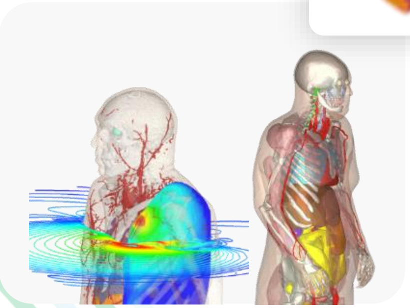


Source: GAO. | GAO-23-106453

The Vision Applied

Personalized physical heart model





Intervention

Medidata Sensor Cloud

Contextualized ECG based Cardiac metrics

Physiological real world monitoring

https://clinicaltrials.gov/ct2/show/NCT05650658

ISCTs and Opportunities for You

What capabilities can this unlock for your company & value delivery?

How can you be on the forefront of applying these concepts to design better trial processes that will differentiate you with sponsors?

New role of “ISCT Data Manager”: bridging the gap between analysts and consumers of simulation data

“It’s time to change the world.”

Be part of the change!

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Sept. 29 – Oct. 2, 2024 | Boston, MA

Transforming FDA Approaches: The Role of In-silico Data, Multiscale Modeling, and Generative AI in Medical Device Product Development

SCDM Live

Generative Virtual Twins for Optimizing Clinical Trial Design

Chaired by

Afrah Shafquat, PhD

Sr. Staff Data Scientist
Medidata Solutions

Steven Levine, PhD

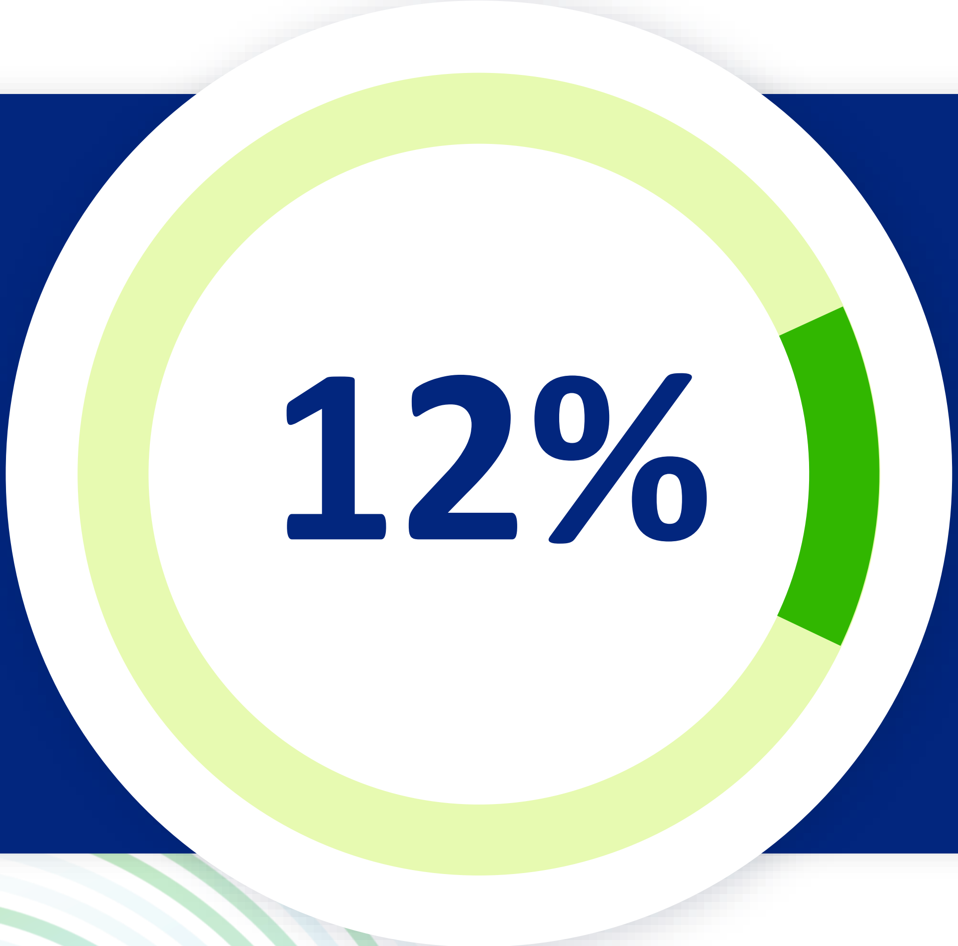
Sr. Director Virtual Human Modelling, Life Sciences and Healthcare
Dassault Systèmes

