# The imperatives of in silico evidence in the digital era

Artificial Intelligence for Regulations,
Computational Modelling and Simulations
or Model-Informed Evidence?


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Grant Support from:


Health Research Board
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What do we know?
1. Have you heard of ISTs? (Single choice)
Yes (7/11)...
No (4/11)...
You did not answer this question
2. Have you utilised ISTs? (Single choice)
Yes (4/11)...
No (7/11)...
You did not answer this question
Close

# Driving Questions

1. How do we continue to improve the safety, quality, efficacy, and durability of products across geographies?

2. How do we manage the risks and opportunities associated with the pace of technologies?

3. How do we help our individual regulators have confidence when engaging technologies in the regulatory review process?

# Outline

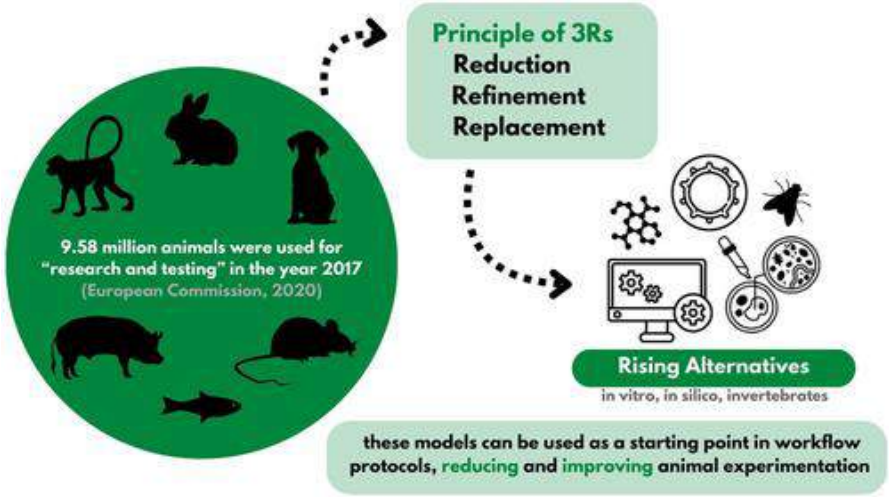
- The Imperatives to Act Now
- The Vision: CM&S aka “in silico”
- The Science: Exemplars
- Ready for Prime Time?
- Computational Model Credibility
- A Call for Action

The Consequences of Inaction

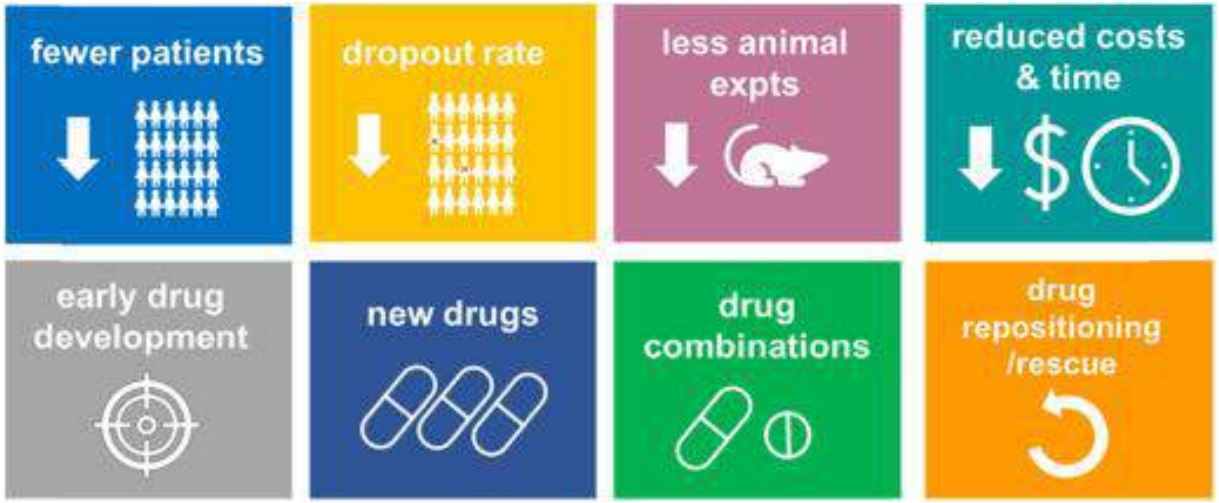
# THE IMPERATIVES

# A Holistic and Market Failure Approach to Ethical & Innovative Medical Development


- Ethical Imperatives: Reducing animal testing across the entire product lifecycle, aligning with broader ethical standards.
- Innovative Synergy: Reducing animal testing can simultaneously reduce patient harm, business risks, and costs.
- Accelerated Access: Approaches speeding up the delivery of lifesaving therapies and interventions.



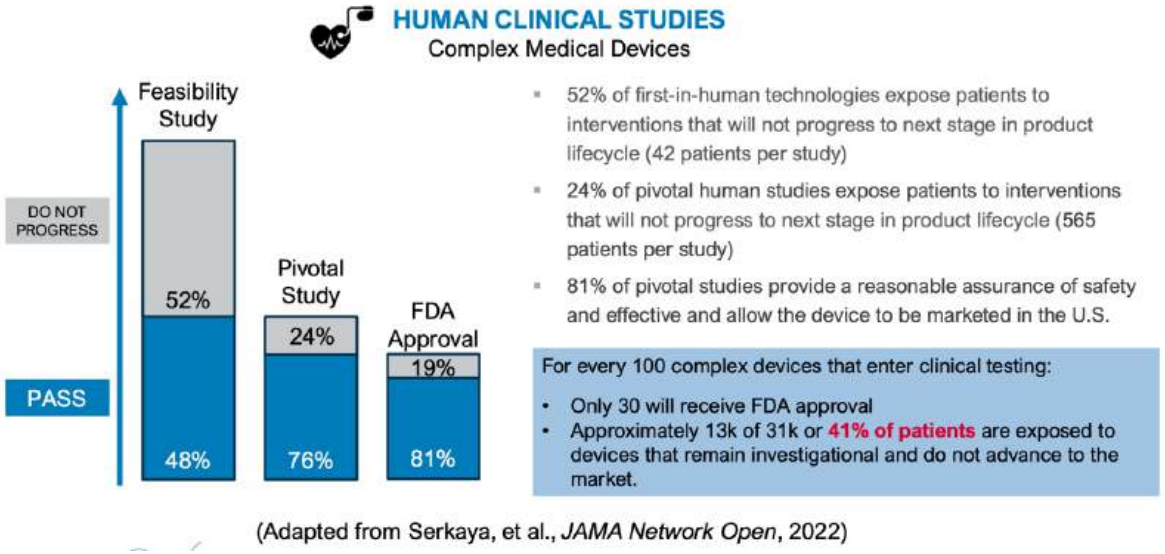

Guimarães AI. Are Animal Models Necessary? Exploring (Dis)advantages and Alternatives. Eur J Neurosci. 2025 Jan;61(1):e16651. doi: 10.1111/ejn.16651.



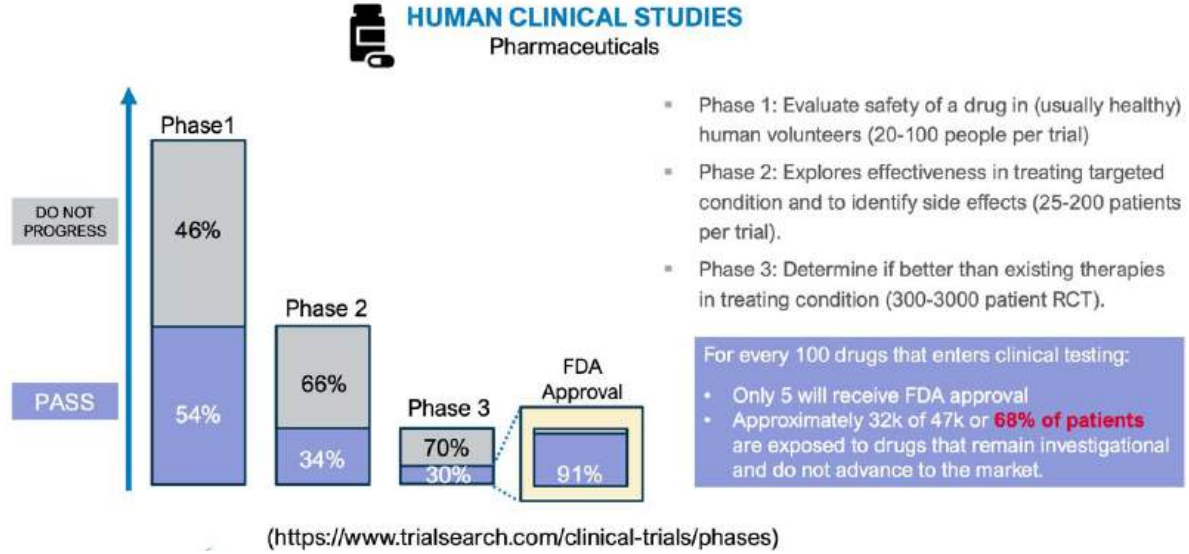

Ogilvie LA, Rieke DT, Lehrach H. A vision: in silico clinical trials without patients. In: Schüler P, editor. Innovation in Clinical Trial Methodologies. Academic Press; 2021. p. 39-48. doi: 10.1016/B978-0-12-824490-6.00020-7.

# The Ethical & Safety Imperative

## Minimise Patient Exposure to Unproven Therapies




(Adapted from Serkaya, et al., *JAMA Network Open*, 2022)




(https://www.trialsearch.com/clinical-trials/phases)

Courtesy of Dr Tina Morrison (FDA) and Dr Mark Palmer (ANSYS)

# The Economic & Financial Imperative

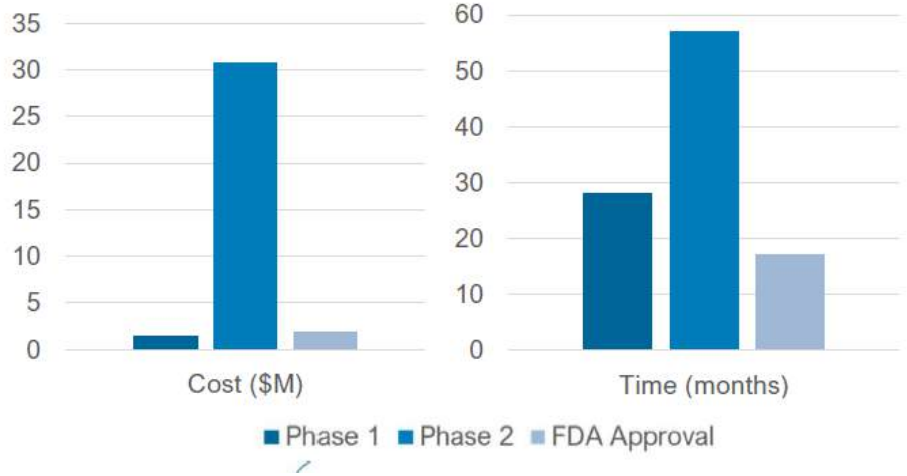
## Sustainable care and affordable innovation

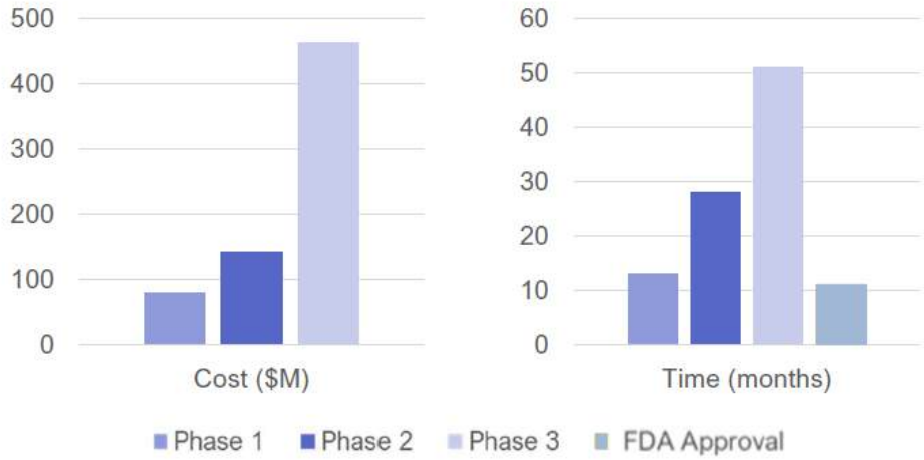
**Complex Medical Devices:**

- Average cost from discovery to launch continues to increase
- Average cost to successfully deliver an asset to market is $0.52B
- Range in cost varies from $0.205B to $3.4B
- Average total time is 13 years

**Pharmaceuticals:**

- Average cost from discovery to launch continues to increase
- Average cost to successfully deliver an asset to market is $2.3B
- Range in cost varies from $0.74B to $6.7B
- Total time is 14-16 years




Courtesy of Dr Tina Morrison (FDA) and Dr Mark Palmer (ANSYS)

WHAT IF….

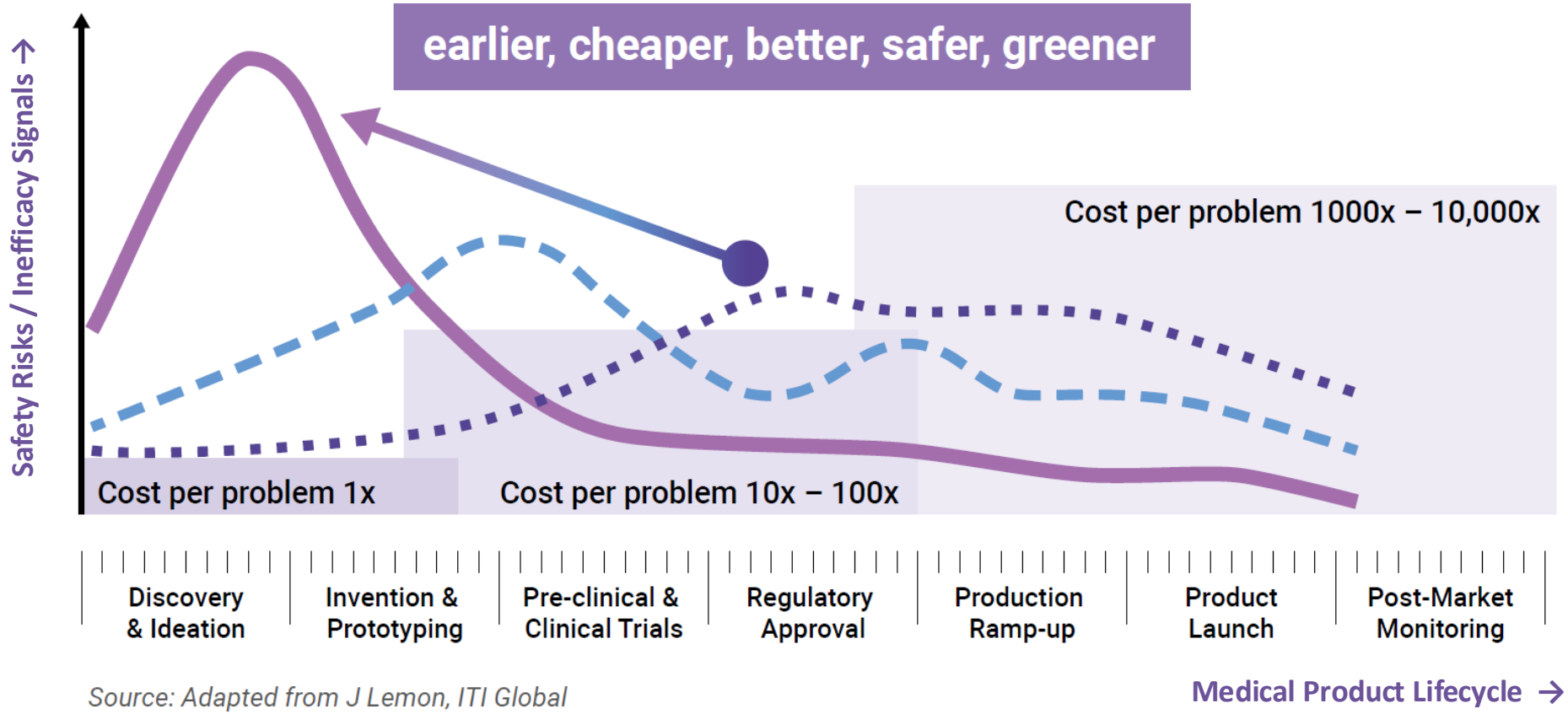
- ❑ We build credible models that surface hidden insights and predict post-market failures early.
- ❑ We then optimise designs to prevent or minimise those failures.
- ❑ Human studies become confirmatory—verifying safety and performance, not estimating them.

The vision

# IN SILICO EVIDENCE

# The Innovation Imperative

## Better Products, Less Failure, Reduced Time to Revenue

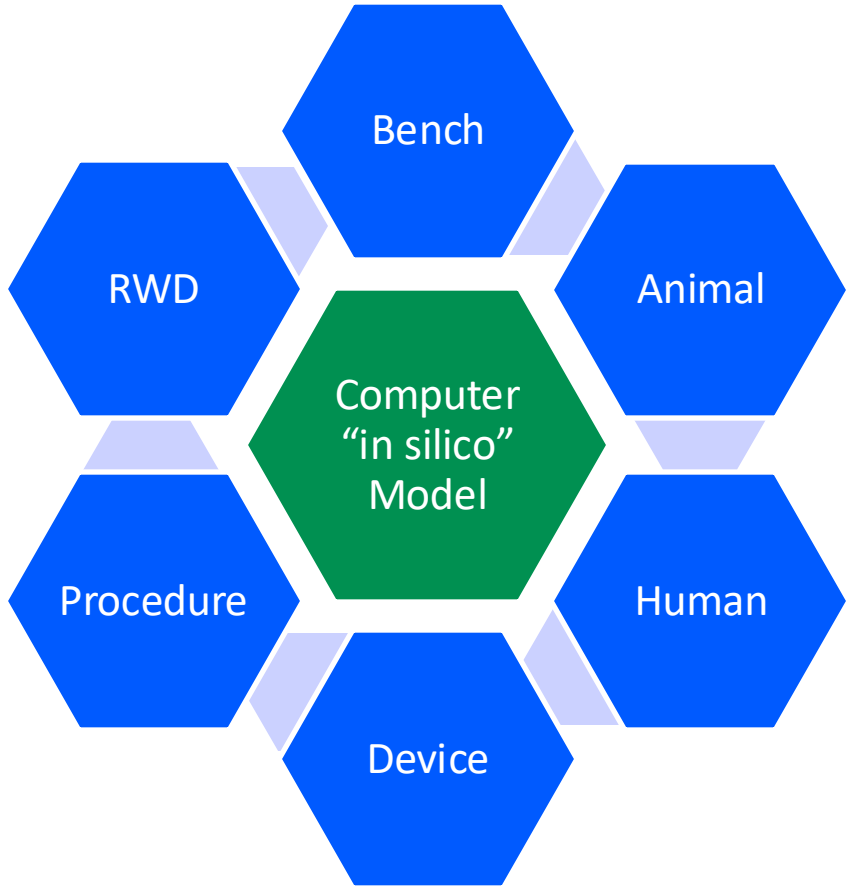



*Source: Adapted from J Lemon, ITI Global*

# Modelling and simulation is a technology integrator

## The foundation of 21st-century design and manufacturing

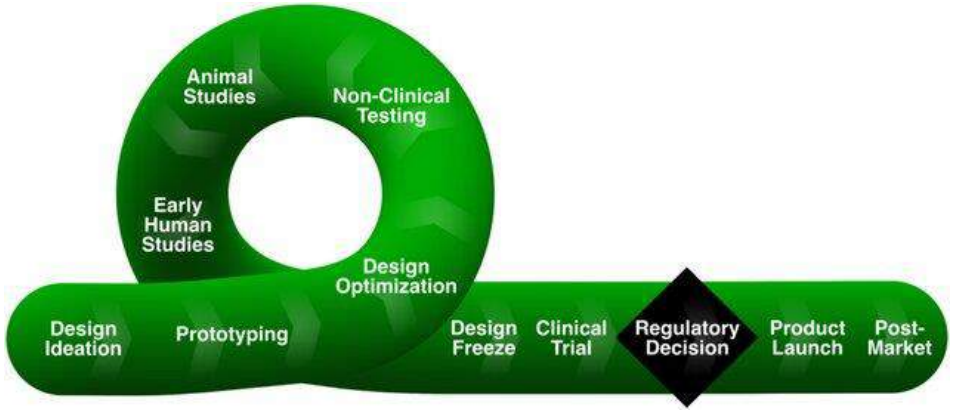
- Models are built to address specific questions of interest
- The better the question is defined, the better the model
- AI (data-driven) + mechanistic (first-principles) modelling
- Models are informed by
  - Physical and Real-World Data
  - Clinical imaging
  - Disease or condition to be treated
  - Digital representation of the device and its operation
  - Manufacturing processes for the device

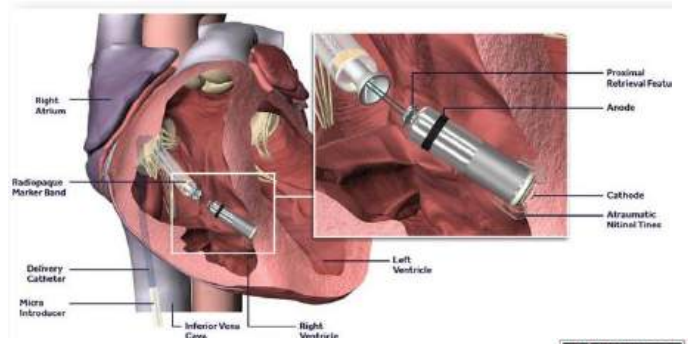


# Regulatory use of modelling and simulation

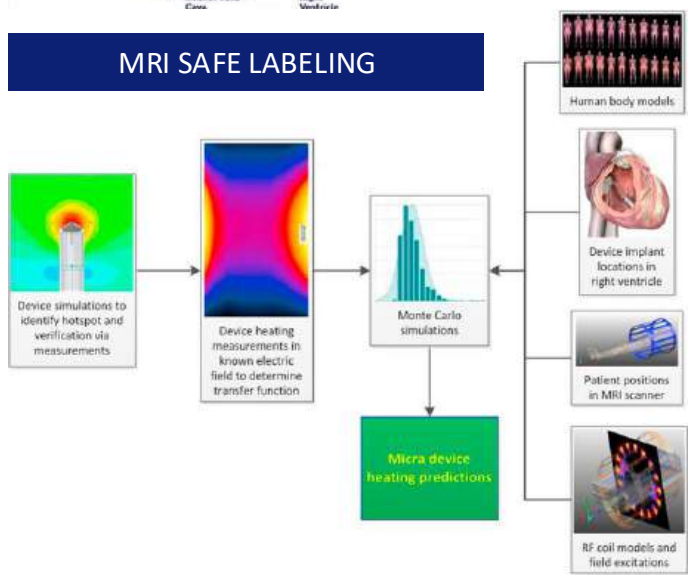
## Benefits to the regulatory ecosystem

- Initial use was for forensic analysis of post-market failures
- Applications moved left in the product life cycle towards manufacturing, R&D, and clinical evidence
- Successful applications have included
  - Reducing the number of questions to be addressed in the study design
  - Augmenting a clinical trial with virtual patients
  - Use of modelling and simulation to expand claims
  - Uses simulation to resolve post-market product safety & efficacy issues




MRI SAFE LABELING





Aycock KI, Battisti T, Peterson A, Yao J, Kreuzer S, Capelli C, Pant S, Pathmanathan P, Hoganson DM, Levine SM, Craven BA. Toward trustworthy medical device in silico clinical trials: a hierarchical framework for establishing credibility and strategies for overcoming key challenges. Front Med (Lausanne). 2024 Aug 12;11:1433372.

