Powering Innovation That Drives Human Advancement

In Silico Trials for Device Development & Regulatory Review: Considerations for Implementation of ISCTs

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Changing the world through the power of simulation

50+ YEARS OF INNOVATION

Shatter Records

Unlock Possibilities

Make the Unmakeable

Save Lives

Traditional Uses of CM&S in Orthopaedics

- Optimize Bench Testing
- MRI safety
- Additive Manufacturing
- Image-Based Modeling
- Materials Intelligence

How to Implement a Solid Approach to Materials Intelligence

Additive Manufacturing

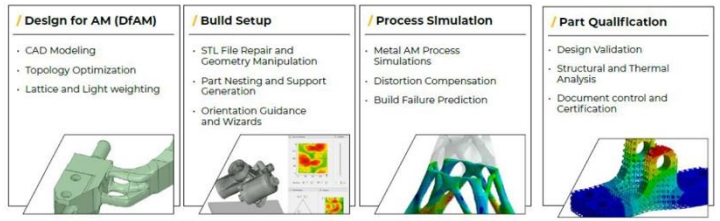
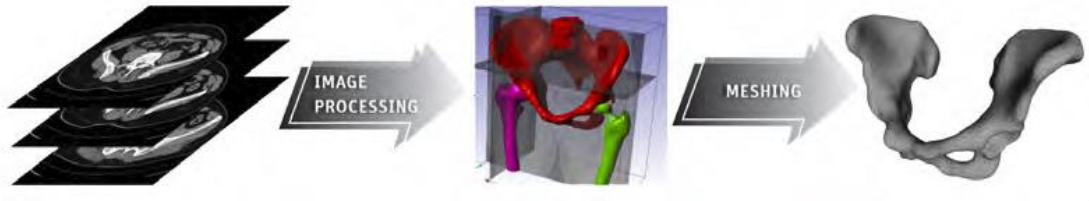
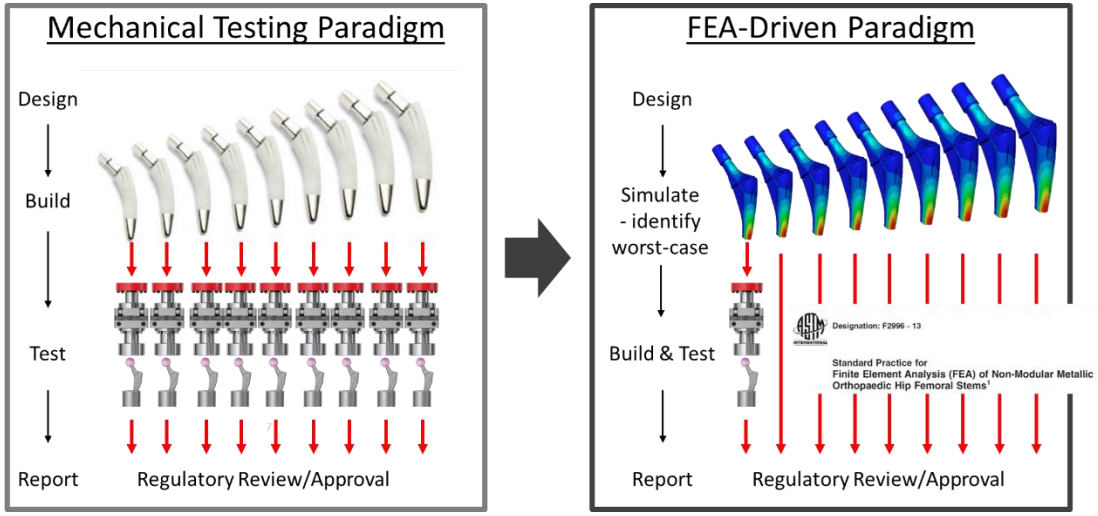
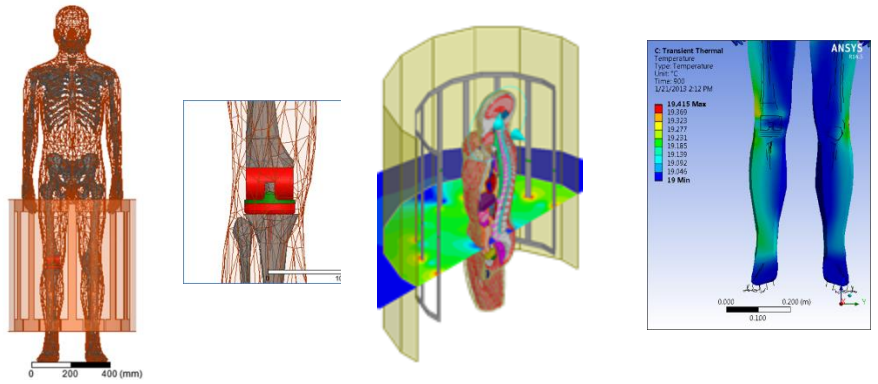


Image-Based Modeling





MRI Safety Workflow



Clinical Trials – Opportunity for Reform

Clinical trial classification

Device Studies	Drug Studies
Pilot: Small study (10-30 patients with the condition) to determine preliminary safety and performance	**Phase I:** Small study (20-100 healthy volunteers or people with condition) to determine preliminary safety and dosage
Pivotal: Larger study (150-300 patients with the condition) to determine efficacy and adverse effects	**Phase II:** Larger study (up to several hundred people with the condition) to determine efficacy and adverse effects
Post-approval: Post-approval study to collect long-term data	**Phase III:** *(sometimes known as pivotal study)* Even larger study (up to thousands of people with the condition) to determine efficacy and monitor adverse effects
	Phase IV: Post-marketing study to collect long-term data

https://premier-research.com/blog-medical-devices-vs-drug-trials/

Clinical trials are models of reality

- Achievement gap between clinical trials, registries and clinical practice
- Problems with double randomized trials for devices (implanted off)
- Ethical issues with mock procedures

Large trials expose many patients to unproven therapies

- Increase patient safety by virtual testing to:
  - Ensure product safety prior to clinical trials
  - Identify/confirm target population

Underserved or underrepresented populations

- Pediatric patients
- Patients with rare diseases
- Women
- Minorities/Ethnic backgrounds

Cost stifles innovation

Regulatory evidence cost outgrows revenue growth

* courtesy Mark Palmer, Medtronic

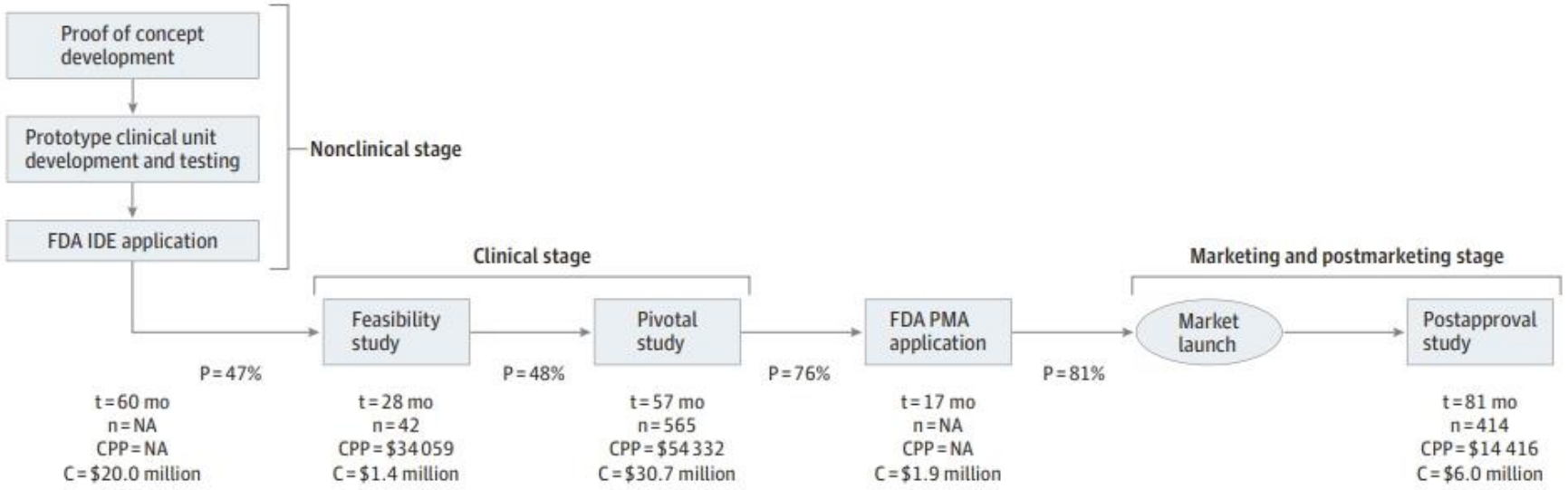
JAMA Network Open

Original Investigation | Health Policy

Estimated Cost of Developing a Therapeutic Complex Medical Device in the US

Aylin Sertkaya, PhD; Rebecca DeVries, ScD; Amber Jessup, PhD; Trinidad Beleche, PhD

Figure 1. Stages of Therapeutic Complex Medical Device Development



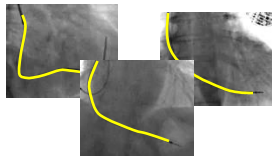
In this flow, these are costs that do not incorporate the cost of capital or failure, or removing the phase probabilities. C indicates phase cost (in $ 2018); CPP, cost per patient (in $ 2018); n, number of patients; NA, not applicable; P, phase transition success probability (%); t, phase duration (in months).

