IN SILICO TRIALS: A SYSTEMATIC APPROACH TO THE ASSESSMENT OF MODEL CREDIBILITY

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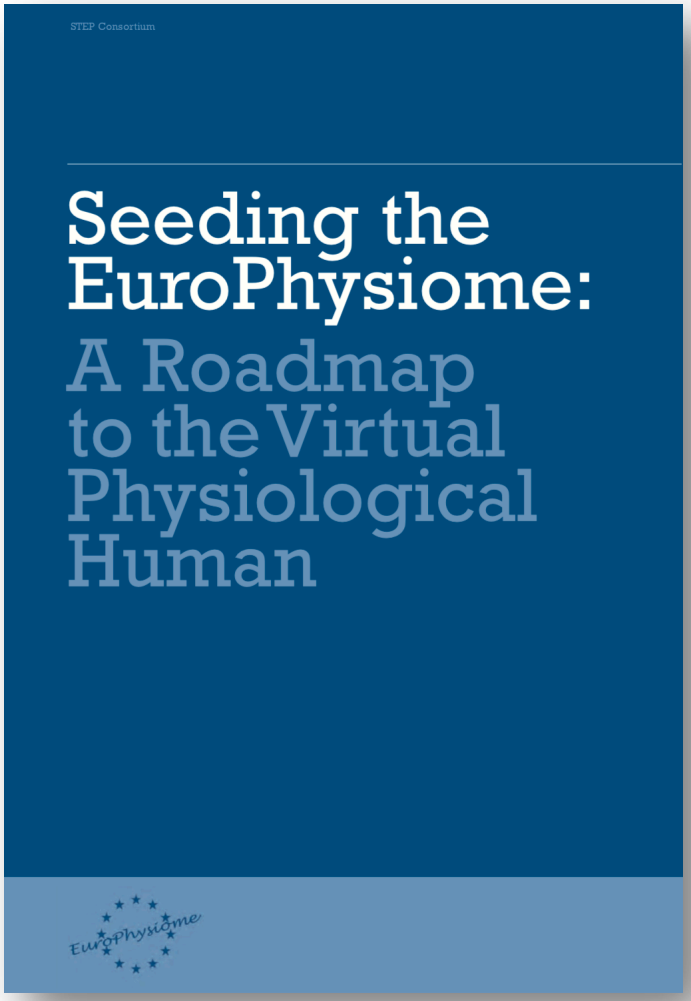
Virtual Physiological Human



2007: VPH Research roadmap

Many called us crazy

SEVENTH FRAMEWORK PROGRAMME

In 2013 (end of FP7) some claimed VPH failed to deliver

In Silico Medicine today

2014: first patient-specific model is FDA-approved

2019: dozen of digital patient products on the market

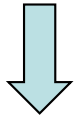
2019: Dassault Systems buys Medidata for US$5.8 BILLIONS

Today we discuss the regulatory aspects of in silico trials

Credibility of a predictive model

$$\hat{O} = f(I)$$

Machine Learning



No epistemic error
No numeric error

$$\begin{cases} |O - \hat{O}| = \alpha_I + \alpha_m \\ \alpha_m = \alpha_f + \varepsilon_f + \nu_{f(I)} \end{cases}$$

Inputs

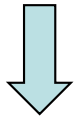
Model

Epistemic

Aleatoric

Numeric

Mechanistic model



All three errors
Aleatoric can brought back to input errors

VV&UQ: Verification

$$\alpha_m = \alpha_f + \varepsilon_f + \nu_{f(I)}$$

- Verification involves code and model
- Code verification is essentially software quality assurance
- Model verification aim to show that the numerical error is negligible when compared to the other errors in the model

$$\nu_{f(I)} = \mathrm{o}\left(\alpha_f + \varepsilon_f\right)$$

$$\alpha_m \approx \alpha_f + \varepsilon_f$$

VV&UQ: validation

$$\alpha_m = \alpha_f + \varepsilon_f + \nu_{f(I)}$$

$$\nu_{f(I)} = \mathrm{o}\left(\alpha_f + \varepsilon_f\right)$$

- Over repeated comparisons:
  - we assume that the error due to the inputs has null average

$$\sum_{i=1}^{n\to\infty} \alpha_I \to 0$$

  - Than the average of the error is only due to the model error

$$ave\left(\left\|O - \hat{O}\right\|\right) \cong ave(\alpha_M)$$

VV&UQ: Uncertainty quantification

$$\alpha_m = \alpha_f + \varepsilon_f + \nu_{f(I)}$$

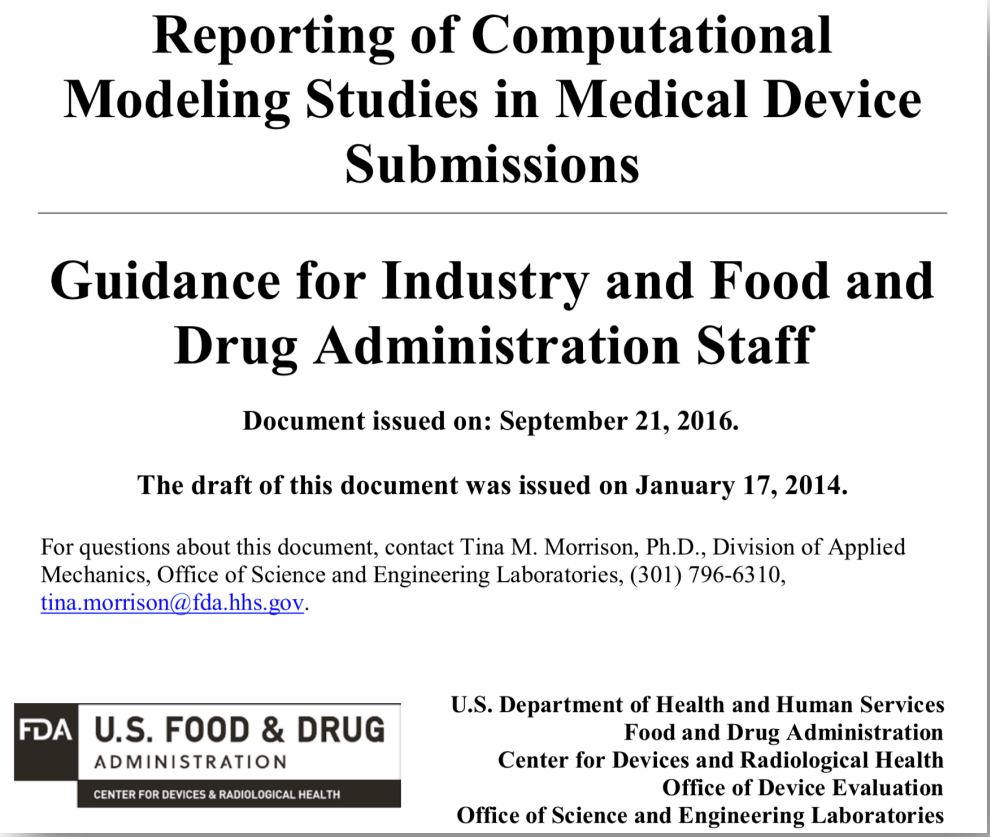
$$\nu_{f(I)} = \mathrm{o}\left(\alpha_f + \varepsilon_f\right)$$

