CompBioMed

A Centre of Excellence in Computational Biomedicine

e-Seminar #31

Assessing the Credibility of Computational Models: Application of the FDA-Endorsed ASME VV-40

26 July 2023

The e-Seminar will start at 2pm CEST / 1pm BST

Presenters:
Alessandra Aldieri (Politecnico di Torino)
Cristina Curreli (University of Bologna)

Moderator:
Jazmin Aguado Sierra (BSC)

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

INSILICO WORLD

https://insilicoworld.slack.com/archives/C0151M02TA4

The e-Seminar series is run in collaboration with: VPH Institute – Building the Virtual Physiological Human

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Welcome!

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VPH Institute
Building the Virtual Physiological Human

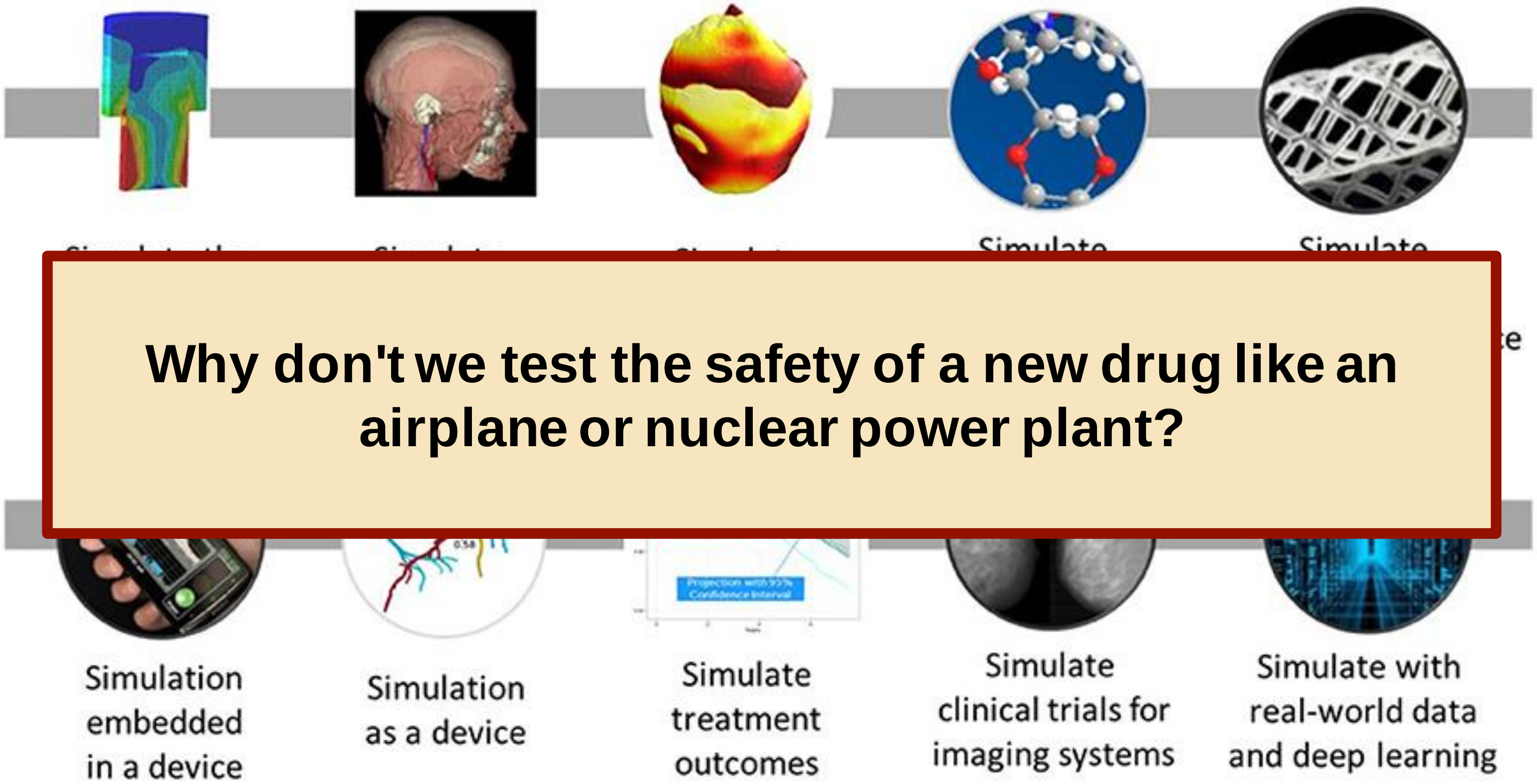
Computer modelling & simulation

Manage information overload

Develop and test faster

Replace problematic experiments

Computer modelling & simulation in healthcare

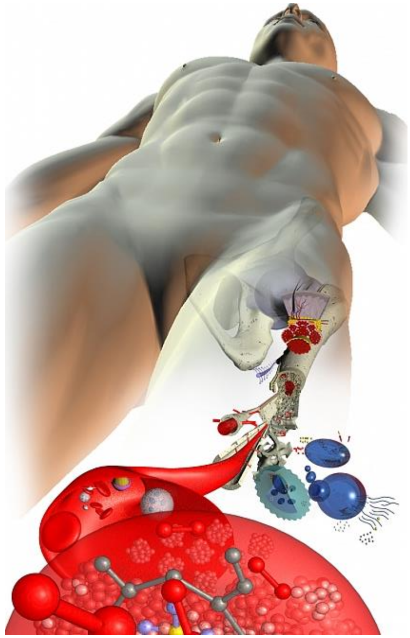


Why don't we test the safety of a new drug like an airplane or nuclear power plant?

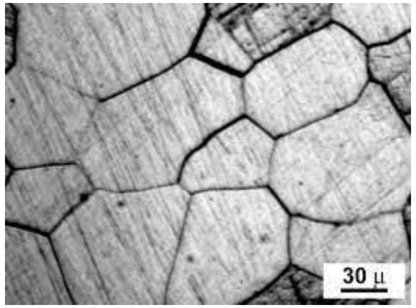
Morrison et al., Advancing Regulatory Science with Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories, Frontiers in Medicine, 2018

1. Complexity

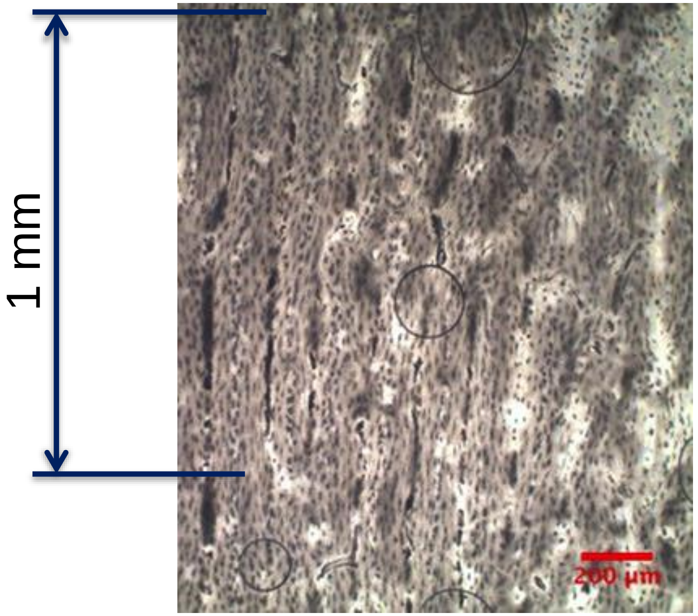
- High dimensionality
- Entanglement: change in one variable/component has an effect on the others
- Scale separation



Scale separation



$$S_s = \frac{6}{60 \cdot 10^{-6}} = 10^5$$



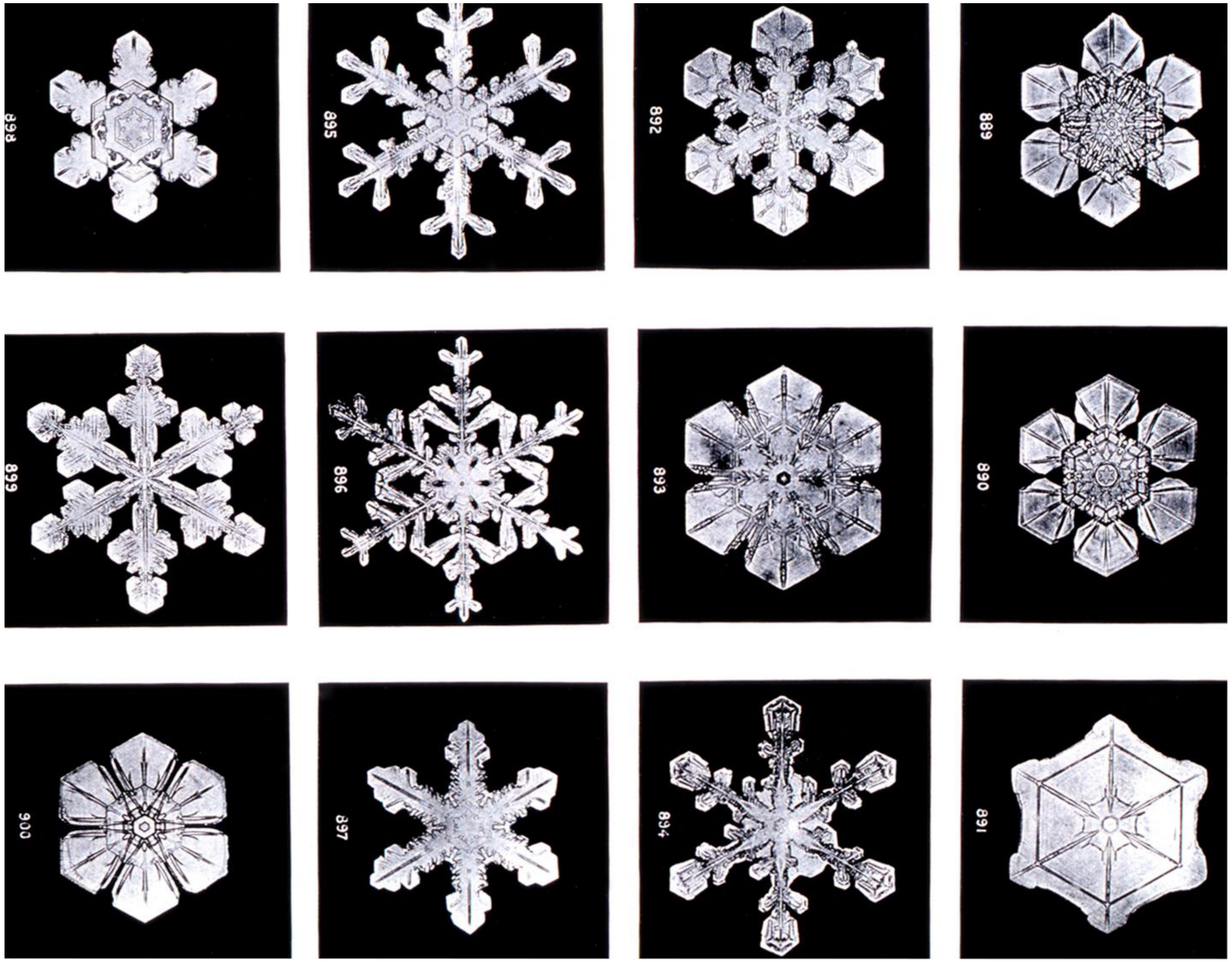
Griesmann U. Microscopy of Bone and Step-by-Step Sample Preparation. © Microscopy UK

$$S_s = \frac{5 \cdot 10^{-1}}{1 \cdot 10^{-3}} = 5 \cdot 10^2$$

2. Redundancy

- Redundancy is only apparent
- Yieast example: 80% of genes do not modify the phenotype under physiological conditions. In chemical/environmental stress conditions, 97% of genes do affect phenotype
- Another example: muscles activation during walking