Case Study:
- Reducing Clinical Trial Size through Virtual Patients

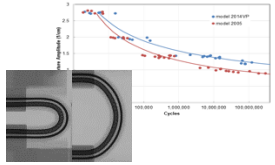
Medical Device Innovation Consortium

MODEL INPUTS

In-vivo curvature

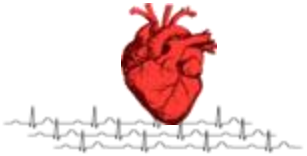


Fatigue strength



Patient activity (heartbeats)

Same for predicate and new lead



Patient age

From device registry

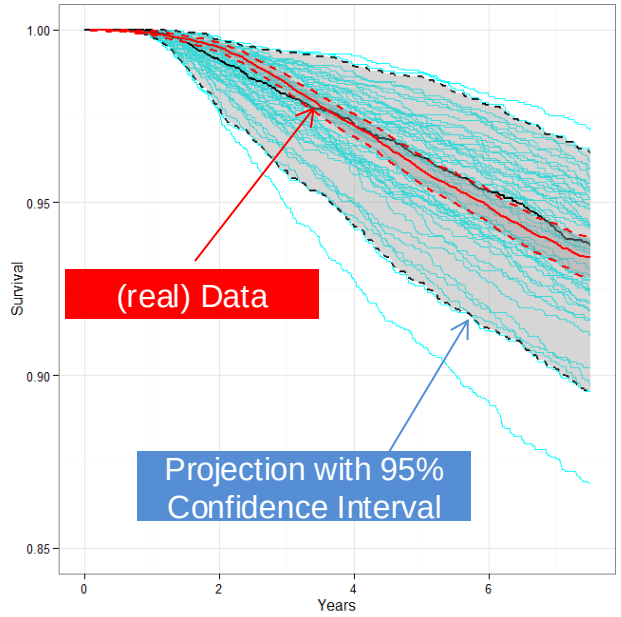
Life expectancy from U.S. Social Security actuarial life table

Same for predicate and new lead

Patient

Simulations

MODEL OUTPUT

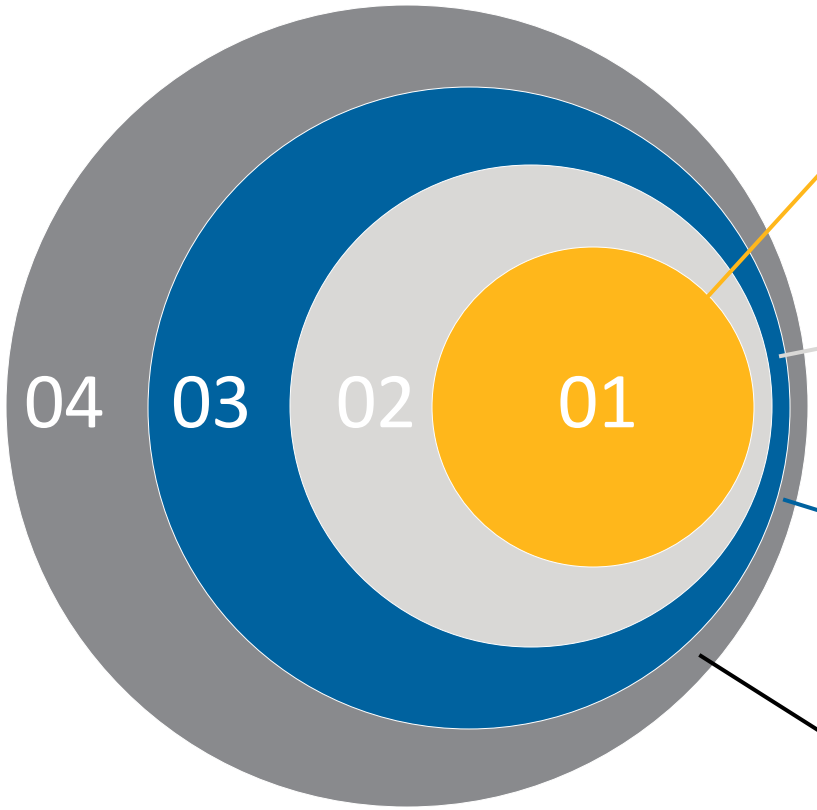


Powering Innovation That Drives Human Advancement

Ansys

Haddad et al. *Rel. Eng Sys Safety* (2014) & Haddad et al. *J. Biopharm. Stat.* (2017)

Virtual Patient Model Benefits



256 Reduction of the number of patients involved in the clinical trial

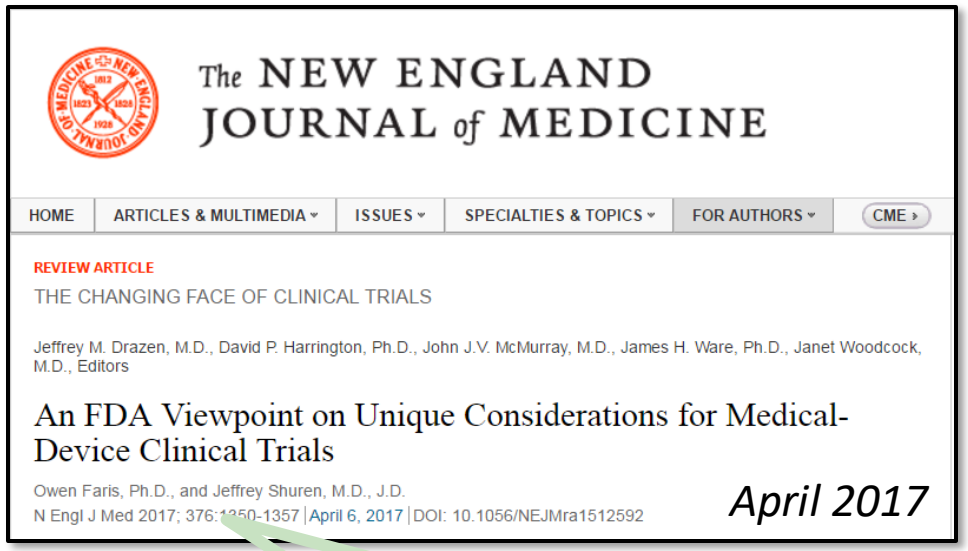
$10M Cost reduction due to the reduced number of patients

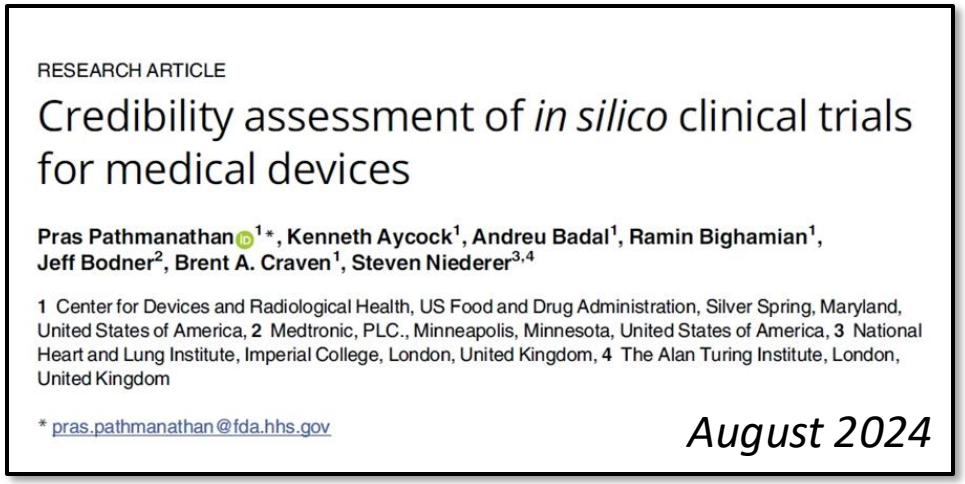
2 The product was released 2 years earlier

