

Ensuring the quality of *in silico* evidence: application to medical devices

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Abstract

The use of *in silico* methods—computational modelling and simulation—to support the development, evaluation, and regulatory approval of medical devices is expanding rapidly. These approaches offer clear benefits in accelerating innovation, reducing development burden, and strengthening safety assessment, yet their regulatory acceptance remains inconsistent across jurisdictions. This variability reflects differences in model maturity, documentation practices, and the absence of globally harmonised criteria for assessing credibility. Building on established standards and regulatory guidance, this position paper outlines a risk-informed framework for the credible generation, assessment, and regulatory utilisation of *in silico* evidence that could be implemented across the medical device lifecycle. The framework emphasises clear definition of a question of interest and context of use, proportional credibility requirements based on model risk, and rigorous application of verification, validation, and uncertainty quantification. Emerging challenges posed by data-driven and hybrid models, including artificial intelligence, highlighting additional governance and data integrity considerations are also addressed. Importantly, the generation of *in silico* evidence increasingly relies on bioinformatics and computational biomedicine workflows, including the integration of heterogeneous biomedical data sources (e.g. medical imaging, real-world data, and population-level datasets), preprocessing and feature extraction pipelines, and hybrid mechanistic–data-driven modelling approaches. In this perspective, the authors argue that the credibility of *in silico* evidence is not determined solely at the level of the executable model, but across the full computational pipeline, encompassing data provenance, preprocessing, model implementation, and reproducible analysis workflows.

Keywords *in silico* evidence, computational modelling and simulation (CM&S), model credibility, risk-informed framework, verification, validation and uncertainty quantification (VUUQ), bioinformatics, hybrid models, data pipelines

Introduction

Medical device manufacturers have traditionally relied on *in vitro* (bench) testing and *in vivo* (animal and human) trials to establish the safety and effectiveness of medical devices. This is true both internally when making decisions about various aspects of a device design and externally when applying for marketing approval. The industry is now increasingly relying on computational modelling and simulation (CM&S) throughout the product lifecycle to accelerate development and provide evidence for the performance and safety. Efforts range from early phase models that support design decisions to models that guide and refine bench testing to image-based multi-scale models of

devices interacting with human anatomy or physiology. This latter class of models is an individualised virtual test of a medical device or other treatment carried out on a virtual cohort of patients, that is commonly referred to as *in silico* clinical trials. One of the primary benefits of an *in silico* clinical trial is that the model predicts the safety or effectiveness of a treatment under conditions replicating the clinical intervention, thereby increasing confidence in the new therapy prior to exposing human subjects. And in contrast to other approaches, *in silico* clinical trials can also provide a physical explanation for the success or failure of a therapy. This is not only a safety benefit, but can also shorten development timelines.

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Although *in silico* evidence is often discussed within the context of regulatory science, its generation increasingly depends on methodological foundations that are central to bioinformatics and computational biomedicine. These include the processing and integration of heterogeneous biomedical data (e.g. medical imaging, physiological signals, and real-world data), the construction of patient-specific or population-level models, and the use of statistical, machine learning, and hybrid modelling approaches. In this sense, assessing the quality of *in silico* evidence is also a bioinformatics problem: the reliability of model predictions depends not only on the mathematical formulation, but also on data provenance, preprocessing pipelines, parameter estimation strategies, and the reproducibility of the computational workflow.

The concepts discussed in this paper are directly relevant to the bioinformatics community, broadly understood as the field concerned with the handling, integration, and interpretation of biomedical data. In the context of *in silico* evidence, this includes (i) the generation and curation of input data from heterogeneous sources (e.g. imaging, experimental, clinical, and real-world data), (ii) the design of computational pipelines for preprocessing, feature extraction, and parameterization, and (iii) the implementation of reproducible workflows that ensure traceability and transparency of model outputs. Consequently, the credibility of *in silico* evidence depends not only on model formulation, but also on the robustness and reproducibility of the underlying data and computational processes.

At this time, the maturity of the *in silico* evidence presented by industry to regulatory agencies, as well as the ability of regulators to conduct a timely and appropriate review, differs significantly between jurisdictions which can adversely impact regulatory strategies for this source of evidence [1]. As it is generally accepted that *in silico* evidence accelerates medical device innovation without negatively impacting patient safety and product efficacy, broader and more predictable acceptance of *in silico* evidence is a commonly expressed goal in all regions [2–4].