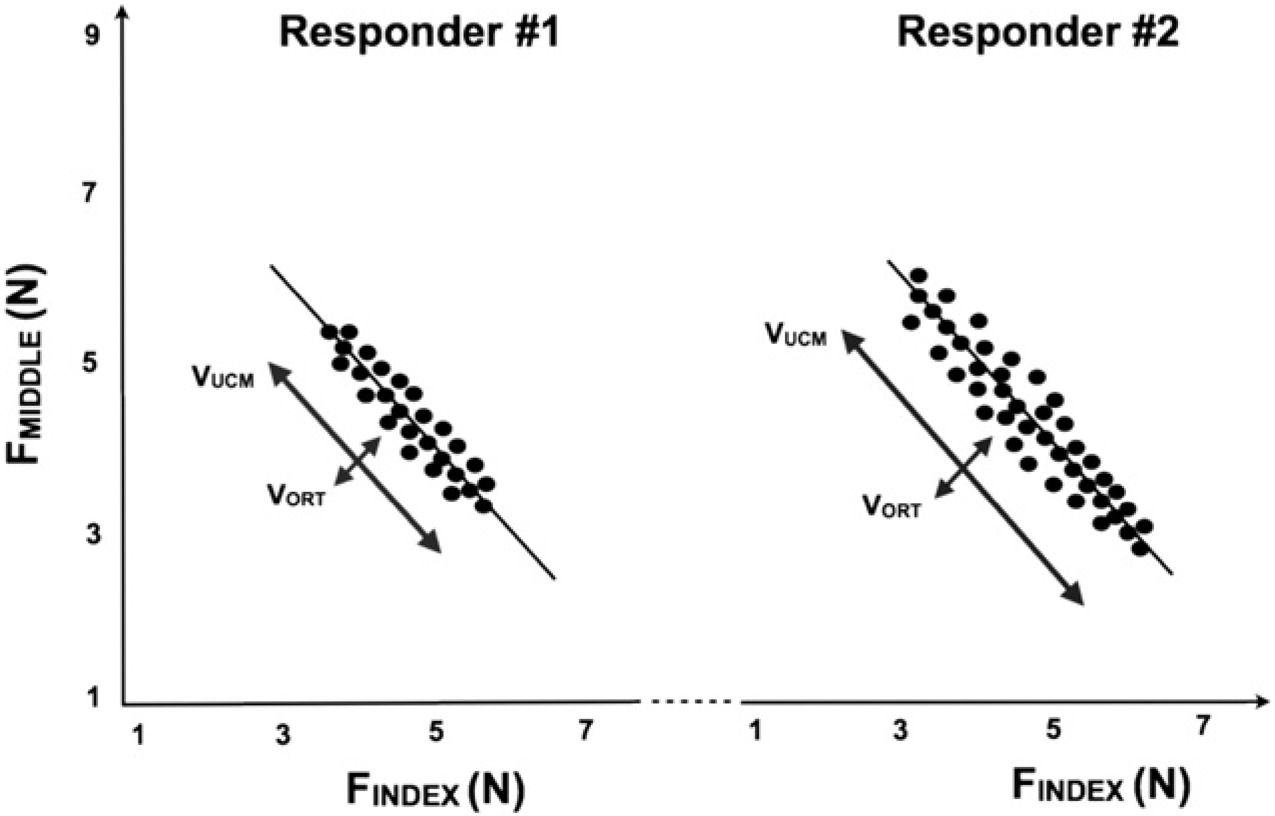
3. Stocasticity



Wilson "Snowflake" Bentley
(Feb 9, 1865 – Dec 23, 1931)
One of the first known photographers of snowflakes

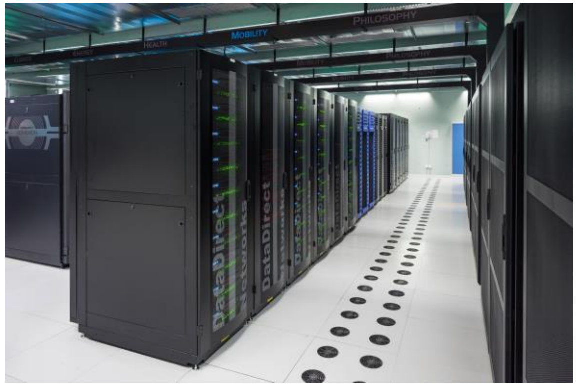
The average patient

3. Stocasticity



Latash ML, et al., Medicina, 2010

4. Culture



In silico medicine is the future

Digital Twins

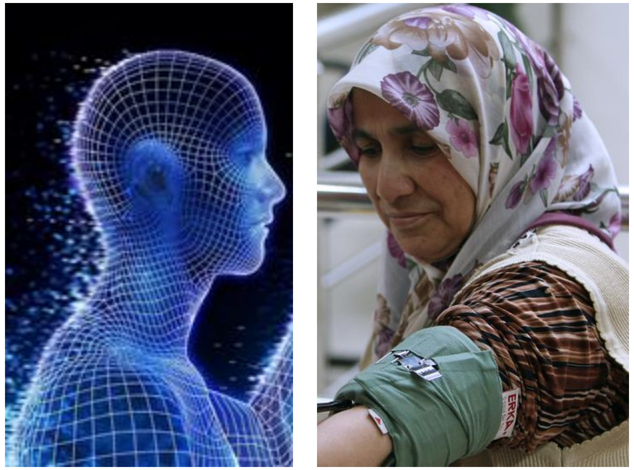
User: Doctor

Use: Clinical Decision Support system

In Silico Trials

User: Medical Industry

Use: Design & de-risking of new medical products



Personal Health Forecast

User: Patient

Use: Self-management of chronic conditions

In silico medicine: taxonomy

Medical device software

- Software inside Medical device
- Software as medical device

Medical product development/evaluation tool

- Medical Device Development Tools
- Drug development Tools

In silico medicine: taxonomy

Medical device software

- Software inside Medical device
- Software as medical device

Predictive software

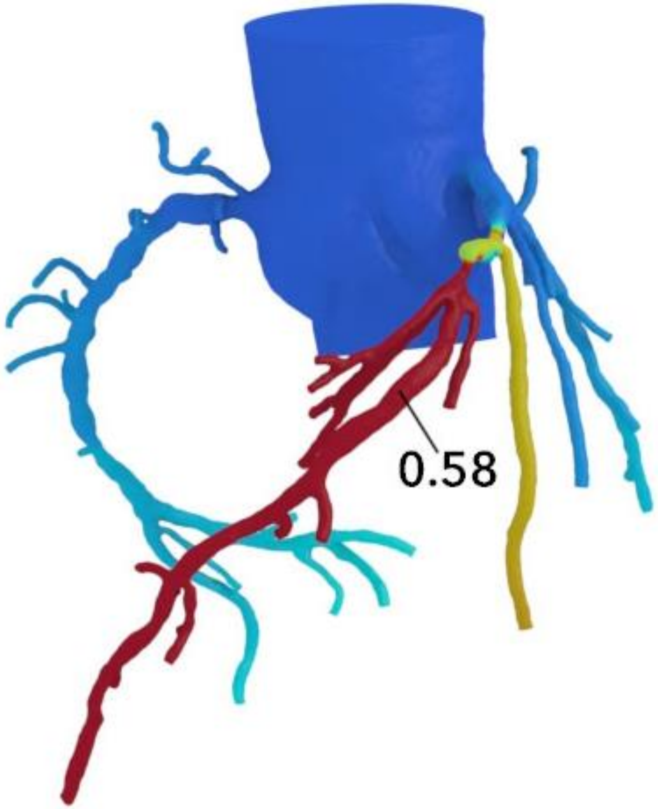
Medical product development/evaluation tool