Jiang Yao, PhD

Biomechanics Application Specialist
Dassault Systèmes

Heidi Sernoff, MD, MBA

Marketing Executive
Dassault Systèmes



# of new therapies entering **Phase I** make it to market

*Congressional Budget Office, Research & Development in the Pharmaceutical Industry, April 2021

Key Considerations

For Designing a Trial

Using Historical Clinical Trial Data to design better trials

Selecting the right patients

- ✔ Unmet medical need
- ✔ Response and tolerance to the drug

Optimal measures

- ✔ Endpoints
- ✔ Rationale behind the endpoints

Identifying the best treatments

- ✔ Con-meds
- ✔ Treating the AEs

Right-size your trials

- ✔ Statistical power
- ✔ Scientific certainty

Value of Historical Clinical Trial Data

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How can Historical Clinical Trial Data Support R&D?

Pre-clinical | Early phase (phase-1) | Mid phase (phase-2) | Late phase (phase-3)

Select the right indication
- Determine patient with unmet medical need under SoC
- Determine which indications to prioritize after basket trial

Optimize eligibility criteria
- Determine relationship between patient characteristics / biomarkers and outcomes
- Pressure test operational feasibility of eligibility criteria
- Identify additional subgroups with unmet medical need

Bolster scientific decision-making
- Right-size trial sample size estimate with more precise estimation of treatment effect
- Make better go/no-go clinical development decisions
- Contextualize single arm trials

Run shorter trials by using surrogate endpoints
- Evidence for regulators to approve drug based of surrogate endpoint
- Determine correlation between endpoints to make the case for a shorter trial

Demonstrate value by assessing safety and efficacy benchmarks
- Determine efficacy and safety benchmarks of patients subgroup
- Assess change in SoC outcomes over time / differences across geographies
- Execute external control arms to replace randomized control patients

Simulate trials by predicting outcomes
- Predict which patients are likely to respond to treatment or drop out
- Identify patients at higher risk of an AE / SAE
- Determine expected efficacy or safety or a planned trial

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Power of Generative AI

Software engineering

Write better code with AI Pair programmer, explain code/documentation, code generation

Healthcare

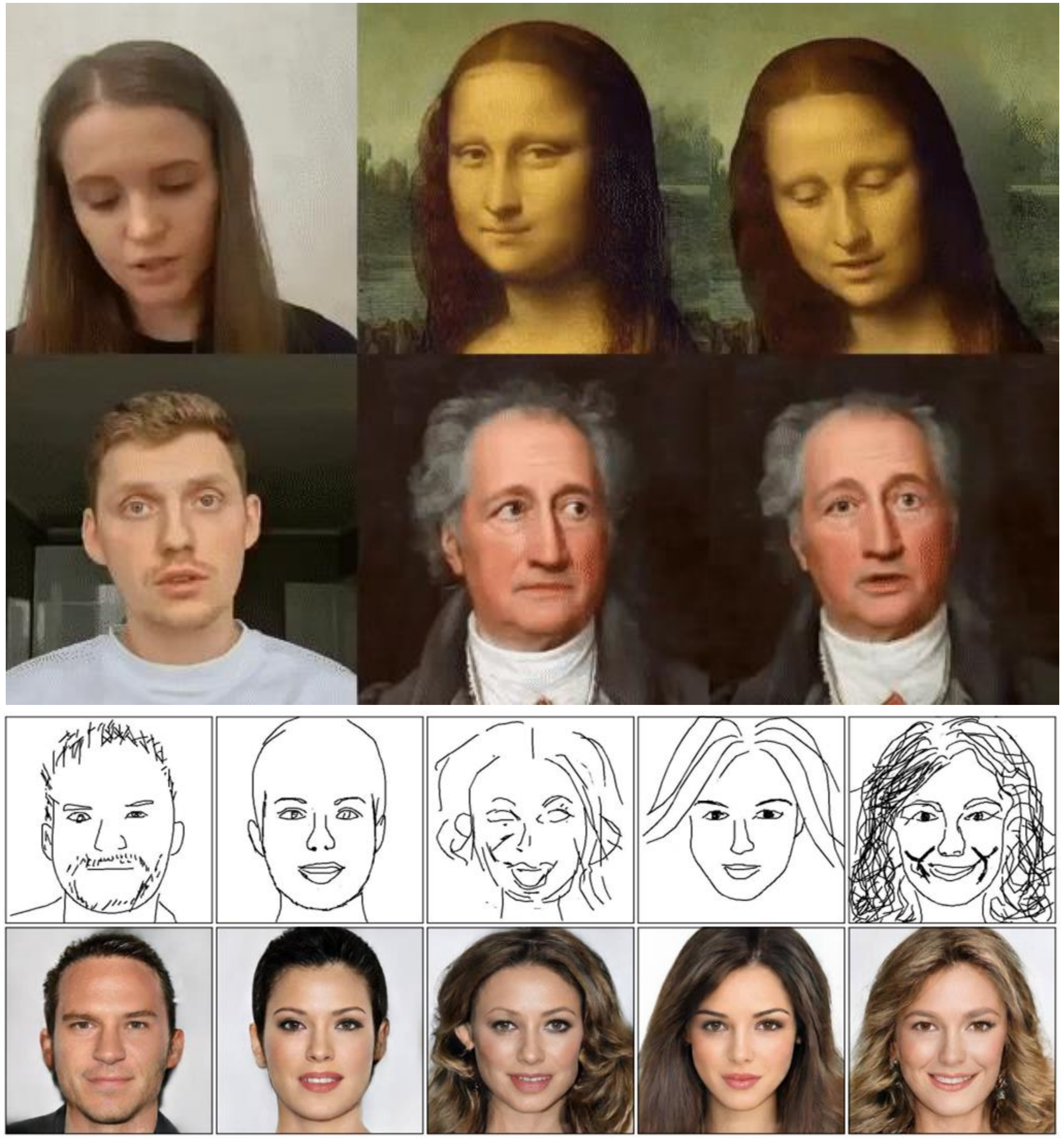
Design better drugs, Build better AI models for disease classification