10,000 Number of patients treated during these 2 years

Source: Avicenna Alliance event at the EU Parliament (Sept 4th, 2018)

The US FDA is Supportive



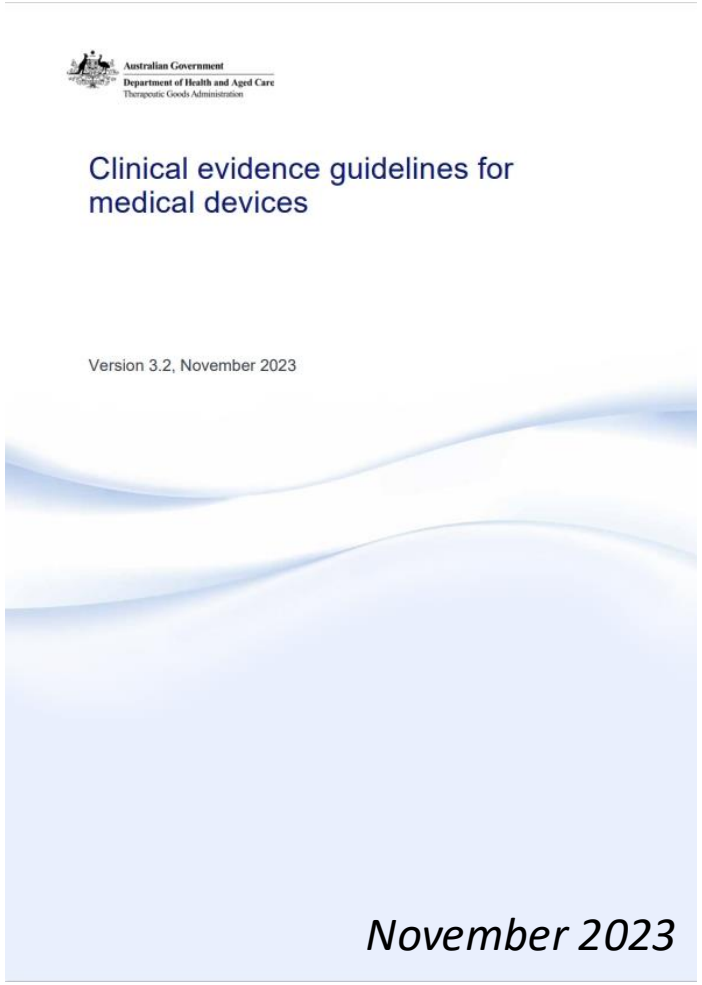


"If it can be shown that these virtual patients are similar, in a precisely defined way, to real patients, ***future trials may be able to rely partially on virtual-patient information****, thus lessening the burden of enrolling additional real patients."*

"ISCTs have the potential to provide cost-effective, time-efficient, and ethically favorable alternatives for evaluating the safety and effectiveness of medical devices. However, ensuring the credibility of ISCT results is a significant challenge."

Faris, O., & Shuren, J. (2017). An FDA viewpoint on unique considerations for medical-device clinical trials. *New England Journal of Medicine*, *376*(14), 1350-1357.

International Support is Also Growing

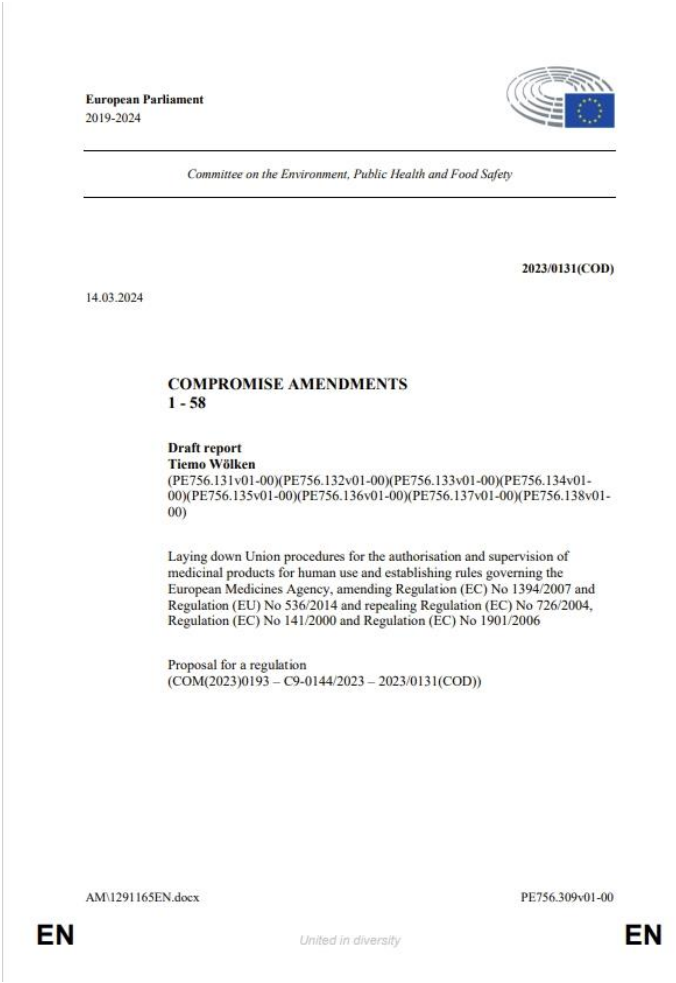


- Document focuses on the clinical evidence that is generated to establish medical device safety

A suitably qualified clinical expert/s who has endorsed the CER should determine the extent to which clinical investigation data can be extrapolated to all potential device specifications within the design envelope. ***Justification of generalisability may involve the use of clinical data, bench testing and/or computer modelling.***

*Generalisability of clinical evidence for the subject device across the entire design envelope has been justified through the identification of worst-case and common-use scenarios (**with the use of computer modelling** and state of the art literature review, respectively).*

International Support is Also Growing



European Parliament
2019-2024

Committee on the Environment, Public Health and Food Safety

2023/0131(COD)

14.03.2024

COMPROMISE AMENDMENTS
1 - 58

Draft report
Tiemo Wölken
(PE756.131v01-00)(PE756.132v01-00)(PE756.133v01-00)(PE756.134v01-00)(PE756.135v01-00)(PE756.136v01-00)(PE756.137v01-00)(PE756.138v01-00)

Laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000 and Regulation (EC) No 1901/2006

Proposal for a regulation
(COM(2023)0193 – C9-0144/2023 – 2023/0131(COD))

AM\1291165EN.docx PE756.309v01-00

EN United in diversity EN

March 2024

- This directive summarizes amendments to previously established EMA legislation related to drug approvals

*…..giving priority to new approach methodologies (NAMs) in place of animal testing. These can include but are not limited to: in vitro models, such as microphysiological systems including organ-on-chips, (2D and 3D) cell culture models, organoids and human stem cells-based models**; in silico tools.***

***Regulatory decision-making on the development, authorisation and supervision** of medicinal products may be supported by access and analysis of health data, including real world data, where appropriate, i.e. health data generated outside of clinical studies, **and/or data generated via in silico methods, such as computational modelling and simulation**, digital molecular representation and mechanistic modelling, digital twin and artificial intelligence (AI).*

What is an In Silico Clinical Trial (ISCT)?

- ISCTs are exploratory trials on the computer that make use of reliable computer models of the treatment (effect of the drug or device on the organism) and its deployment (administration of the drug or surgical procedure), together with reliable computer models of the patient's characteristics.