Soejima K, Edmonson J, Ellingson ML, Herberg B, Wiklund C, Zhao J. Safety evaluation of a leadless transcatheter pacemaker for magnetic resonance imaging use. Heart Rhythm. 2016 Oct;13(10):2056-63

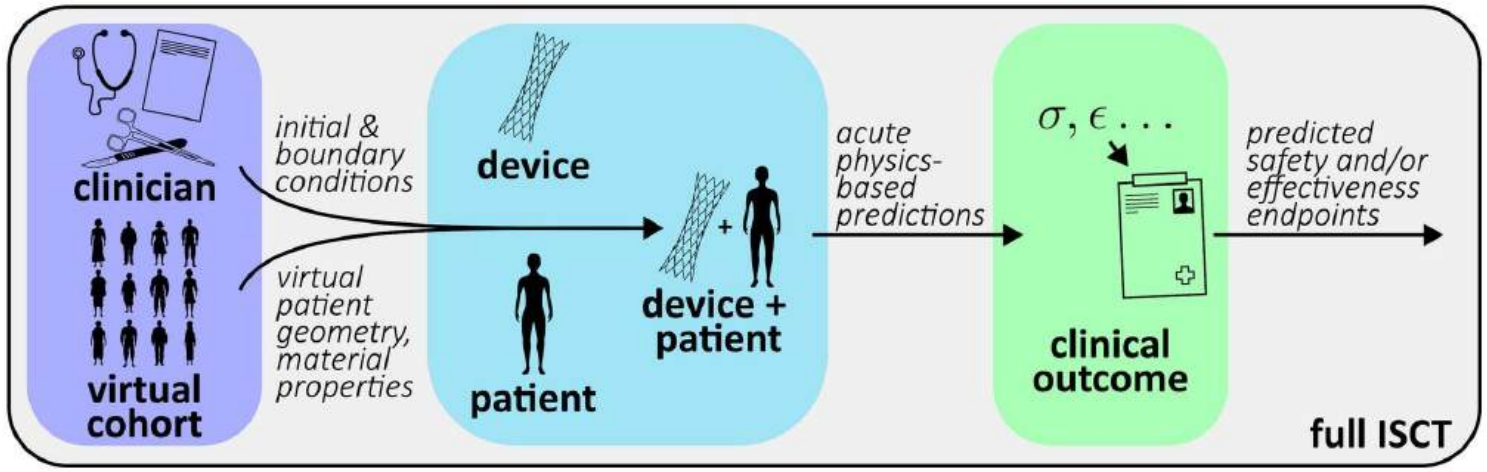
# High-value Evidence for the entire Product Lifecycle

Value Proposition: ***Reduce RDR from "Years to Months" & Safety Risks "Failing fast & earlier "***

## In-silico testing/trials:

computer-based tests/trials using detailed prediction models on highly controlled virtual conditions or virtual cohorts

representing realistic operational conditions or target populations for the intended use



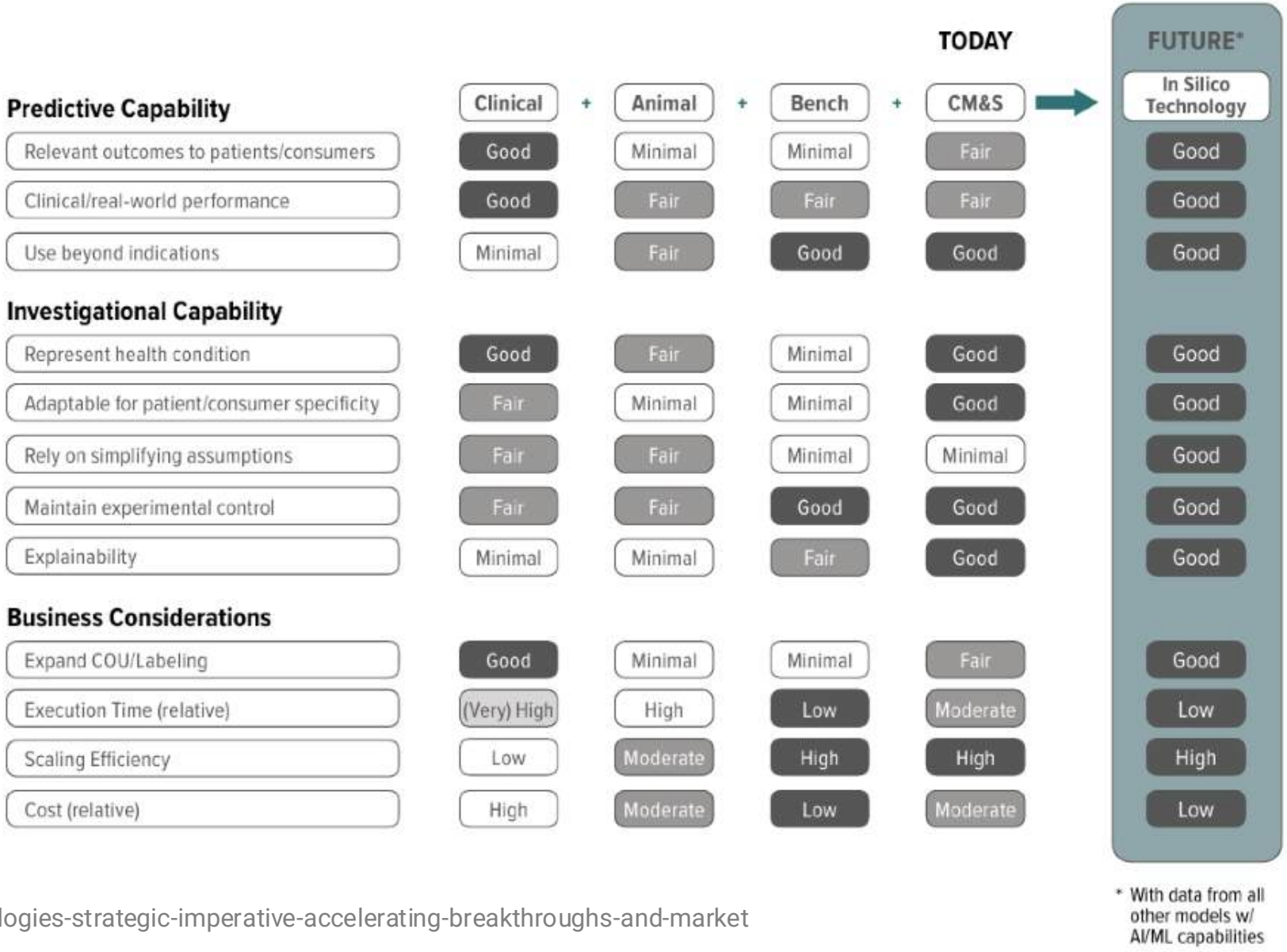

IN SILICO = evidence derived from real-world data plus computational modelling and simulation, including AI


Aycock KI, Battisti T, Peterson A, Yao J, Kreuzer S, Capelli C, Pant S, Pathmanathan P, Hoganson DM, Levine SM, Craven BA. Toward trustworthy medical device *in silico* clinical trials: a hierarchical framework for establishing credibility and strategies for overcoming key challenges. Front Med (Lausanne). 2024 Aug 12;11:1433372.

# The Future?

Proportionate and risk-informed evidence framework

*No single source of evidence provides the highest evidence rigour for all categories*



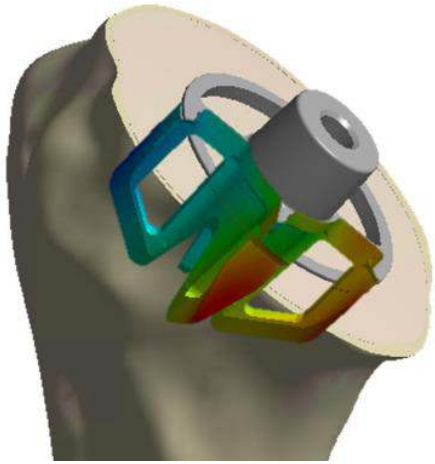

https://reaganudall.org/publications/silico-technologies-strategic-imperative-accelerating-breakthroughs-and-market

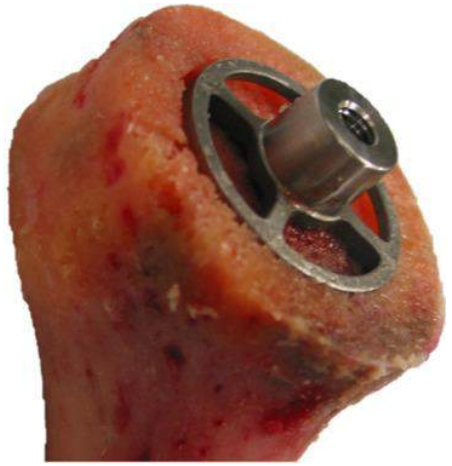
This is happening, Regulators just don’t assess it

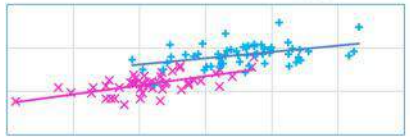
# EXEMPLARS

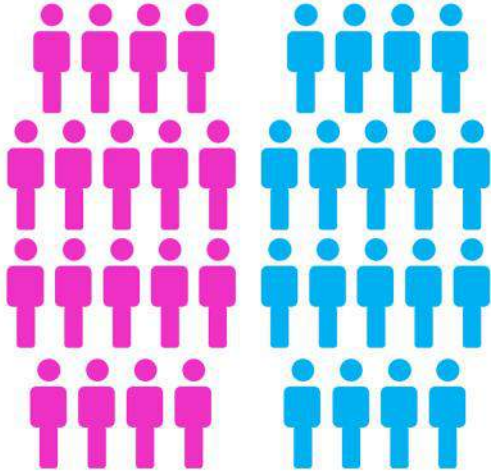
# Orthopaedic implants

> in silico bench test on realistic regimes









*Annals of Biomedical Engineering*, Vol. 49, No. 12, December 2021 (© 2021) pp. 3213–3226
https://doi.org/10.1007/s10439-021-02787-y

*Virtual Physiological Human*

## *In Silico* Clinical Trials in the Orthopedic Device Industry: From Fantasy to Reality?

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(*Received 29 January 2021; accepted 24 April 2021; published online 10 May 2021*)

Associate Editor Joel Stitzel oversaw the review of this article.

**Abstract**—The orthopedic device industry relies heavily on clinical evaluation to confirm the safety, performance, and clinical benefits of its implants. Limited sample size often prevents these studies from capturing the full spectrum of patient variability and real-life implant use. The device industry is accustomed to simulating benchtop tests with numerical methods and recent developments now enable virtual "in silico clinical trials" (ISCT). In this article, we describe how the advancement of computer modeling has naturally led to ISCT; outline the potential benefits of ISCT to patients, healthcare systems, manufacturers, and regulators; and identify how hurdles associated with ISCT may be overcome. In particular, we highlight a process for defining the relevant patient risks to address with ISCT, the utility of a versatile software pipeline, the necessity to ensure model credibility, and the goal of limiting regulatory uncertainty. By complementing—not replacing—traditional clinical trials with computational evidence, ISCT provides a viable tech-

| | |
|---|---|
| FE | Finite element |
| ISCT | In silico clinical trials |
| MDR | Medical Devices Regulation |
| Clinical investigation (trial, study) | Systematic investigation in one or more human subjects, undertaken to assess the clinical performance, effectiveness or safety of a medical device |
| Clinical data | Safety, clinical performance and/or effectiveness information that is generated from the clinical use of a medical device |
| Clinical evaluation | Systematic and planned process |

Favre P, Maquer G, Henderson A, Hertig D, Ciric D, Bischoff JE. In Silico Clinical Trials in the Orthopedic Device Industry: From Fantasy to Reality? Ann Biomed Eng. 2021 Dec;49(12):3213-3226. doi: 10.1007/s10439-021-02787-y.

# Personalised high tibial osteotomy

*> realignment surgery with bespoke vs generic devices*

**Table 2 Maximum von Mises stress (Stress) in the plates, maximum Von Mises strain (Strain) in the bone adjacent to the plates screws and maximum inter-fragmentary movement (IFM) for the two arms, and the differences between the arms for each of the three healing stages (HS), all cases are for screw configuration 3.**

| | Generic[a] | | Personalised[a] | | Adjusted Difference (95% CIs)[b] Generic—Personalised | |
|---|---|---|---|---|---|---|
| | *n* | Mean (SE) | *n* | Mean (SE) | | *p* values |
| Stress (MPa) | | | | | | |
| HS2 | 391 | 331.8 (13.55) | 410 | 345.1 (9.54) | −12.5 (−70.0, 45.0) | 0.67 |
| HS3 | 410 | 90.6 (3.56) | 392 | 108.3 (3.81) | −17.1 (−26.2, −7.9) | <0.001 |
| HS4 | 416 | 37.0 (1.64) | 419 | 48.3 (1.60) | −11.1 (−15.3, −6.8) | <0.001 |
| Strain (unitless) | | | | | | |
| HS2 | 391 | 0.015 (0.00071) | 365 | 0.017 (0.00067) | −0.0011 (−0.0030, 0.0008) | 0.27 |
| HS3 | 410 | 0.011 (0.00065) | 392 | 0.011 (0.00056) | −0.0002 (−0.0024, 0.0021) | 0.88 |
| HS4 | 416 | 0.0096 (0.00067) | 419 | 0.0090 (0.00055) | 0.0005 (−0.0020, 0.0031) | 0.67 |
| IFM (mm) | | | | | | |
| HS2 | 391 | 0.31 (0.012) | 410 | 0.33 (0.015) | −0.014 (−0.045, 0.017) | 0.37 |
| HS3 | 410 | 0.12 (0.005) | 392 | 0.12 (0.004) | −0.005 (−0.010, 0.001) | 0.10 |
| HS4 | 416 | 0.04 (0.002) | 419 | 0.06 (0.003) | −0.036 (−0.054, −0.018) | <0.001 |

[a]Data are presented for all observations, which are clustered within participants.
[b]Estimates are based on a multi-level logistic model using repeated measures over time and allowing for additional clustering within participants using robust standard errors.

Interesting points

- Obesity has been shown to be a significant independent predictor of major complications following HTO surgery (p= 0.001). TomoFix plate not recommended in obese individuals.
- Despite this fact, 88% of patients in a previous clinical study were overweight or obese.
- The study included 92.9% overweight and 78.6% obese patients and is representative of the typical patient demographics.

communications medicine

ARTICLE

https://doi.org/10.1038/s43856-021-00001-7 OPEN

## Personalised high tibial osteotomy has mechanical safety equivalent to generic device in a case-control in silico clinical trial

Alisdair R. MacLeod[1], Nicholas Peckham[2], Gil Serrancolí[3], Ines Rombach[2], Patrick Hourigan[4], Vipul I. Mandalia[4], Andrew D. Toms[4], Benjamin J. Fregly[5] & Harinderjit S. Gill[1,6]✉

**Abstract**

**Background** Despite favourable outcomes relatively few surgeons offer high tibial osteotomy (HTO) as a treatment option for early knee osteoarthritis, mainly due to the difficulty of achieving planned correction and reported soft tissue irritation around the plate used to stablise the osteotomy. To compare the mechanical safety of a new personalised 3D printed high tibial osteotomy (HTO) device, created to overcome these issues, with an existing generic device, a case-control in silico virtual clinical trial was conducted.

**Methods** Twenty-eight knee osteoarthritis patients underwent computed tomography (CT) scanning to create a virtual cohort; the cohort was duplicated to form two arms, Generic and Personalised, on which virtual HTO was performed. Finite element analysis was performed to calculate the stresses in the plates arising from simulated physiological activities at three healing stages. The odds ratio indicative of the relative risk of fatigue failure of the HTO plates between the personalised and generic arms was obtained from a multi-level logistic model.

**Results** Here we show, at 12 weeks post-surgery, the odds ratio indicative of the relative risk of fatigue failure was 0.14 (95%CI 0.01 to 2.73, $p = 0.20$).

**Conclusions** This novel (to the best of our knowledge) in silico trial, comparing the mechanical safety of a new personalised 3D printed high tibial osteotomy device with an existing generic device, shows that there is no increased risk of failure for the new personalised design compared to the existing generic commonly used device. Personalised high tibial osteotomy can overcome the main technical barriers for this type of surgery, our findings support the case for using this technology for treating early knee osteoarthritis.

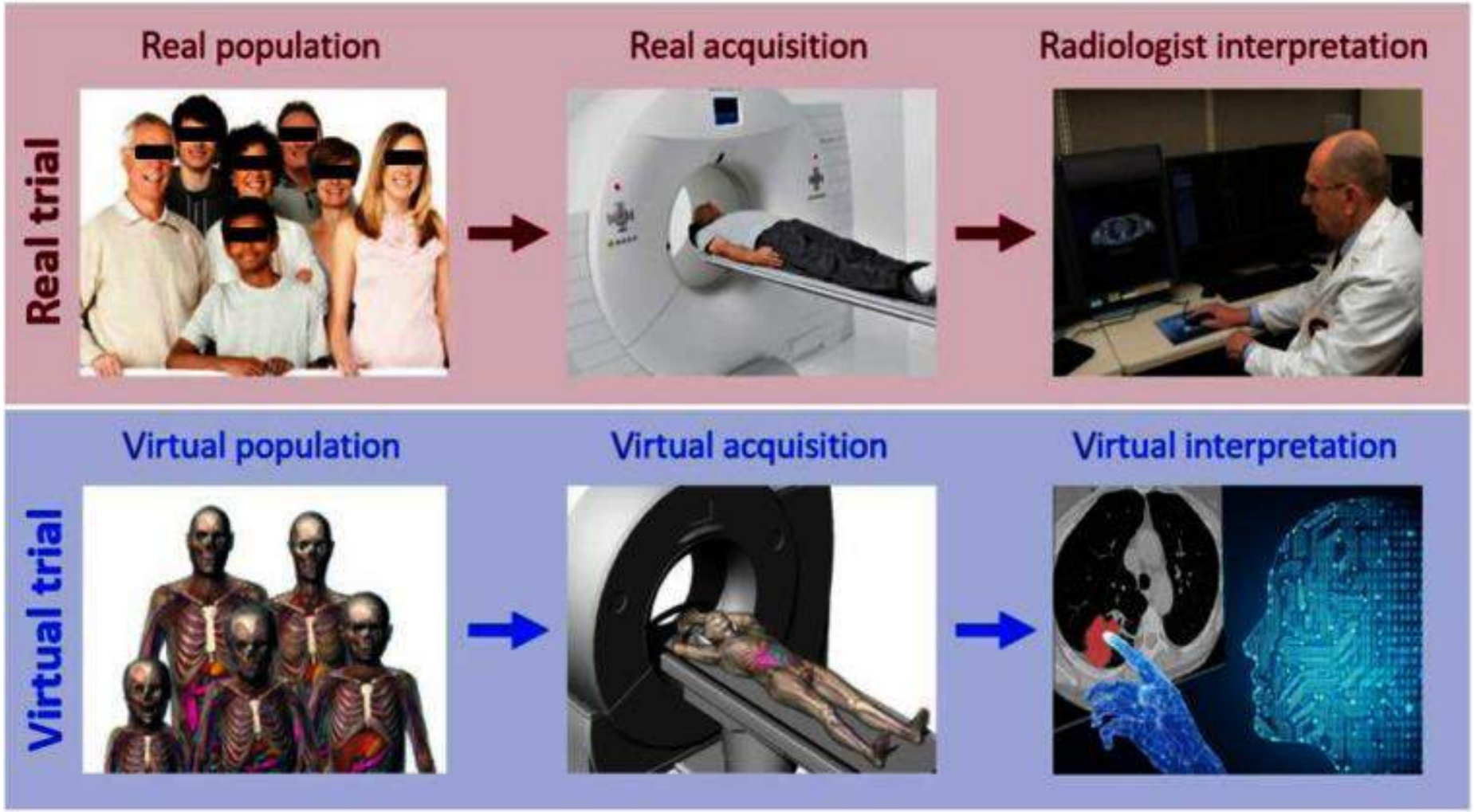
**Plain Language Summary**

Surgical treatment to realign the knee, called a high tibial osteotomy, is effective at relieving symptoms of knee osteoarthritis but the operation is difficult. A new personalised treatment with simpler surgery has been designed. The aim of this study was to investigate the safety of the new personalised treatment compared to the standard treatment. For the first time, a detailed computer simulation clinical trial was performed, using imaging data from 28 real patients. The computer simulation compared the risk of the implant failure between the personalised and standard treatments. The personalised treatment did not have a higher risk of implant failure than standard treatment. This supports further clinical studies looking at the benefits of personalised over standard realignment surgery. The personalised treatment has the potential to allow much more widespread use of realignment surgery to treat early knee osteoarthritis.

MacLeod, A.R., Peckham, N., Serrancolí, G. et al. Personalised high tibial osteotomy has mechanical safety equivalent to generic device in a case–control in silico clinical trial. Commun Med 1, 6 (2021).