Media

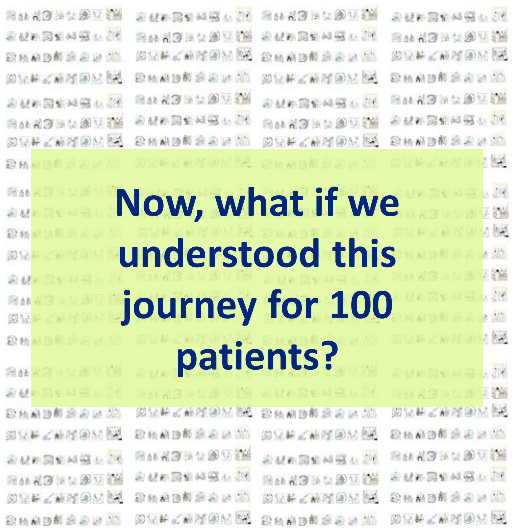
Text summarization, content copywriting, market content generation

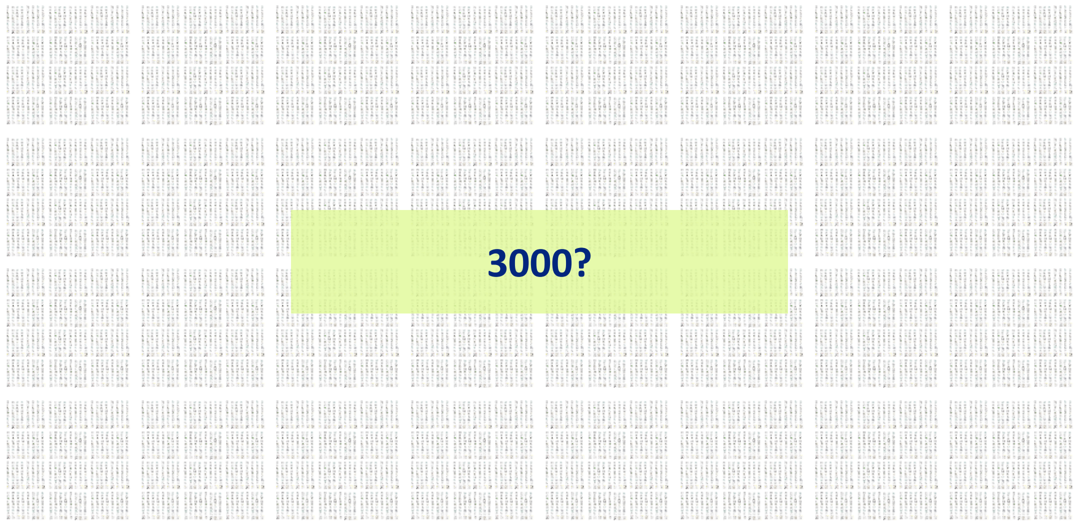
Art

Virtual photoshoots, 2D sketches to digital renderings and artwork



Virtual twins for patient journeys in clinical trials





Medidata

Powerful, artificial intelligence … making trial data available … across all major indications