$$\sum_{i=1}^{n\to\infty} \alpha_I \to 0$$

If all above are true, then the variance of the error over repeated comparison is only due due to the variance of the inputs

$$var\left(\left\|O - \hat{O}\right\|\right) \cong var(\alpha_I)$$

In Silico Trials: medical devices



Reporting of Computational Modeling Studies in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on: September 21, 2016.

The draft of this document was issued on January 17, 2014.

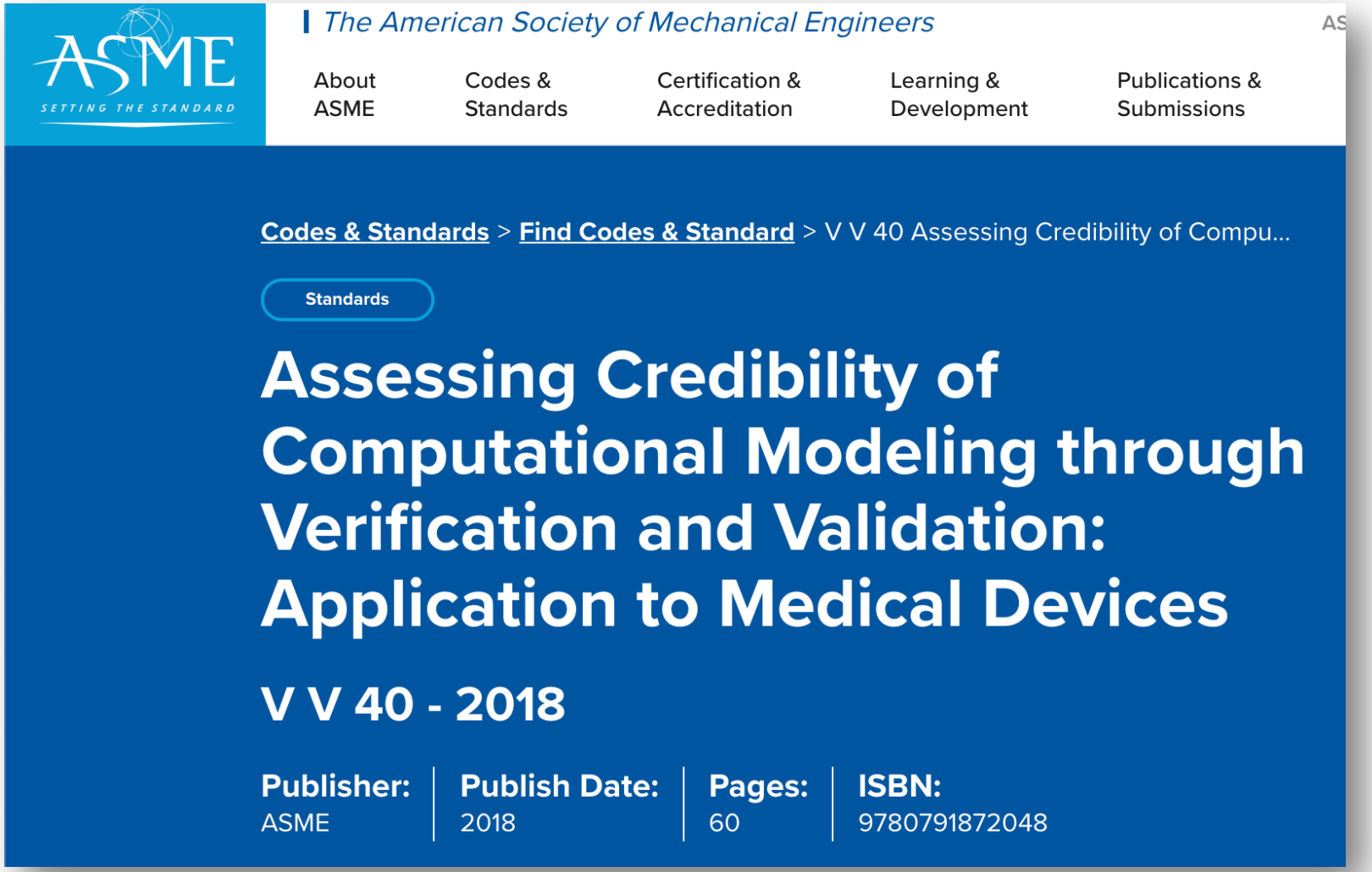
For questions about this document, contact Tina M. Morrison, Ph.D., Division of Applied Mechanics, Office of Science and Engineering Laboratories, (301) 796-6310, tina.morrison@fda.hhs.gov.

FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Office of Device Evaluation
Office of Science and Engineering Laboratories

- Code Verification
- System Configuration
- Governing Equations, Constitutive Laws
- System Properties
- System Conditions
- System Discretization
- Numerical Implementation
- Validation