- Medical Device Development Tools
- Drug development Tools

HeartFlow: first DT-SaMD

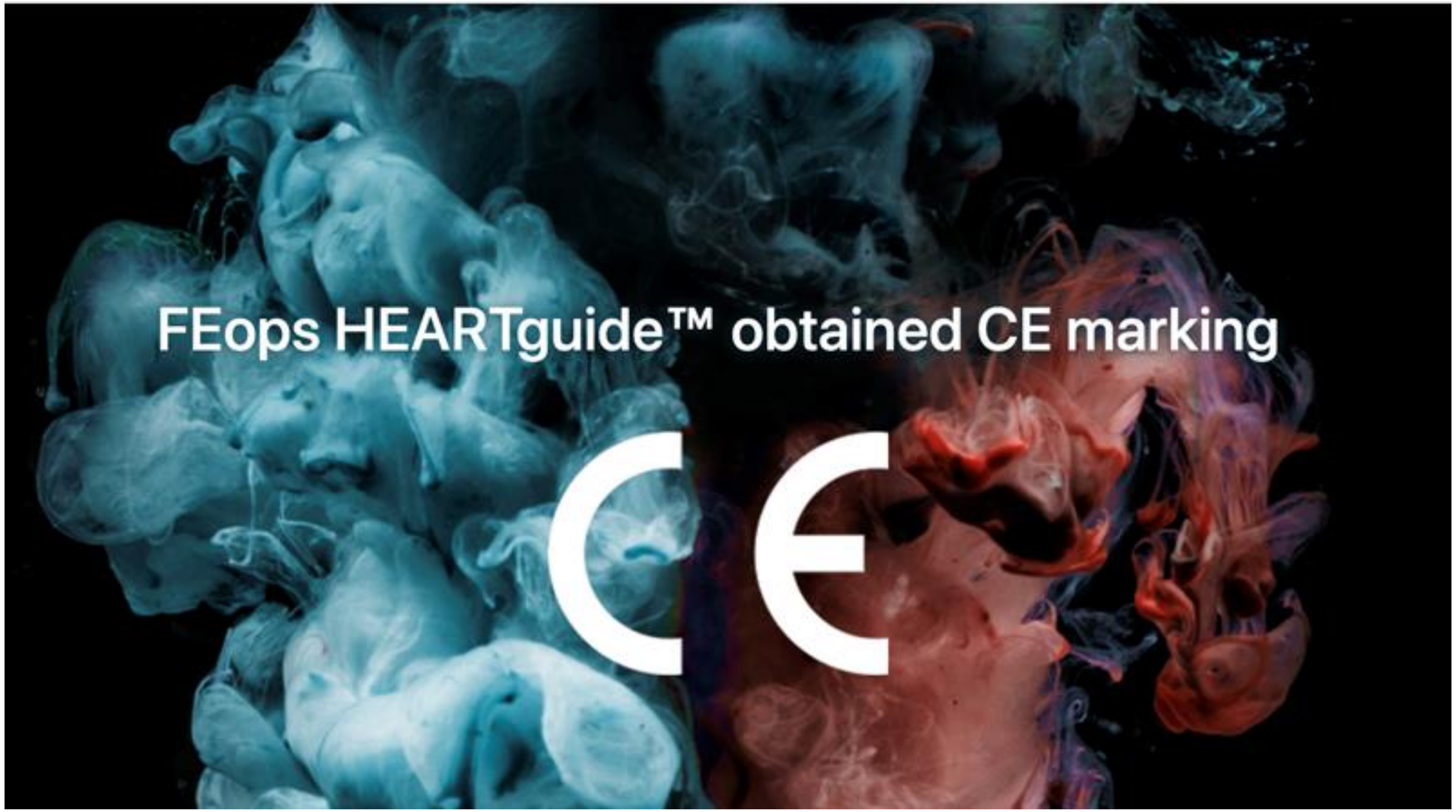
Coronary CT Angiography

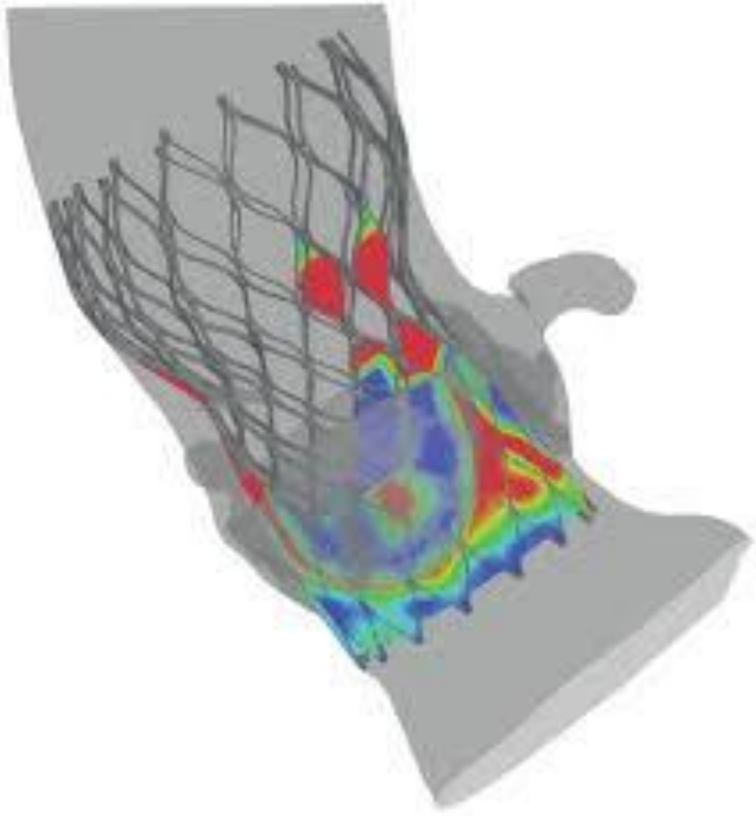
La Barbera M. Noninvasive Cardiac Imaging: Coronary CT Angiography
https://www.clinicalcorrelations.org/?p=679



HeartFlow FFRCT. Courtesy of HeartFlow Inc.

FEOPS HEARTguide





Transcatheter Aortic Valve Implantation

Bone fracture prediction

FDA-approved in 2018

CE marked in 2019

[VirtuOst Video]

In silico medicine: taxonomy

Medical device software

- Software inside Medical device
- Software as medical device

Medical product development/evaluation tool

- Medical Device Development Tools
- Drug development Tools

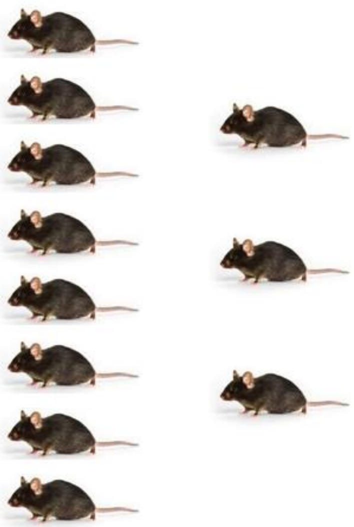
In silico trials


IEEE JOURNAL OF BIOMEDICAL AND HEALTH INFORMATICS, VOL. 25, NO. 10, OCTOBER 2021 3977

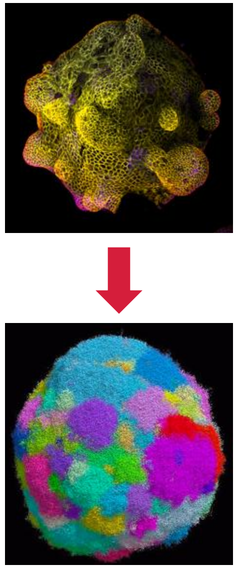
Possible Contexts of Use for *In Silico* Trials Methodologies: A Consensus-Based Review

Marco Viceconti, Luca Emili, Payman Afshari, Eulalie Courcelles, Cristina Curreli, Nele Famaey, Liesbet Geris, Marc Horner, Maria Cristina Jori, Alexander Kulesza, Axel Loewe, Michael Neidlin, Markus Reiterer, Cecile F. Rousseau, Giulia Russo, Simon J. Sonntag, Emmanuelle M. Voisin, and Francesco Pappalardo

"The use of individualised computer simulation in the development or regulatory evaluation of a medicinal product or medical device/medical intervention" **Avicenna Roadmap**

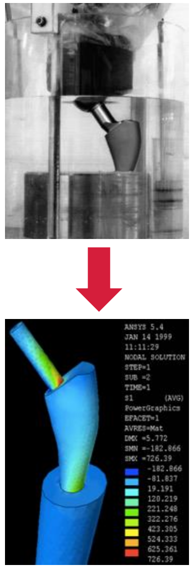


Reduce



Refine

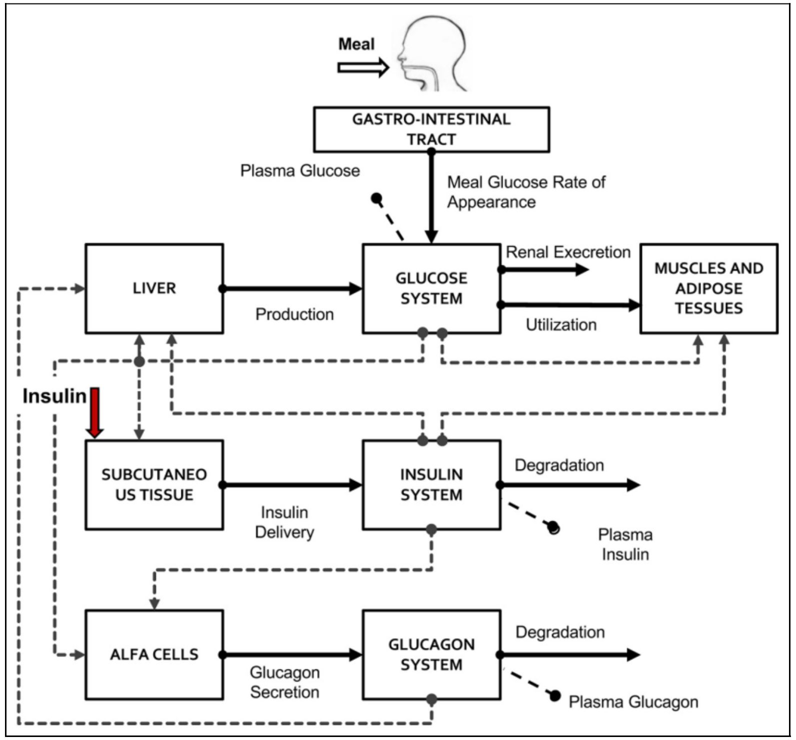
Reduce suffering
improve accuracy

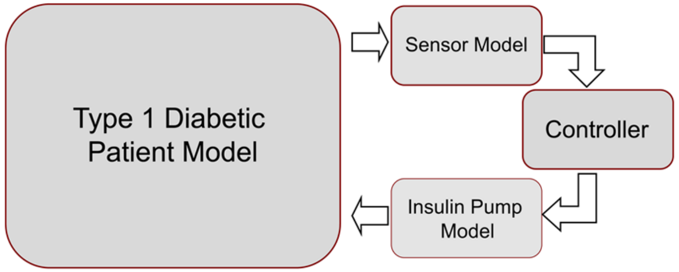


Replace

UVA/Padua T1DM simulator

- 2006: Juvenile Diabetes Research Foundation starts the Artificial Pancreas Project
- FDA requires algorithms to be tested on dogs before human trials are allowed
- UVA/Padua simulator virtual patient cohort includes 100 adults, 100 adolescents, and 100 children, spanning the variability of the T1DM population observed in vivo
- 2008: FDA approves investigational device exemption supported only by simulator results





Reduction of human experiments

In 2018 FDA accepts an in silico augmented clinical trial as evidence of low risk of fatigue fracture in Quad LV leads

JOURNAL OF BIOPHARMACEUTICAL STATISTICS
2017, VOL. 27, NO. 6, 1089–1103
http://dx.doi.org/10.1080/10543406.2017.1300907

Taylor & Francis
Taylor & Francis Group

OPEN ACCESS

Incorporation of stochastic engineering models as prior information in Bayesian medical device trials

Tarek Haddad[a], Adam Himes[a], Laura Thompson[b], Telba Irony[b,c], Rajesh Nair[b]; and on Behalf of MDIC Computer Modeling and Simulation Working Group Participants[d,e]

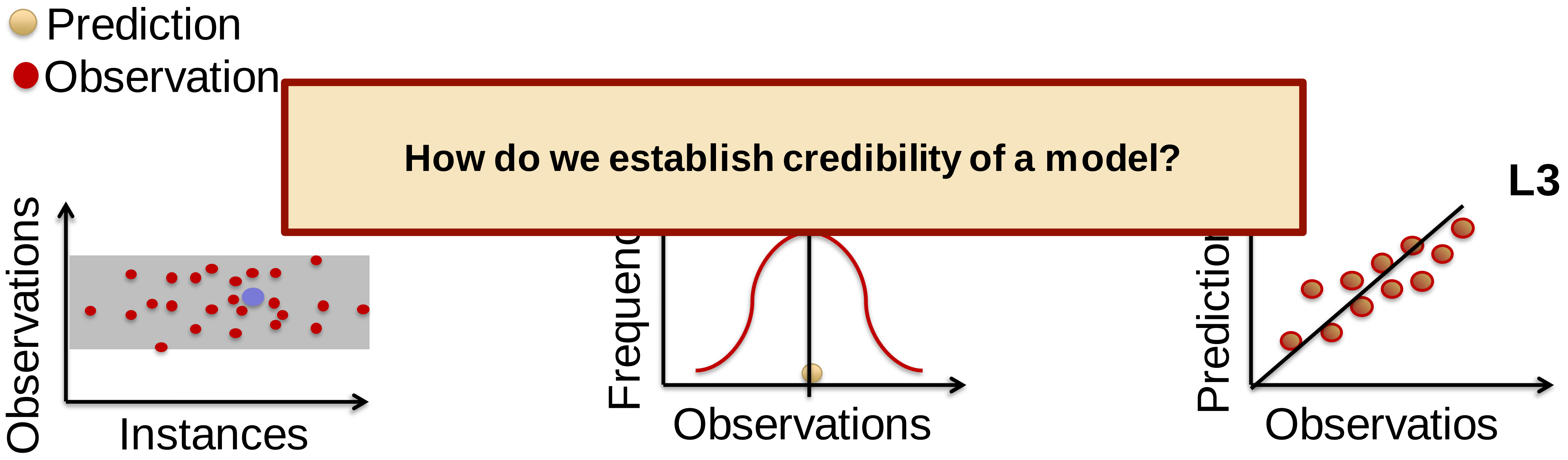
[a]Medtronic, plc, Mounds View, Minnesota, USA; [b]Center for Devices and Radiological Health, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [c]Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA; [d]Medical Device Innovation Consortium Clinical Trials Powered by Bench and Simulation Working Group; [e]See online supplement for a complete list of participants