For each patient in the patient cohort

Physiology Layer

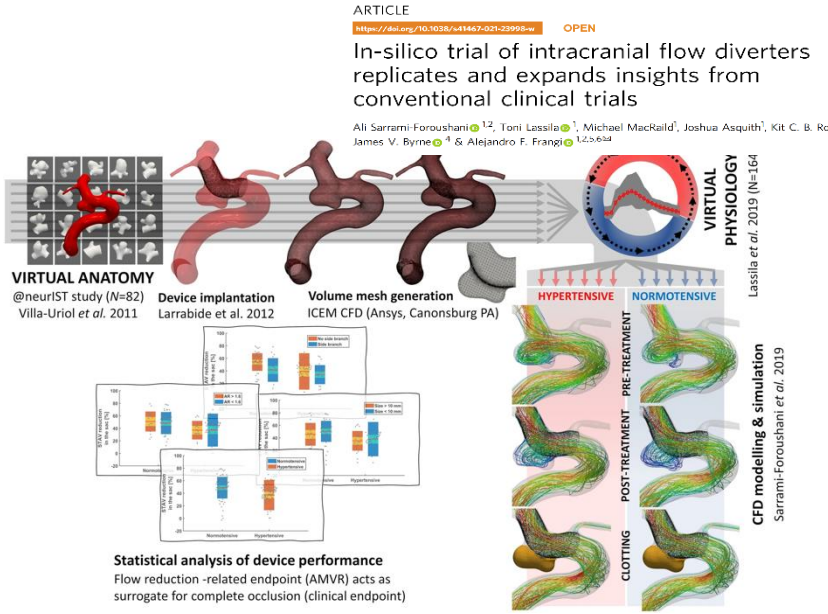
- Models patient physiology

Pathology Layer

- Models disease processes, incl. treatment response

Treatment Layer

- Models delivery of the therapy/intervention



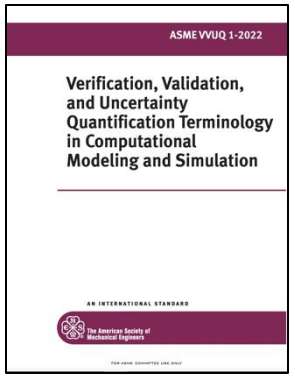
But is the Valid Scientific Evidence Valid?

ASME Committee on VVUQ in CM&S

COMMITTEE CENTRAL › VVUQ VERIFICATION, VALIDATION, AND UNCERTAINTY QUANTIFICATION IN COMPUTATIONAL MODELING AND SIMULATION

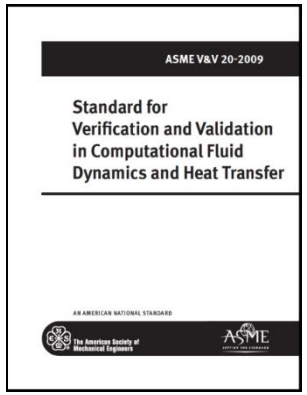
Standards Committee

- **Provide procedures for assessing and quantifying the accuracy and credibility of computational modeling and simulation**

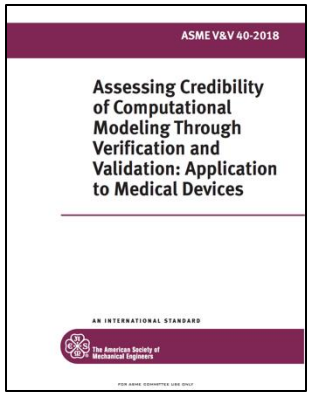


ASME VVUQ 1

ASME V&V10



ASME V&V20

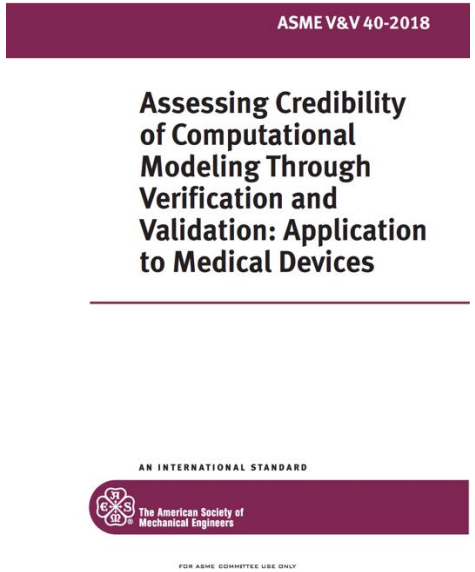


ASME V&V40

VVUQ Standards Committee in Computational Modeling and Simulation

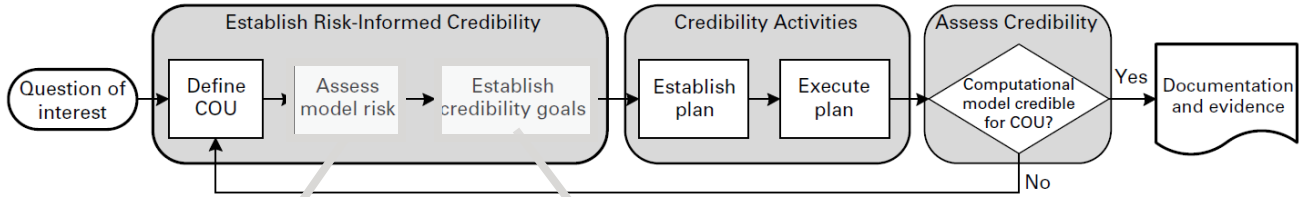
- **VVUQ 10** – VVUQ in Computational Solid Mechanics
- **VVUQ 20** – VVUQ in Computational Fluid Dynamics and Heat Transfer
- **VVUQ 30** – VVUQ in Computational Simulation of Nuclear System Thermal Fluids Behavior
- **VVUQ 40** – VVUQ in Computational Modeling of Medical Devices
- **VVUQ 50** – VVUQ of Computational Modeling for Advanced Manufacturing
- **VVUQ 60** – VVUQ of Computational Modeling for Energy Systems
- **VVUQ 70** – VVUQ of Machine Learning
- **VVUQ 80** – VVUQ in Computational Modeling of Pharmaceutical Products

A Risk-Based Approach to Establishing Model Credibility



The ASME V&V 40 standard provides a risk-based framework for establishing the credibility of CM&S

Figure 2.4-1 Process Diagram of the Risk-Informed Credibility Assessment Framework



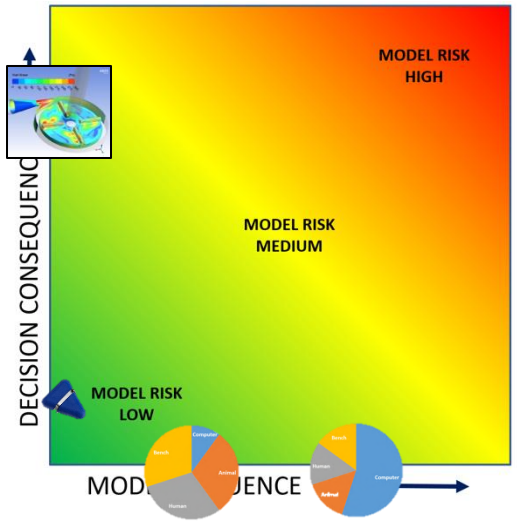
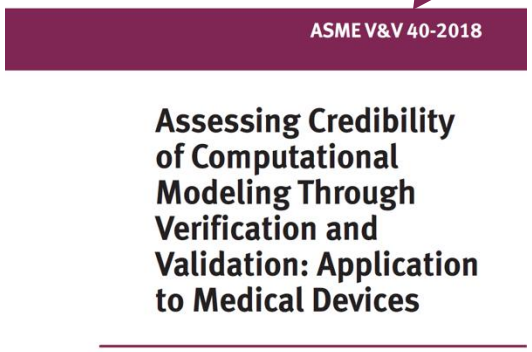


Table 5-1 Verification, Validation, and Applicability Activities and Their Associated Credibility Factors

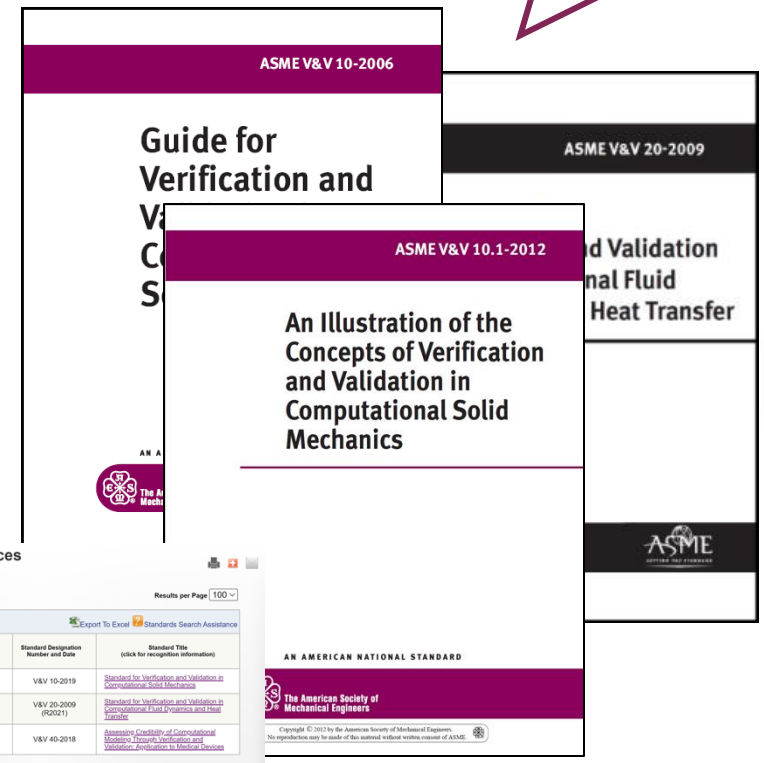
Activity (Paragraph)	Credibility Factor (Paragraph)
Verification (5.1)	
Code (5.1.1)	Software quality assurance (5.1.1.1)
	Numerical code verification (5.1.1.2)
Calculation (5.1.2)	Discretization error (5.1.2.1)
	Numerical solver error (5.1.2.2)
	Use error (5.1.2.3)
Validation (5.2)	
Computational model (5.2.1)	Model form (5.2.1.1)
	Model inputs (5.2.1.2)
Comparator (5.2.2)	Test samples (5.2.2.1)
	Test conditions (5.2.2.2)
Assessment (5.2.3)	Equivalency of input parameters (5.2.3.1)
	Output comparison (5.2.3.2)
Applicability (5.3)	Relevance of the quantities of interest (5.3.1)
	Relevance of the validation activities to the COU (5.3.2)