ASME V&V-40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Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices
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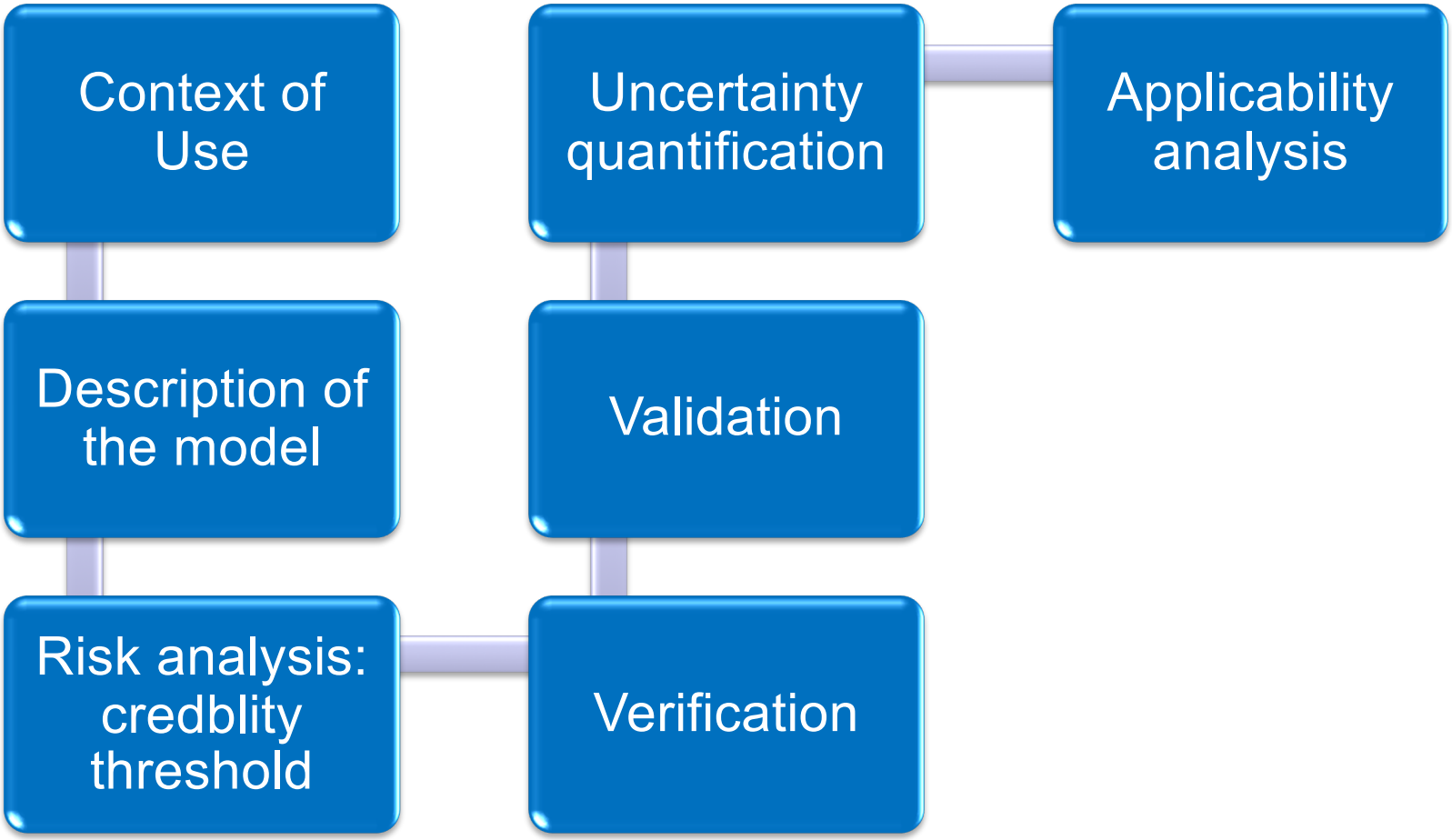
ISBN: 9780791872048

VV40 structure



Risk analysis

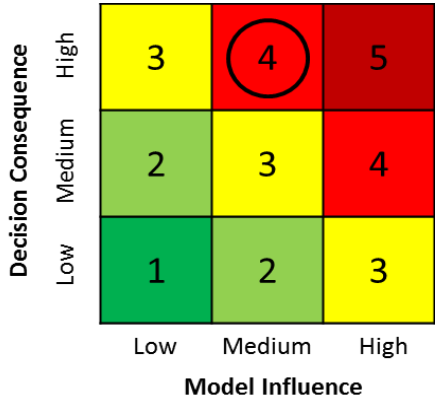
Purpose

Define Context of Use

Use the model to predict the outcome of ISO7206-4 on Ti6Al4V cementless hip stem

FEM model to predict peak cyclic stress, and form that predict the risk of fatigue fracture

Assess model risk



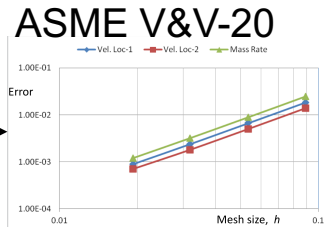
Prediction error <10% of fatigue limit

Establish credibility threshold

Establish VV&UQ plan

Verification

Numerical Code Verification



Software QA


CERTIFICATE

This is to certify that

ANSYS, Inc.

275 Technology Drive
Canonsburg, PA 15317
United States of America
Reference No. 10003741

Plot No. 34/1,
Rajiv Ghandi Infotech Park,
MIDC Hinjewandi
Pune 411057
India
Reference No. 10005556

10 Cavendish Court
Lebanon, NH 03766
United States of America
Reference No. 10005557

1007 Church Street
Suite 250
Evanston, IL 60201
United States of America
Reference No. 10005558

West Central 127
Milton Park, Abingdon
Oxfordshire OX14 4SA
United Kingdom
Reference No. 10005559

225 West Station Square Drive
Pittsburgh, PA 15219
United States of America
Reference No. 10010983

has implemented and maintains a **Quality Management System**.

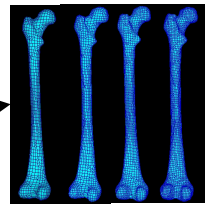
Scope:
The development, delivery, and support of software products and training for engineering simulation. The provision of Quality Assurance and verification services for software products.

Through an audit, documented in a report, it was verified that the management system fulfills the requirements of the following standard:

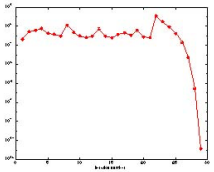
ISO 9001 : 2008

Code Verification

Discretisation error



Solver error

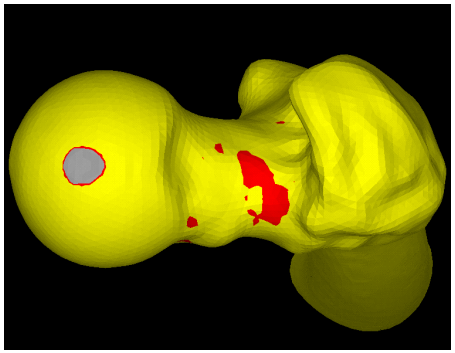
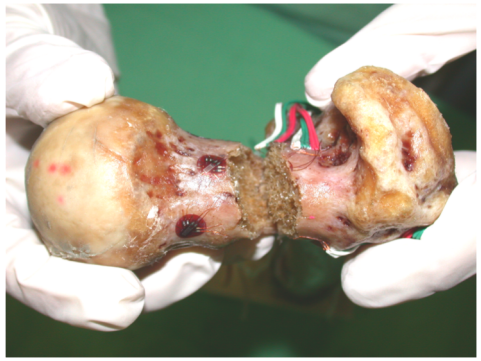
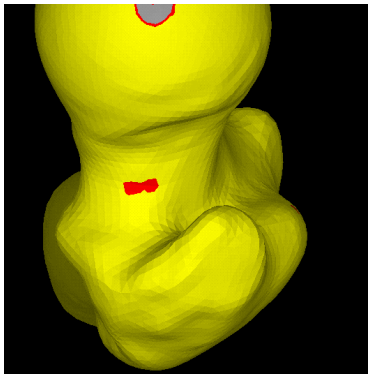
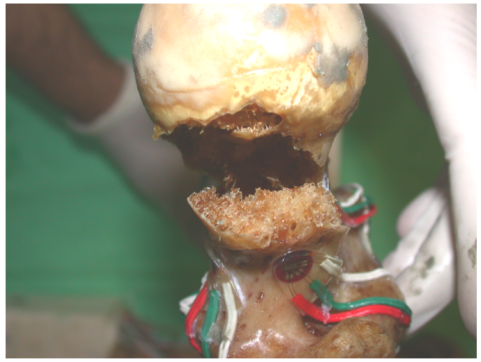
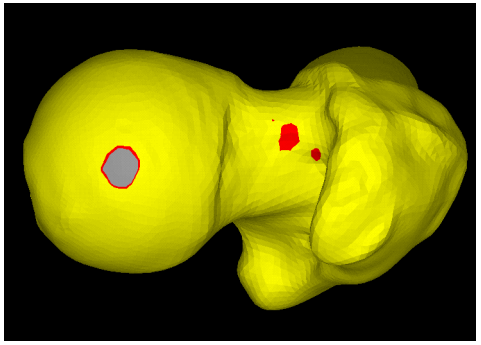
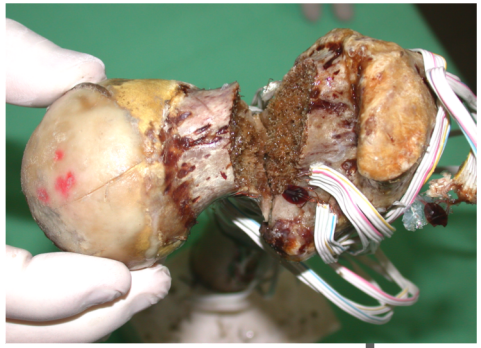


Use error
(Human)

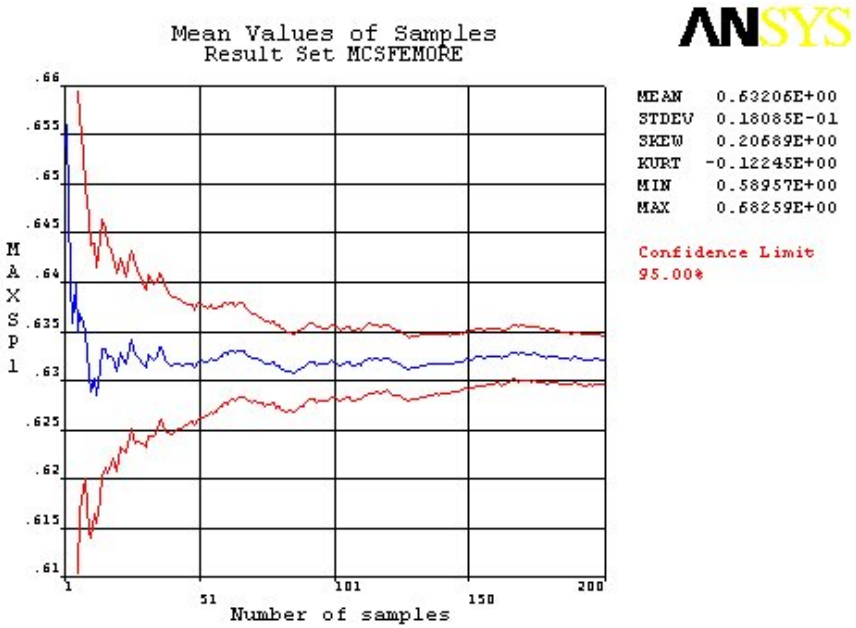
Model Verification

Validation

- Credibility factors
  - Model Form
    - governing equations
    - system configuration (i.e. geometry)
    - system properties (i.e. materials)
    - system conditions (i.e. loads)
  - Model Inputs
  - Comparator
    - In vitro, ex vivo, in vivo
  - Assessment