It is all about trust

https://www.forbes.com/sites/matthewerskine/2022/08/05/what-is-a-trust/

Credibility

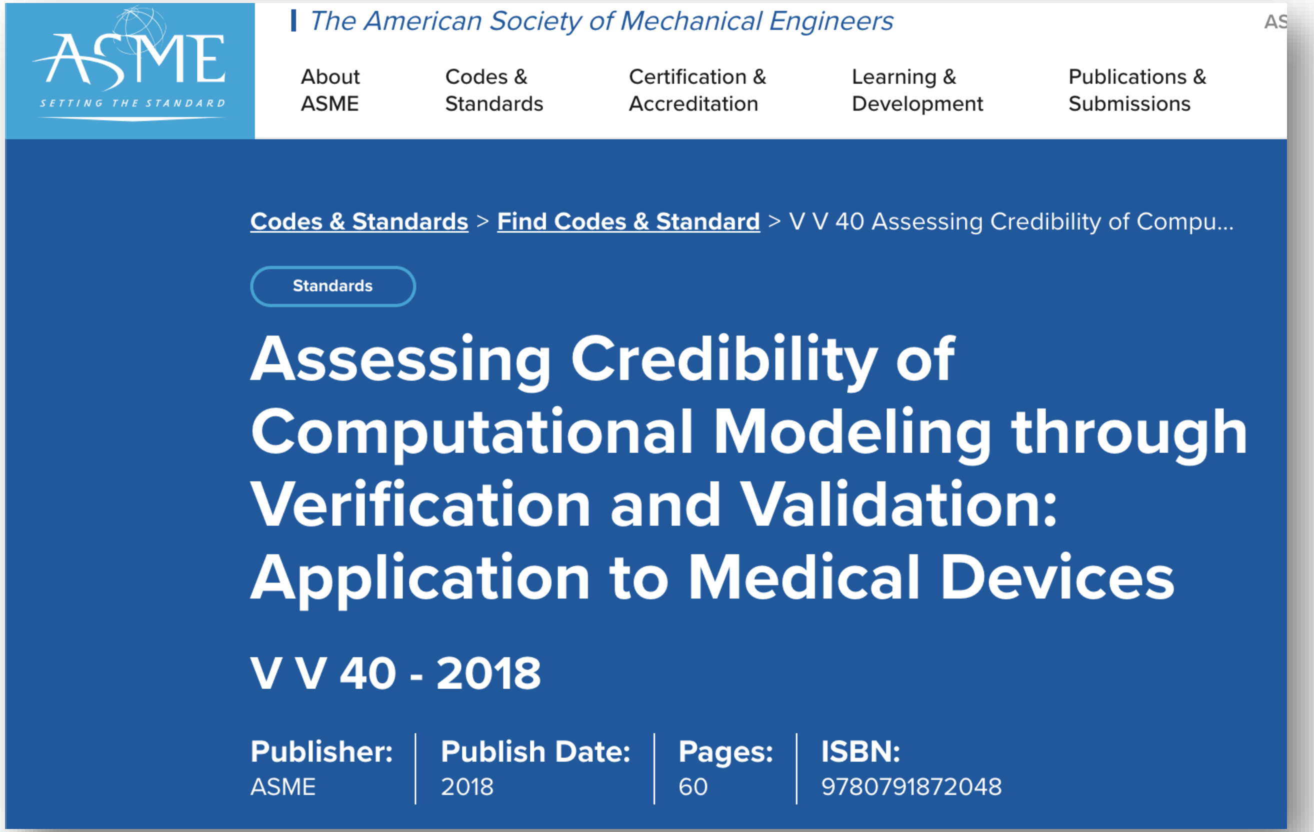
Ability of a model to elicit belief or trust in its results also accounting for its risk level



ASME V&V-40 2018

Assessing credibility of computational modelling through verification and validation: Application to medical devices

ASME V&V-40



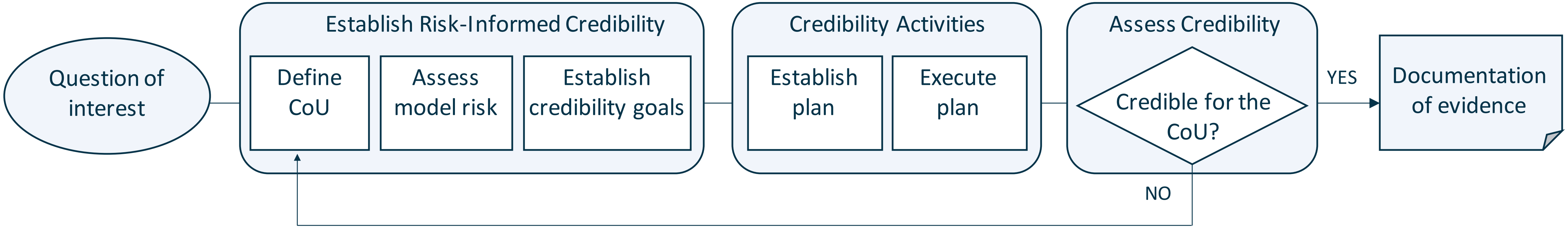
- Published by the ASME in 2018
- Is my model credible for the CoU?

- Work in progress..

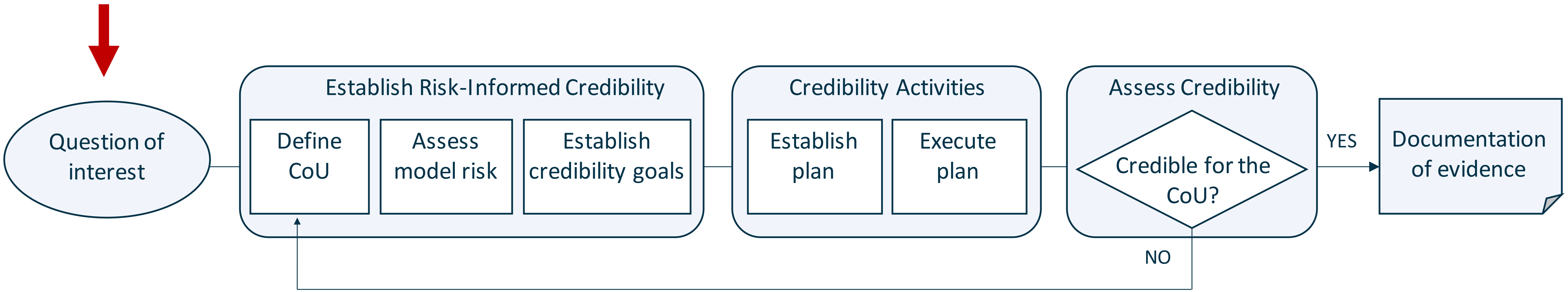
WG1 Using Historical Clinical Data As A Comparator
WG2 End-to-End Example
WG3 Patient-Specific Models
WG4 Verification Best Practices in Code and Calculation
WG5 Mock Submission – V&V 40 Practice in Regulatory Applications
WG6 Revisions for V&V40 – General Methodology Work Item

[Assessing Credibility of Computational Modeling through Verification & Validation: Application to Medical Devices | 2018 | DRM Enabled PDF | ASME]

V&V-40 Credibility framework



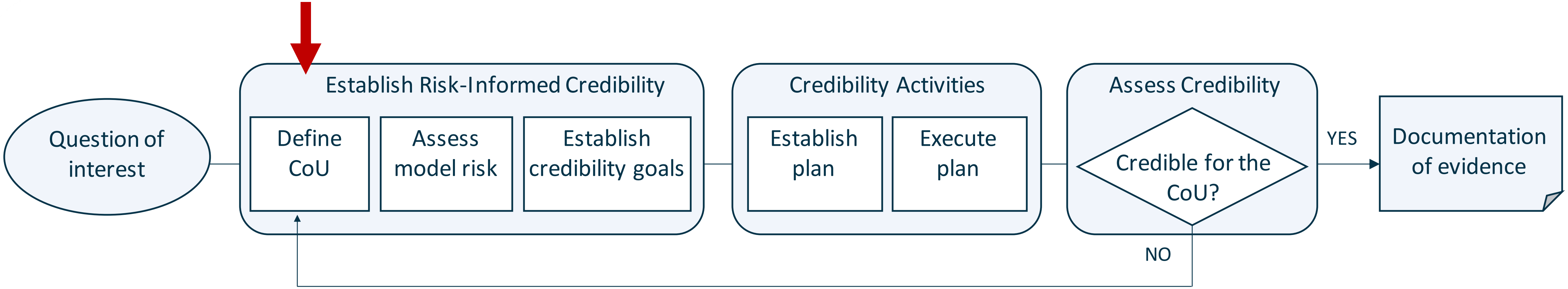
Question of Interest



Describes the *specific* question, decision or concern that is being addressed

What problem are you solving / addressing, irrespective of the model?

Context of Use

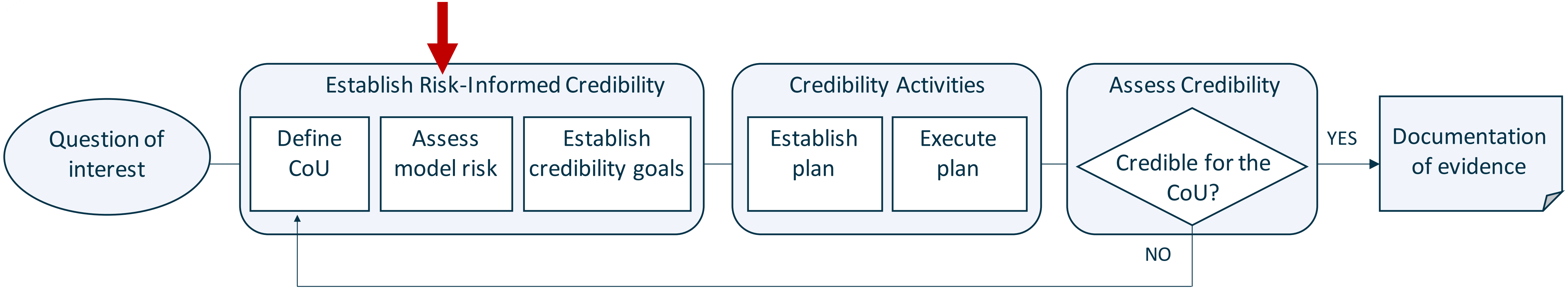


Defines the specific role and scope of the computational model used to address the problem in relation to other evidences.

Model will *do this*, by *using that*, to *decide this*.

General | Strategy | Decision

Assess model risk



Is the possibility that the model may lead to a false/incorrect conclusion about device performance, resulting in adverse outcomes

Assess model risk

- **Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.

(Low, Medium, High)

- Delay in Surgery
- Revision Surgery
- Severe Death

Decision Consequence				
	High	3	4	5
	Medium	2	3	4
	Low	1	2	3
		Low	Medium	High
		Model Influence		

- **Model influence** is the contribution of the computational model to the decision relative to other available evidence.

(Low, Medium, High):

- Model is a minor factor in the decision.
- Model is a moderate factor in the decision.
- Model is a significant factor in the decision.

Assess model risk

Model Risk = medium-high

- **Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision.