# Cheaper, faster, better, safer and more scalable

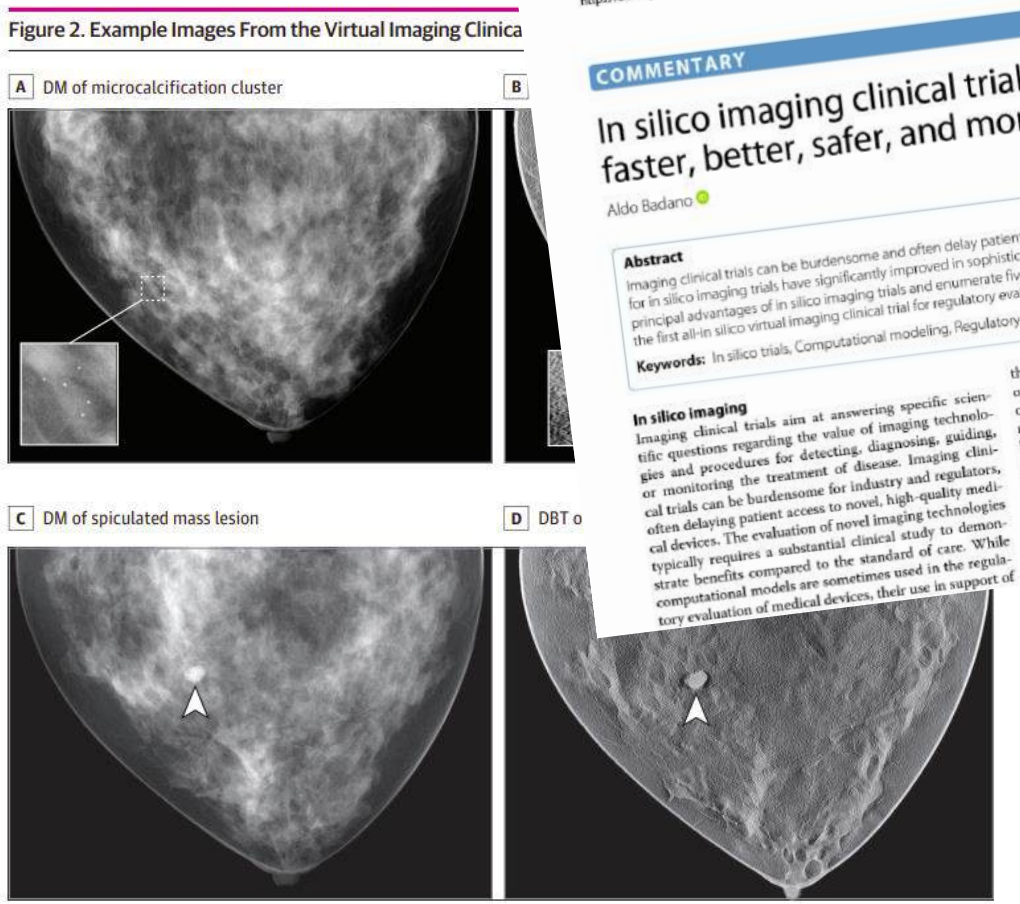
## VICTRE Trial – Digital Breast Mammography vs DB Tomosynthesis




Abadi E, Segars WP, Tsui BMW, Kinahan PE, Bottenus N, Frangi AF, Maidment A, Lo J, Samei E. Virtual clinical trials in medical imaging: a review. J Med Imaging (Bellingham). 2020 Jul;7(4):042805

# Digital Breast Tomosynthesis

> comparative diagnostic efficacy




A and B, Digital mammography (DM) (A) and selected digital breast tomosynthesis (DBT) slice (B) of a case corresponding to a breast with scattered areas of fibroglandular density containing a microcalcification cluster (inserts). C and D, Digital mammography (C) and selected DBT slice (D) of a case corresponding to a breast with scattered areas of fibroglandular density containing a spiculated mass lesion (arrowheads). Lesions have been made more conspicuous for display purposes by artificially increasing their radiography attenuation during image acquisition.

Trials

Badano Trials (2021) 22:64
https://doi.org/10.1186/s13063-020-05002-w

Open Access

COMMENTARY

## In silico imaging clinical trials: cheaper, faster, better, safer, and more scalable

Aldo Badano

**Abstract**

Imaging clinical trials can be burdensome and often delay patient access to novel, high-quality medical devices. Tools for in silico imaging trials have significantly improved in sophistication and availability. Here, I describe some of the principal advantages of in silico imaging trials and enumerate five lessons learned during the design and execution of the first all-in silico virtual imaging clinical trial for regulatory evaluation (the VICTRE study).

**Keywords:** In silico trials, Computational modeling, Regulatory evaluation

**In silico imaging**

Imaging clinical trials aim at answering specific scientific questions regarding the value of imaging technologies and procedures for detecting, diagnosing, guiding, or monitoring the treatment of disease. Imaging clinical trials can be burdensome for industry and regulators, often delaying patient access to novel, high-quality medical devices. The evaluation of novel imaging technologies typically requires a substantial clinical study to demonstrate benefits compared to the standard of care. While computational models are sometimes used in the regulatory evaluation of medical devices, their use in support of the more conventional applications in research and development of new imaging technology into areas where computer simulation has not yet been applied at any significant level. For instance, simulation tools can be used by industry and regulators to better understand modifications to existing devices and to predict the performance of new technology.

While many investigations on the use of in silico imaging to study the performance of radiation imaging systems (see, for instance, [2]) have been reported, no all-in silico clinical imaging trial has been reported until recently [3].

The VICTRE study consisted of an in silico replication

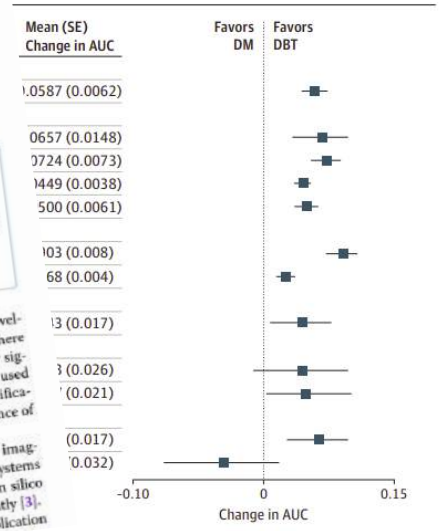
JAMA Network | Open

Original Investigation | Imaging

## Evaluation of Digital Breast Tomosynthesis as Replacement of Full-Field Digital Mammography Using an In Silico Imaging Trial

Aldo Badano, PhD; Christian G. Graff, PhD; Andreu Badal, PhD; Diksha Sharma, MSc; Rongping Zeng, PhD; Frank W. Samuelson, PhD; Stephen J. Glick, PhD; Kyle J. Myers, PhD

**Abstract**




y regulatory evaluation of innovative
l products. Simulation is increasingly
pplications.

l evaluating digital breast tomosynthesis
o compare the results with a

tual Imaging Clinical Trial for Regulatory
trial that used human patients and
d DBT systems via fast Monte Carlo x-ray
ting the presence of lesions. A total of
es and radiographic densities
icknesses from 3.5 to 6 cm were
ructures are randomly created within a
dal orientation. A positive cohort
culated mass.

s the difference in area under the
or lesion detection. The trial was sized
, half the uncertainty in the comparative

5 DM and 27 960 DBT cases from 2986
and Data System densities: 286 (9.6%)
00 (40.2%) scattered fibroglandular
E) change in AUC was 0.0587 (0.0062)
in favor of DBT. The change in AUC was larger for masses (mean [SE], 0.0903 [0.008])
calcifications (mean [SE], 0.0268 [0.004]), which was consistent with the findings of the
tive trial (mean [SE], 0.065 [0.017] for masses and −0.047 [0.032] for calcifications).

**SIONS AND RELEVANCE** The results of the simulated VICTRE trial are consistent with the
nce seen in the comparative trial. While further research is needed to assess the
ability of these findings, in silico imaging trials represent a viable source of regulatory
for imaging devices.

ork Open. 2018;1(7):e185474. doi:10.1001/jamanetworkopen.2018.5474

**Key Points**

**Question** Can in silico imaging trials play a role in the evaluation of new medical imaging systems?

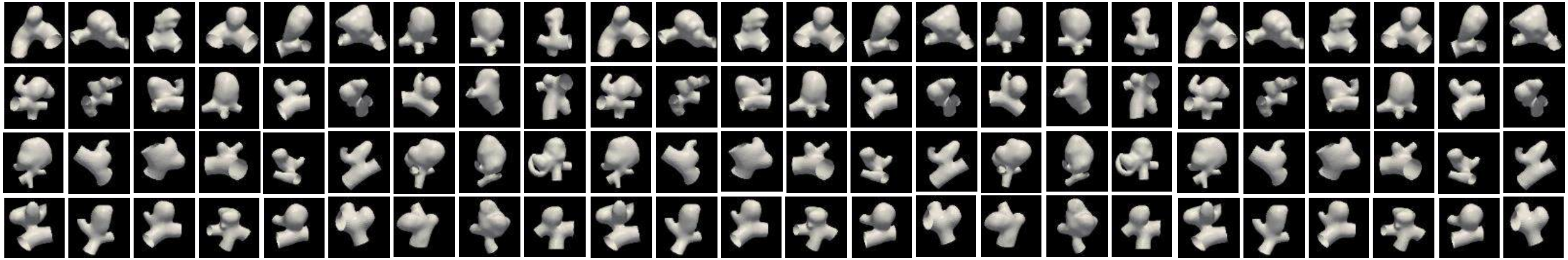
**Findings** This diagnostic study used computer-simulated imaging of 2986 synthetic image-based virtual patients to compare digital mammography and digital breast tomosynthesis and found an improved lesion detection performance favoring tomosynthesis for all breast sizes and lesion types. The increased performance for tomosynthesis was consistent with results from a comparative trial using human patients and radiologists.

**Meaning** The study's findings suggest that in silico imaging trials and imaging system computer simulation tools can in some cases be considered viable sources of evidence for the regulatory evaluation of imaging devices.

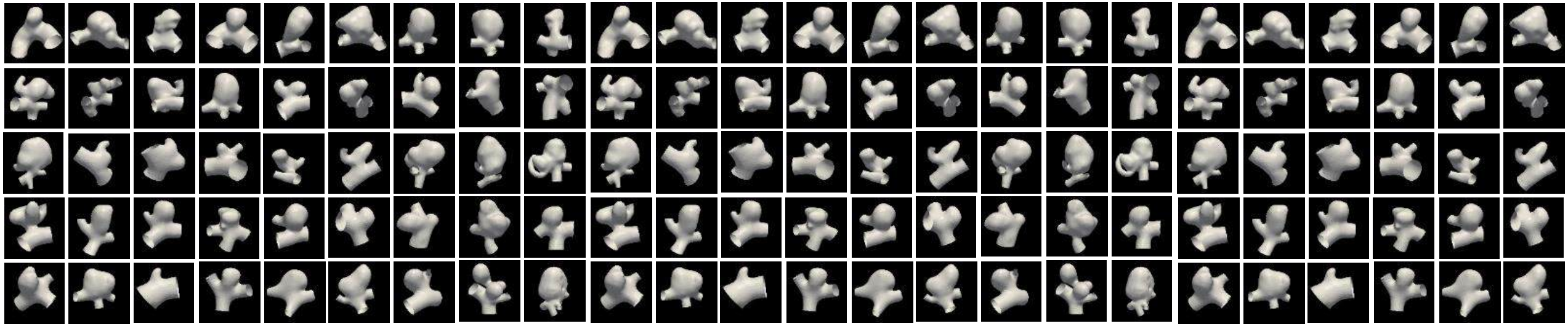
Supplemental content

Author affiliations and article information are listed at the end of this article.

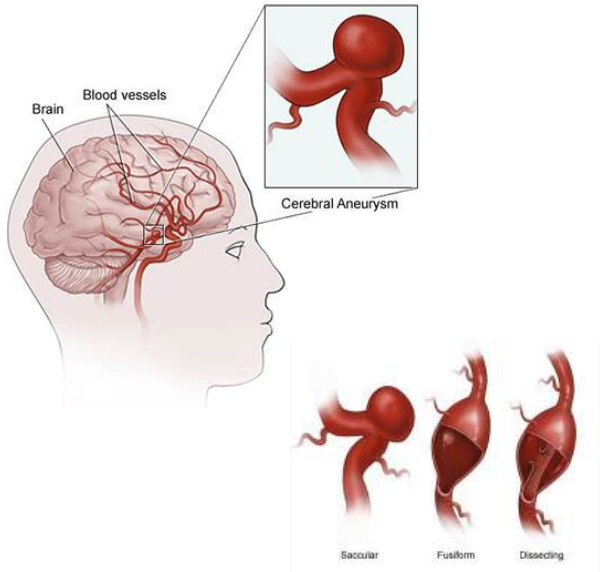
no A, Graff CG, Badal A, Sharma D, Zeng R, Samuelson FW, Glick SJ, s KJ. Evaluation of Digital Breast Tomosynthesis as Replacement of ield Digital Mammography Using an In Silico Imaging Trial. JAMA Netw . 2018 Nov 2;1(7):e185474. doi: 10.1001/jamanetworkopen.2018.5474.



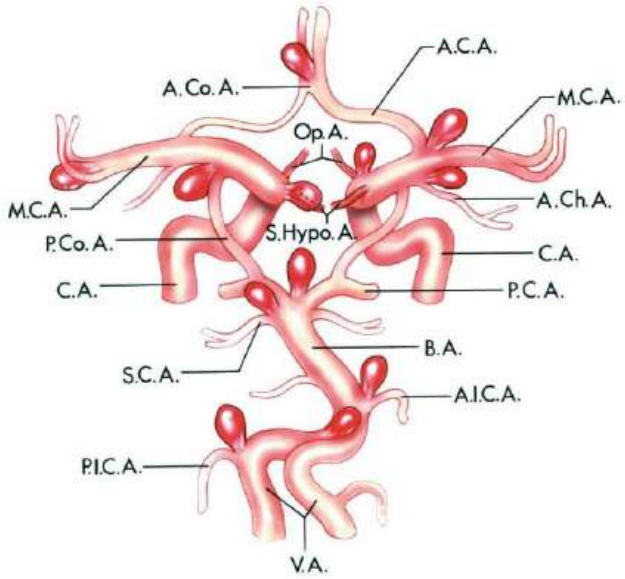
# Can in-silico trials replicate and expand conventional clinical trials?



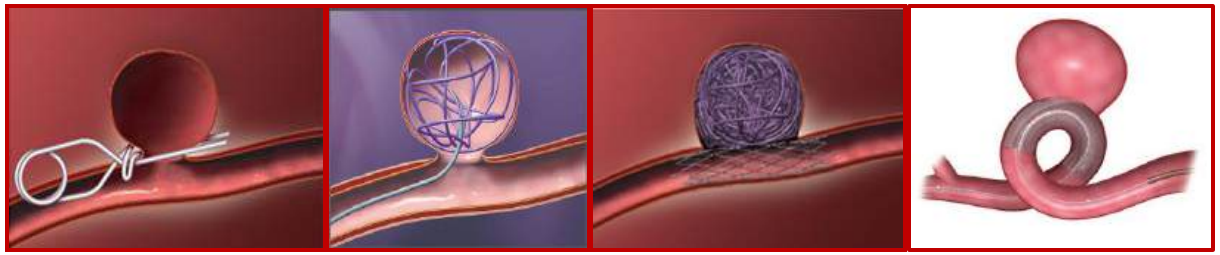
# Haemorrhagic stroke: intracranial aneurysms

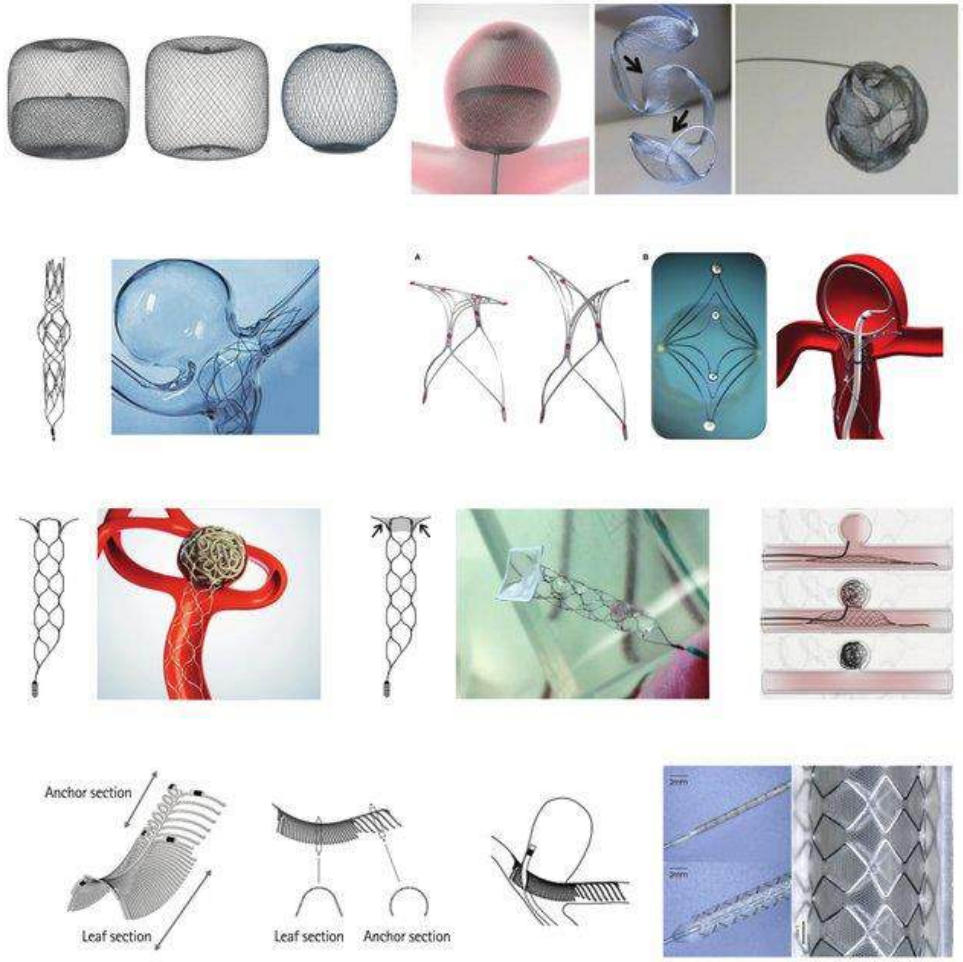



www.rwjbh.org/rwj-university-hospital-new-brunswick/treatment-care/neurosciences/neurosurgery/for-patients/new-jersey-brain-aneurysm-avm-program/what-is-a-brain-aneurysm-/



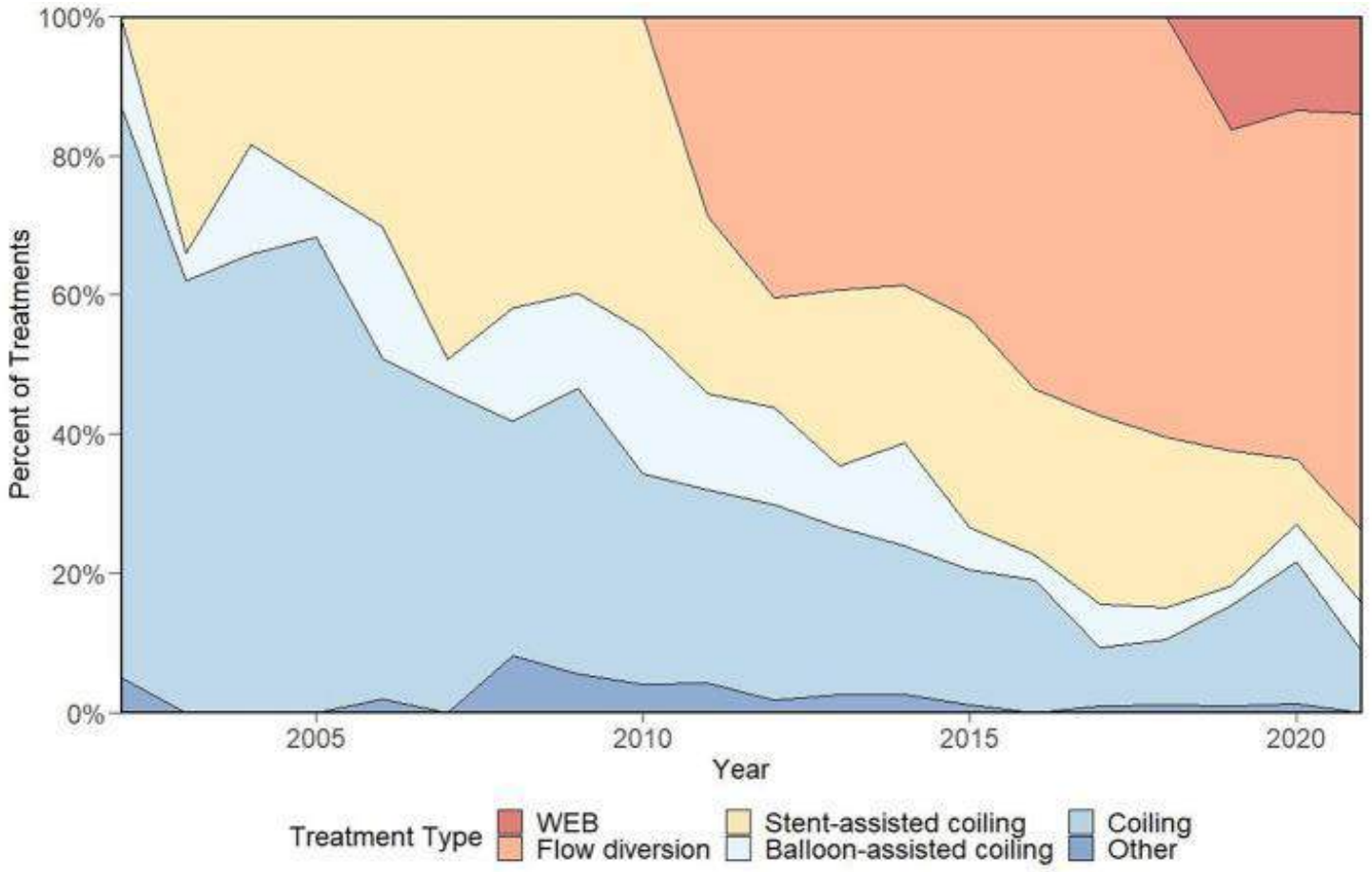

www.neurosurgicalatlas.com/neuroanatomy/most-common-sites-of-saccular-aneurysms






Jia ZY, Shi HB, Miyachi S, Hwang SM, Sheen JJ, Song YS, Kim JG, Lee DH, Suh DC. Development of New Endovascular Devices for Aneurysm Treatment. J Stroke. 2018 Jan;20(1):46-56. doi: 10.5853/jos.2017.02229.
Dandapat S, Mendez-Ruiz A, Martínez-Galdámez M, Macho J, Derakhshani S, Foa Torres G, Pereira VM, Arat A, Wakhloo AK, Ortega-Gutierrez S. Review of current intracranial aneurysm flow diversion technology and clinical use. J Neurointerv Surg. 2021 Jan;13(1):54-62.