Uncertainty quantification

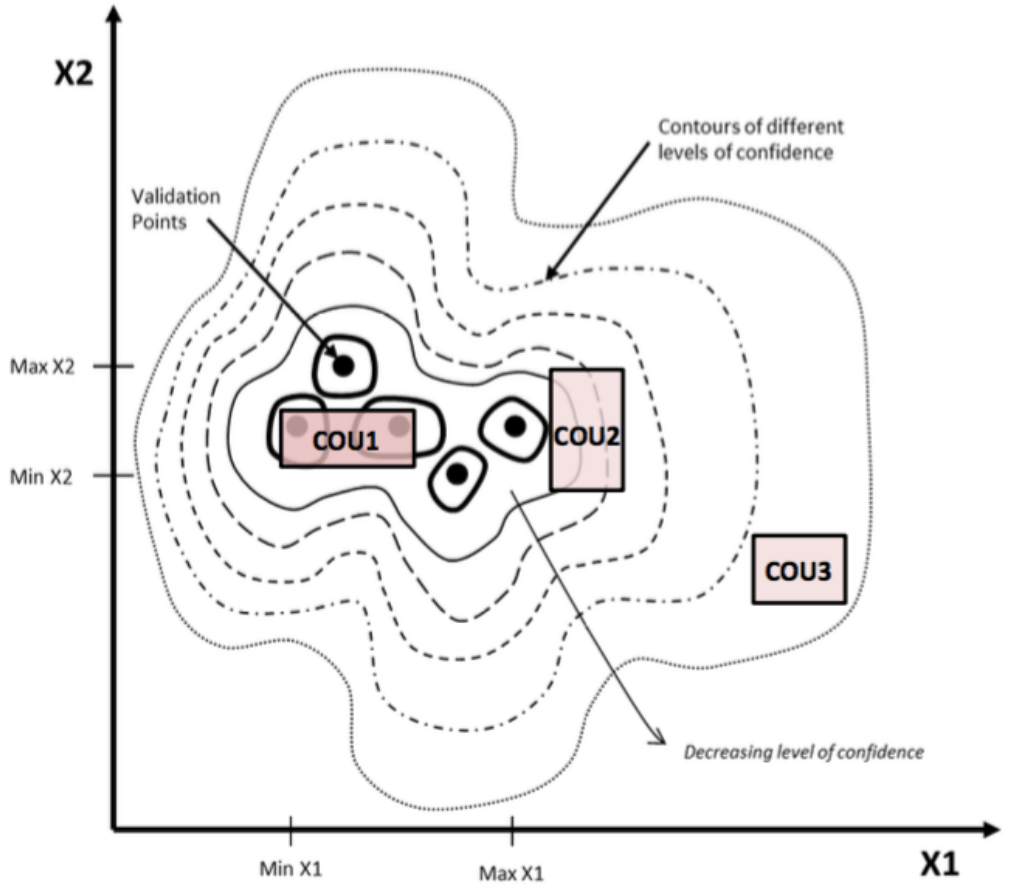


	Achilles	Peroneus Longus			Tibialis Anterior			Tibialis Posterior		
	I	via1	via2	via3	via1	via2	I	via1	via2	I
Patient 1										
Anterior	10.6	-0.6	-2.8	-0.6	-0.6	-3.0	-2.9	-1.3	5.2	-0.6
Posterior	-8.2	-0.6	2.5	-2.2	-0.6	3.0	3.3	0.7	-4.3	-0.6
Superior	-1.7	-0.6	-3.8	-0.6	-0.6	-3.1	-2.4	-1.0	-1.5	-0.6
Inferior	1.4	-0.6	5.3	-2.0	-0.6	4.1	2.2	-0.6	1.5	-0.6
Lateral	13.4	-0.6	-3.4	-0.9	-0.6	-3.8	-5.5	1.0	8.2	-0.6
Medial	-12.0	-0.6	3.8	0.8	-0.6	3.9	5.8	-1.0	-5.4	-0.6
Patient 2										
Anterior	9.6	1.2	-2.0	1.3	1.2	-2.7	-2.8	-1.0	4.4	1.2
Posterior	-7.9	1.2	1.5	-1.2	1.2	2.4	2.2	2.0	-3.8	1.2
Superior	-1.5	1.2	-2.5	1.3	1.2	-2.5	-1.5	-1.0	2.1	1.2
Inferior	1.6	1.2	2.6	1.1	1.2	2.4	1.5	2.0	-1.5	1.2
Lateral	11.5	1.2	-3.5	1.3	1.2	-4.5	-4.6	2.8	4.8	1.2
Medial	-11.9	1.2	3.8	1.1	1.2	3.8	3.9	-2.1	-3.5	1.2
Patient 3										
Anterior	12.9	-0.8	-1.0	-0.8	-0.8	3.2	-2.3	-0.9	7.8	-0.8
Posterior	-9.9	-0.8	-0.9	-0.8	-0.8	-3.0	2.4	0.6	-6.5	-0.8
Superior	2.0	-0.8	-2.6	-0.8	-0.8	-2.6	-1.6	-0.9	-1.6	-0.8
Inferior	-2.4	-0.8	-2.4	-0.8	-0.8	-3.1	-1.0	-0.6	0.9	-0.8
Lateral	-9.3	-0.8	-1.3	-0.8	-0.8	-3.4	3.3	-1.0	-5.0	-0.8
Medial	9.4	-0.8	-2.3	-0.8	-0.8	3.8	2.0	0.9	6.7	-0.8

Hannah I., *et al.* Proc Inst Mech Eng H. 2017 May;231(5):415-422.