(Low, Medium, High)

- Delay in Surgery
- Revision Surgery
- Severe Death

Decision Consequence		Model Influence: Low	Model Influence: Medium	Model Influence: High
	High	3	4	5
	Medium	2	3	4
	Low	1	2	3

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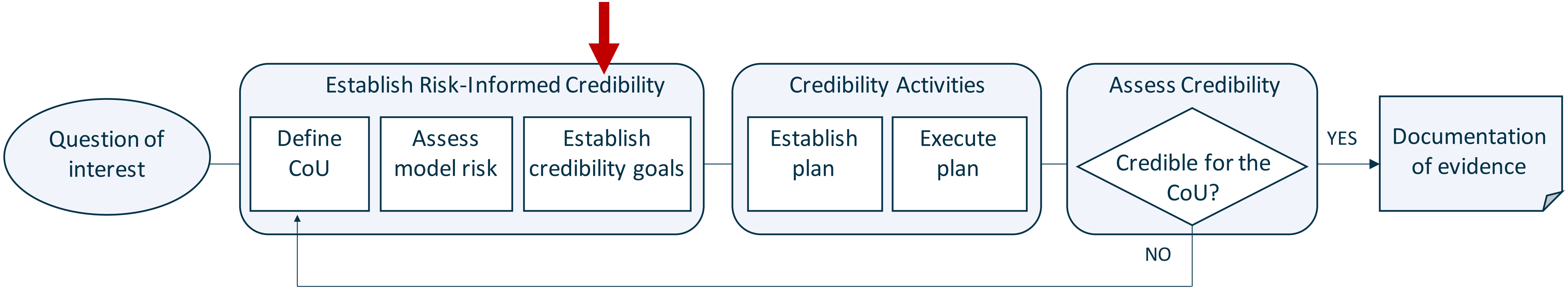
Establish credibility goals



V&V40 core principle: model credibility is commensurate with the risk!

Establish credibility goals

Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Inputs
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency of Input Parameters
		Output Comparison

Adapted from V&V40 Document

Establish credibility goals

Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Inputs
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency of Input Parameters
		Output Comparison

Quantification of Sensitivities

Quantification of Uncertainties

Adapted from V&V40 Document

Example gradation of activities: QoU

5.2.1.2.2 Quantification of Uncertainties. This component of the credibility factor examines the degree to which known or assumed uncertainties in the model inputs are propagated to uncertainties in the simulation results.

LOW

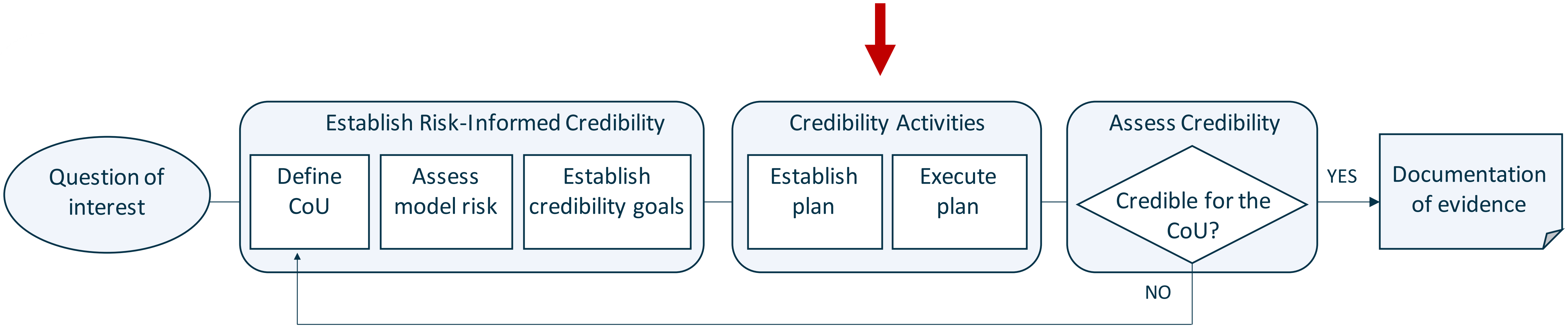
↓

HIGH

(a) Uncertainties were not identified.
(b) Uncertainties on expected key inputs were identified and quantified but were not propagated to quantitatively assess the effect on the simulation results.
(c) Uncertainties on all inputs were identified and quantified, and were propagated to quantitatively assess the effect on the simulation results.

Adapted from V&V40 Document

Define and perform the credibility plan



! Specific for the context of use and for the type of model!

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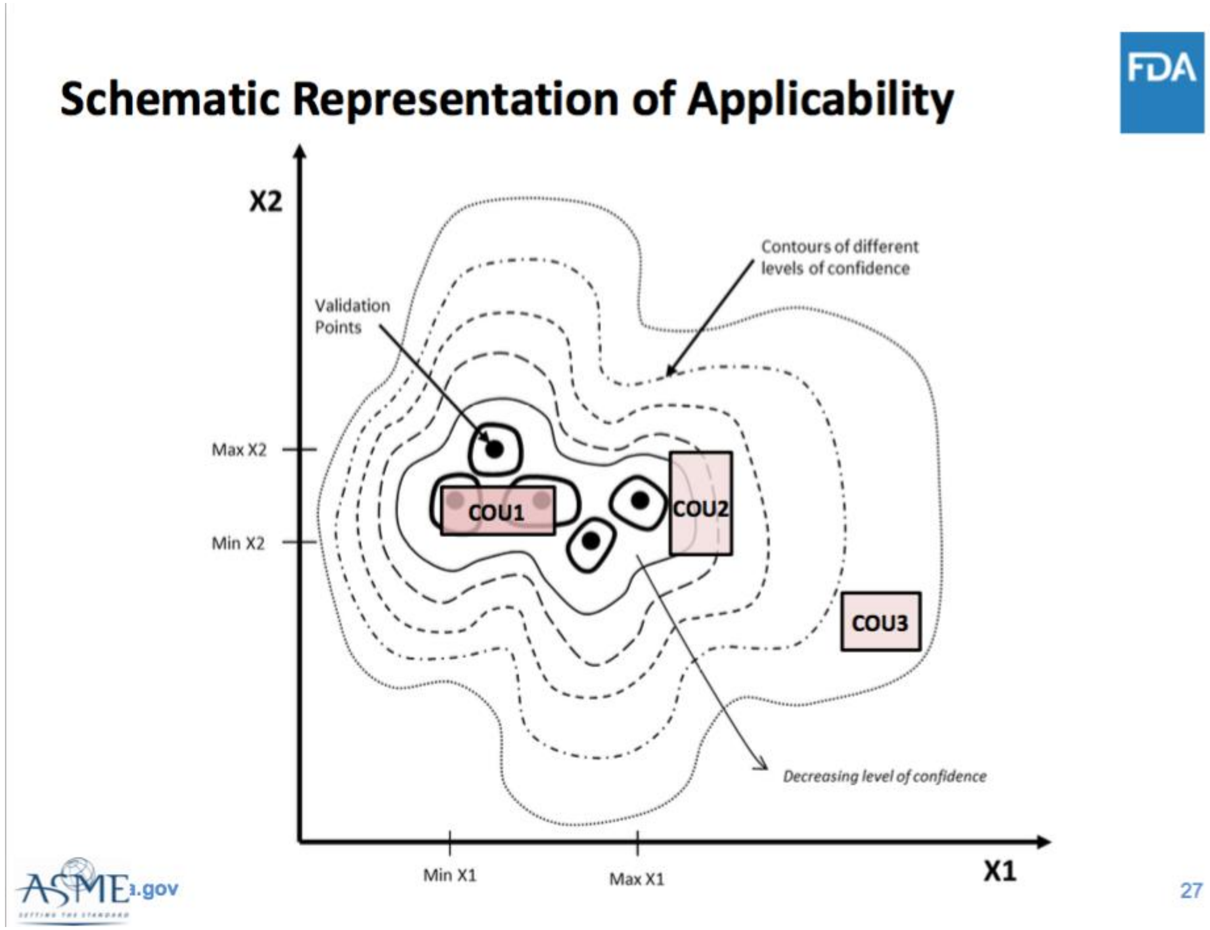
SCIENCE MEDICINES HEALTH

FDA U.S. FOOD & DRUG ADMINISTRATION

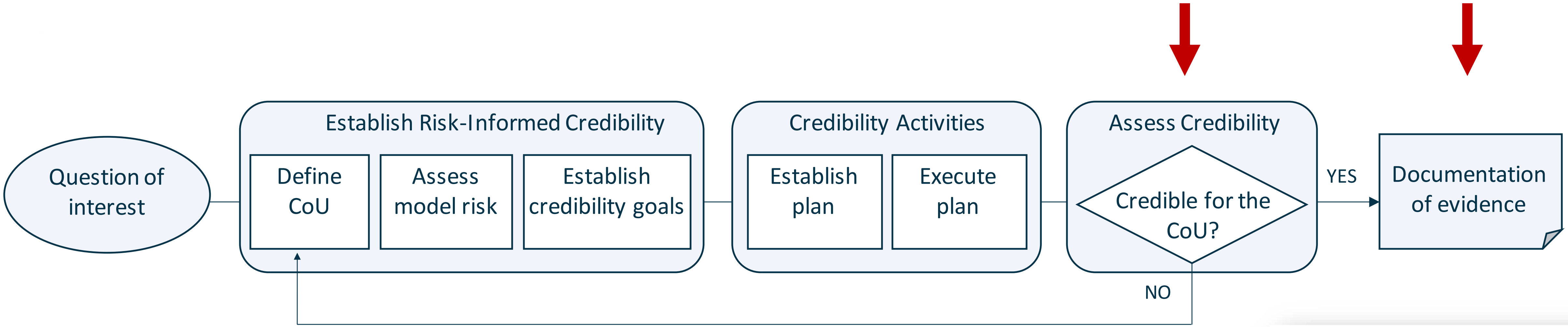
! Interactive feedback from regulators!

Applicability

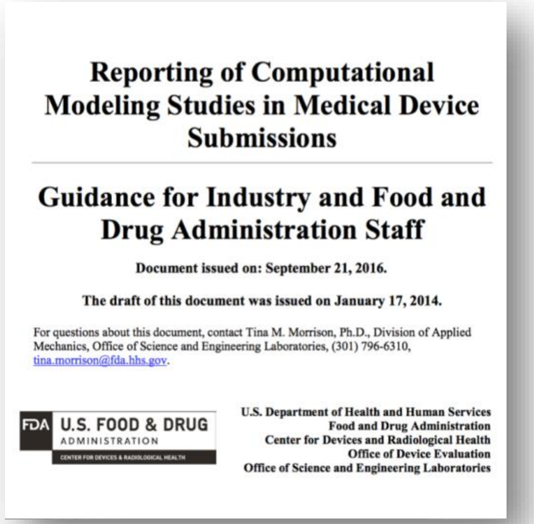


- Relevance of the V&V Activity to the COU model
- Relevance of the quantities of interest

Assess credibility and document evidences



Review the Cou, model risk, goals, credibility activities and results…



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

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

Standard accepted by regulators..

U.S. FOOD & DRUG ADMINISTRATION

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Contains Nonbinding Recommendations
Draft – Not for Implementation

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Draft Guidance for Industry and Food and Drug Administration Staff

DRAFT GUIDANCE
This draft guidance document is being distributed for comment purposes only.

Document issued on December 23, 2021.

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

DRAFT

.. More about clinical validation...