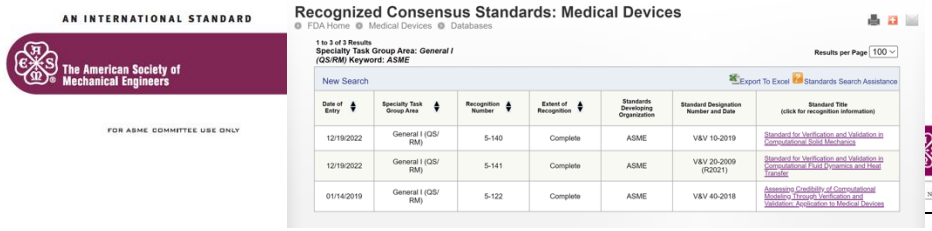
A Framework for CM&S in Regulatory Submissions

HOW MUCH VVUQ

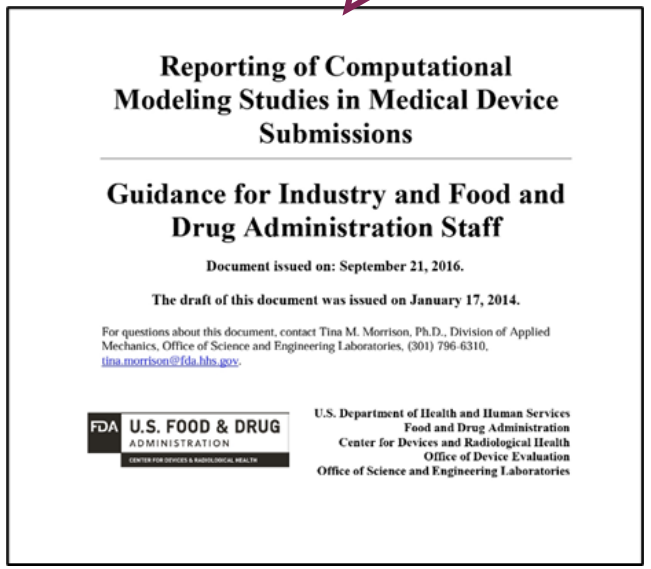


HOW TO DO VVUQ

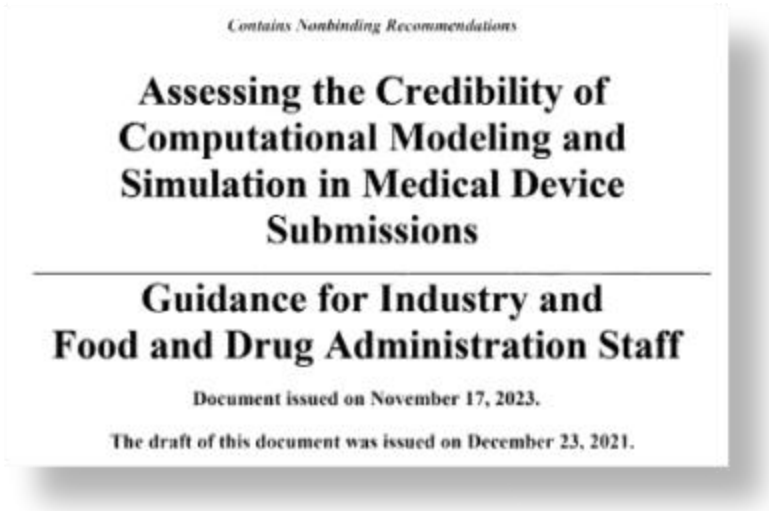




REPORT YOUR MODEL



US FDA Credibility Guidance (2023)



Contains Nonbinding Recommendations

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

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

The draft of this document was issued on December 23, 2021.

"This guidance provides a general risk-informed framework that can be used in the credibility assessment of computational modeling and simulation (CM&S) used in medical device regulatory submissions"

- The guidance expands upon the ASME V&V 40 standard by:
  - Expanding the number of comparators used for model validation (beyond bench testing)
  - Discussing the need for prospective and post-study credibility assessments
  - Providing reporting recommendations for computational model information included in submissions

Evidence Sources

Evidence Supporting Model Form
Evidence Supporting Inputs
Implant Evaluation

Table 4.1 Eight categories of credibility evidence. Reprinted from FDA guidance "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions", Nov 2023

Category	Definition	Definition
1	Code verification results	Results showing that a computational model implemented in software is an accurate implementation of the underlying mathematical model
2	Model calibration evidence	Comparison of model results with the same data used to calibrate model parameters
3	Bench test validation results	Validation results using a bench test comparator. May be supported by calculation verification and/or UQ results using the validation conditions
4	In vivo validation results	Same as previous category except using in vivo data as the comparator
5	Population-based validation results	Comparison of population-level data between model predictions and a clinical data set. No individual-level comparisons are made
6	Emergent model behaviour	Evidence showing that the model reproduces phenomena that are known to occur in the system at the specified conditions but were not pre-specified or explicitly modelled by the governing equations
7	Model plausibility evidence	Rationale supporting the choice of governing equations, model assumptions, and/or input parameters only
8	Calculation verification/ UQ results using CoU evidence	Calculation verification and/or UQ results obtained using the CoU simulations, that is, the simulations performed to answer the question of interest

CM&S Reporting Structures

Possible Content to include in a Q-submission on a Credibility Assessment Plan:

1. **Purpose:** The overall purpose of the Q-Submission including goals for the outcome of the interaction with FDA.
2. **Background:** e.g., clinical context or other relevant background information for the device.
3. **Device Description**
4. **Proposed Indications for Use**
5. **Regulatory History**
6. **Description of Computational Model**
7. **Credibility Assessment Plan**
   a. Summary of overall approach
   b. Question of Interest (see Section VI.A.(1))
   c. COU (see Section VI.A.(2))
   d. Model Risk Assessment (see Section '
   e. Planned Credibility Evidence. For eac provide the following:
      i. Categorization of evidence per
      ii. Description of evidence to be

Recommended Content for a Credibility Assessment Report:

1. **Executive Summary:** Include a brief description of the device, the model, the question of interest that the model is used to address, the model COU, the assessed model risk, a summary of the categories of the credibility evidence provided, and a summary of the adequacy assessment with a brief rationale.
2. **Background:** e.g., clinical context or other relevant background for the device. Either provide here or refer to another section in the regulatory submission.
3. **Device Description:** Include within the report or refer to another section in regulatory submission.
4. **Proposed Indications for Use:** Include within the report or refer to another section in regulatory submission.
5. **Description of Computational Model:** If model details are included elsewhere in the regulatory submission, we recommend referencing accordingly. We recommend providing details on governing equations, model parameter values, methods used to determine parameter values, numerical methods used for solving the governing equations, and other information that could be relevant in evaluating model credibility.
6. **Model Credibility Assessment**
   a. Summary of overall approach
   b. Question of Interest (see Section VI.A.(1))
   c. COU (see Section VI.A.(2))
   d. Model Risk Assessment (see Section VI.A.(3))
   e. Credibility Evidence. For each type of credibility evidence provided, provide the