10M
Trial Participants

33,000
Clinical Trials

110+
Clinical variables

Oncology

Lung, breast, skin, gastrointestinal, genitourinary, brain

Cardiometabolic

Diabetes, hypertension, obesity, hyperlipidemia, kidney disease, cardiovascular

Autoimmune

Skin, connective tissue, gastrointestinal, musculoskeletal

CNS

Pain, movement, auto-immune, degenerative

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Simulants

Gen AI based technology to create and share synthetic data

Data Sharing

Access high value datasets w/o privacy/regulatory concerns

SW Testing & Demo

Generate high quality test, UAT data for efficient SW engineering

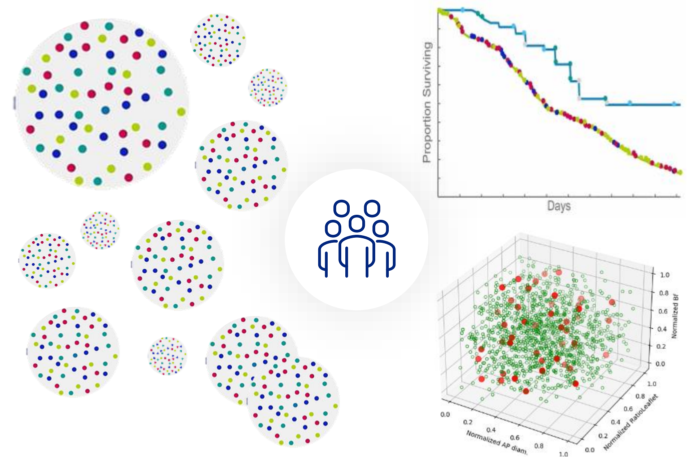
Modeling & Simulation

Augment model, generate balanced data at low cost, address bias

Virtual Patients: A New Era of Digital Evidence

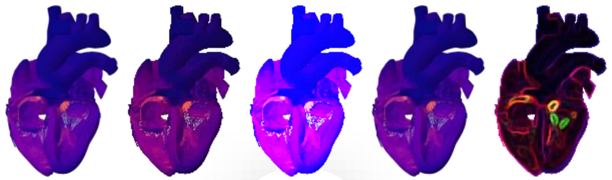
Merging *in vitro, in vivo + in silico*

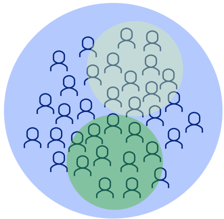
Synthesized Control Arm based on *Real* Patient Data