WHITE PAPER

Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility

Flora T. Musuamba[1,2,3] | Ine Skottheim Rusten[1,4] | Raphaëlle Lesage[5,6] | Giulia Russo[7] | Roberta Bursi[8] | Luca Emili[8] | Gaby ... Kristin E. Karlsson[1,11] | Alexander ... Jean-Pierre Boissel[12] | Cécile F. Rouss...

starting from mechanisms, see Table in Section 2 for a full definition) is scarce. The EMA and FDA physiology-based guidelines on pharmacokinetics (PBPK) models can be cited as pioneers in this domain.[16,17] With the aforementioned increase in model technologies used in drug development, there is an unmet need to provide an environment that would permit establishing the credibility of mechanistic *in silico* models and their adequate (regulatory) evaluation in a consistent manner.

This white paper aims to provide input on rigorous scientific and regulatory evaluation strategy for the expanding range of *in silico* technologies currently used in drug development. We will present a high-level framework, inspired by the ASME V&V40 for medical devices,[18] that could guide the evaluation process of models and associated simulations in a holistic and comprehensive manner without necessary

Received: 9 February 2021 | Revised: 18 August 2021 | Accepted: 24 August 2021
DOI: 10.1002/psp4.12708

WHITE PAPER

Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework

Ine Skottheim Rusten[1,2] | Flora Tshinanu Musuamba[2,3]

[1]The Norwegian Medicines Agency, Oslo, Norway
[2]EMA Modelling and Simulation Working Party, Amsterdam,

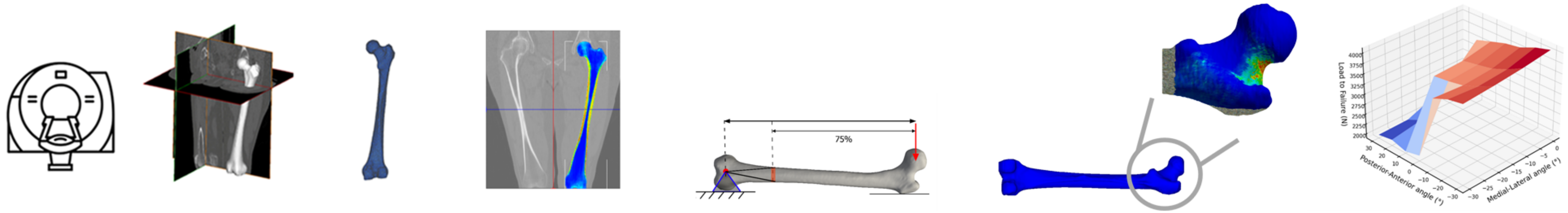
Abstract
Empirical pharmacometric models are part of practically every regulatory submission for a new drug. The use of the models often exceeds descriptory roles a...

.. Also for in silico model in drug development...

ASME V&V-40 2018 application to Bologna Biomechanical Computed Tomography (BBCT)-hip model

BBCT-hip model

Finite Element model



QCT | Geometry extraction | Meshing | HU-based material properties | Boundary condtions | Principal strains based load to failure | Load to failure map

Mathematical stochastic model

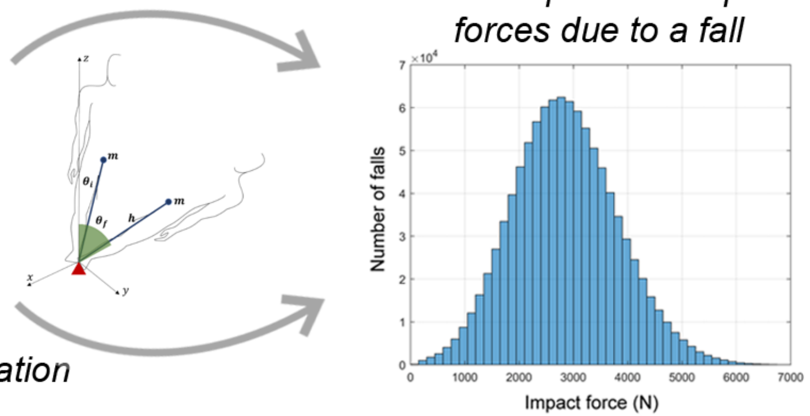
Deterministic variables

Patient-specific height
Patient-specific weight

Stochastic variables

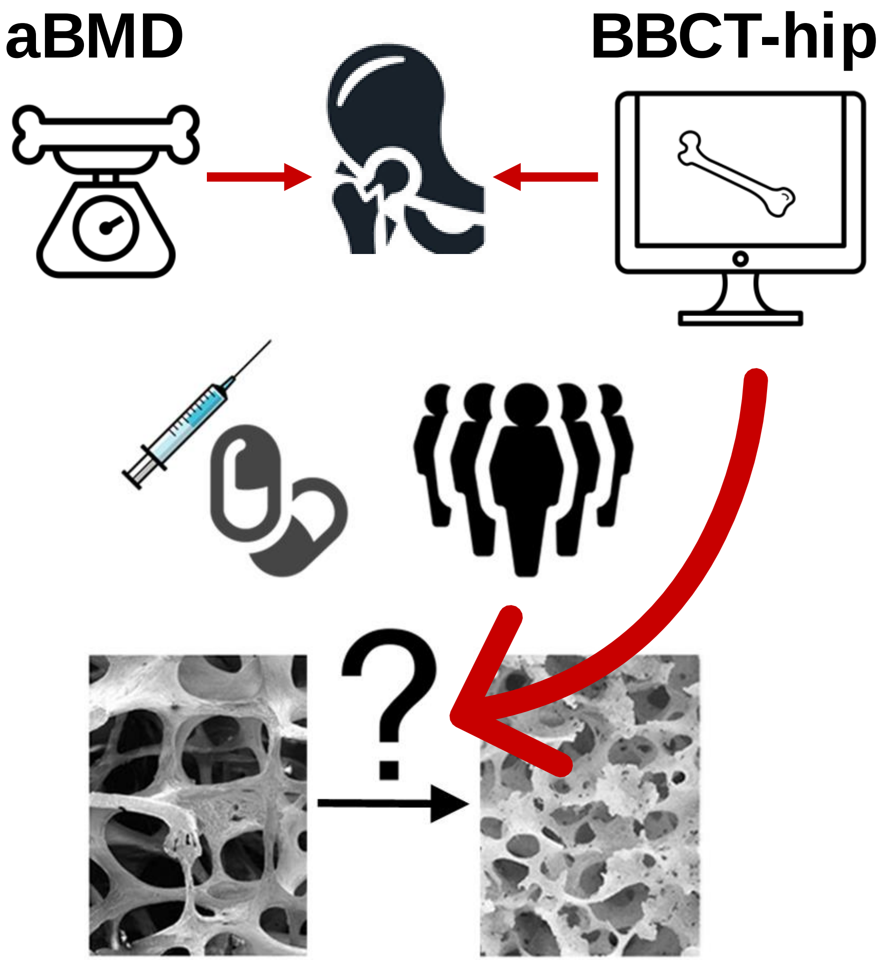
Initial & final velocity
Initial and final accleration
Postural attenuation
External impact force attenuation

1 million possible impact forces due to a fall



ARF0: fraction of impact forces causing fracture

BBCT-hip methodology: in silico trial



QUALIFICATION

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insight into the ***reliability, accuracy, precision, clinical validity, generalizability and clinical applicability*** *of the methodology to be qualified*

Qualification of novel methodologies

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10 November 2014
EMA/CHMP/SAWP/72894/2008
Revision 1: January 2012[1]
Revision 2: January 2014[2]
Revision 3: November 2014[3]
Revision 4: October 2020[4]
Scientific Advice Working Party of CHMP

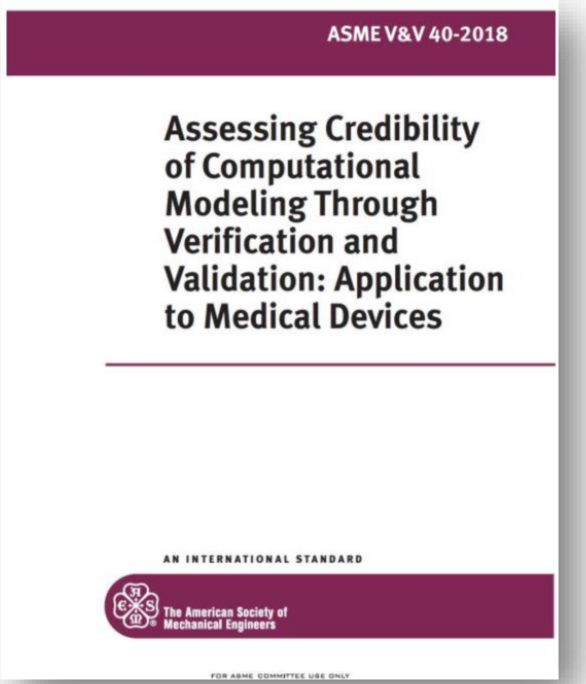
Qualification of novel methodologies for drug development: guidance to applicants

“A qualification submission **should provide insight into the reliability, accuracy, precision, clinical validity, generalisability and clinical applicability** of the methodology to be qualified, at a level of detail that is sufficient for assessment, yet not so detailed as to invalidate the qualification when, for example, minor software updates are implemented.”

BBCT-hip model credibility

No shared framework for establishing the credibility of mechanistic in silico models used in drug development

BBCT-hip credibility assessment following ASME V&V-40 2018

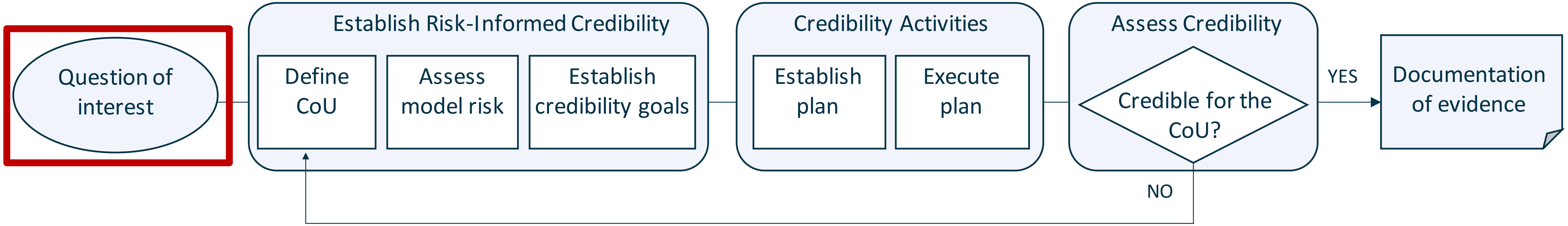

ASME V&V 40-2018

Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices

AN INTERNATIONAL STANDARD

The American Society of Mechanical Engineers

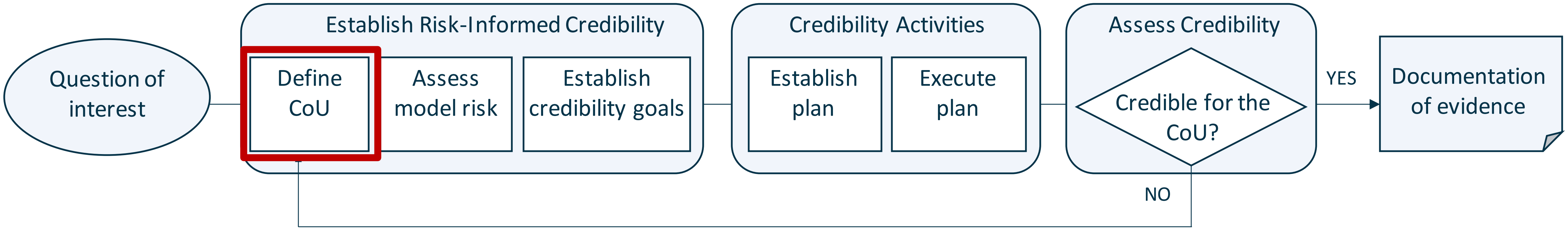
Application of ASME V&V-40 to BBCT-hip



Which is the optimal effective dose for a new anti-osteoporosis drug in adults and older adults (from 55 years) according to multi-dose Phase II studies?