An ISCT Framework

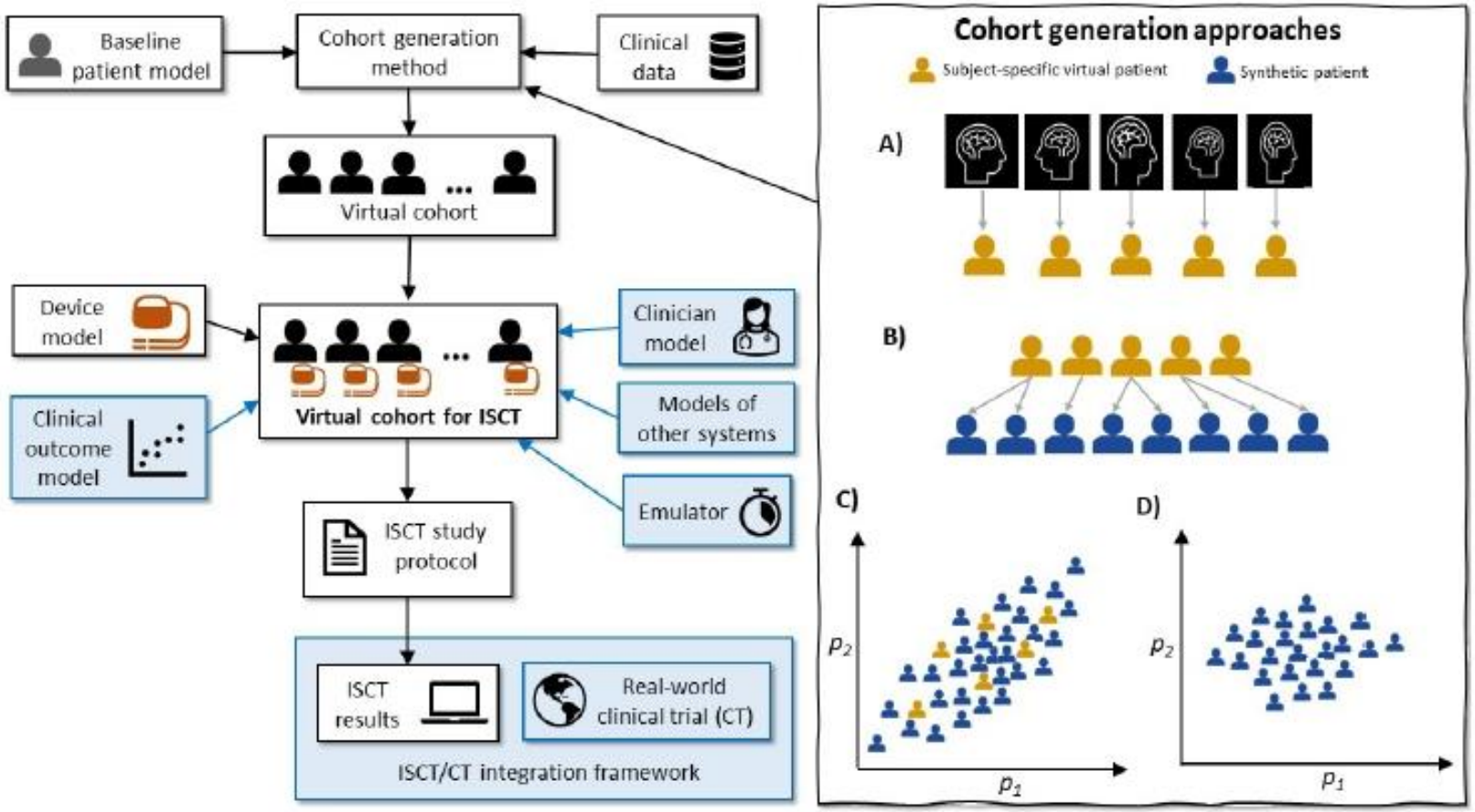
RESEARCH ARTICLE

Credibility assessment of *in silico* clinical trials for medical devices

Pras Pathmanathan[1]*, Kenneth Aycock[1], Andreu Badal[1], Ramin Bighamian[1], Jeff Bodner[2], Brent A. Craven[1], Steven Niederer[3,4]

1 Center for Devices and Radiological Health, US Food and Drug Administration, Silver Spring, Maryland, United States of America, **2** Medtronic, PLC., Minneapolis, Minnesota, United States of America, **3** National Heart and Lung Institute, Imperial College, London, United Kingdom, **4** The Alan Turing Institute, London, United Kingdom

* pras.pathmanathan@fda.hhs.gov



Establishing Credibility through Hierarchical Validation

- ISCTs are exploratory trials on the computer that make use of reliable computer models of the treatment (effect of the drug or device on the organism) and its deployment (administration of the drug or surgical procedure), together with reliable computer models of the patient's characteristics.

For each patient in the patient cohort

Physiology Layer

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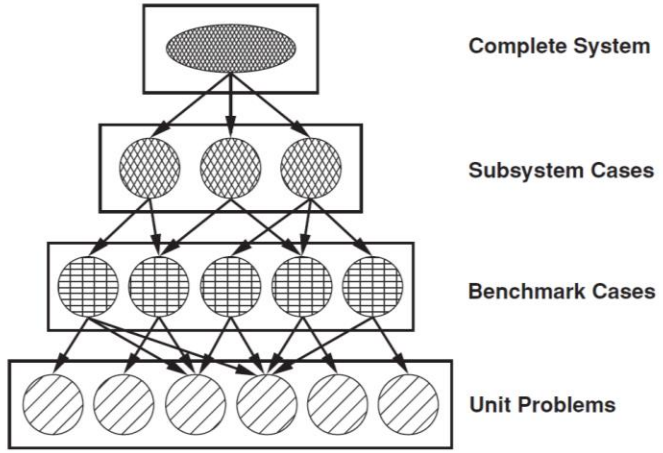


Validation must be performed within each component of the hierarchy

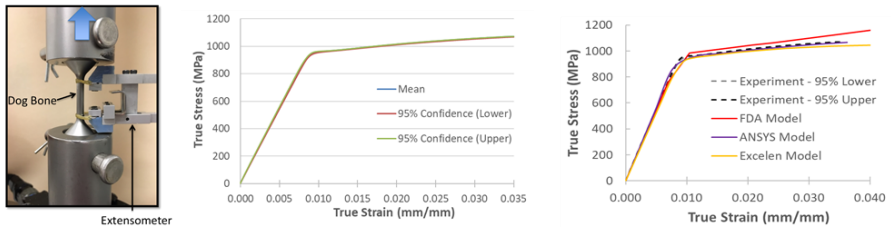
Hierarchical Validation Example – Spinal Implant Modeling

PROJECT GOAL

Demonstrate how to apply the ASME V&V 40 standard to answer a regulatory question of interest.

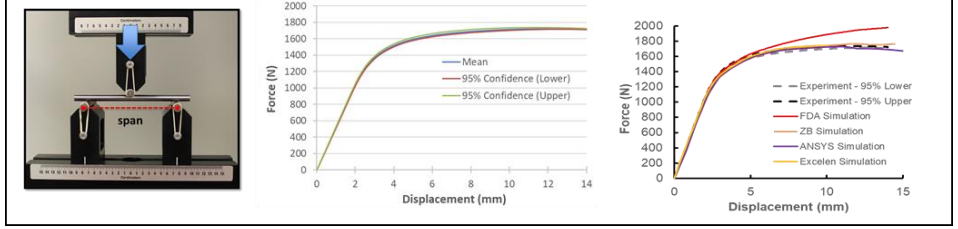
Step 1: Material Characterization

Tensile Testing (ASTM E8)



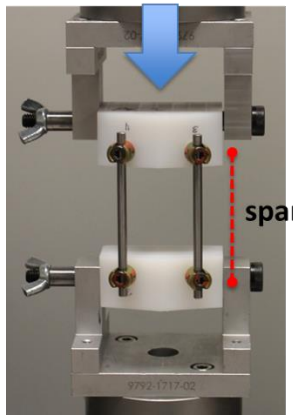
Step 2: 3-point Bending Validation

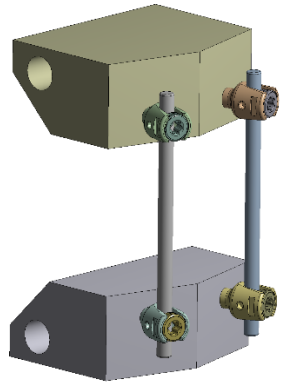
Three-Point Bend Testing (ASTM F2193)