Simulant™ Generative AI

Synthesized Treatment Arm based on *Virtual* Patient Data

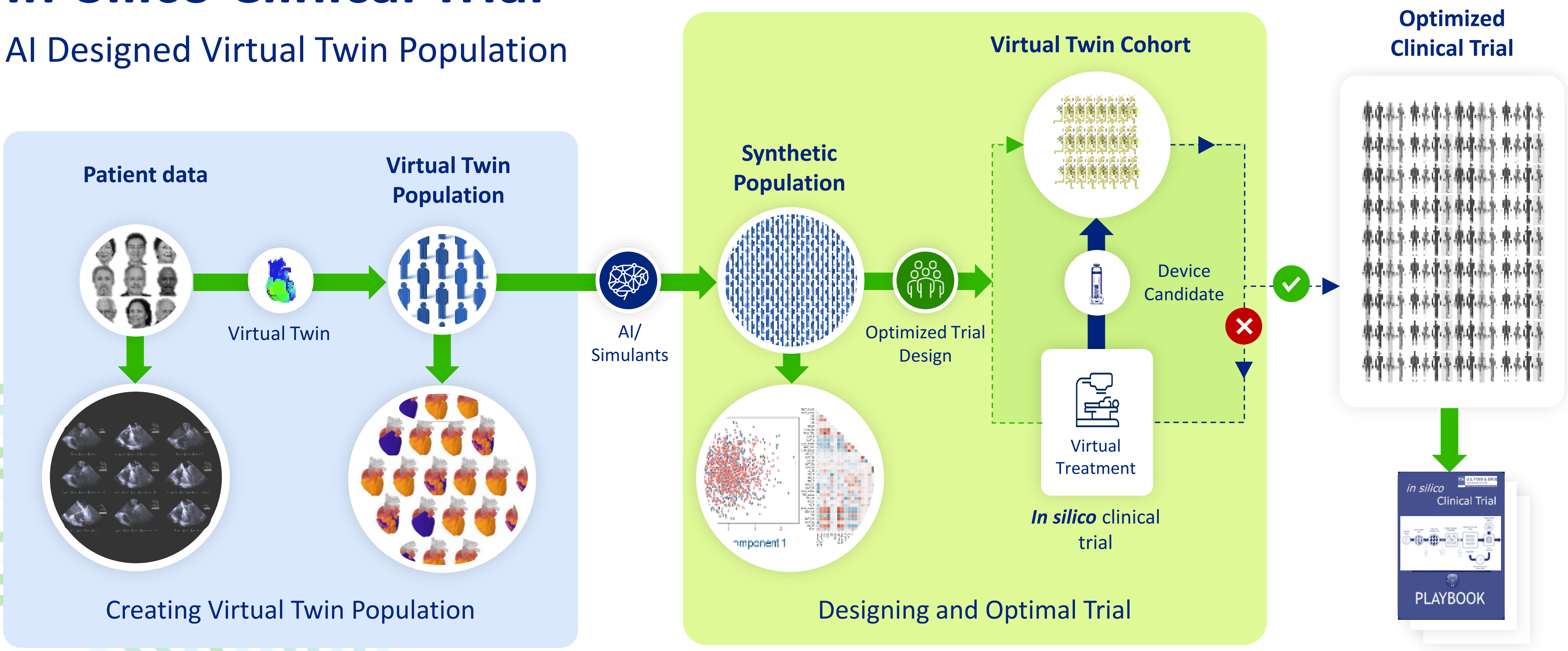




Smaller, Safer, Predictable Clinical Trials

In-Silico Clinical Trial

AI Designed Virtual Twin Population



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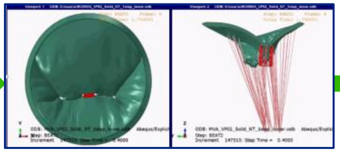
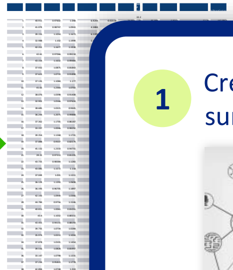
Virtual Patient Engine Schematic

Input

Virtual Twin of Real Patients

A collection of (physics-based) patient model definitions & pre-operative simulation results

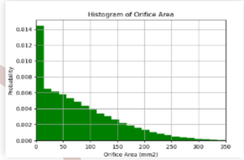




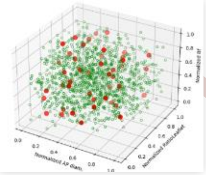
AI Powered
Virtual Patient Engine

1 Create AI surrogate model

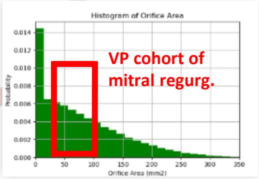
2 Generate surrogate population



3 Virtual Population for ISCT

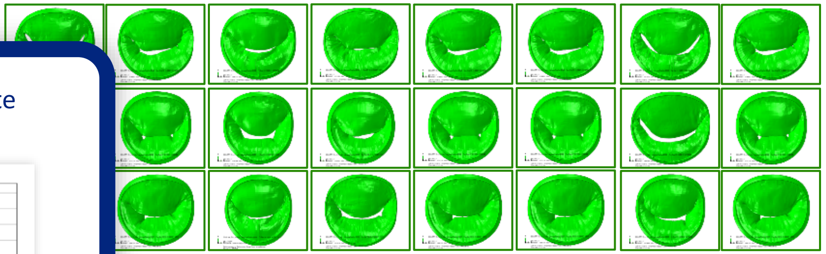


4 Filter w/defined inclusions criteria



Output

A Virtual Patient Cohort with precise pre-operative characteristics to be treated in an iSCT

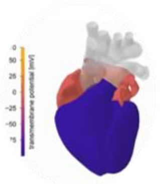


Slide adapted from the SIG 35 readout:
https://www.3ds.com/products-services/simulia/solutions/life-sciences-healthcare/the-living-heart-project/

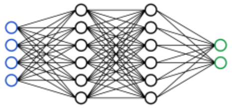
Create Surrogate: Testing Results

Input parameters of patient data

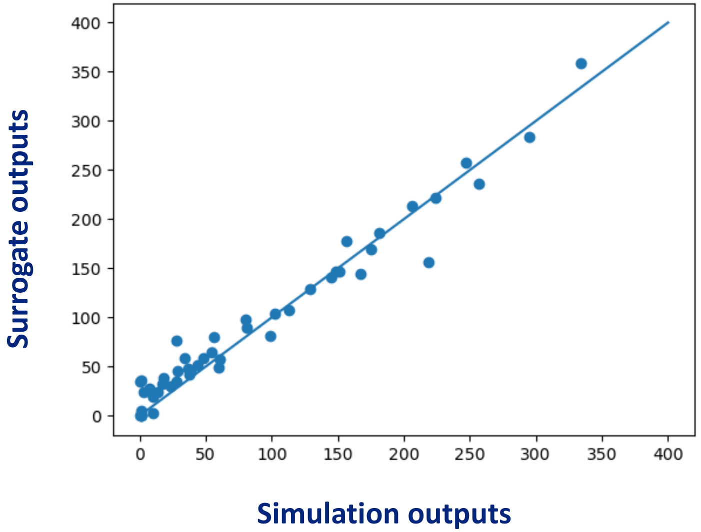
Surrogate Model Validation



Physics-based Population → Simulation outputs (days)