# Device selection for elective aneurysm treatments at a US center over 20-year



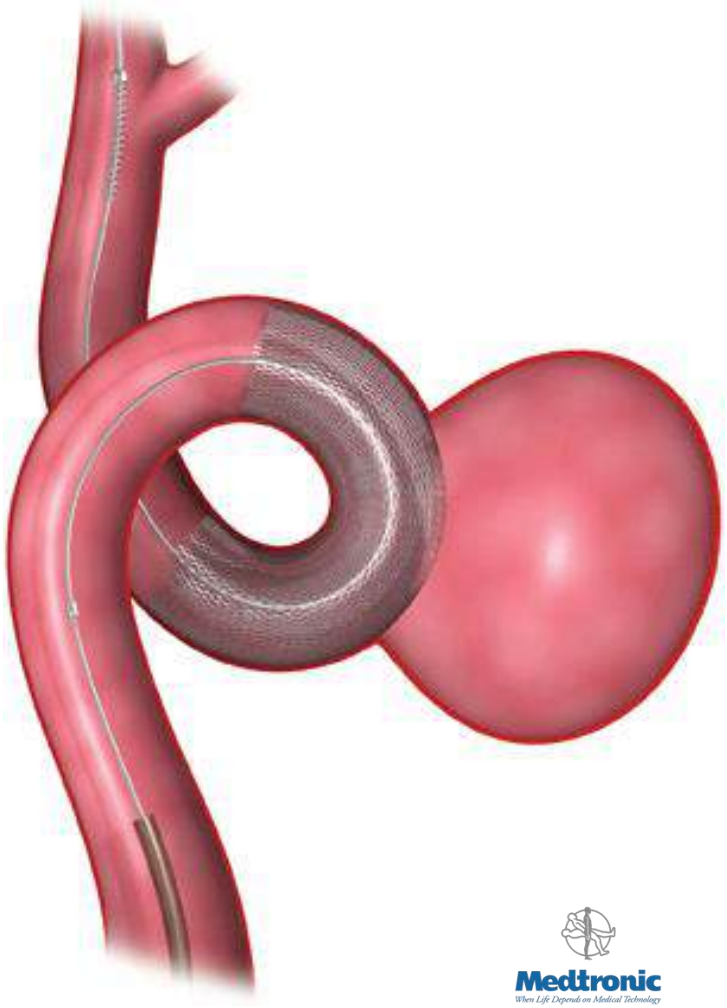

| Device | Manufacturer and year of FDA approval | Material | Detachment |
|---|---|---|---|
| **Coils** | | | |
| Target (Guglielmi) detachable coil | Target, 1995 | Bare platinum | Electrolytic |
| Micrus microcoil | Micrus, 2003 | Bare platinum | Mechanical (using resistive heating) |
| HydroCoil embolic system | Microvention, 2002 | Hydrogel-coated bare platinum coils | V-grip detachment controller with self-contained (integral) power supply |
| Orbit detachable coil | Cordis, 2003 | Bare Platinum | Mechanical (Guidant) |
| Matrix bioactive coil | Boston Scientific/Target, 2003 | Polyglycolic acid–coated bare platinum coils | Electrolytic |
| Genesis coil | Micrus, 2004 | Platinum coils with polyglycolic acid coating through lumen of primary platinum wind | Mechanical (using resistive heating) |
| Orbit Galaxy coil | Cordis, 2010 | Bare platinum | Mechanical (using resistive heating) |
| POD coil | Penumbra, 2011 | Bare platinum | Mechanical |
| Cashman Trufill coil | Johnson and Johnson, 2013 | Bare platinum | Mechanical (hydraulic) |
| Axium | Medtronic, 2014 | Bare platinum | Mechanical |
| Barricade coil | Balt, 2015 | Bare platinum | Electrolytic |
| Axium prime | Medtronic, 2017 | Bare platinum | Mechanical |
| Optima coil | Balt, 2020 | Bare platinum | Thermal |
| **Stents** | | | |
| Device | Manufacturer and Year of FDA Approval | Material | Delivery System Size) |
| Neuroform stent | Boston Scientific/Target, 2002 | Nitinol, open-cell design | 0.027-inch microcatheter |
| Enterprise stent | Cordis Neurovascular, 2007 | Nitinol, closed-cell design coated with resulting polymer (Part two C) | 0.021-inch microcatheter |
| LVIS, LVIS Jr | Microvention, 2014 | Nitinol, closed-cell braided design | 0.021-inch, 0.0165-inch microcatheter, respectively |
| LVIS EVO | Microvention | Nitinol, closed-cell braided design | 0.0165-inch microcatheter |
| Neuroform Atlas | Stryker Neurovascular, 2019 | Nitinol, laser-cut open-cell design | 0.0165-inch microcatheter |
| **Flow diverters** | | | |
| Device | Manufacturer and year of FDA approval | Material | Delivery catheter size |
| Pipeline Embolization Device | Medtronic Neurovascular, 2011 | 36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio | 0.027-inch microcatheter |
| Pipeline Flex Embolization Device | Medtronic Neurovascular, 2018 | 36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio | 0.027-inch microcatheter |
| Pipeline Flex with Shield | Medtronic Neurovascular, 2021 | 36 cobalt-chromium strands, 12 platinum-tungsten strands woven in 3:1 ratio, phosphorylcholine polymer surface coating | 0.027-inch microcatheter |
| Pipeline Vantage | Medtronic Neurovascular | 36 or 48 cobalt-chromium strands, 12 or 16 platinum-tungsten strands woven in 3:1 ratio, phosphorylcholine polymer surface coating | 0.021-inch or 0.027-inch microcatheter |
| FRED | Microvention, 2019 | Self-expanding braided 48 nitinol wires | 0.027-inch microcatheter |
| FRED Jr | Microvention, 2019 | Self-expanding braided 34 nitinol wires | 0.021-inch microcatheter |
| FRED X | Microvention | Self-expanding braided 34 or 48 nitinol wires, proteolytic nano-polymer hydration layer | 0.021-inch or 0.027-inch microcatheter |
| Surpass Streamline | Stryker Neurovascular, 2018 | 72 or 96 cobalt-chromium wires | 0.053-inch intermediate catheter, passed over 0.014-inch microwire |
| Surpass Evolve | Stryker Neurovascular, 2020 | 48 cobalt-chromium wires | 0.027-inch microcatheter |
| Silk | Balt Extrusion | 48 braided nitinol wires | 0.021-inch or 0.025-inch microcatheter |
| Silk Vista | Balt Extrusion | 48 braided nitinol wires | 0.021-inch or 0.025-inch microcatheter |
| Silk Vista Baby | Balt Extrusion | 48 braided nitinol wires | 0.017-inch microcatheter |
| **Other** | | | |
| Device | Manufacturer and year of FDA approval | Material | Delivery catheter size |
| Onyx HD-500 | ev3, 2007 | 20% Ethylene vinyl alcohol copolymer dissolved in DMSO with suspended micronized tantalum powder | 0.014-inch microcatheter |
| PulseRider Device | Cerenovus, 2018 | Nitinol, T or T-shape | 0.021-inch microcatheter |
| pCONUS | Phenox | Nitinol, radially flowing distal petals | 0.021-inch microcatheter |
| pCONUS 2 | Phenox | Nitinol, radially flowing distal petals | 0.021-inch microcatheter |
| pCONUS 2 HPC | Phenox | Nitinol, radially flowing distal petals with hydrophilic coating | 0.021-inch microcatheter |
| WEB | Microvention, 2019 | Nitinol wires with platinum coil, wire single layer of mesh | 0.017, 0.021, 0.027, or 0.033-inch microcatheter |
| Contour | Cerus | Dual-layered structure of 2 or 72 nitinol wires | 0.021-inch or 0.027-inch microcatheter |
| **Balloons** | | | |
| Device | Manufacturer and Year of FDA Approval | Lumen type | DAMD compatible? |
| Cerecyte | Cordis Neurovascular, 1998 | Single lumen | No |
| Equinox | Micro Therapeutics, 2000 | Single lumen | No |
| Scout | Micrus, 2008 | Single lumen | No |
| HyperGlide | Medtronic Neurovascular, 2010 | Single lumen | Yes |
| HyperForm | Medtronic Neurovascular, 2010 | Single lumen | Yes |
| Scepter | Microvention, 2012 | Dual lumen | Yes |
| Transform | Stryker Neurovascular, 2013 | Single lumen | No |
| Eclipse | Balt, 2019 | Dual lumen | Yes |

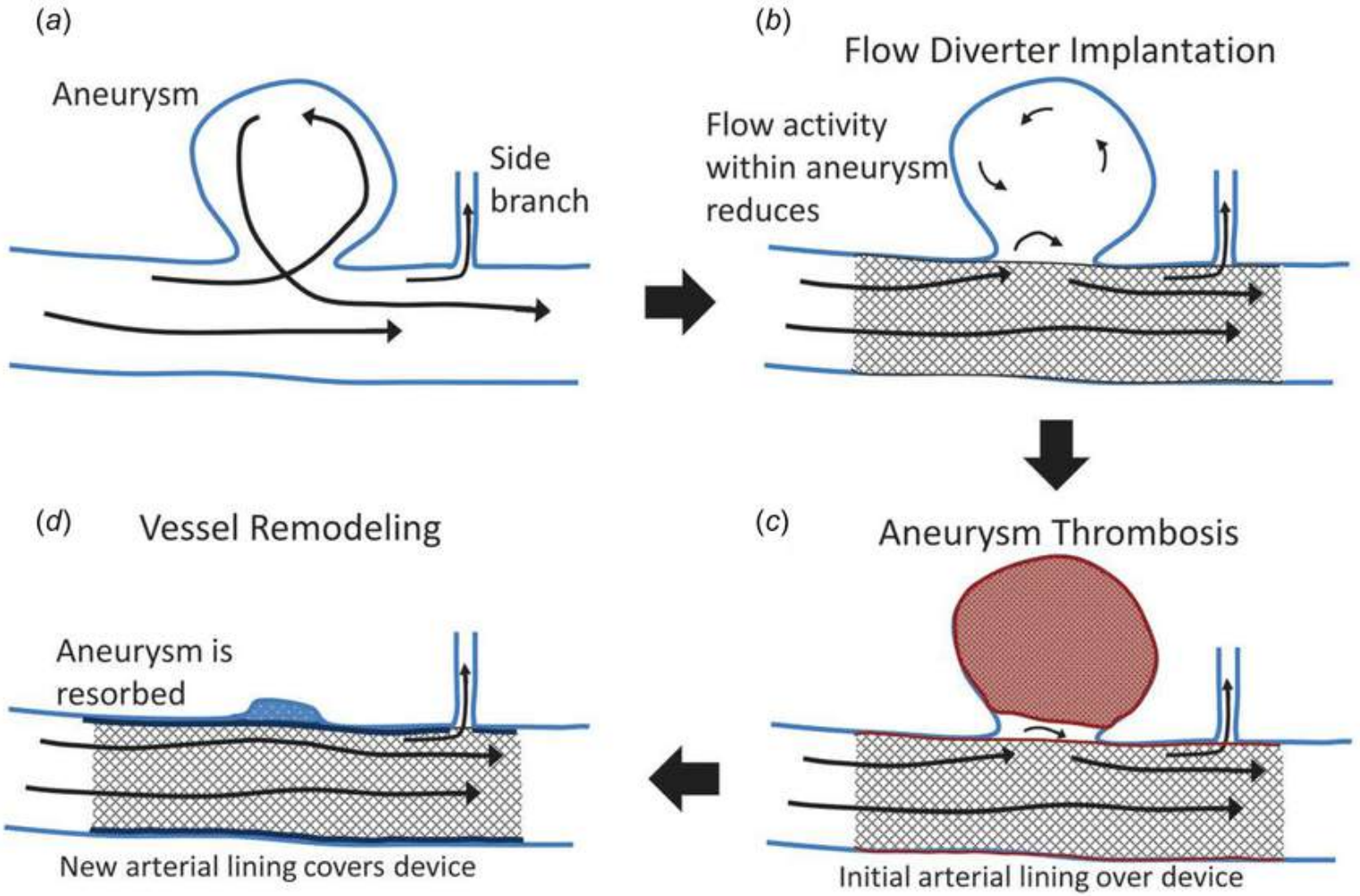
Year of FDA approval provided for devices available in the United States.
Similar to device evolution, there have been dramatic changes in device manufacturers with many mergers and buyouts. For example, Micrus originally was acquired by tech Cordis was acquired by Medtronic. Target was acquired by Boston Scientific, which in turn was acquired by Stryker, and Micrus was acquired by Cordis in turn by a subsidiary of Johnson and Johnson.



Lauzier DC, Huguenard AL, Srienc AI, Cler SJ, Osbun JW, Chatterjee AR, Vellimana AK, Kansagra AP, Derdeyn CP, Cross DT, Moran CJ. A review of technological innovations leading to modern endovascular brain aneurysm treatment. Front Neurol. 2023 Apr 11;14:1156887. doi: 10.3389/fneur.2023.1156887.

# Flow-Diverter Mechanism of Action



# Pipeline for Uncoilable or Failed Aneurysms (PUFS) Trial

ORIGINAL RESEARCH ■ NEURORADIOLOGY

## Pipeline for Uncoilable or Failed Aneurysms: Results from a Multicenter Clinical Trial[1]

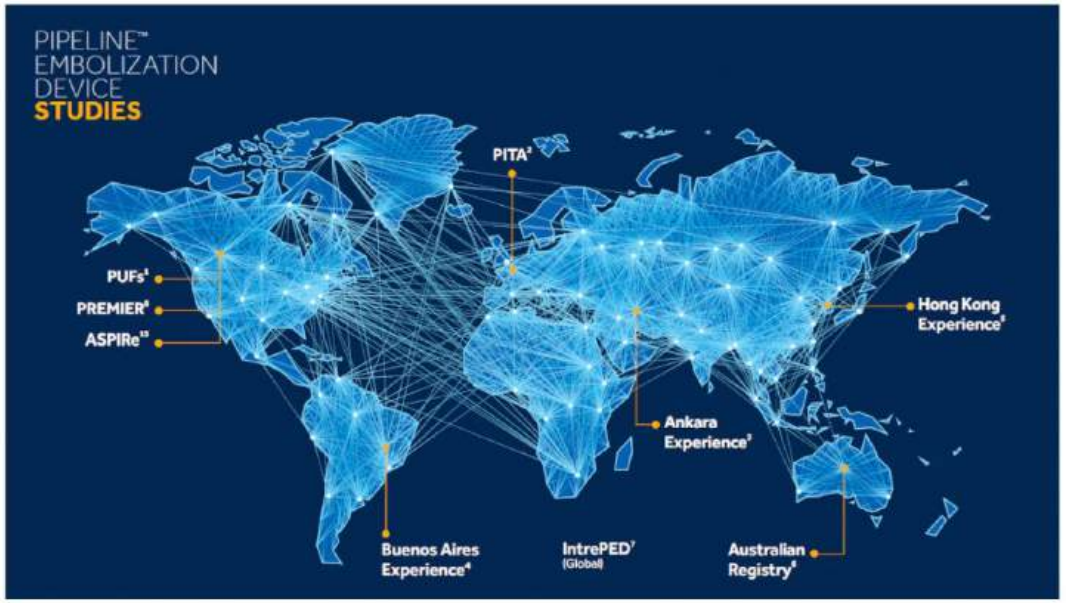
Tibor Becske, MD
David F. Kallmes, MD
Isil Saatci, MD
Cameron G. McDougall, MD
István Szikora, MD, PhD
Giuseppe Lanzino, MD
Christopher J. Moran, MD
Henry H. Woo, MD
Demetrius K. Lopes, MD
Aaron L. Berez, MD
Daniel J. Cher, MD
Adnan H. Siddiqui, MD, PhD
Elad I. Levy, MD
Felipe C. Albuquerque, MD
David J. Fiorella, MD, PhD
Zsolt Berentei, MD

**Purpose:** To evaluate the safety and effectiveness of the Pipeline Embolization Device (PED; ev3/Covidien, Irvine, Calif) in the treatment of complex intracranial aneurysms.

**Materials and Methods:** The Pipeline for Uncoilable or Failed Aneurysms is a multicenter, prospective, interventional, single-arm trial of PED for the treatment of uncoilable or failed aneurysms of the internal carotid artery. Institutional review board approval of the HIPAA-compliant study protocol was obtained from each center. After providing informed consent, 108 patients with recently unruptured large and giant wide-necked aneurysms were enrolled in the study. The primary effectiveness endpoint was angiographic evaluation that demonstrated complete aneurysm occlusion and absence of major stenosis at 180 days. The primary safety endpoint was occurrence of major ipsilateral stroke or neurologic death at 180 days.

Radiology

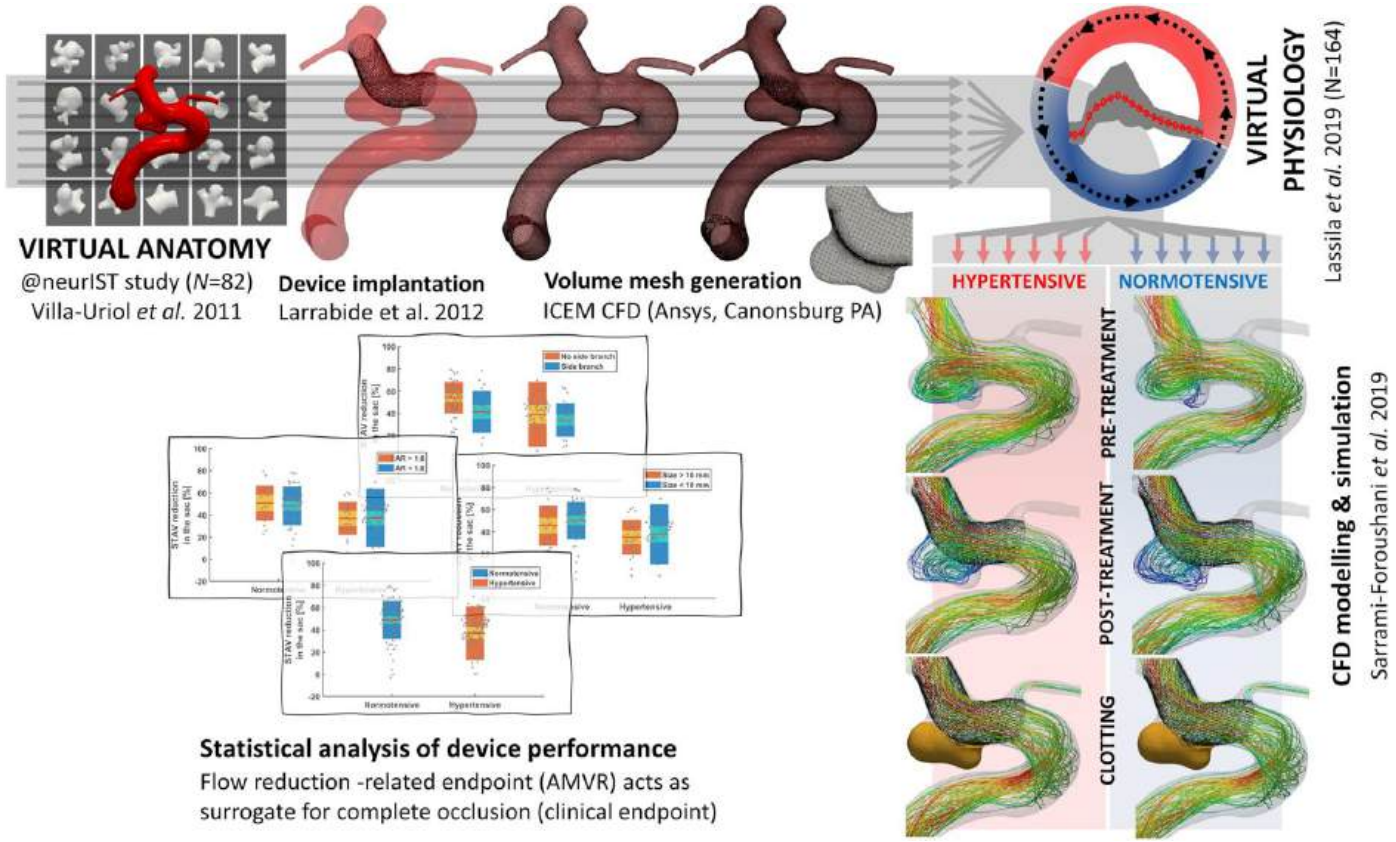
Design to Publication 8 years
Recruitment 6 years
108 patients ca. £30-40m
https://clinicaltrials.gov/ct2/show/NCT00777088




| | | | |
|---|---|---|---|
| PREMIER[7] n=141 | PUFs[1,2] n=106 | Buenos Aires Experience n=53 | Hong Kong Experience[15] n=178 |
| ASPIRe[11] n=191 | PITA[13] n=31 | Ankara Experience[14] n=251 | Australian Registry[16] n=5 |

# FD-PASS

## *Our first in silico clinical trial*




nature COMMUNICATIONS

Medtronic

ARTICLE

https://doi.org/10.1038/s41467-021-23998-w OPEN

Check for updates

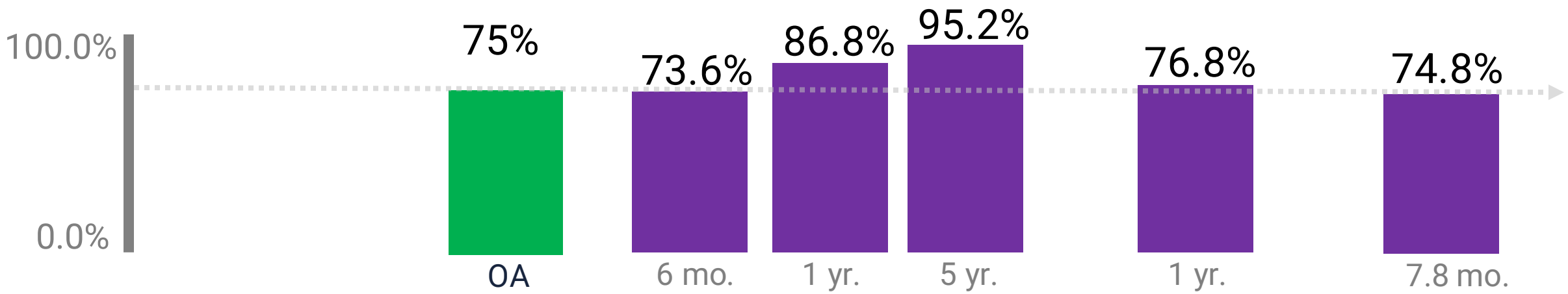
### In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials

Ali Sarrami-Foroushani[1,2], Toni Lassila[1], Michael MacRaild[1], Joshua Asquith[1], Kit C. B. Roes[3], James V. Byrne[4] & Alejandro F. Frangi[1,2,5,6]✉

The cost of clinical trials is ever-increasing. In-silico trials rely on virtual populations and interventions simulated using patient-specific models and may offer a solution to lower these costs. We present the flow diverter performance assessment (FD-PASS) in-silico trial, which models the treatment of intracranial aneurysms in 164 virtual patients with 82 distinct anatomies with a flow-diverting stent, using computational fluid dynamics to quantify post-treatment flow reduction. The predicted FD-PASS flow-diversion success rates replicate the values previously reported in three clinical trials. The in-silico approach allows broader investigation of factors associated with insufficient flow reduction than feasible in a conventional trial. Our findings demonstrate that in-silico trials of endovascular medical devices can: (i) replicate findings of conventional clinical trials, and (ii) perform virtual experiments and sub-group analyses that are difficult or impossible in conventional trials to discover new insights on treatment failure, e.g. in the presence of side-branches or hypertension.

Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861. doi: 10.1038/s41467-021-23998-w.

# FD-PASS:
## replicated the occlusion rates of three studies




| FDPASS | PUFS | PREMIER | ASPIRe |
|---|---|---|---|
| 2021<br>In-silico trial<br>Small, large, and giant aneurysms | 2008-2014<br>Clinical trial<br>Large & giant aneurysms (size > 10mm) | 2014-2015<br>Clinical trial<br>Small & medium aneurysms (size < 12mm) | 2016<br>Observational registry<br>Small, large, and giant aneurysms |

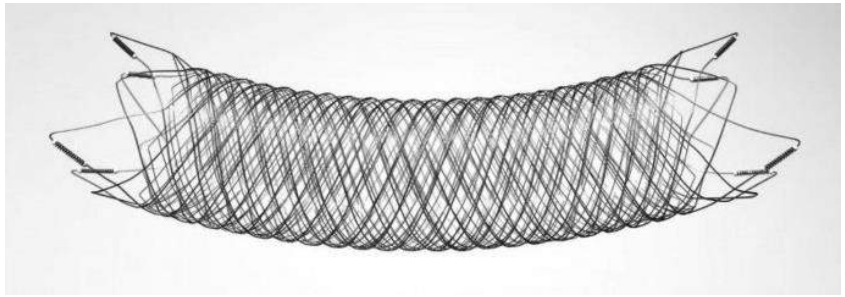
PUFS—Outcome improvement over time—Three possible explanations:
1/ The aneurysm occlusion process can be prolonged in some cases. As time passes, more aneurysms heal.
2/ Some cases received re-treatments: 6 aneurysms re-treated
3/ Dropouts or failure in follow-ups Y1: 86.8% (79/91), Y3: 93.4% (71/76), and Y5: 95.2% (60/63).

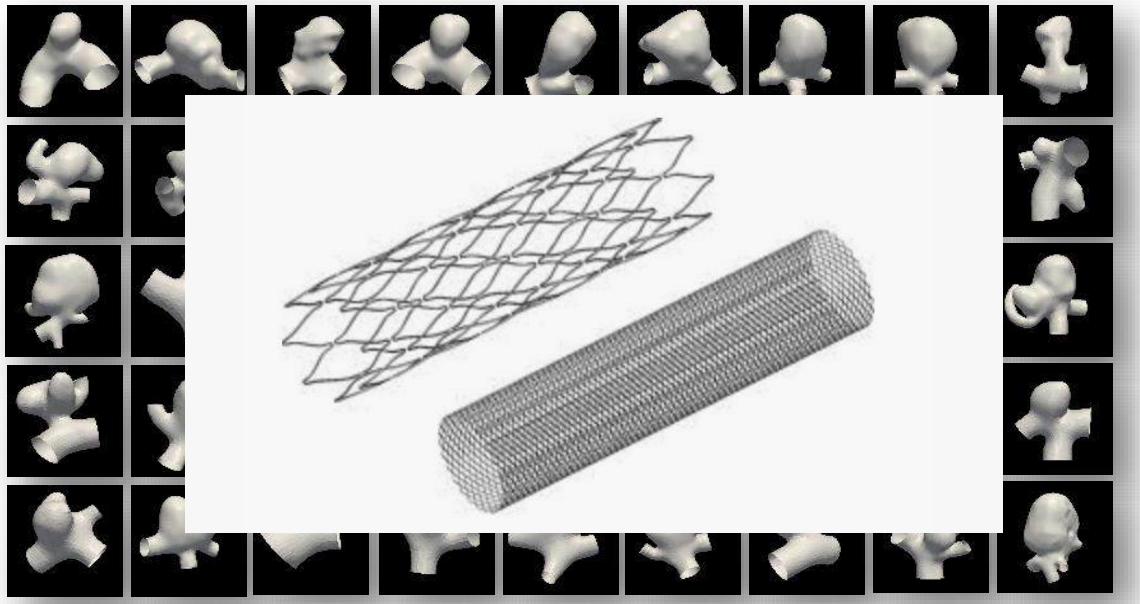


Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

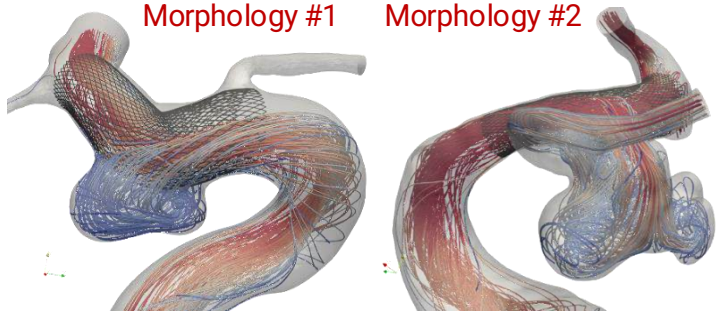
# **In silico trials** – Concrete example: cerebrovascular flow diversion devices

## Systematically explore design space & test it against available knowledge

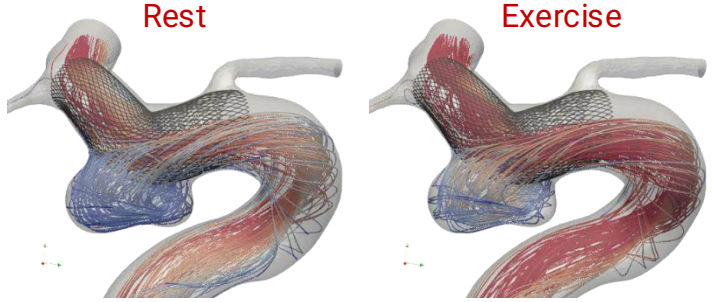




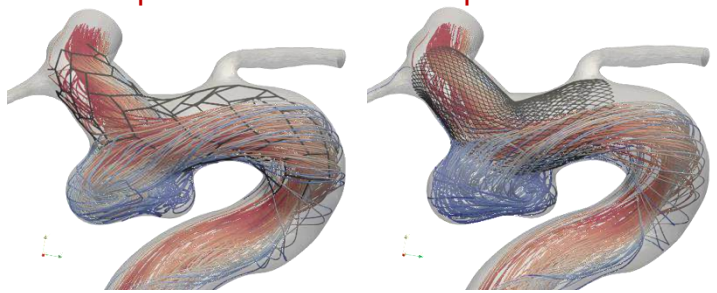
Morphology #1 Morphology #2



Rest Exercise



Enterprise device Pipeline device



**Surrogate end point**: Reduction in max time-averaged velocity at the neck

Anatomy #1: 64%
Anatomy #2: 27%

| | |
|---|---|
| Rest | 64% |
| Exercise | 56% |

| | |
|---|---|
| Enterprise: | 10% |
| Pipeline: | 64% |



Sarrami-Foroushani A, Lassila T, MacRaild M, Asquith J, Roes KCB, Byrne JV, Frangi AF. In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021 Jun 23;12(1):3861.

# The In-Silico Trial Space

> From virtual twin to virtual chimera populations

**Population Data**

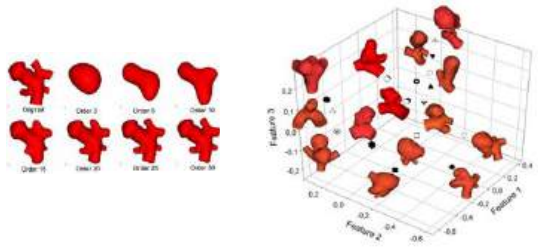
biobank uk
Improving the health of future generations

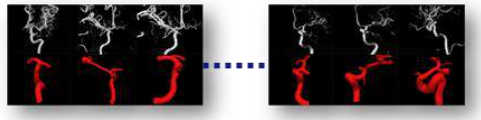
Yorkshire IMAGING COLLABORATIVE
Every image. Anywhere

LEEDS CARE RECORD
Shared information. Better care for you.

Yorkshire & Humber Care Record

LIVING IN LEEDS.
Better data. Better health.

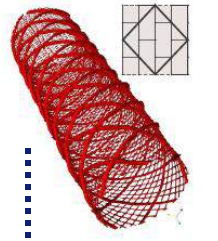


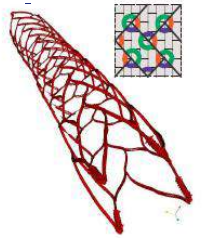


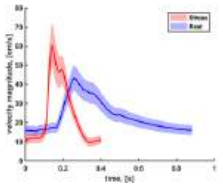
Anatomical, Mechanical & Rheological envelope

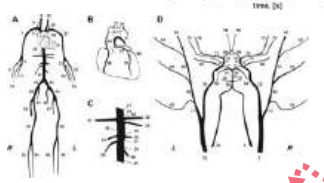
Device Design & Delivery envelope

virtual experiment






Lifestyle, Physiological & Operational envelope

**Device Specs**

**Population Data**

# Real-world datasets – intracranial aneurysms

aneurIST

NHS
The Leeds Teaching Hospitals
NHS Trust

| | |
|---|---|
| Brain angiographic data (3D rotational angiography, CTA, and/or MRA).<br>Approximately **600** patients. | Consecutive brain angiographic data (3D rotational angiography, CTA, and/or MRA) and radiology reports from the past 10 years have been retrieved in LTHT.<br><br>Approximately **36,000** patients. |
| **Exams/Interventions**<br>When available, aneurysm rupture status.<br>When available, information about coiling treatment. | **Exams/Interventions**<br>When available, aneurysm rupture status<br>Flow diversion or coiling treatment of aneurysms.<br>Device information (type/make, size, numbers) |
| **Demographics & clinical data**<br>Age, gender, smoking status, and BMI | **Demographics & clinical data**<br>Age, gender, ethnicity, smoking status, and BMI |

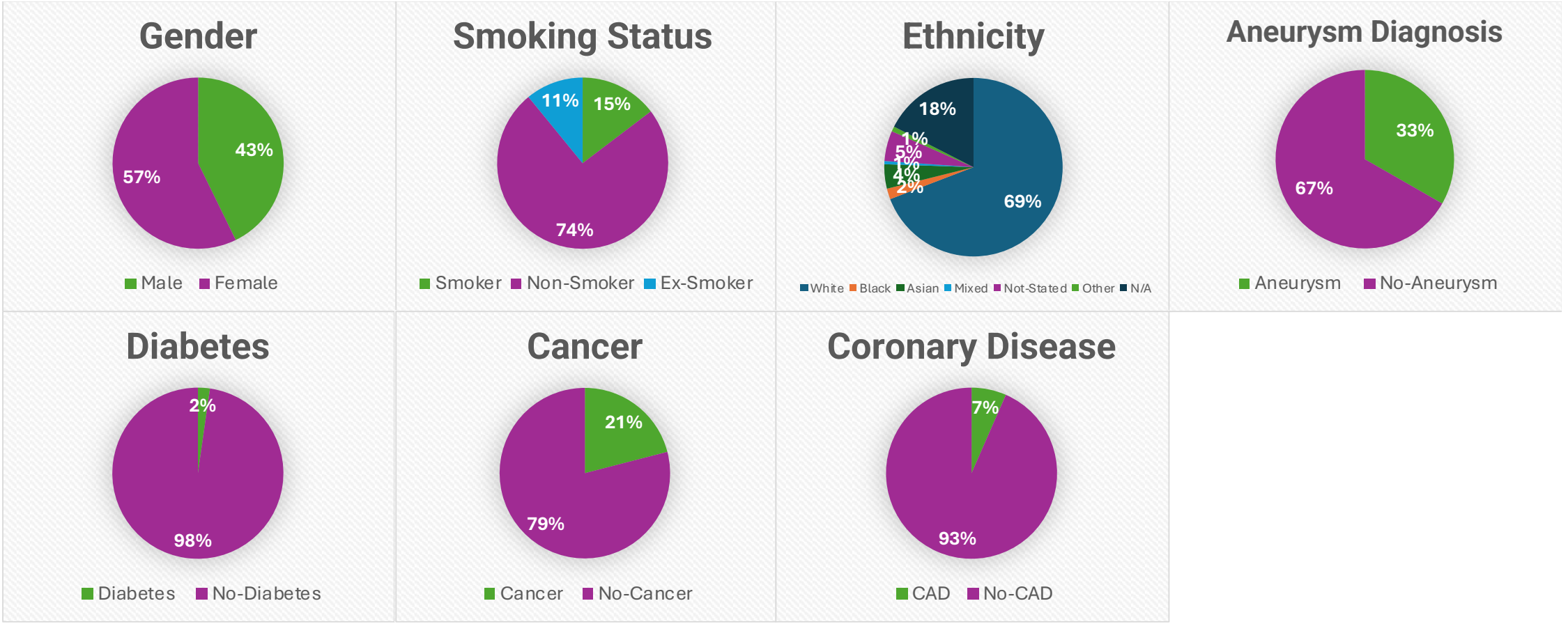
**Blood analytics**
Information re RBCs, WBCs, platelets, etc.

**Comorbidities**
Diabetes, (controlled) hypertension, hyperlipidemia, coronary artery disease, polycystic kidney disease, atrial fibrillation, and cancer.

**Medicines**
Anticoagulant and antiplatelet medicines like heparin, warfarin, aspirin, clopidogrel, ticagrelor, and prasugrel.

# Real-world datasets – intracranial aneurysms

Example: Population– 35,891 cases (examined 2014-2024). Mean age = 59 yo [17-92 yo]



# Reference at-scale datasets – aortic valve stenosis

Boston Scientific

1,000

REPRISE III
Lotus Valve System

A randomized, controlled trial to evaluate the safety and effectiveness of the Lotus™ Valve System for TAVR in symptomatic subjects with calcific, severe native aortic valve stenosis who are considered at extreme or high risk for surgical valve replacement

**Study Design:**

- 2:1 Randomization of **Lotus Valve vs. CoreValve® Transcatheter Aortic Valve Replacement Platform**
- N=1032
- Annulus size: 20 mm-27 mm (utilizing the 23, 25, and 27 mm Lotus valves)

**Primary Safety Endpoint:** Composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications at 30 days

**Primary Efficacy Endpoint:** Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year

**Secondary Endpoint:** Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year

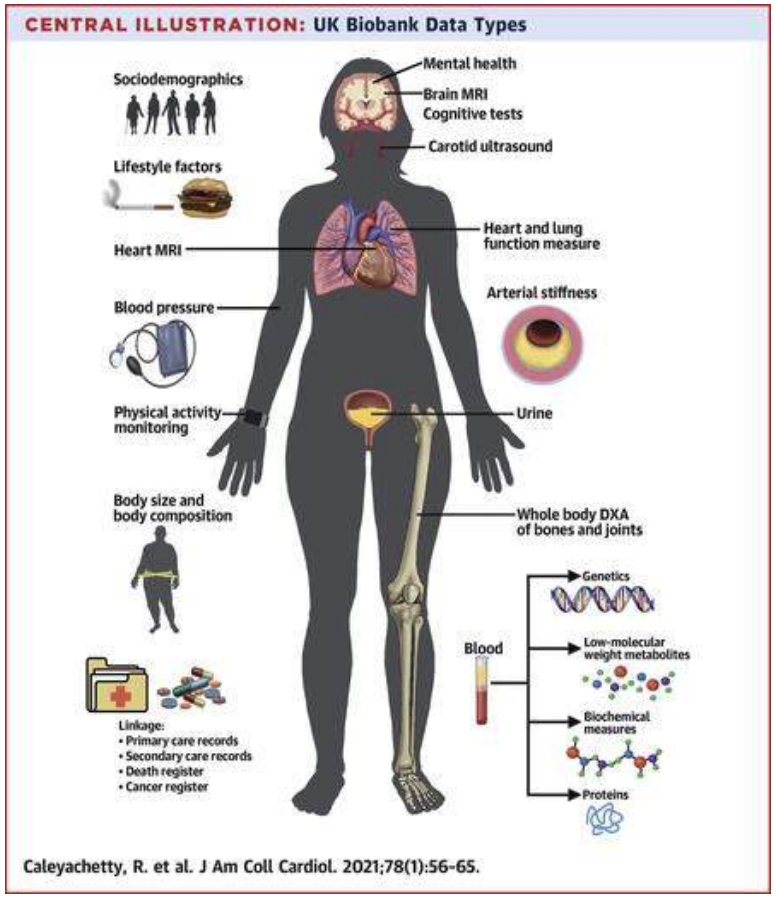
Up to 60 Centers
United States, Canada, Western Europe and Australia

A prospective, multicenter, 2:1 randomised (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System, controlled trial

85,000

biobank uk

A very large, population-based prospective study, established to allow detailed investigations of the genetic and nongenetic determinants of the diseases of middle and old age. 500k (100k imaging enhancement)



# Health Data as a Sovereign Asset

## UK: Health Data Research Service to provide single point of access to NHS data in the United Kingdom

https://www.gov.uk/government/news/prime-minister-turbocharges-medical-research

GOV.UK

Home > Business and industry > Industrial strategy

Press release

### Prime Minister turbocharges medical research

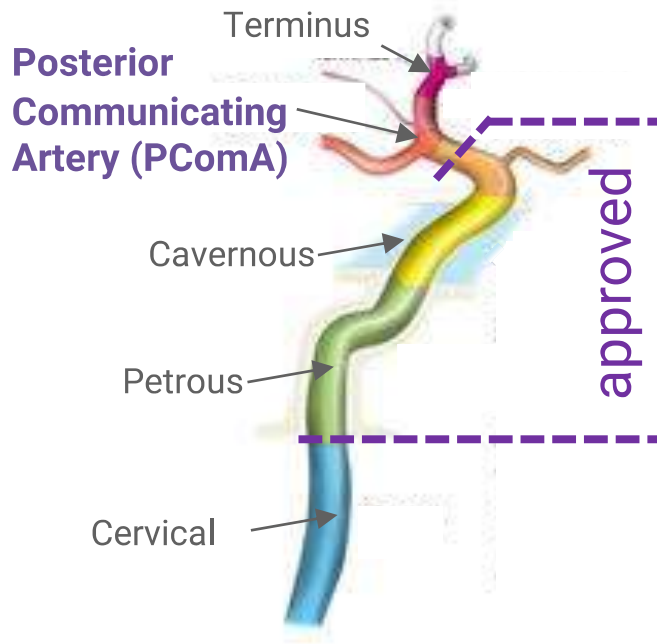
Better and faster access to NHS data for researchers, with gold standard security and privacy measures.

From: Department of Health and Social Care, Prime Minister's Office, 10 Downing Street, Department for Science, Innovation and Technology, Office for Life Sciences, The Rt Hon Sir Keir Starmer KCB KC MP, The Rt Hon Wes Streeting MP and The Rt Hon Peter Kyle MP

Published 7 April 2025

Last updated 7 April 2025 — See all updates

- Latest in a series of pro-growth measures to build a strong, resilient economy with more well-paid jobs
- Changes will help make Britain the best country in the world for medical research driving growth that puts more money in people's pockets as part of the Plan for Change




## Exemplar II

# IN SILICO TRIAL FOR OFF-LABEL USE

INCREMENTAL INNOVATION / UNDERSERVED PATIENT GROUPS

OPEN ACCESS

Original research

# Off-label in-silico flow diverter performance assessment in posterior communicating artery aneurysms

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► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jnis-2024-022000).

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Received 18 May 2024
Accepted 13 September 2024

## ABSTRACT

**Background** The posterior communicating artery (PComA) is among the most common intracranial aneurysm locations, but flow diverter (FD) treatment with the widely used pipeline embolization device (PED) remains an off-label treatment that is not well understood. PComA aneurysm flow diversion is complicated by the presence of fetal posterior circulation (FPC), which has an estimated prevalence of 4–29% and is more common in people of black (11.5%) than white (4.9%) race. We present the FD-PComA in-silico trial (IST) into FD treatment performance in PComA aneurysms. ISTs use computational modeling and simulation in cohorts of virtual patients to evaluate medical device performance.

**Methods** We modeled FD treatment in 118 virtual patients with 59 distinct PComA aneurysm anatomies, using computational fluid dynamics to assess post-treatment outcome. Boundary conditions were prescribed to model the effects of non-fetal and FPC, allowing for comparison between these subgroups.

**Results** FD-PComA predicted reduced treatment success in FPC patients, with an average aneurysm space and time-averaged velocity reduction of 67.8% for non-fetal patients and 46.5% for fetal patients ($P<0.001$). Space and time-averaged wall shear stress on the device surface was 29.2 Pa averaged across fetal patients and 23.5 Pa across non-fetal ($P<0.05$) patients, suggesting FD endothelialization may be hindered in FPC patients. Morphological variables, such as the size and shape of the aneurysm and PComA size, did not affect the treatment outcome.

**Conclusions** FD-PComA had significantly lower treatment success rates in PComA aneurysm patients with FPC. We suggest that FPC patients should be treated with an alternative to single PED flow diversion.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Flow diverter (FD) treatment of posterior communicating artery (PComA) aneurysms using the pipeline embolization device (PED) is an off-label indication with poorly understood low treatment success rates in patients with fetal posterior circulation (FPC).

### WHAT THIS STUDY ADDS

⇒ The FD-PComA in-silico trial used computer modeling and simulation in 118 virtual patients to determine that PED treatment of PComA aneurysms was less effective in patients with FPC and was due to the increased flow rate through the PComA in this scenario.

⇒ Morphological variables, such as PComA size, aneurysm maximum diameter, aneurysm aspect ratio, aneurysm neck width, and aneurysm non-sphericity index did not influence treatment outcomes.

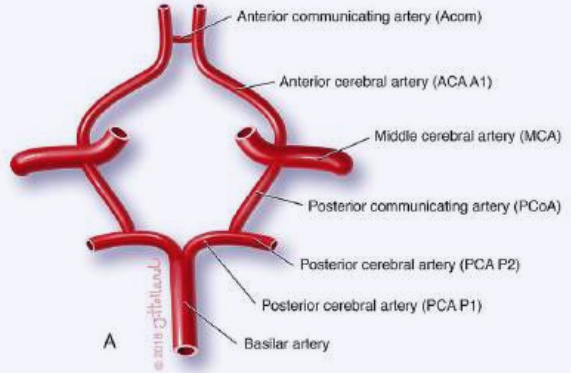
### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

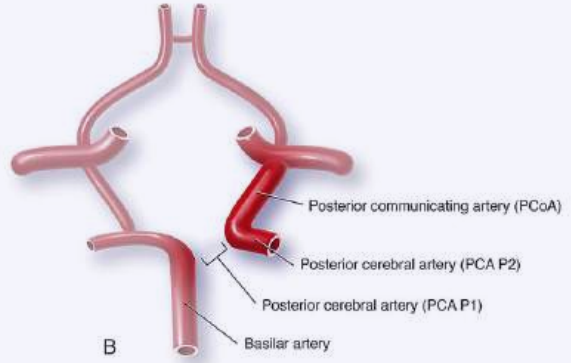
⇒ Alternative treatment to single PED flow diversion is recommended for PComA aneurysms with FPC.