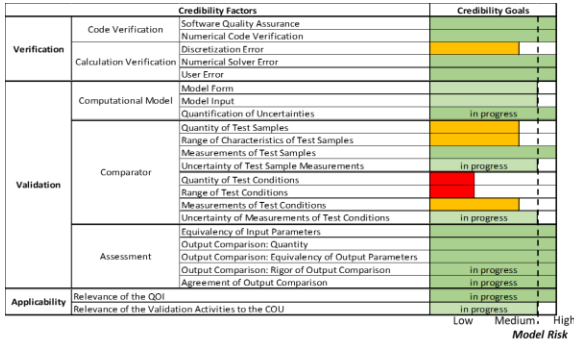
* Nagaraja et al. *J VVUQ* (2022)

Step 3: ASTM F1717 Validation

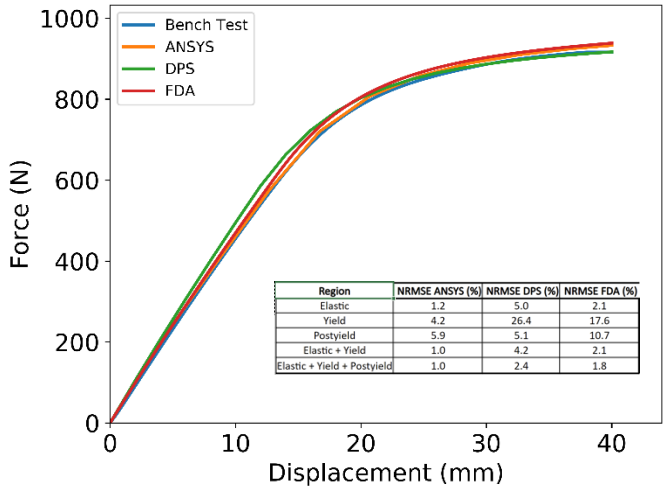




Question of Interest:
Does adding a 1.6 mm cannulation to an existing 7.5 mm pedicle screw design compromise mechanical performance of the rod-screw construct in static compression-bending?

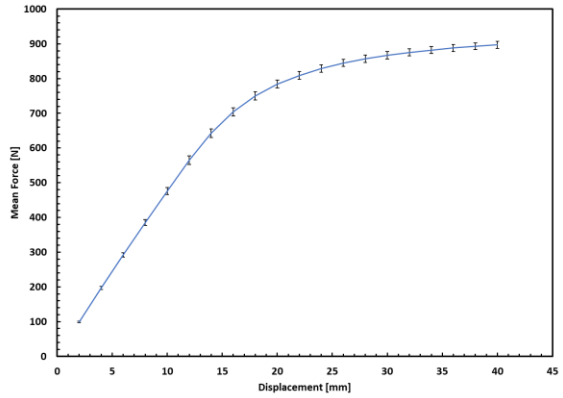


Non-Cannulated PS System



Region	NRMSE ANSYS (%)	NRMSE DPS (%)	NRMSE FDA (%)
Elastic	1.2	5.0	2.1
Yield	4.2	26.4	17.6
Postyield	5.9	5.1	10.7
Elastic + Yield	1.0	4.2	2.1
Elastic + Yield + Postyield	1.0	2.4	1.8

UQ in Ansys optiSLang



* Nagaraja et al *Methods* (2024)

One “Limitation” of the ASME V&V 40 Standard

- The framework presented in the ASME V&V 40 standard was *demonstrated* using *in vitro* testing as the primary source of validation evidence.

Table 5-1 Verification, Validation, and Applicability Activities and Their Associated Credibility Factors

Activity (Paragraph)	Credibility Factor (Paragraph)
Verification (5.1)	
Code (5.1.1)	Software quality assurance (5.1.1.1)
	Numerical code verification (5.1.1.2)
Calculation (5.1.2)	Discretization error (5.1.2.1)
	Numerical solver error (5.1.2.2)
	Use error (5.1.2.3)
Validation (5.2)	
Computational model (5.2.1)	Model form (5.2.1.1)
	Model inputs (5.2.1.2)
Comparator (5.2.2)	Test samples (5.2.2.1)
	Test conditions (5.2.2.2)
Assessment (5.2.3)	Equivalency of input parameters (5.2.3.1)
	Output comparison (5.2.3.2)
Applicability (5.3)	Relevance of the quantities of interest (5.3.1)
	Relevance of the validation activities to the COU (5.3.2)

ASME V&V40 credibility factor	Example gradation in ASME V&V40	Potential interpretation for some PSM cases	Potential new gradations for some PSM-CT cases	Potential new gradations for some PSM-VC cases
Quantity of Test Samples	(a) A single sample was used. (b) Multiple samples were used, but not enough to be statistically relevant. (c) statistically relevant number of samples were used	Number of validation subjects	(a) Single subject (b) Multiple subjects, not enough to be statistically relevant (c) Statistically relevant number of subjects	(a) Validation not performed for any subject in original cohort (b) Validation performed for some subjects in original cohort (c) Validation performed for all subjects in original cohort
Range of Characteristics of Test Samples	(a) One or more samples with a single set of characteristics were included. (b) Samples representing a range of characteristics near nominal were included. (c) Samples representing the expected extreme values of the parameters were included. (d) Samples representing the entire range of parameters were included.	Range of characteristics of validation subjects	(a) All validation subjects similar (b) Limited range of characteristics in validation subjects (c) Wide range of characteristics in validation subjects	(a) All validation subjects similar (b) Limited range of characteristics in validation subjects (c) Wide range of characteristics in validation subjects
Characteristics of Test Samples	(a) Test samples were not measured and/or characterized. (b) One or more key characteristics of the test samples were measured. (c) All key characteristics of the test samples were measured.	Patient data collected	(a) Key patient data missing *[e.g., because retrospective study]* (b) Most key patient data was obtained. (c) All key patient data was obtained.	(a) Key patient data missing *[e.g., because retrospective study]* (b) Most key patient data was obtained. (c) All key patient data was obtained.
Measurements of Test Samples	(a) Samples were not characterized or were characterized with gross observations, and measurement uncertainty was not addressed.	Patient measurements	(a) Patient measurements were not characterized or were characterized with gross observations, and measurement uncertainty was not addressed.	(a) Patient measurements were not characterized or were characterized with gross observations, and measurement

Expansion of the ASME V&V 40 Framework

- Clinical validation activities require a comparison to clinical outcomes to establish credibility
  - Builds upon the benchtop validation activities performed for the device
  - This also requires expansion of the ASME V&V 40 framework

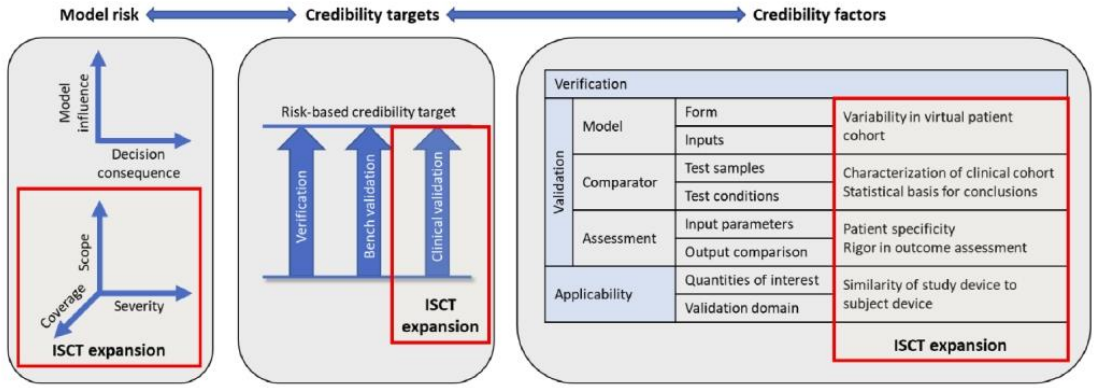


Fig. 1. Aspects of the proposed risk-based credibility framework for ISCT applications. Areas of expansion relative to existing guidance are highlighted in red.