Surrogate model population → Surrogate outputs (seconds)



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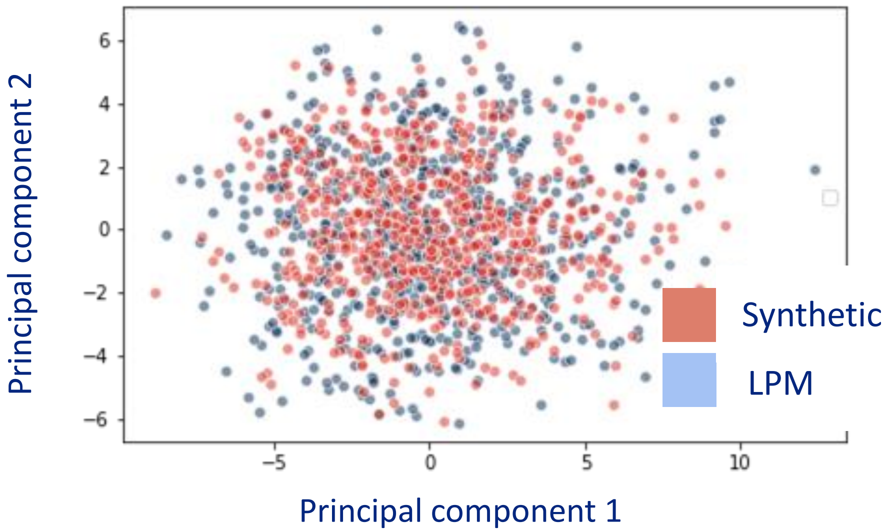
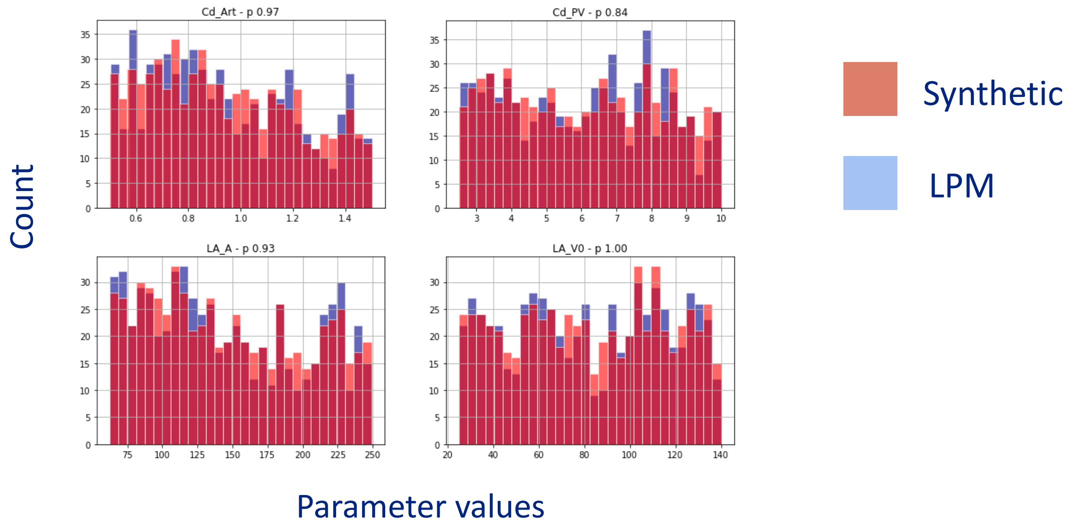
Synthetic (AI) POPULATION aligns with (physical) Virtual Twins

Synthetic vs. physics-based simulated data



Alignment between source/template and Simulants generated synthetic dataset indicates synthesis reflects the source population well

100% alignment across input parameters between datasets



Alignment between input parameters is evaluated by performing the K-S test for input parameters produced by Simulants and the physics-based model. All 14 input parameters had non-statistically significant differences using the K-S test.