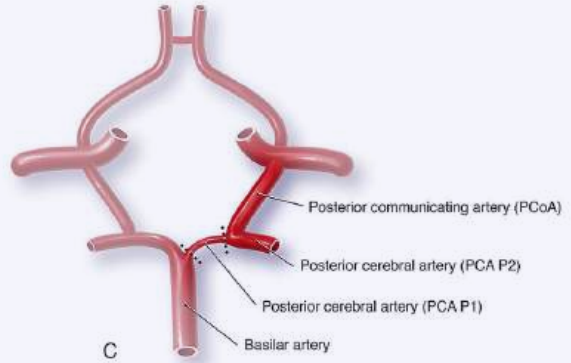
⇒ This study highlights how in-silico trials can generate evidence on medical device performance in less studied treatment scenarios.

neointima along the device itself, ultimately leading to aneurysm occlusion. Neointimal proliferation can also lead to parent vessel remodelling, which led to concerns that the PED has the potential to



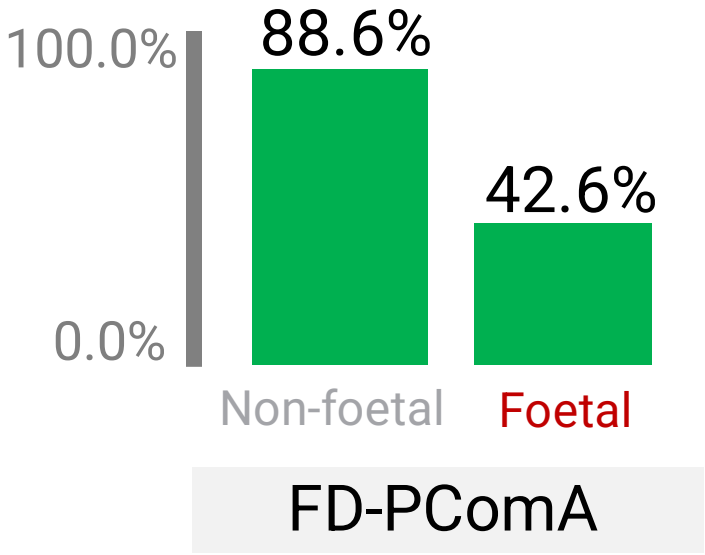


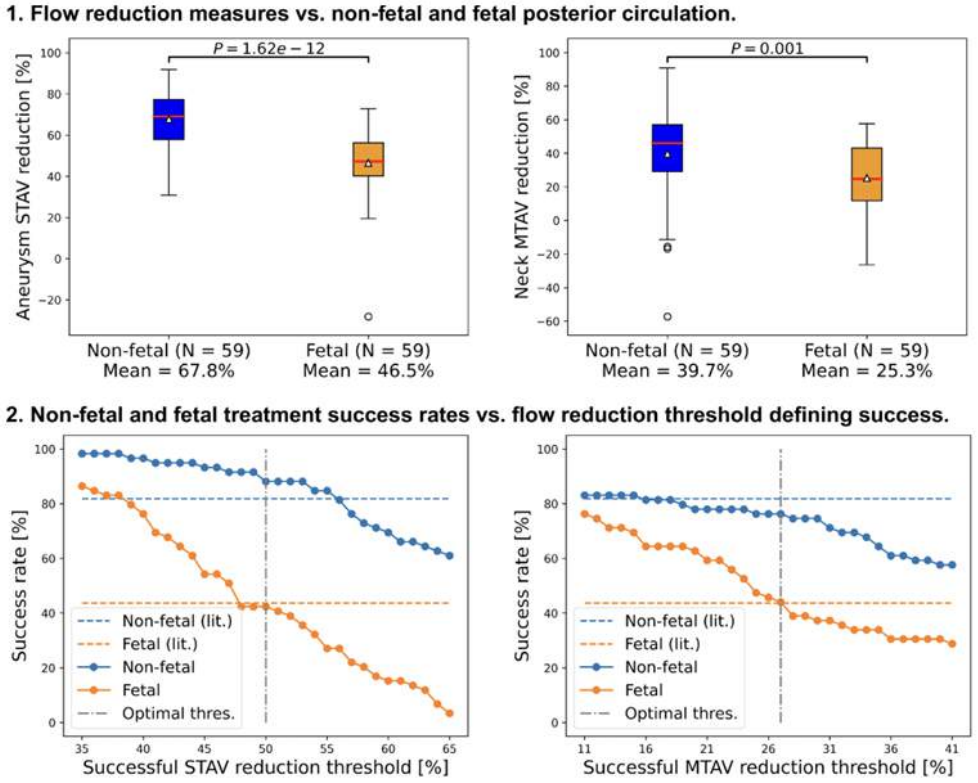



# FD-PComA complete occlusion rates

Flow reduction & thus, the success rate is reduced in PComA aneurysms with foetal posterior circulation.




Flow reduction (STAV) > 50% threshold.




Flow reduction = space and time-averaged velocity (STAV) in the aneurysm sac.



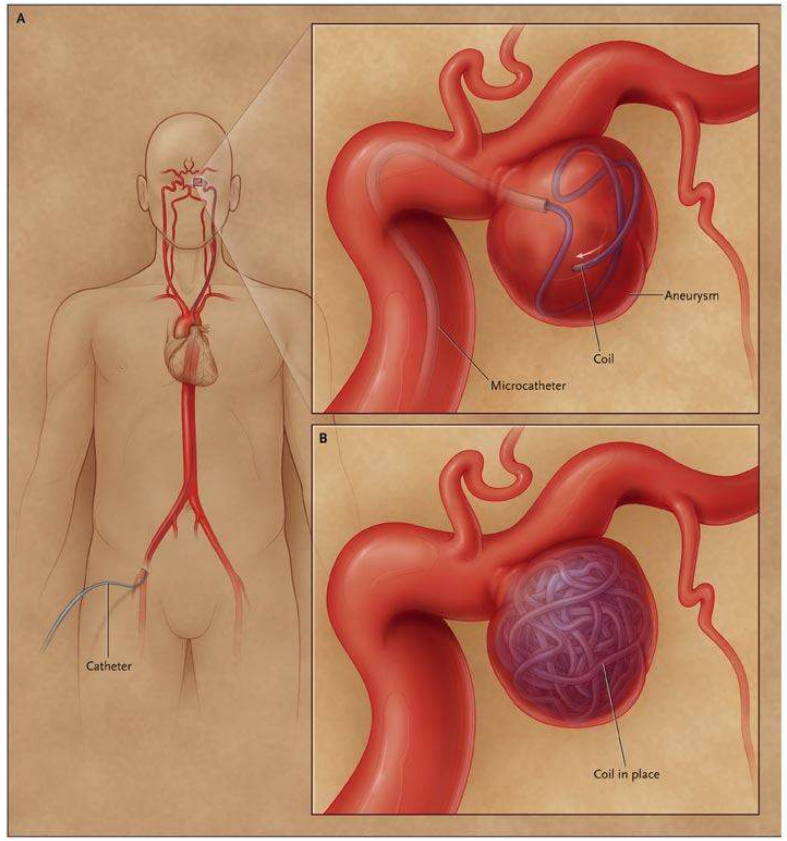
MacRaild M, Sarrami-Foroushani A, Song S, Liu Q, Kelly C, Ravikumar N, Patankar T, Lassila T, Taylor ZA, Frangi AF. Off-label in-silico flow diverter performance assessment in posterior communicating artery aneurysms. J Neurointerv Surg. 2025 Jan 26:jnis-2024-022000.

## Exemplar III

# IN SILICO TREATMENT STRATIFICATION

OPERATOR INFLUENCE / COST EFFECTIVENESS
EMERGING BEHAVIOUR

# Coiling: the basics




[Penumbra Smart Coil Insertion]
[Generic Call Insertion (short)]

**Packing density** is defined as **the ratio between the inserted coils and aneurysm volume**.




Morales HG, Kim M, Vivas EE, et al. How do coil configuration and packing density influence intra-aneurysmal hemodynamics?. AJNR Am J Neuroradiol. 2011;32(10):1935-1941. doi:10.3174/ajnr.A2635

ORIGINAL RESEARCH

# How Do Coil Configuration and Packing Density Influence Intra-Aneurysmal Hemodynamics?

H.G. Morales
M. Kim
E.E. Vivas
M.-C. Villa-Uriol
I. Larrabide
T. Sola
L. Guimaraens
A.F. Frangi

**BACKGROUND AND PURPOSE:** Endovascular coiling is a well-established therapy for treating intracranial aneurysms. Nonetheless, postoperative hemodynamic changes induced by this therapy remain not fully understood. The purpose of this work is to assess the influence of coil configuration and packing density on intra-aneurysmal hemodynamics.

**MATERIALS AND METHODS:** Three 3D rotational angiography images of 3 intracranial aneurysms before and after endovascular coiling were used. For each aneurysm, a 3D representation of the vasculature was obtained after the segmentation of the images. Afterward, a virtual coiling technique was used to treat the aneurysm geometries with coil models. The aneurysms were coiled with 5 packing densities, and each was generated by using 3 coil configurations. Computational fluid dynamics analyses were carried out in both untreated and treated aneurysm geometries. Statistical tests were performed to evaluate the relative effect of coil configuration on local hemodynamics.

**RESULTS:** The intra-aneurysmal blood flow velocity and wall shear stress were diminished as packing density increased. Aneurysmal flow velocity was reduced >50% due to the first inserted coils (packing density <12%) but with a high dependency on coil configuration. Nonsignificant differences ($P > .01$) were found in the hemodynamics due to coil configuration for high packing densities (near 30%). A damping effect was observed on the intra-aneurysmal blood flow waveform after coiling.

**CONCLUSIONS:** Intra-aneurysmal hemodynamics are altered by coils. Coil configuration might reduce its influence on intra-aneurysmal hemodynamics as the packing density increases until an insignificant influence could be achieved for high packing densities.

**ABBREVIATIONS:** 3DRA = 3D rotational angiography; ANOVA = analysis of variance; CFD = computational fluid dynamics; DSA = digital subtraction angiography; WSS = wall shear stress

Intracranial aneurysms are balloon-like dilations of arteries often occurring at branching points in the circle of Willis. In most cases, these stay asymptomatic and are only diagnosed through medical imaging or after spontaneous rupture. Aneurysm rupture typically leads to subarachnoid hemorrhage producing rates of mortality of approximately 50%.[1] The existing therapeutic options seek isolating the aneurysm from the bloodstream and preventing its rupture. The most important therapies are surgical clipping and endovascular interventions,[2] such as coiling and stent placement.

Coiling has been the most popular endovascular option for the last 15 years.[1-3] This minimally invasive treatment consists of the placement of biocompatible metal alloy coils to block the blood flow into the aneurysm and to prevent rupture. Although coiling is associated to lower mortality and morbidity rates compared with surgical clipping,[2] its outcome is not always predictable.[1-5] Packing density is thought to have a strong influence in postcoiling outcome, and usually the aneurysms are packed as dense as possible.[6-8] Packing density is defined as the ratio between the inserted coils and aneurysm volume.

Moreover, the success of coiling is intimately related to the biologic responses to hemodynamics inside the aneurysm.[9] Certainly, CFD is an effective and well-accepted technique to investigate intravascular hemodynamics in silico.[10] However, the use of this technique in the presence of endovascular coils is still challenging, due to the geometric complexity of the devices, their small size (diameters of 0.010–0.015 inch),[11] and their unpredictable distribution inside the aneurysm.

To simulate the hemodynamics in coiled aneurysm geom-

INTERVENTIONAL ORIGINAL RESEARCH

Morales HG, Kim M, Vivas EE, Villa-Uriol MC, Larrabide I, Sola T, Guimaraens L, Frangi AF. How do coil configuration and packing density influence intra-aneurysmal hemodynamics? AJNR Am J Neuroradiol. 2011 Nov-Dec;32(10):1935-41.

# Coiling: *in silico* trials /device understanding

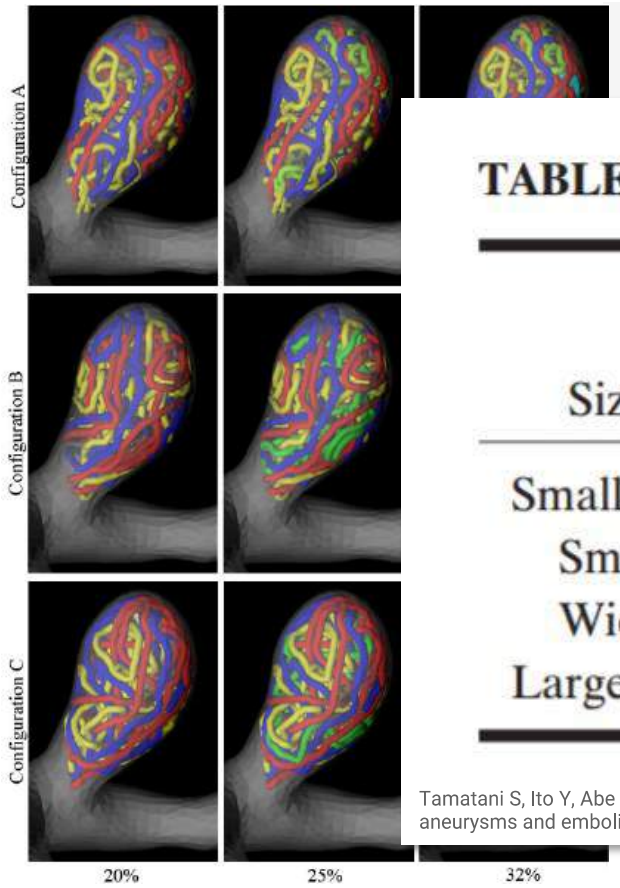
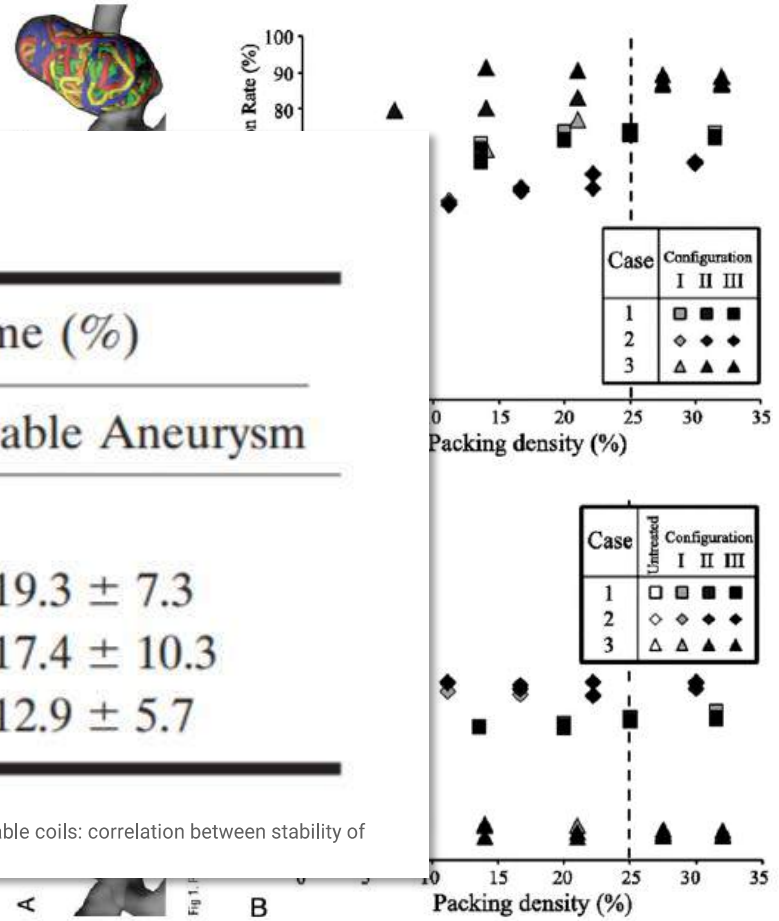



**TABLE 2: Embolized volume of aneurysms**

| Size of Aneurysm | Embolized Volume (%) | |
|---|---|---|
| | Stable Aneurysm | Unstable Aneurysm |
| Small (n = 71) | | |
| Small neck (n = 47) | 32.5 ± 9.8 | 19.3 ± 7.3 |
| Wide neck (n = 13) | 27.7 ± 11.4 | 17.4 ± 10.3 |
| Large (n = 27) | 20.2 ± 8.2 | 12.9 ± 5.7 |

Tamatani S, Ito Y, Abe H, Koike T, Takeuchi S, Tanaka R. Evaluation of the stability of aneurysms after embolization using detachable coils: correlation between stability of aneurysms and embolized volume of aneurysms. AJNR Am J Neuroradiol. 2002 May;23(5):762-7.




Morales HG, Larrabide I, Geers AJ, San Roman L, Blasco J, Macho JM, Frangi AF. A virtual coiling technique for image-based aneurysm models by dynamic path planning. IEEE Trans Med Imaging. 2013 Jan;32(1):119-29.
Morales HG, Kim M, Vivas EE, Villa-Uriol MC, Larrabide I, Sola T, Guimaraens L, Frangi AF. How do coil configuration and packing density influence intra-aneurysmal hemodynamics? AJNR Am J Neuroradiol. 2011 Nov-Dec;32(10):1935-41.


Better population coverage
Complex or Rare Diseases
Underserved communities
Pediatric applications
Combination therapies – co-simulation
Off-label or Foreseeable Misuse
Dose–Device Coupling
Virtual First-in-Body
Communicating RCT risk to patients
…
Fragile Physiology Zone
Pregnancy Protected Window
Comorbidity Jigsaw
Evidence for the Global South
Pre-test inclusion/exclusion
Incremental Equivalence Proof
Supply Chain Substitute Swap
Reprocessing & Reuse Validator
Operator Variability Reactor
…
Magnetic Environment Immunity
Extreme Physiology Checker
Recall Scope Optimiser
Recurrence Predictor Sandbox
Adaptive Arm Optimiser
Non-Inferiority Cushion Finder
Bespoke Manufactured Devices
Bioresorbable Horizon Scan
Clinician Learning Curve
…
The tip of the
iceberg

Why should regulators and industry get involved?

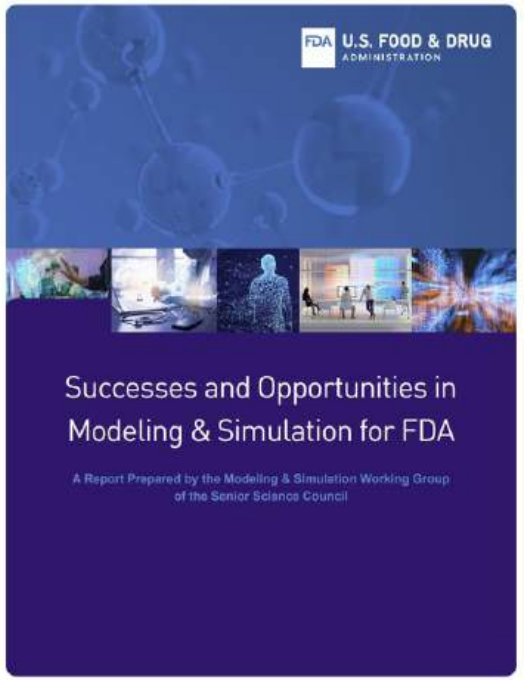
# READY FOR PRIME TIME?

# In Silico Medicine/Trials – Ready for prime time?

> Computational Modelling & Simulation, Model-Informed or In Silico Evidence in FDA


"**Model-informed [product] development** is the way of the future [at FDA]! [...] **Modelling will become the leading science.**"

— *Food & Drug Administration, Dr Patrizia Cavazzoni*





NEWS | IN DEPTH

ANIMAL RESEARCH

## FDA no longer has to require animal testing for new drugs

Agency can rely on animal-free alternatives before human trials

By **Meredith Wadman**

New medicines need not be tested in animals to receive U.S. Food and Drug Administration (FDA) approval, according to legislation signed by President Joe Biden in late December 2022. The change—long sought by animal welfare organizations—could signal a major shift away from animal use after more than 80 years of drug safety regulation.

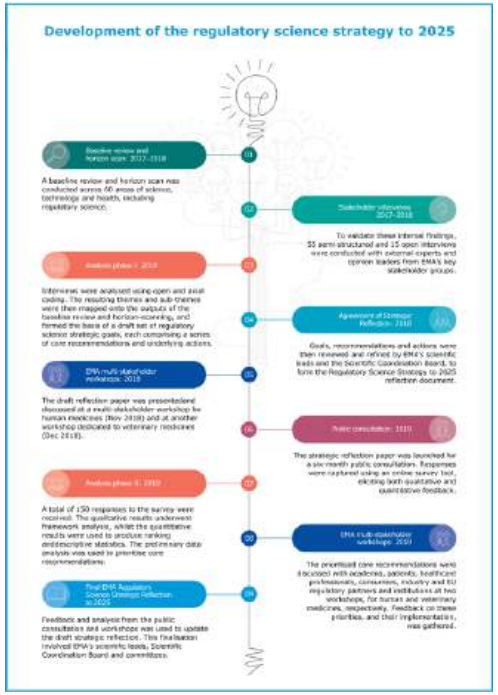
"This is huge," says Tamara Drake, director of research and regulatory policy at the Center for a Humane Economy, a nonprofit animal welfare organization and key driver of the legislation. "It's a win for industry. It's a win for patients in need of cures."

In place of the 1938 stipulation that potential drugs be tested for safety and

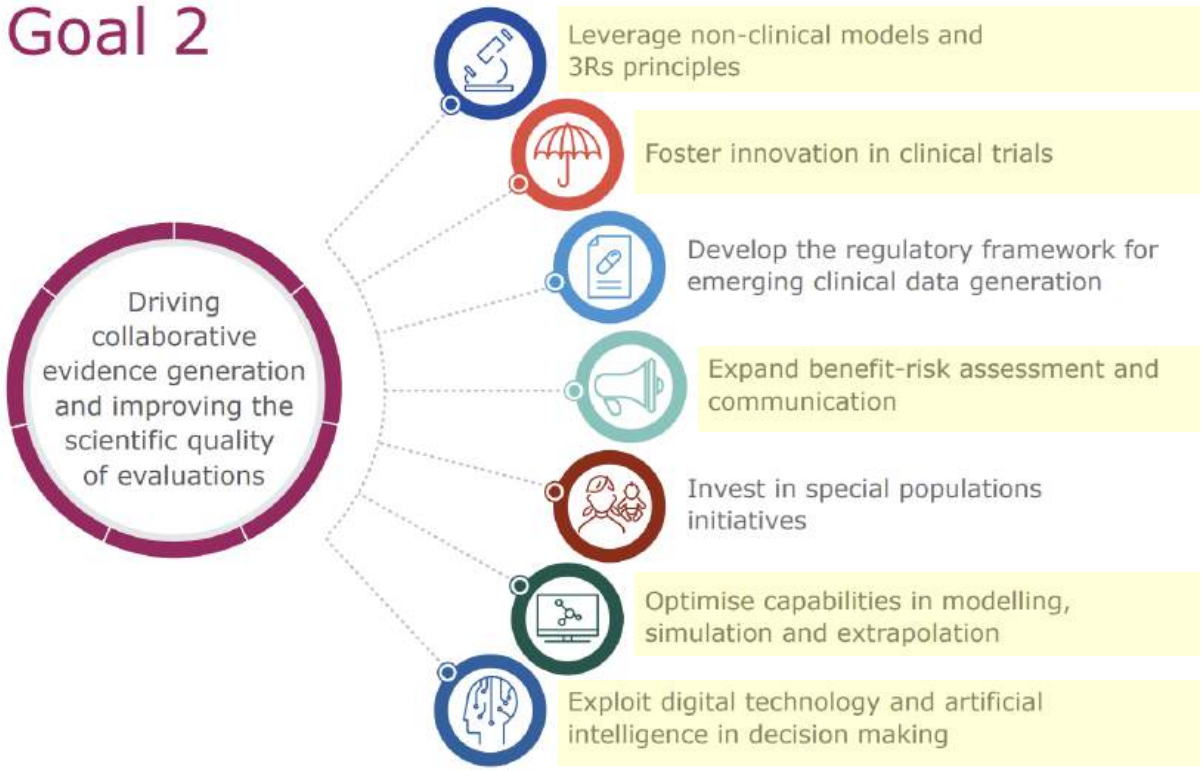
Wadman M. FDA no longer has to require animal testing for new drugs. *Science*. 2023 Jan 13;379(6628):127-128.