Applicability analysis

Schematic Representation of Applicability



27

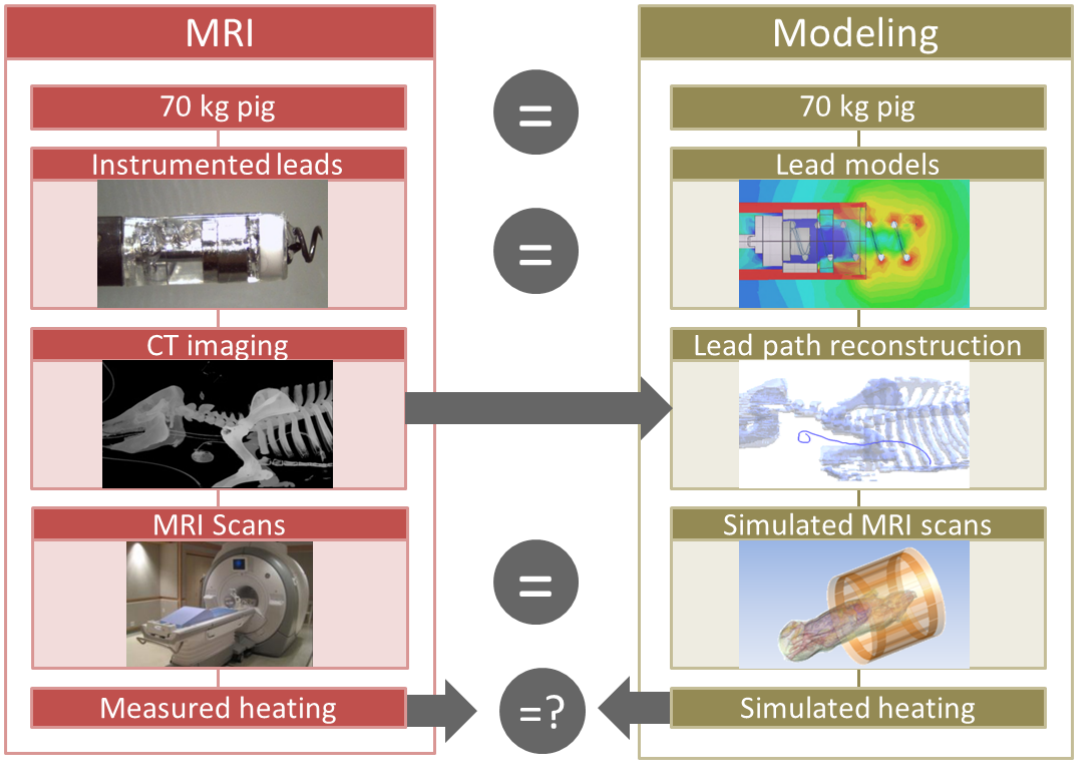
Courtesy of Tina Morrison, FDA

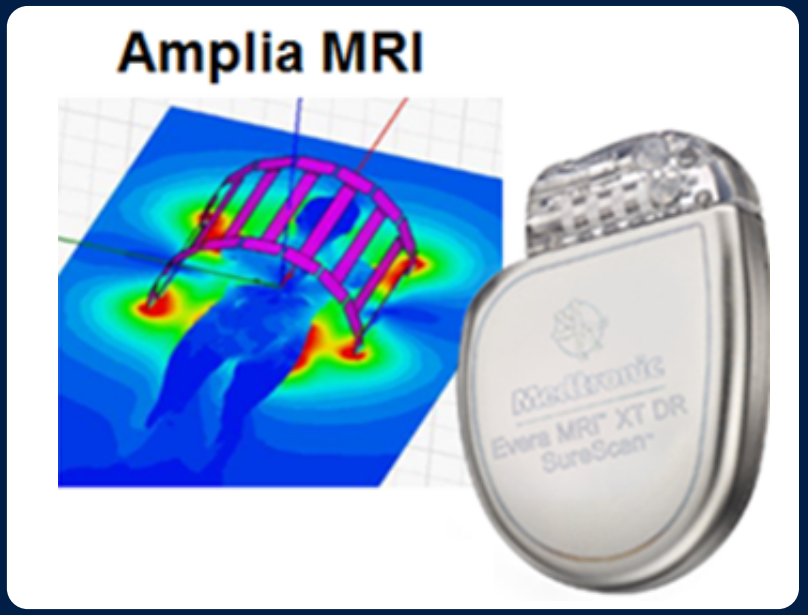
AVOID CLINICAL TRIAL

ADVISA SR APPROVAL CRT-D MRI, 3T MRI

Significant cost and time savings due to **clinical trial avoidance** leading to valuable incremental revenue gain and **earlier patient access**

In Vivo Model Validation





- Advisa SR approved with no clinical
- No clinical required for CRT-D MRI, 3T MRI, and future MRI programs

Courtesy of Markus Reiterer

Credit: CRHF MRI

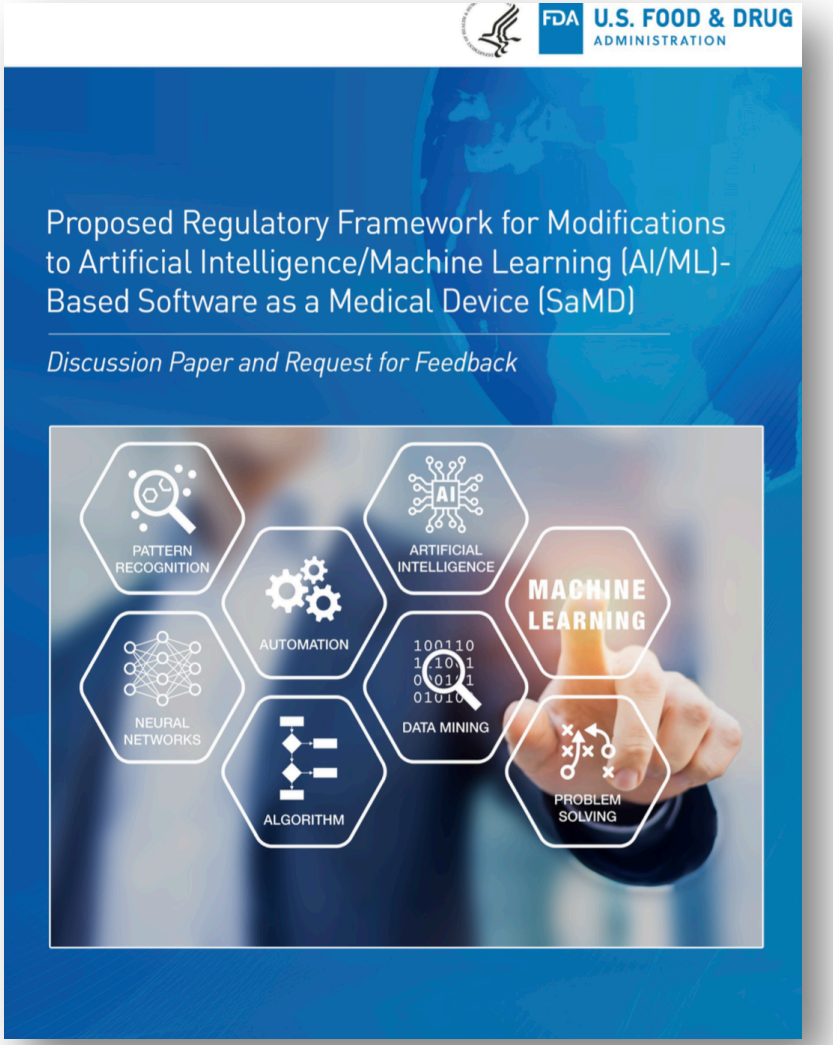
Medtronic

Limits of the VV40

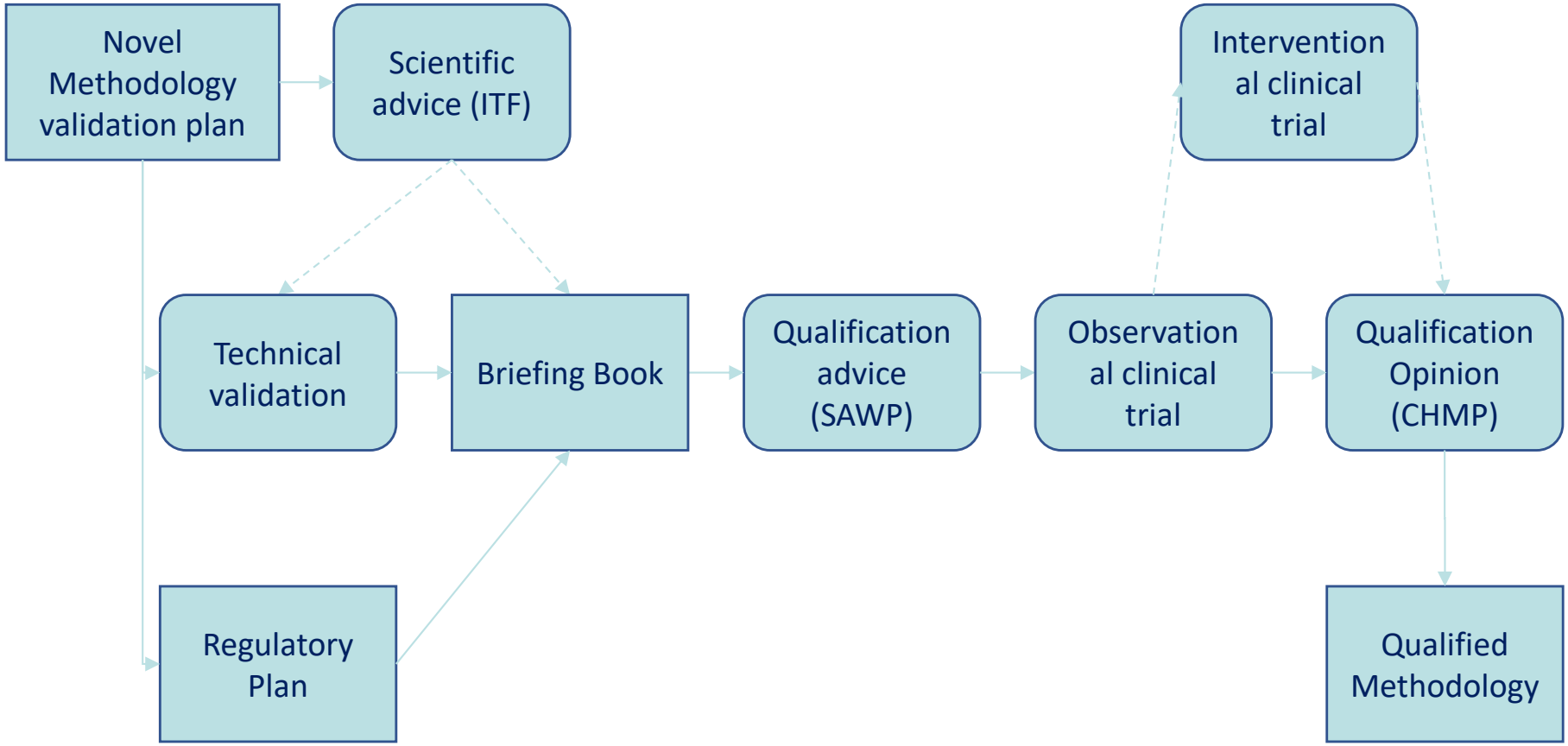
- Applicability approach assumes physics-based models
- Primary target is replacement of bench tests
- No explicit provision for replacement of clinical trials