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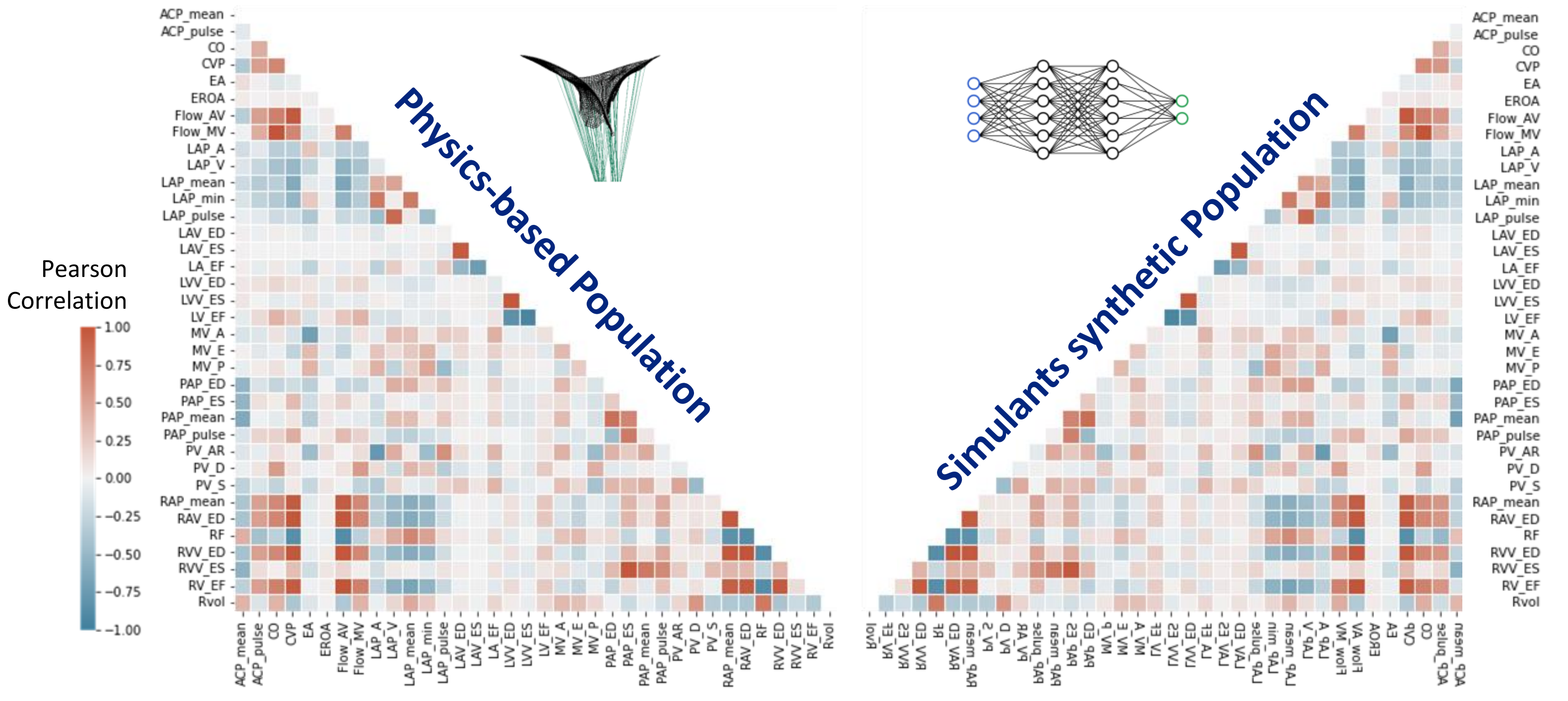
Preservation of bidirectional relationships in synthetic data



Heatmaps confirm the essential bidirectional relationships

Patient biomarkers ⟷ Outcome metrics

are preserved in SIMULANTS population

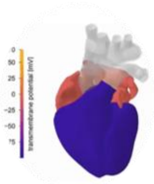
Correlations drive weighting factors for ISCT population

Generative Virtual Twins: From Years to Seconds

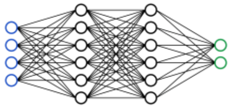
Input parameters of patient data

Model Validation

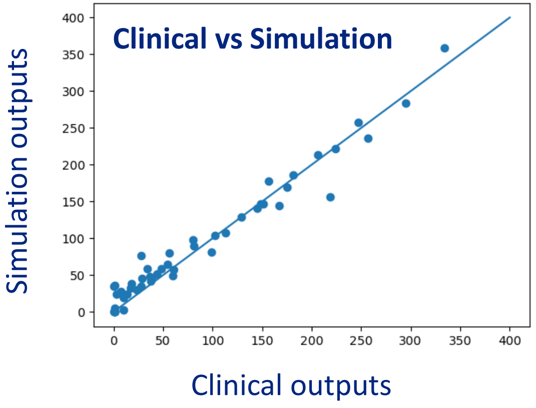
Clinical Trial Population → Clinical outputs **(years)**