# In Silico Medicine/Trials – Ready for prime time?

> Modelling & Simulation, 3Rs, … in EMA


Hines PA, Gonzalez-Quevedo R, Lambert AIOM, Janssens R, Freischem B, Torren Edo J, Claassen IJTM, Humphreys AJ. Regulatory Science to 2025: An Analysis of Stakeholder Responses to the European Medicines Agency's Strategy. Front Med (Lausanne). 2020 Sep 23;7:508.




"**In Silico Trials should be at the core of the EMA 2025 strategy**."

— *Efthymios Manolis, Scientific Advise Office, European Medicines Agency*.

https://www.ema.europa.eu/en/about-us/how-we-work/regulatory-science-strategy

# In Silico Medicine/Trials – Ready for prime time?

> Clinical Evidence, Modelling & Simulation, … in TGA

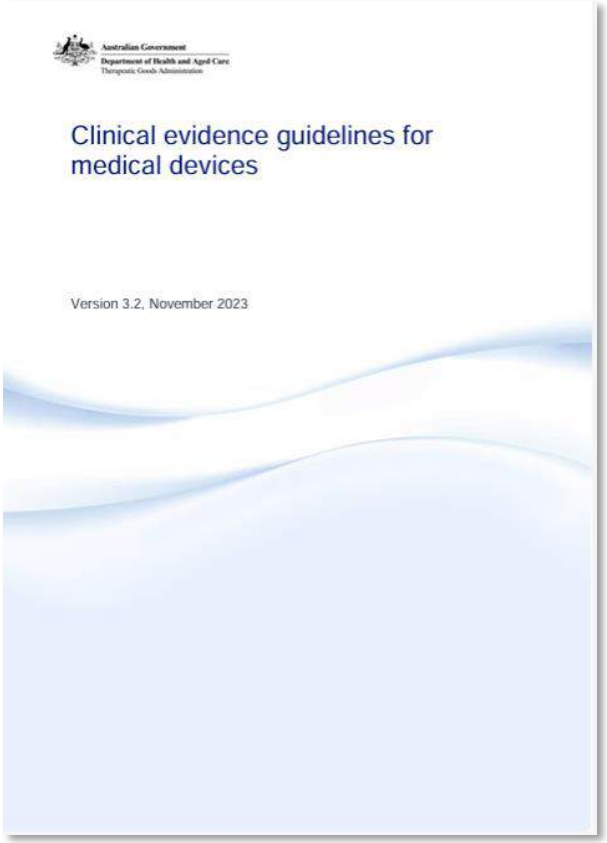
Australian Government
Department of Health
Therapeutic Goods Administration

**Example – Adaptable medical device**

Louise is a dentist and clinical expert for a manufacturer of temporary stainless-steel crowns that are used as an interim measure whilst patients await fitting of patient-matched dental crowns. One new device is a mass-produced stainless steel molar crown that comes in a range of sizes. Dentists are required to trim the edges with crown scissors and "crimp" the device with crimping pliers for the individual patient. The device is then cemented to the tooth.

The IFU contains detailed instructions for acceptable point-of-care manipulation of the subject device with respect to sizing. The greatest extent of trimming and crimping supported by the IFU are considered worst-case scenarios (justified through computer modelling).

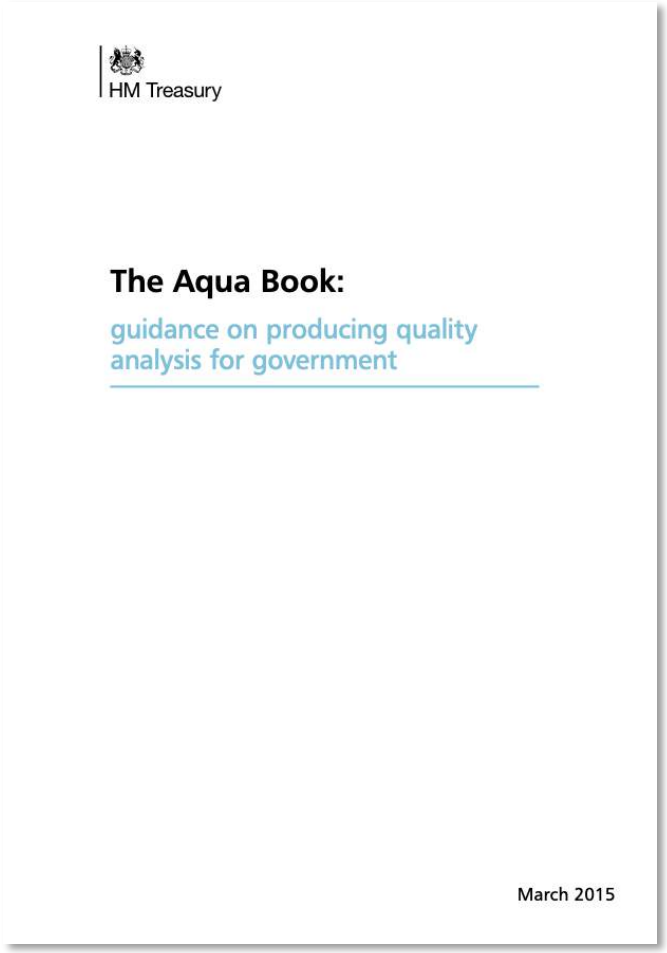
Louise has conducted a state-of-the-art literature review and from the literature is satisfied that temporary stainless steel and acrylic resin dental crowns are the accepted standard of care when patients are awaiting a more permanent, patient-matched crown.




www.tga.gov.au/resources/guidance/clinical-evidence-guidelines-medical-devices

# Model-Informed Evidence: Credibility Principles?

## Quality Analysis Principles for Analytical Models


HM Treasury

**The Aqua Book:**

guidance on producing quality analysis for government

March 2015

1.10 No single piece of guidance can provide a route to a definitive assessment of whether a piece of analysis is of sufficient quality for an intended purpose. However, the Aqua Book sets out the following principles of analytical quality assurance that will help to support commissioning and delivery of fit-for-purpose analysis:

- **Proportionality of response**: The extent of the analytical quality assurance effort should be proportionate in response to the risks associated with the intended use of the analysis. These risks include financial, legal, operational and reputational impacts. In addition, analysis that is frequently used to support a decision-making process may require a more comprehensive analytical quality assurance response.
- **Assurance throughout development**: Quality assurance considerations should be taken into account throughout the life cycle of the analysis and not just at the end. Effective communication is crucial when understanding the problem, designing the analytical approach, conducting the analysis and relaying the outputs.
- **Verification and validation**: Analytical quality assurance is more than checking that the analysis is error-free and satisfies its specification (verification). It must also include checks that the analysis is appropriate, i.e. fit for the purpose for which it is being used (validation).
- **Analysis with RIGOUR**: Quality analysis needs to be repeatable, independent, grounded in reality, objective, have understood and managed uncertainty, and the results should address the initial question robustly. In particular, it is important to accept that uncertainty is inherent within the inputs and outputs of any piece of analysis. It is important to establish how much we can rely upon the analysis for a given problem.

### Quality = RIGOUR:

Repeatable,
Independent,
Grounded in reality,
Objective,
understood and managed
Uncertainty,
address the initial question
Robustly.

AQuA Handbook - https://www.gov.uk/government/publications/the-aqua-book-guidance-on-producing-quality-analysis-for-government

# PAGIT Framework

## Proportionate and Adaptive Governance of Innovative Technologies

Executive Summary

### Proportionate and adaptive governance of innovative technologies

The role of regulations, guidelines and standards

Joyce Tait and Geoffrey Banda
Innogen Institute, University of Edinburgh

**Figure 1** – Framework for proportionate and adaptive governance of innovative technologies

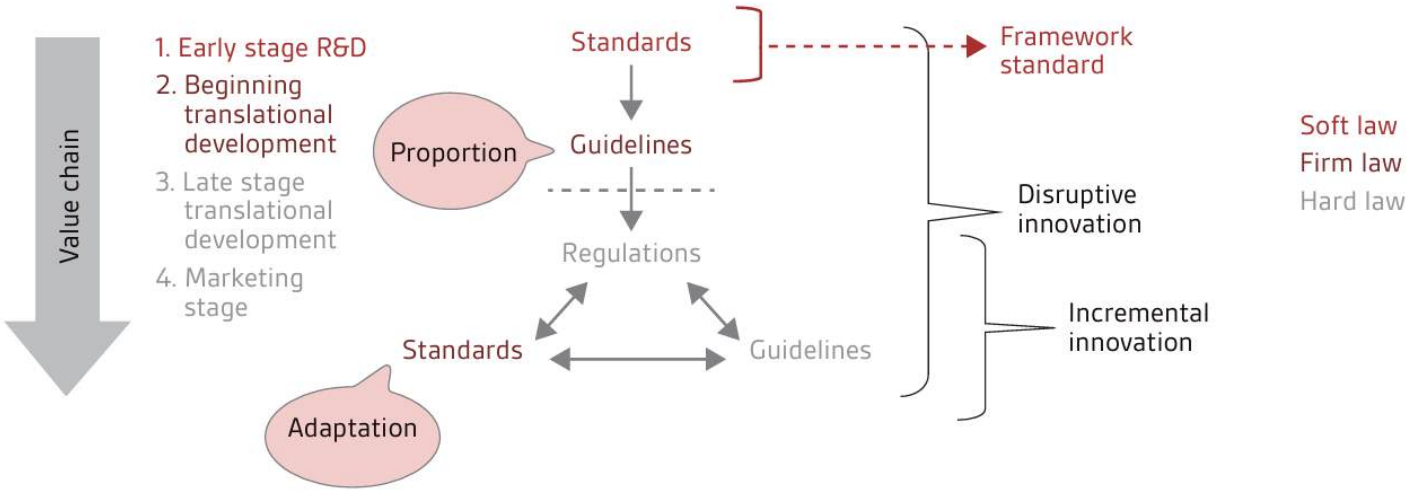



**Table 1** – Differences between standards and regulations/guidelines

| Standards | Regulations/Guidelines |
|---|---|
| Based on recommendations | Based on legislation |
| Adoption is usually voluntary | Adoption is mandatory for regulations and potentially so for guidelines (soft law) |
| Established by consensus of all parties concerned, including relevant industry sectors | Developed by a regulatory authority, usually involving consultation |
| Based on consolidated results of science, technology and experience | Guidelines provide technical specifications either directly or by reference, e.g. to standards |
| Approved and published by recognized standardization body | Adopted by a legal authority |
| Oversight by independent third party certification | Oversight by formal government-appointed regulatory bodies |

See also Allen and Sriram, (2000), Langlois and Savage (2001)[2]

**Table 2** – Relative advantages of standards and regulations/guidelines

| Advantages of standards | Advantages of regulations/guidelines |
|---|---|
| Standards can act as infrastructures for coordination; a common language for interoperability and compatibility | Regulations have the force of law, and compliance is compulsory and enforceable |
| Standards as routines (usually internal standards) can govern behaviour required for certain activities/routines | Easier to diffuse through inter-country, regional or international treaties and conventions |
| Standards as technology can reduce variety and enhance economies of scale thereby reducing transaction costs | Regulations are prescriptive, and sometimes are linked to specific guidelines and/or standards which, if adhered to, constitute compliance |
| Standards can be an innovation to achieve market dominance | |

See also Allen and Sriram, (2000), Langlois and Savage (2001)[2]

Tait, J., Banda, G., Watkins, A.: Proportionate and Adaptive Governance of Innovative Technologies (PAGIT): A Framework to Guide Policy and Regulatory Decision Making, Innogen Institute Report to the British Standards Institution. (2017). https://www.innogen.ac.uk/reports/1222.

# Openness to Computational Modeling & Simulation for regulatory approval: a global initiative

Avicenna Alliance
Association for Data Driven Medicine

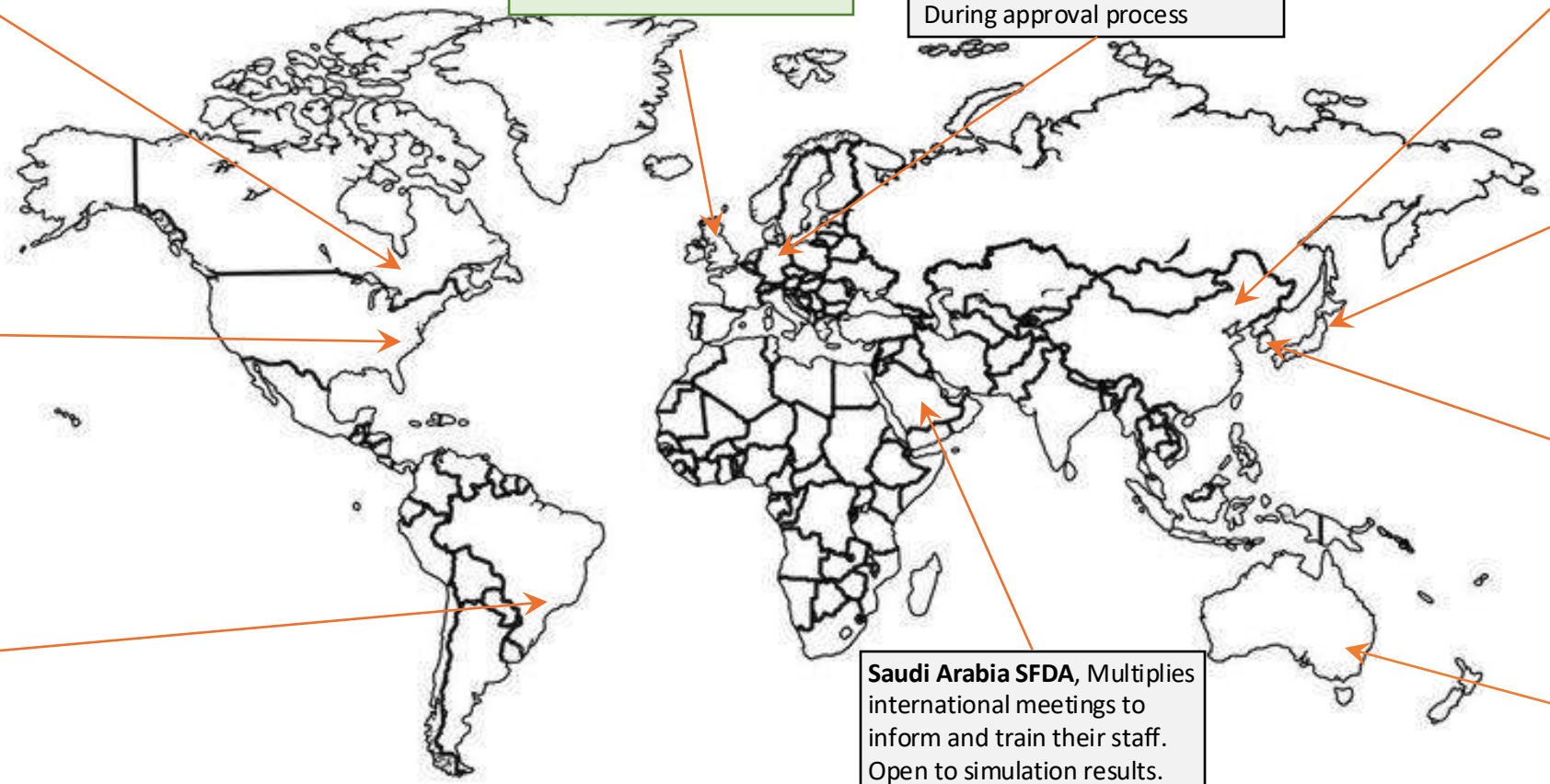
**Health Canada**, in favor of adopting procedures similar to those accepted by the FDA; open to the use of numerical methods and accept Digital Evidence.

**US FDA,** , the first to adopt and regulate in silico methods (Guidance 2016). Many cardiovascular device submissions include simulation results.

**Brazil ANVISA**, encourages the investigation of digital methods and legislates in this direction (session in the Brazilian Parliament on October 4, 2023).

**UK MHRA**, very dynamic for the validation and use of numerical methods. Actively promoting this discussion.

**Germany TuV SuD**, This Notified Body has the expertise and understanding of simulation results that they often receive. During approval process



**Saudi Arabia SFDA**, Multiplies international meetings to inform and train their staff. Open to simulation results.

**China NMPA**, Authorities very engaged in information, evaluation and training of their staff for numerical methods.

Avicenna Documents available in Chinese

**Japan PMDA**, Evaluation of numerical methods and their verification. Networking with key players.

Avicenna Documents available in Japanese

**South Korea KFDA** , Develop a strong expertise in numerical methods within their staffs.

Avicenna Documents available in Korean

**Australia TGA**, Collects information related to numerical methods; cautious opening for Digital Evidence in the context of submissions.



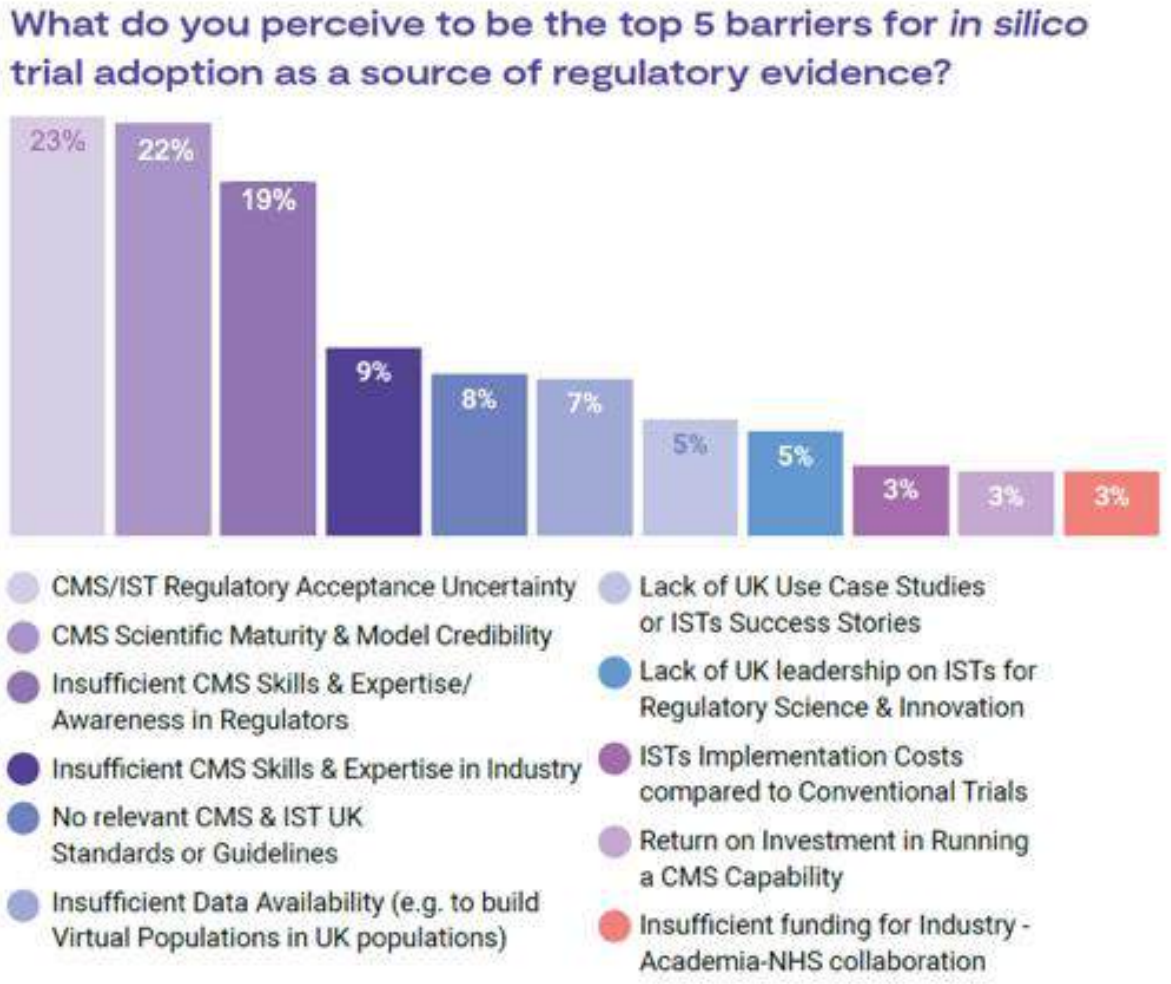
Non exhaustive, illustrates some Avicenna engagements

Cross-sector Co-creation In Practice

# IN SILICO REGULATORY AIRLOCK

# Mapping Barriers


Frangi, A., Denison, T., Myles, P., Ordish, J., Brown, P., Turpin, R., Kipping, M., Palmer, M., Flynn, D., Afshari, P., Lane, C., de Cunha, M., Horner, M., Levine, S., Marchal, T., Bryan, R., Tunbridge, G., Pink, J., Macpherson, S., … Thompson, M. (2023). Unlocking the power of computational modelling and simulation across the product lifecycle in life sciences: A UK Landscape Report. InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.8325274




Adapted from a presentation by Prof AF Frangi at the InSilicoUK Innovation Network Launch Event,[88] InSilicoUK Community Survey #1: Enablers and Barriers.