Machine learning models

- ML regulatory framework proposal acknowledge the issue of “concept drift”
- Recommend a continuous QA process ➔ collection of clinical outcomes
- Cast shadow on “locked ML” systems



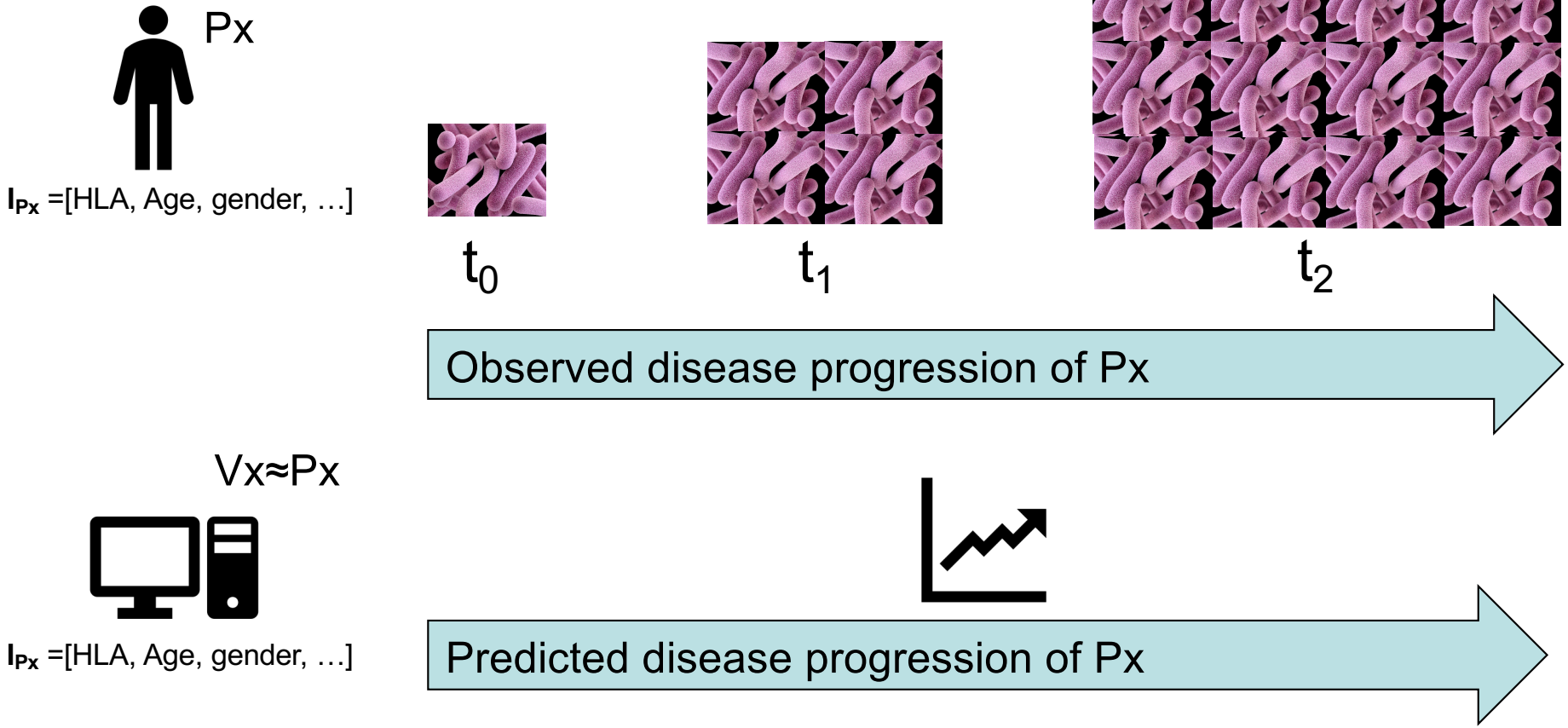
EMA Qualification process



STriTuVaD

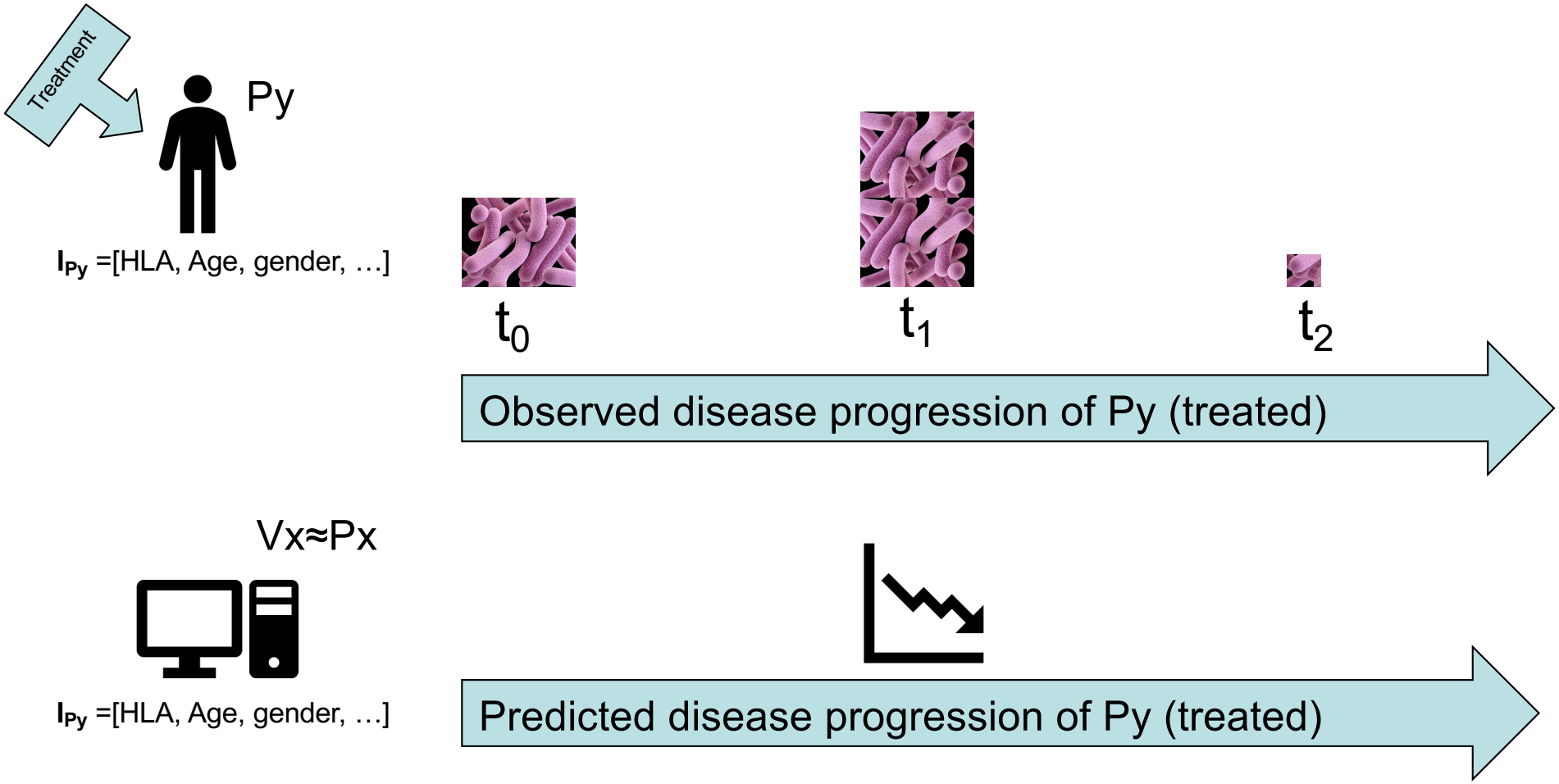
- Universal Immune System Simulator (UISS), U. of Catania
- UISS-TB to be used to reduce duration and cohort size of clinical trials of new therapeutic vaccines

Qualification of UISS-TB /1



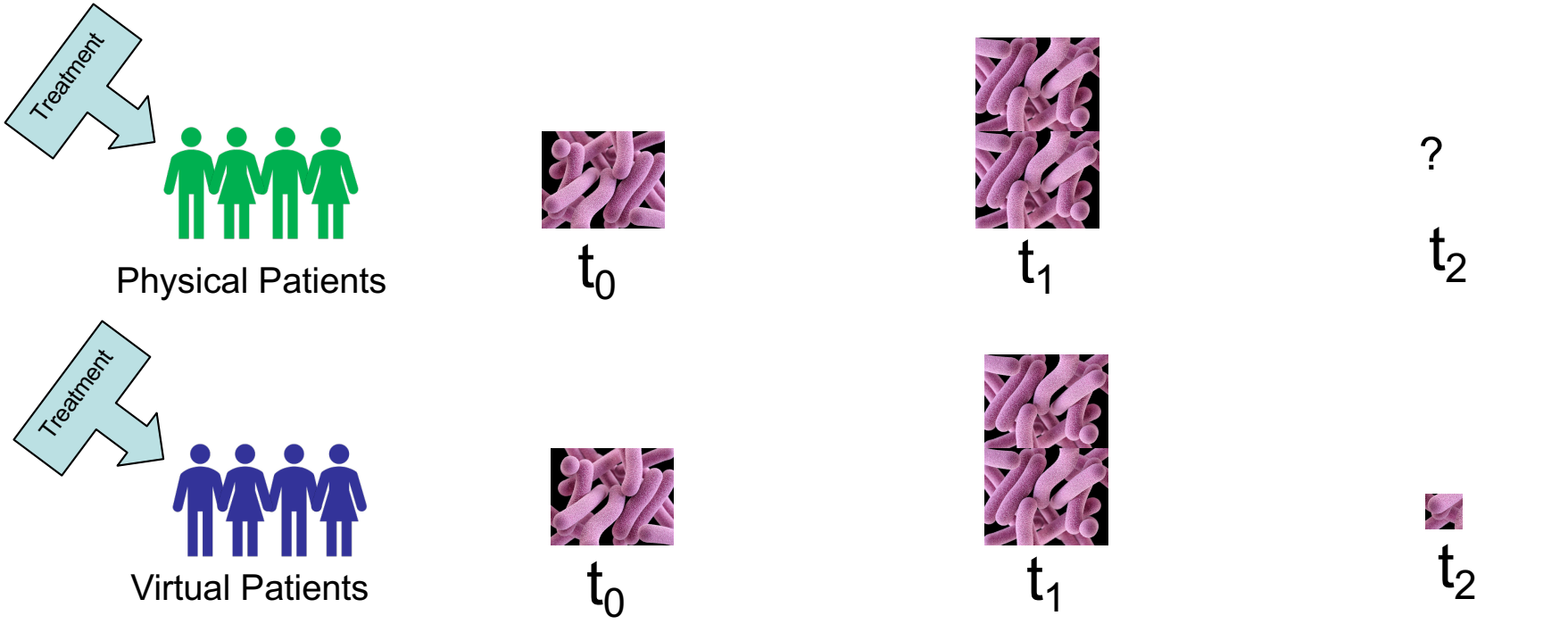
Validated patient-specific model of disease progression

Qualification of UISS-TB /2



Validated patient-specific model of treatment response

Simplest use: time extrapolation



Conclusions

- “First in Kind” qualification of In Silico Trials methods will complete the cycle started in 2005 with the idea of the VPH
- In Silico Medicine research should now enters a maturity stage where:
  - Clear distinction between models for hypothesis falsification and models for problem-solving
  - Problem-solving models should undergo same levels of VV&UQ required by standards before publication

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