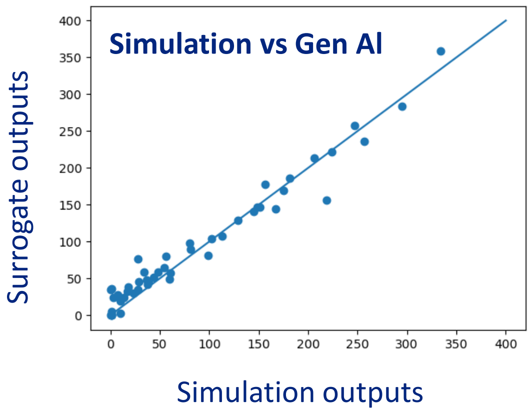


Physics-based Population → Simulation outputs **(days)**



AI Surrogate Population → Surrogate outputs **(seconds)**





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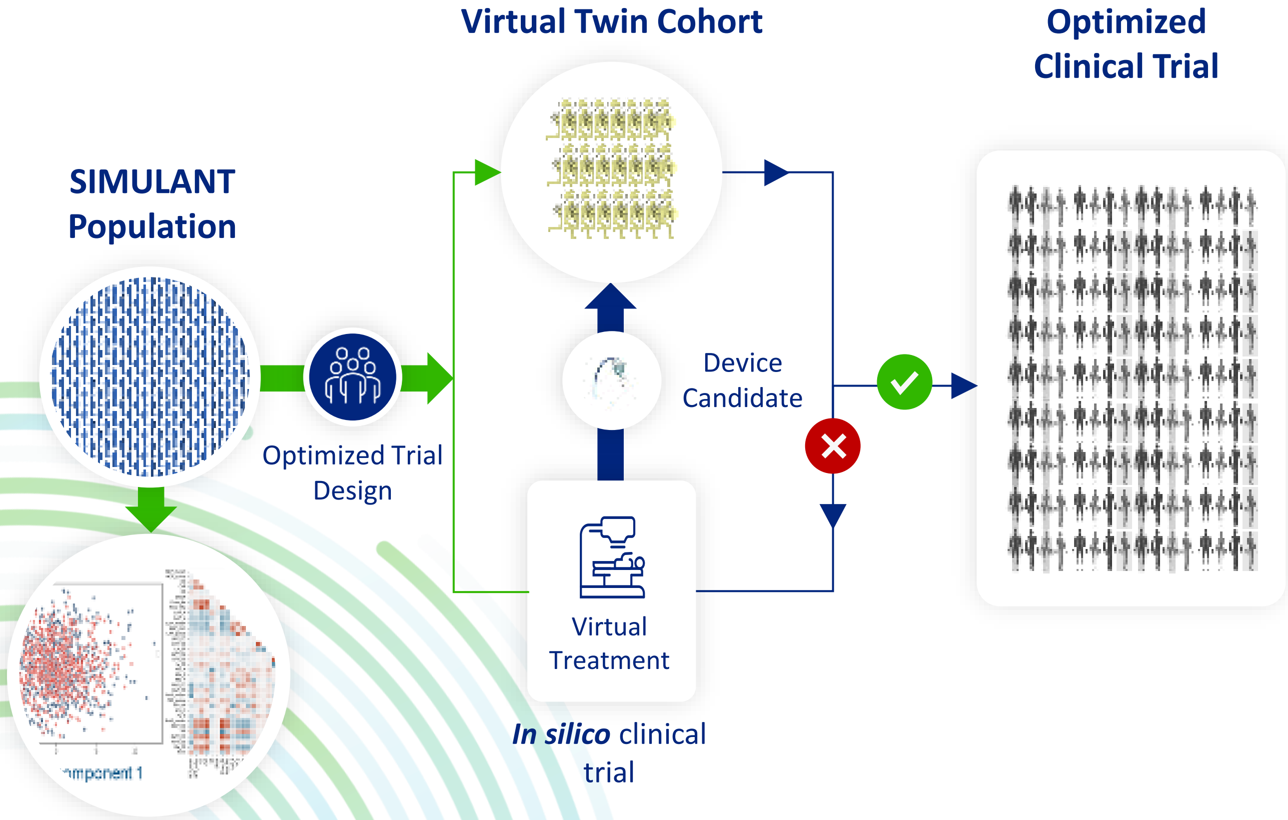
In-Silico Clinical Trial

AI Designed Virtual Twin Population



Simulant Optimized Trials Offer

- Selecting the right indication
- Optimized eligibility criteria
- Increased diversity
- Smaller/shorter trials
- Improved safety/efficacy analytics & decisions making
- Streamlined regulatory review