# UK CEiRSI Community of Interest

## Medical Devices & Pharmaceutical Companies

Medtronic, Boston Scientific, stryker, PHILIPS, element, AstraZeneca, GSK, ZIMMER BIOMET Moving You Forward, Edwards, ucb Pharma, SIEMENS Healthineers, varian, apc, GRAU INNOVATIVE METALLE, AMBER THERAPEUTICS, IMPULSE DYNAMICS, MatOrtho, ResMed, DePuy Synthes PART OF THE Johnson & Johnson FAMILY OF COMPANIES, Elekta

CEiRSI Centre of Excellence on in-silico Regulatory Science & Innovation

## Supply Chain

Ansys, aws, IBM, DASSAULT SYSTEMES, adsilico, ddn, ALTAIR, NVIDIA, Exponent, CERTARA, Simcyp, esqLABS WE EMPOWER HEALTH CARE, SYNOPSYS

## Catalysts

INDUSTRIAL BIOTECHNOLOGY INNOVATION CATALYST, TURING INNOVATION CATALYST MANCHESTER, HIRANI Advocate • Collaborate • Integrate

## Capital

LocalGlobe, praetura VENTURES, AlbionCapital, NORTHERN GRITSTONE THE VALUE OF IDEAS

## Consultant

KPMG, MILLS & REEVE Achieve more. Together., NEXXER, RLS

## Funders, Charities & Academies

UKRI Innovate UK, UKRI Engineering and Physical Sciences Research Council, UKRI Medical Research Council, NIHR National Institute for Health Research, NC3Rs National Centre for the Replacement Refinement & Reduction of Animals in Research, British Heart Foundation, CANCER RESEARCH UK, Royal Academy of Engineering, The Royal Society of Medicine

## Clinical Needs, National Data Controllers & Providers

NHS England, HDRUK Health Data Research UK, ukbiobank Enabling scientific discoveries that improve human health, GM Care Record We are better together, North West SECURE DATA ENVIRONMENT, NHS Great Ormond Street Hospital for Children NHS Foundation Trust, NUFFIELD DEPARTMENT WOMEN'S & REPRODUCTIVE HEALTH, bsci, Manchester Rare Conditions Centre, NICOR, NHS Greater Manchester, NHS Manchester University NHS Foundation Trust, National Joint Registry Working for patients, committed to excellence, NHS Nottingham University Hospitals NHS Trust, NHS Oxford University Hospital NHS Foundation Trust, NHS Barts Health NHS Trust, MIDLANDS HEALTH ALLIANCE, Health Innovation Manchester, nhsa A Health Partnership for Northern England

## Research Organisations & Infrastructures

MANCHESTER 1824 The University of Manchester, HENRY ROYCE INSTITUTE, CANCER RESEARCH UK Manchester Centre, University of York, UCL, THE UNIVERSITY of EDINBURGH, University of Oxford, University of Nottingham UK | CHINA | MALAYSIA, Queen Mary University of London, Swansea University Prifysgol Abertawe, UNIVERSITY OF LIVERPOOL, University of Sheffield, AMRC ADVANCED MANUFACTURING RESEARCH CENTRE, UNIVERSITY OF SURREY, UNIVERSITY OF LEEDS, University of Strathclyde Glasgow, UNIVERSITY OF BIRMINGHAM, cpi, NIHR Leicester Biomedical Research Centre, NIHR Barts Biomedical Research Centre, NIHR HealthTech Research Centre Accelerated surgical care, NIHR Greater Manchester Patient Safety Research Collaboration, NIHR Manchester Biomedical Research Centre, Ollscoil na Gaillimhe University of Galway, Duke, UNIVERSITY OF MARYLAND, AUCKLAND BIOENGINEERING INSTITUTE THE UNIVERSITY OF AUCKLAND NEW ZEALAND, Fraunhofer IMTE, Triangle CERSI, CERSI University of Maryland, DTNet, UNDERSTANDING THE Physics of Life, BIOREDE

## Membership Organisations

ABHI HealthTech for Life, NAFEMS, abpi Bringing medicines to life, techUK FOR WHAT COMES NEXT, I•M3 Institute of Materials, Minerals & Mining, bionow, CRITICAL PATH INSTITUTE, MDIC Medical Device Innovation Consortium, Avicenna Alliance Association for Data Driven Medicine, VPH Institute Building the Virtual Physiological Human, TOPRA

## Policymakers, Standardisation, Regulators & Health System

MHRA, NHS Health Research Authority, NICE, Department for Science, Innovation, & Technology, Department of Health & Social Care, Office for Life Sciences, Office for Product Safety & Standards, Food Standards Agency, HSE, UK Health Security Agency, GMCA GREATER MANCHESTER COMBINED AUTHORITY, NPL, TEAM AB, TÜV SÜD, bsi., intertek Total Quality. Assured., FDA U.S. FOOD & DRUG ADMINISTRATION, ASME SETTING THE STANDARD, ISO, IEC

# In-Silico Regulatory Airlock Initiative

We focus on applying and evaluating the strengths and limitations of existing **international model credibility frameworks**.

**Why do we need a Regulatory Airlock Initiative?**

- Double-derisking: managing change in regulators and industry
- Problem-based learning boosts awareness, confidence & competence
- Precompetitive co-creation builds trust among stakeholders
- Collaborative learning enhances engagement and learning
- Focused primarily on early regulatory impacts
- Consider broader socio-technical questions

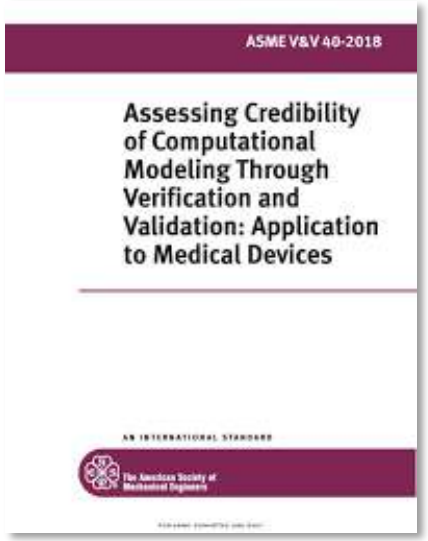
| Pilot Convenors | # | Theme |
|---|---|---|
| Resmed | 1 | CPAP Mask Evaluation: CO2 Venting and Rebreathing Performance Using In-Silico Techniques for Regulatory Compliance |
| stryker | 2 | Flow-Diverter Device: Pre/Post Implantation Intracranial Aneurysm Blood Flow & Clotting Models for In-Silico Trials |
| Boston Scientific | 3 | Transcatheter Aortic Valve Implantation: Conditional Generative Virtual Populations of Heart Anatomy for Targeted In-Silico Trials |
| Edwards | 4 | Transcatheter Aortic Valve Implantation: Frame Release and Pre/Post Implantation Blood Flow Models Predicting Aortic Stresses and Valve Leakage for In-Silico Trials |
| AMBER THERAPEUTICS | 5 | Deep Brain Stimulation: Closed-Loop Physiological Bidirectional Control System Model for Early Safety/Performance Assessment |
| DePuy Synthes | 6 | Spinal Pedicle Screw System: In-Silico Bench Testing for Confirming System Integrity after Introduction of a Cannulation |
| MatOrtho | 7 | Total Hip-Joint Replacement: Computational Simulator for Patient-Centered Wear Testing of Orthopaedic Device |
| ZIMMER BIOMET Moving You Forward | 8 | Total Knee Replacement Device: Augmentation of National Joint Registry with Data Derived from In-Silico Trial Insights |
| GSK | 9 | Vaccines: Quantitative systems pharmacology (QSP) computational models for finding optimal dosing regimens |
| SIEMENS Healthineers varian | 10 | Radiotherapy treatment system: in-device integration of treatment data and models of radiobiology for optimised radiotherapy performance |

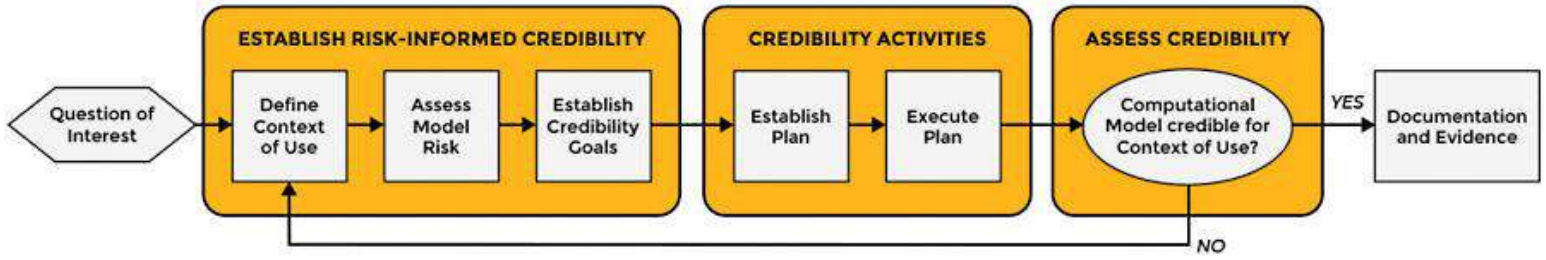
Frangi, A. F. (2024). The In-Silico Regulatory Airlock Initiative for Advancing Model-Informed Evidence Adoption (v 6). InSilicoUK Pro-Innovation Regulations Network. https://doi.org/10.5281/zenodo.12745437

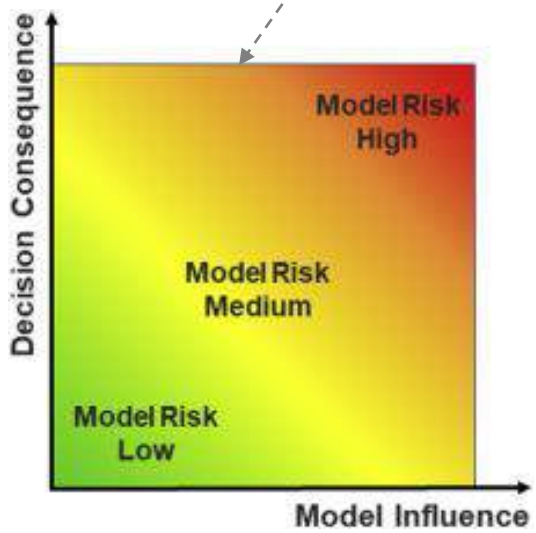
# Core Approach to CM&S Evidence & Model Credibility

A Risk-informed Validation, Verification & Uncertainty Quantification Framework

**Establishes that model credibility should be commensurate with the risk associated with a decision based, in part, on the computational model.**



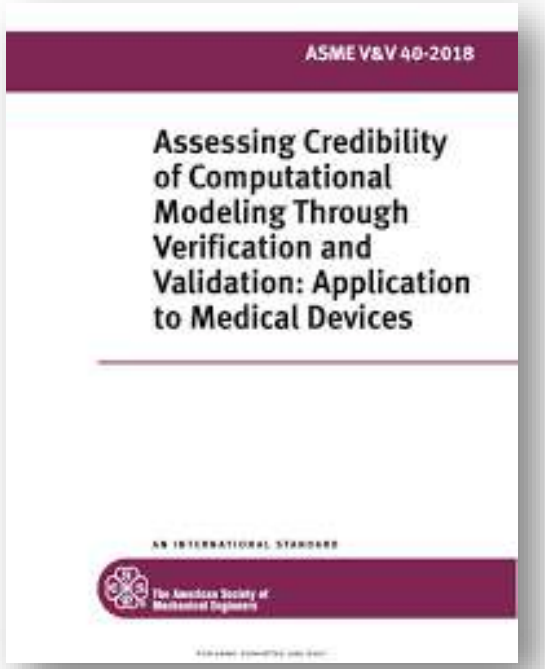




| Activities | | Credibility Factors |
|---|---|---|
| Verification | | |
| | Code | Software quality assurance |
| | | Numerical code verification |
| | Calculation | Discretization error |
| | | Numerical solver error |
| | | Use error |
| Validation | | |
| | Computational model | Model form |
| | | Model inputs |
| | Comparator | Test samples |
| | | Test conditions |
| | Assessment | Equivalency of input parameters |
| | | Output comparison |
| Applicability | | Relevance of the quantities of interest |
| | | Relevance of the validation activities to the COU |


Viceconti M, Pappalardo F, Rodriguez B, Horner M, Bischoff J, Musuamba F. In silico trials: Verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. Methods. 2021 Jan;185:120-127.

Viceconti M, Emili L, Afshari P, Courcelles E, Curreli C, Famaey N, Geris L, Horner M, Jori MC, Kulesza A, Loewe A, Neidlin M, Reiterer M, Rousseau CF, Russo G, Sonntag SJ, Voisin EM, Pappalardo F. Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review. IEEE J Biomed Health Inform. 2021 Oct;25(10):3977-3982.

# Standards and Guidance to industry and regulatory staff




From 2018…

Jul/Nov 2023


ASME SETTING THE STANDARD

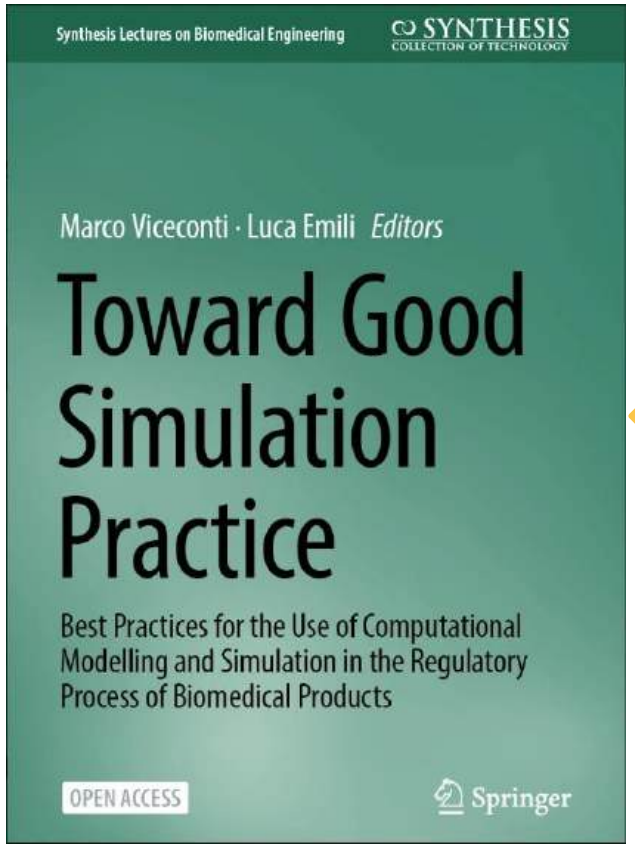
ASME V&V 40 Verification and Validation

V&V Standards Committee on Verification and Validation in Modeling and Simulation

# Best Practices – from practitioners

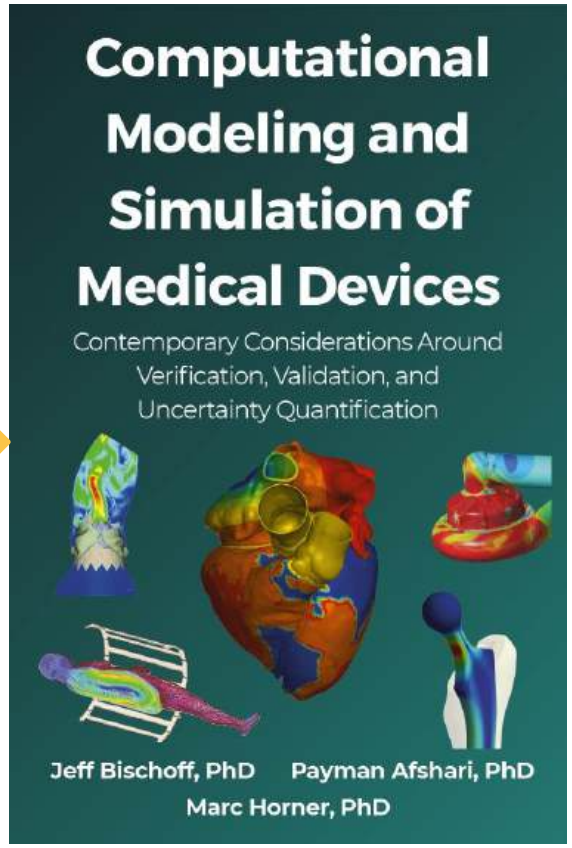
Led by:

INSILICO WORLD




Springer






Springer

Published Feb 2024
Open Access

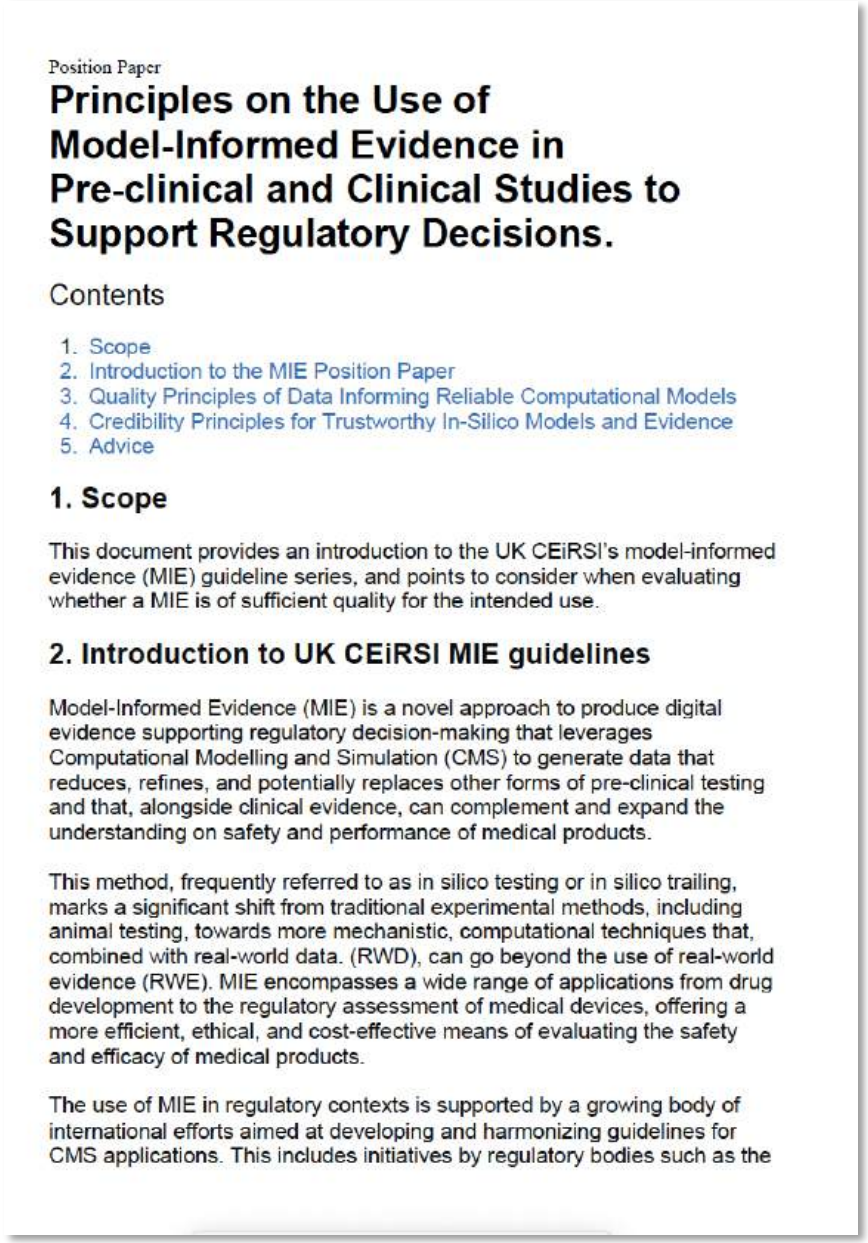
Expected Publication date: Jan 2026
Open Access

# Model-Informed Evidence (MIE)

## Position Paper

- **We are striving to launch an In-Silico Regulatory Airlock Initiative**.
- This initiative will involve a collaborative learning process that engages all stakeholders and taps into their expertise.
- Our ultimate aim is to present the MHRA, NICE, and HRA with preliminary guidance on the Use of MIE in Preclinical and Clinical Studies to support Regulatory Decisions.
- This guidance will be underpinned by the analysis of 10 realistic case studies or in-silico regulatory Pilots.

Additionally, we will deliver a host of activities and reports that cover technical and socio-technical regulatory considerations and a sustainability plan to scope and prioritise and continue the work of the UK CEiRSI beyond 12 months



Position Paper

**Principles on the Use of Model-Informed Evidence in Pre-clinical and Clinical Studies to Support Regulatory Decisions.**

Contents



**1. Scope**

This document provides an introduction to the UK CEiRSI's model-informed evidence (MIE) guideline series, and points to consider when evaluating whether a MIE is of sufficient quality for the intended use.

**2. Introduction to UK CEiRSI MIE guidelines**

Model-Informed Evidence (MIE) is a novel approach to produce digital evidence supporting regulatory decision-making that leverages Computational Modelling and Simulation (CMS) to generate data that reduces, refines, and potentially replaces other forms of pre-clinical testing and that, alongside clinical evidence, can complement and expand the understanding on safety and performance of medical products.

This method, frequently referred to as in silico testing or in silico trailing, marks a significant shift from traditional experimental methods, including animal testing, towards more mechanistic, computational techniques that, combined with real-world data. (RWD), can go beyond the use of real-world evidence (RWE). MIE encompasses a wide range of applications from drug development to the regulatory assessment of medical devices, offering a more efficient, ethical, and cost-effective means of evaluating the safety and efficacy of medical products.

The use of MIE in regulatory contexts is supported by a growing body of international efforts aimed at developing and harmonizing guidelines for CMS applications. This includes initiatives by regulatory bodies such as the

# OUTLOOK AND CONCLUSIONS

# Outlook

- Medical product innovation and regulatory processes – at an inflexion point
- CM&S: essential new ingredient well positioned in current regulatory pathways
- Both a technical and a cultural transformation – where to start?
  - Focus on how in silico studies enhance the type of evidence regulators currently receive and how evidence gaps (e.g., in paediatrics, rare diseases, combination devices, etc.) can be filled
- Transformation is already taking place, needing cross-stakeholder engagement.
- Catalysing uptake relies on the pull from regulators and push from the industry
- Work alongside patients – they expect better regulatory pathways.

# Discussion

1. Integration of In Silico Models
   - Question: How do you envision integrating in silico models with existing clinical trial protocols, and what specific challenges do you foresee in aligning model outputs with clinical endpoints?

2. Data Requirements and Sources
   - Question: What types of clinical data are currently underutilised in your trials that could enhance the predictive accuracy of in silico simulations, and how can we ensure these data sources are adequately captured and validated?

3. Regulatory Considerations
   - Question: What regulatory hurdles do you anticipate for the acceptance of in silico trials as part of the clinical development process, and what methodological innovations do you believe are necessary to address these concerns effectively?

4. Adaptive Trial Design
   - Question: How can we incorporate adaptive trial design principles into in silico trials to enhance flexibility and efficiency in responding to emerging data, and what specific methodological frameworks do you think are necessary to support this integration?

# Contact us

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CEiRSI Centre of Excellence on in-silico Regulatory Science & Innovation

The University of Manchester