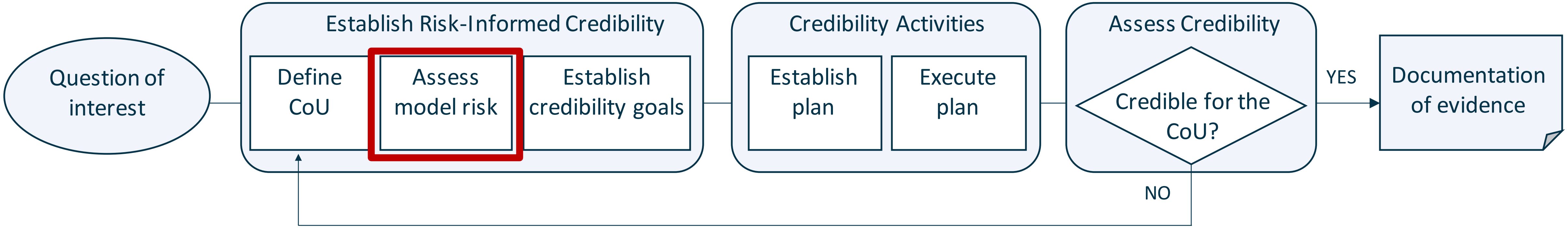
Adapted from V&V40 Document - Draft v11 – Public Comment (Fall 2017)

Application of ASME V&V-40 to BBCT-hip



BBCT-hip is a methodology where a stochastic biophysics model provides an estimate, for a given subject, of the Absolute Risk of proximal femur Fracture upon falling at time zero (ARF0), from their height, weight, and a Quantitative Computed Tomography (QCT) scan of the hip region. This ARF0 is to be used as a ***response variable in multi-dose Phase II studies in place of the measured DXA-based aBMD****. The average change in ARF0 over the period of treatment for all subjects treated with a given dose* **($Ave_{\Delta ARF0}$) can be used as response variable, by assuming the optimal dose among those tested is the one for which $Ave_{\Delta ARF0}$ is most positive (or least negative).**

Application of ASME V&V-40 to BBCT-hip



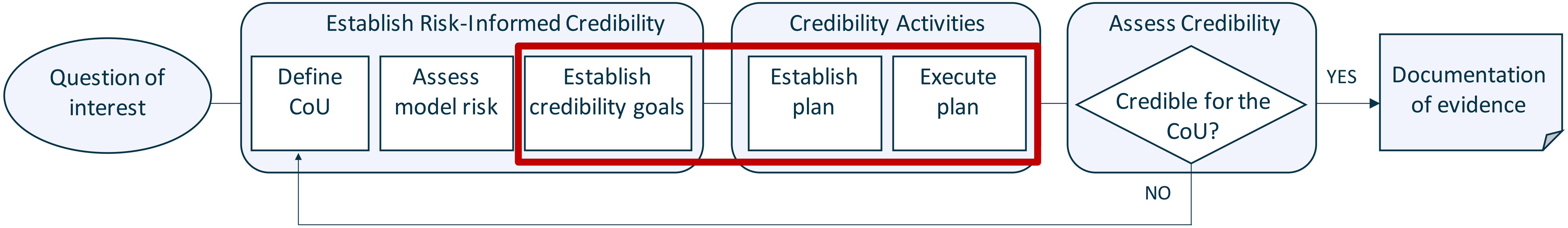
Decision consequence		Regulatory Impact: Low	Regulatory Impact: Medium	Regulatory Impact: High
	High	3	4	5
	Medium	2	3	4
	Low	1	2	3

Low **decision consequence**

High **regulatory impact**

Skottheim Rusten et al., CPT: Pharmacomet. Syst. Pharmacol., 2021

Application of ASME V&V-40 to BBCT-hip



Activities		Credibility Factors
Verification	Code	Software Quality Assurance
		Numerical Code Verification
	Calculation	Discretization Error
		Numerical Solver Error
		Use Error
Validation	Computational Model	Model Form
		Model Inputs
	Comparator	Test Samples
		Test Conditions
	Assessment	Equivalency of Input Parameters
		Output Comparison
Applicability		Relevance of the Validation to the COU
		Relevance of the Quantities of Interest

Adapted from V&V40 Document - Draft v11 – Public Comment (Fall 2017)

BBCT-Hip credibility

Activities		Credibility Factors
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Technical validation

Verification

Uncertainty/sensitivities quantification

Experimental tests

Retrospective clinical cohort

Adapted from V&V40 Document - Draft v11 – Public Comment (Fall 2017)

BBCT-Hip credibility

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BBCT-Hip credibility: Validation

Activity	Credibility factor	Rigor		
		Available Range	Selected	Achieved Credibility
Verification				
Code Verification	Software Quality Assurance (SQA) (5.1.1.1)	a-c	b: SQA procedures from the vendors are referenced.	Medium
	Numerical Code Verification (NCV) (5.1.1.2)	a-d	b: multiple benchmark test cases are used to verify the numerical solution.	Medium
Calculation verification	Discretization error (5.1.2.1)	a-c	c: conservation equation balances are checked, and mesh sensitivity study conducted.	High
	Numerical solver error (5.1.2.2)	a-c	c: problem-specific sensitivity study performed on solver parameters.	High
	User error (5.1.2.3)	a-d	b: inputs and outputs verified by practitioner.	Medium

BBCT-Hip credibility: Verification

Code verification **Calculation verification**

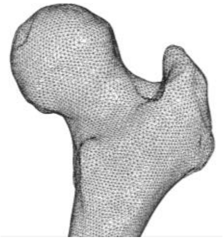
Mathematical model ⟷ Computational model ⟷ Simulation results

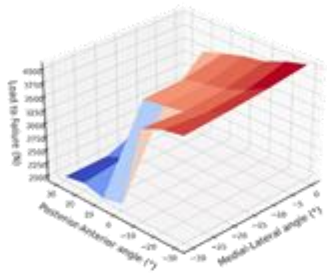
- SQA procedures from the vendors are referenced

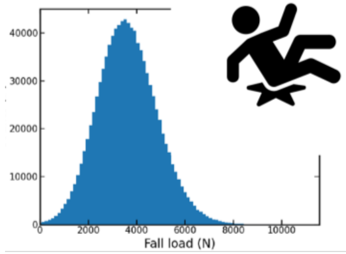
Ansys MATLAB

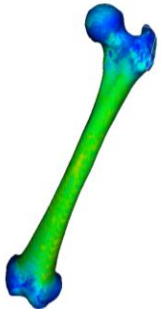
- Multiple benchmark test cases are used to verify the numerical solution

- Newton-Raphson convergence criteria
- Discretization error









BBCT-Hip credibility: Validation

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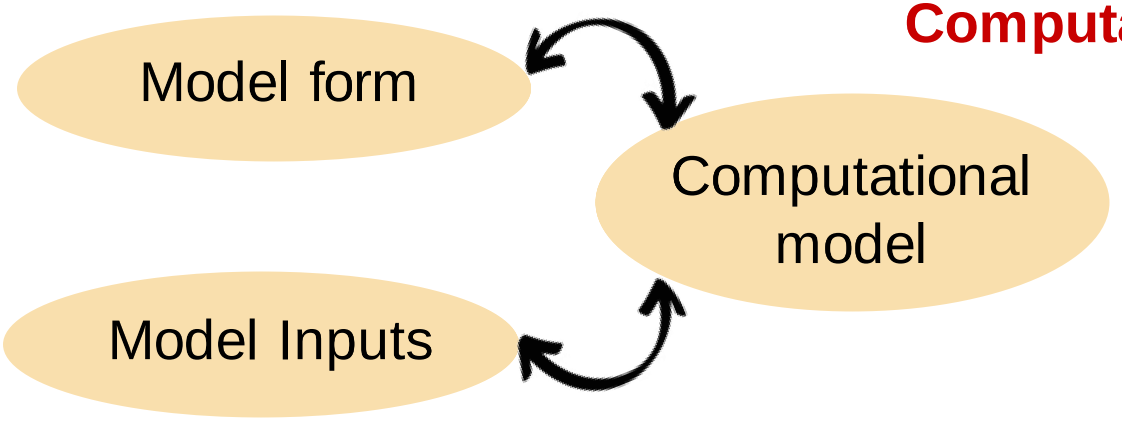
BBCT-Hip credibility: Validation

Activity	Credibility factor	Rigor		
		Available Range	Selected	Achieved Credibility
Validation				
Computational model	Model Form (5.2.1.1)	a-c	c: comprehensive evaluation of model form performed **(segmented geometry, density-elasticity relationship, principal strains-based fracture criteria, boundary conditions).**	High
	Model Inputs			
	Quantification of sensitivities (5.2.1.2.1)	a-c	c: comprehensive sensitivity analysis performed.	High
	Quantification of Uncertainties (5.2.1.2.2)	a-c	c: input uncertainties identified and propagated.	High

Aldieri et al., Comput. Methods Programs Biomed., Accepted

BBCT-Hip credibility: Validation



Computational Model

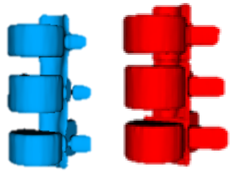
Model form

- Governing equations: density–elasticity relationship
- System configuration: CT-derived femur geometry
- System conditions: applied boundary conditions to simulate a fall on the side

Model inputs

- Governing equations: $\mathrm{E} = A \cdot \rho_{App}^{B}$
- Governing equations:

$$\rho_{QCT} = C + HU \cdot D$$



- System configuration: anatomical landmarks

- System conditions: boundary conditions
- System conditions: contact parameters

BBCT-Hip credibility: Validation

Activity	Credibility factor	Rigor: Available Range	Rigor: Selected	Rigor: Achieved Credibility
Comparator – Observed data	**Test samples**			
	Quantity of test samples (5.2.2.1.1)	a-c	c: statistically relevant number of samples used.	High
	Range of characteristic test samples (5.2.2.1.2)	a-d	b: samples with range of characteristics near nominal (*in vitro* data). c: samples representing expected extreme values included (*in vivo* data).	Medium
	Measurements of test samples (5.2.2.1.3)	a-c	c: all key characteristics measured.	High
	Uncertainty of test sample measurements (5.2.2.1.4)	a-d	c: statistical treatment of repeated measurements (*in vitro* data).	Medium
	Test Condition			
	Quantity of test conditions (5.2.2.2.1)	a-c	b: two test conditions examined (*in vitro* data).	Medium