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A risk and credibility framework for *in silico* clinical trials of medical devices

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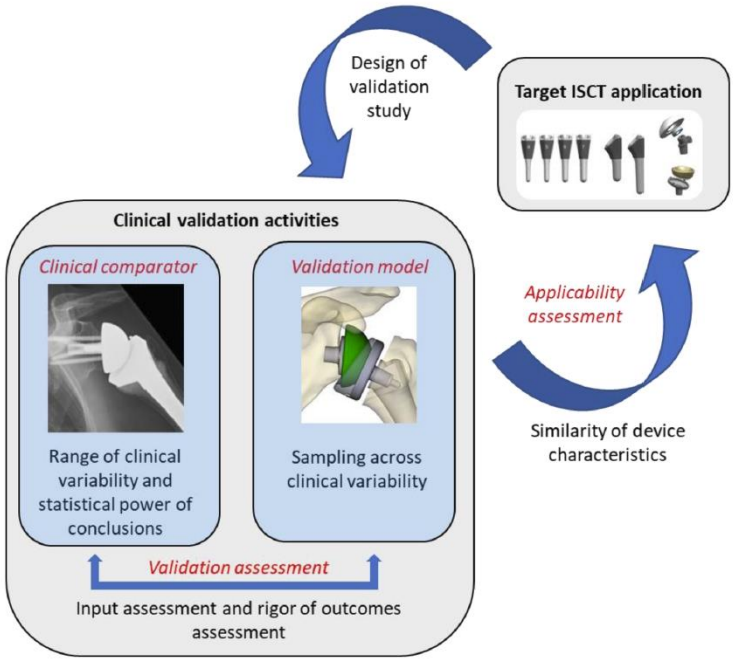
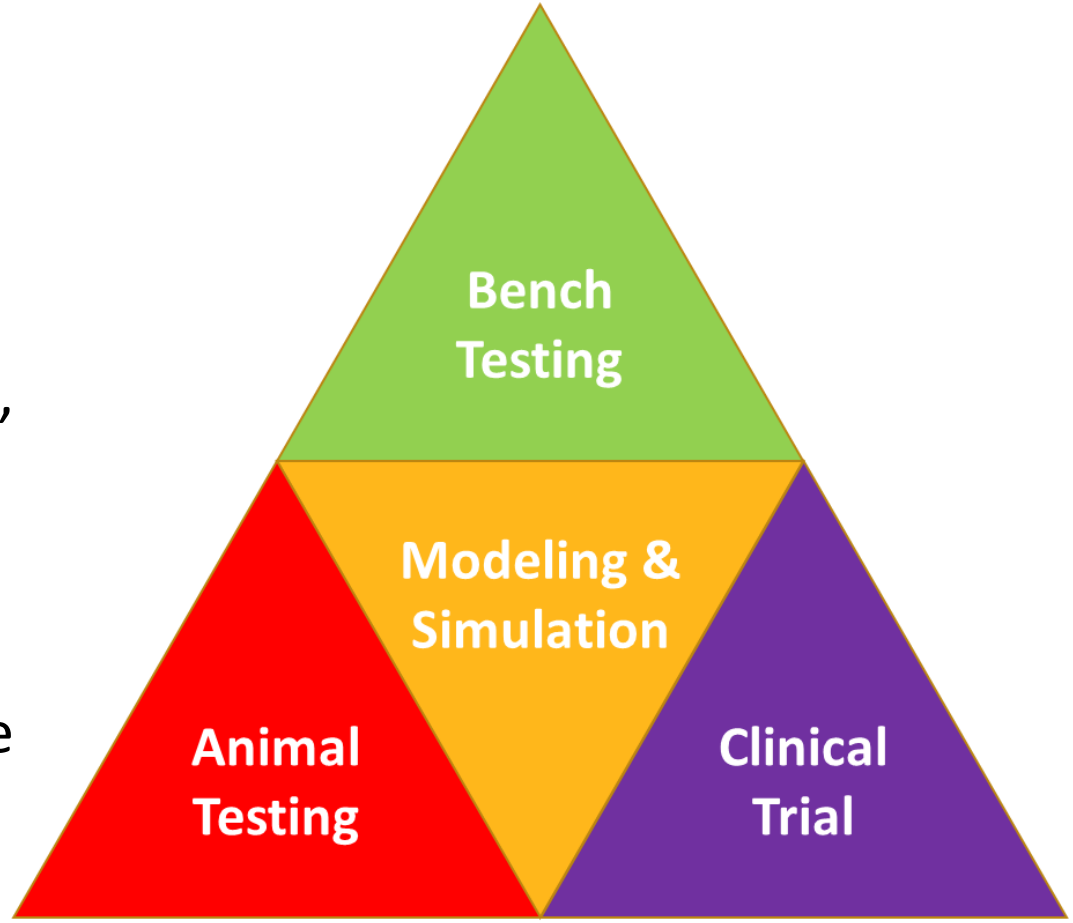


Fig. 8. Illustration of key credibility factors (clinical comparator, validation model, validation assessment, and applicability assessment) for assessing credibility of clinical validation activities, and considerations to grade each factor. Radiographic image of scapular notching reprinted with permission from [23].

In Conclusion

- The cost of device development and clinical trials continues to put pressure on device companies to innovate faster and more efficiently.
- In silico clinical trials (ISCTs) can reduce, refine, or even replace our reliance on animal and human testing.
- Globally recognized standards and regulatory frameworks will be required for the healthcare industry to take full advantage of ISCTs.



New Work Item – IEC/ISO Co-Branded Standard on CM&S Credibility

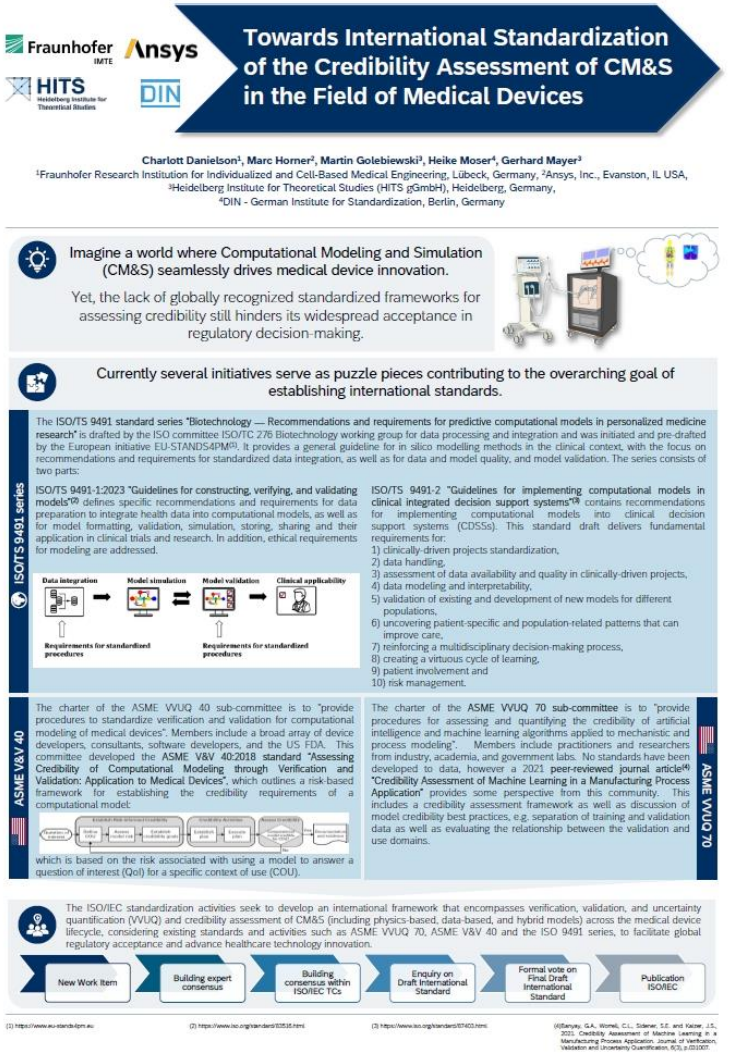
First Meeting: October 16, 2024

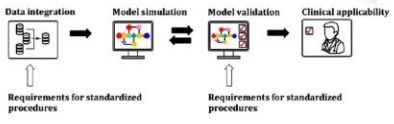
- IEC TC 62 focuses on medical equipment, software, and systems

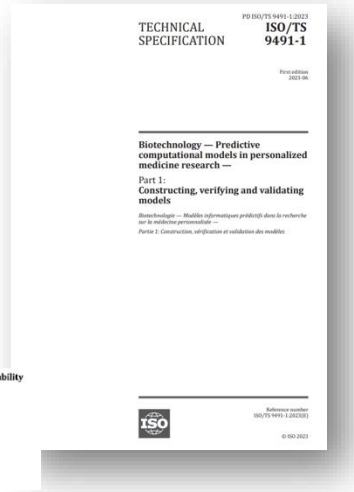
  CHARTER: To prepare international standards, and other publications, with focus on safety and performance of medical equipment, software, and systems.

- ISO TC 276 focuses on biotechnology applications

  CHARTER: Standardization in the field of biotechnology processes that includes the following topics:
  - Terms and definitions;
  - Biobanks and bioresources;
  - Analytical methods;
  - Bioprocessing;
  - Data processing including annotation, analysis, validation, comparability and integration;
  - Metrology.







THANK YOU

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