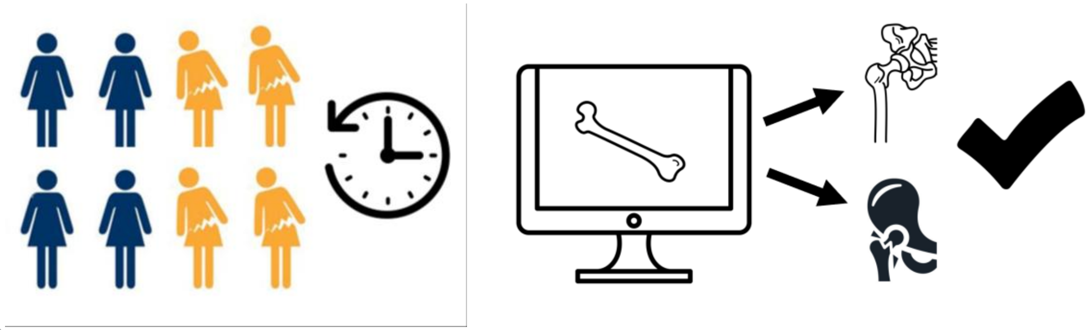
BBCT-Hip credibility: Validation

Comparator – Observed Data

Computational model → Simulation outcomes ⟷ Experimental outcomes

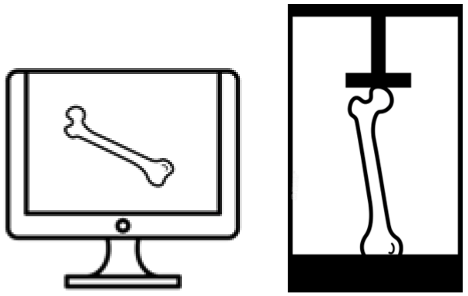
In vivo comparator:

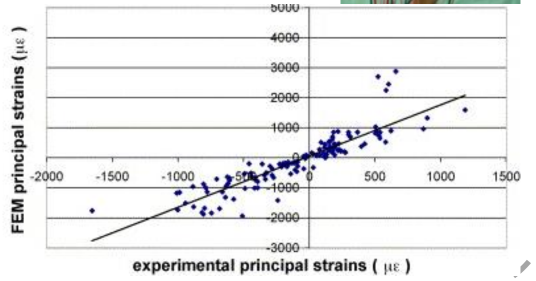
stratification accuracy



In vitro comparator:

predictive accuracy





BBCT-Hip credibility: Assessment

Activity	Credibility factor	Rigor		
		Available Range	Selected	Achieved Credibility
Assessment	Equivalency of Input parameters (5.2.3.1)	a-c	c: types and inputs equivalent (*in vitro* data).	High
	Output comparison			
	Quantity (5.2.3.2.1)	a-b	b: multiple outputs compared.	High
	Equivalency of output parameters (5.2.3.2.2)	a-c	c: types of outputs were equivalent (*in vitro* data). b: types of output were similar (*in vivo* data).	Medium
	Rigor of Output comparison (5.2.3.2.3)	a-d	b: comparison performed determining the difference between experimental and computational results. **The comparison was performed based on the Standard Error of Estimate (SEE) for in vitro data, Area Under Curve (AUC) for in vivo data.**	Medium
	Agreement of output comparison (5.2.3.2.4)	a-c	c: level of agreement satisfactory for all comparison	High

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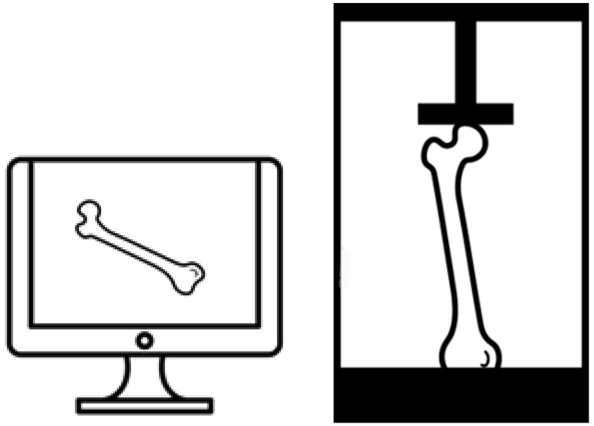
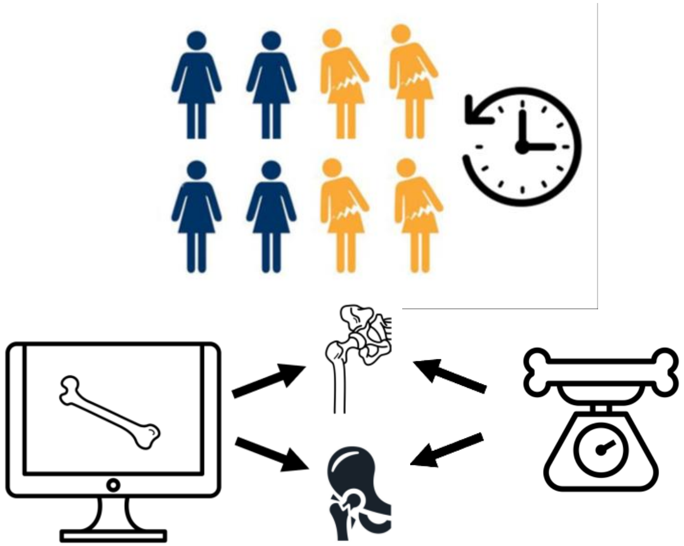
BBCT-Hip credibility: Assessment

Predictive accuracy



- Strain prediction accuracy: 7%
- Load to failure prediction accuracy: 15-16%

Stratification accuracy



- BBCT-hip AUC: 85.2%
- aBMD AUC: 75%

BBCT-Hip credibility: Applicability

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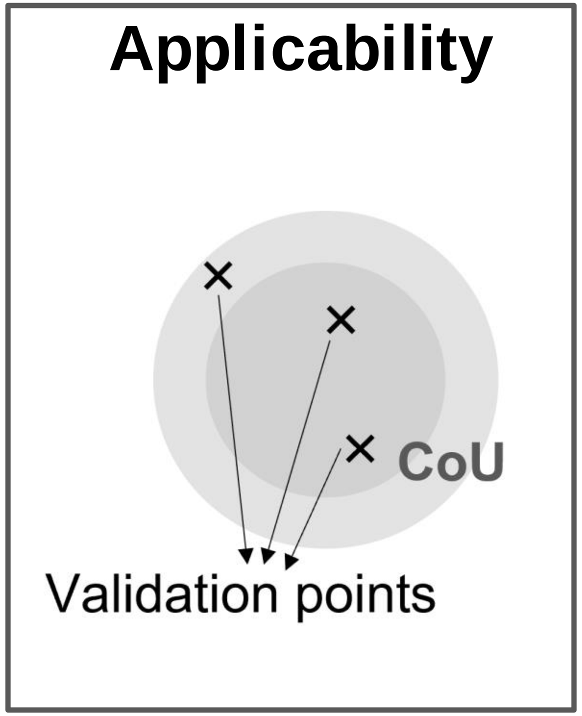
BBCT-Hip credibility: Applicability



Activity	Credibility factor	Rigor		
		Available Range	Selected	Achieved Credibility
Applicability	Relevance of the Quantity of Interest (5.3.1)	a-c	a: the quantities of interest from the validation activities were related to those for the CoU (*in vitro* data) b: the quantities of interest used for the validation activities was equivalent to those for the CoU but the way it was adopted different (*in vivo* data)	Low-Medium
	Relevance of the Validation Activities on the CoU (5.3.2)	a-d	b: there was partial overlap between the ranges of the validation points and the CoU	Low-Medium

Aldieri et al., Comput. Methods Programs Biomed., Accepted

BBCT-Hip credibility

Was this enough?

BBCT-Hip credibility assessment

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Clinical validation must be designed like a clinical trial:

Prospective
Randomised
Double blind
Statistically powered
Validity against established outcomes

Clinical validation

Prospective clinical cohort

Conclusions

- Importance of a standardized credibility assessment framework
- Flexibility of ASME V&V-40 allows it to be translated to different contexts
- Robust V&V and credibility activities to be carried out throughout the development of computational models
- Need of interactive feedback from regulators

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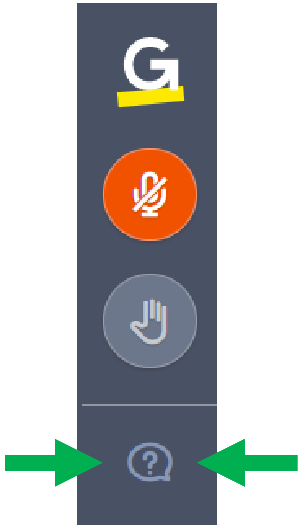
Q&A

To pose a question, please click on the symbol and send your question via the 'Ask the staff a question' panel



This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 823712

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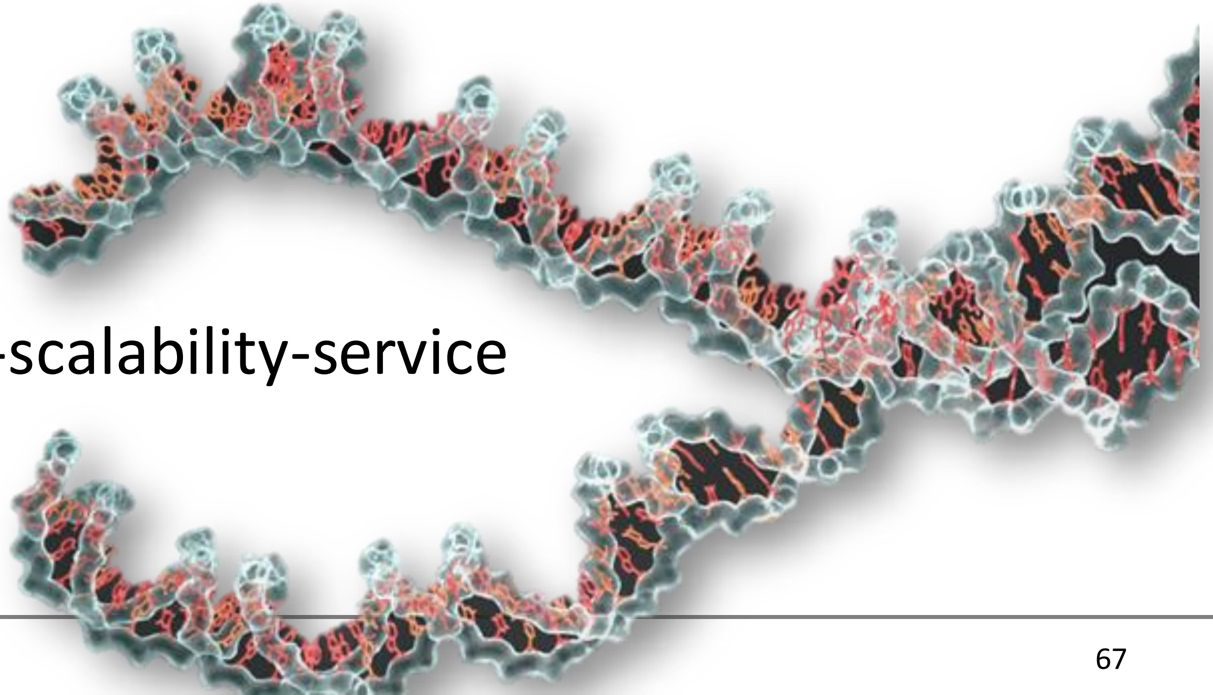

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Expertise	• The community is invitation only: in this way we ensure only interested experts have access
Collaboration	• Join teams and collaboratively work on shared goals, projects, concerns, problems or topics
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