Various regulatory agencies have taken steps to ensure the rigorous application and implementation of *in silico* evidence as part of their decision-making processes [5–9]. For example, the European Union Regulation (EU) 2017/745, also known as the Medical Device Regulation (MDR), explicitly mentions ‘computer modelling’ as an allowable form of pre-clinical evidence [6]. The European AI Act (EU 2024/1689) is another regulation that takes a risk-based approach to establishing the rules and requirements for accurate, reliable, and safe artificial intelligence (AI) systems [10]. In the United States, 21 CFR 860.7 (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-H/part-860>) lists the accepted forms of scientific evidence without explicitly mentioning CM&S. However, several documents published by the FDA list ‘bench testing, animal testing, human testing (clinical trials), and computational modeling’ as four forms of accepted science-based regulatory evidence [11–14]. [Supplementary Tables 1–3](#) list and compare a selection of additional documents published (or recognized) by various regulatory authorities that support the use of *in silico* as part of the regulatory evaluation of medical devices. Similarly, see [Supplementary Table 4](#) for a selection of documents supporting the use of *in silico* evidence in drug development and manufacturing. A comprehensive review of best practices supporting the credible use of *in silico* methods during medical product development and regulatory evaluation can be found in the book ‘Computational Modeling and Simulation of Medical Devices: Verification, Validation, and Uncertainty Quantification’ [15].

More recently, the adoption of ICH M15 (Model-Informed Drug Development) (<https://www.ema.europa.eu/en/ich-m15-guideline-general-principles-model-informed-drug-development-step-2b-scientific-guideline>) provides a harmonised international framework for the use of modelling and simulation in the development and regulatory evaluation of medicinal products. While primarily focused on pharmacological and clinical development, ICH M15 reinforces key principles that are directly relevant to *in silico* evidence more broadly, including the explicit definition of the question of interest, the context of use (COU), and the structured integration of model-derived evidence within regulatory decision-making.

But in spite of this progress, current regulatory frameworks regarding CM&S may not (i) translate across geographies, (ii) address the public health risks posed by the use of *in silico* methods, or (iii) ensure an appropriate balance between patient/consumer protection and the promotion of public health by facilitating innovation. A detailed regulatory pathway for CE marking, as outlined by Pappalardo et al. [16], suggests a structured approach for the potential integration of *in silico* trials into the European regulatory framework, with the aim of using these trials effectively in conjunction with, or in place of, traditional clinical trials. In addition to the transitional adoption of the ASME V&V 40 standard, the article suggests the development of a globally harmonised standard that outlines model credibility best practices (Such a standard is currently in the early stages of development under an IEC TC 62 ah16 Working Group). This standard could then be used by global regulatory bodies to evaluate the credibility of CM&S evidence. Moreover, an EU qualification program for medical device development tools (MDDTs), similar to the existing FDA MDDT (<https://www.fda.gov/medical-devices/medical-device-development-tools-mddt>) and EMA medicinal (<https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/opinions-letters-support-qualification-novel-methodologies-medicine-development>) programs, was suggested as a part of the approach that would provide a clear process for qualifying new *in silico* methods.

Lastly, successful utilisation of *in silico* evidence as part of the market authorization process will require primary legislation that formally recognizes the use of *in silico* evidence that is supported by regulations/guidance/standards that describe how to develop, employ, report, and assess the results of computer simulations. To address the latter requirement, this paper aims to provide a common framework for regulators to incorporate as a harmonised approach into their regulatory processes for evaluating *in silico* evidence. This document also provides regulators (and notified bodies) with some of the supporting information that will be needed when relying on *in silico* evidence during regulatory decision-making.

On the use of *in silico* evidence in the medical device lifecycle

Nonclinical investigations, investigations using laboratory animals, or investigations involving human subjects represent the conventionally accepted forms of evidence for demonstrating the safety and effectiveness of a medical device [17]. *In silico* evidence represents an additional form of evidence that can be used in lieu of, or in conjunction with, conventional evidence sources. In 2021, the Medical Device Innovation Consortium (MDIC) surveyed 41 medical device companies about their use of CM&S in the product lifecycle [4]. As shown in [Fig. 1](#), survey respondents indicated that CM&S is primarily

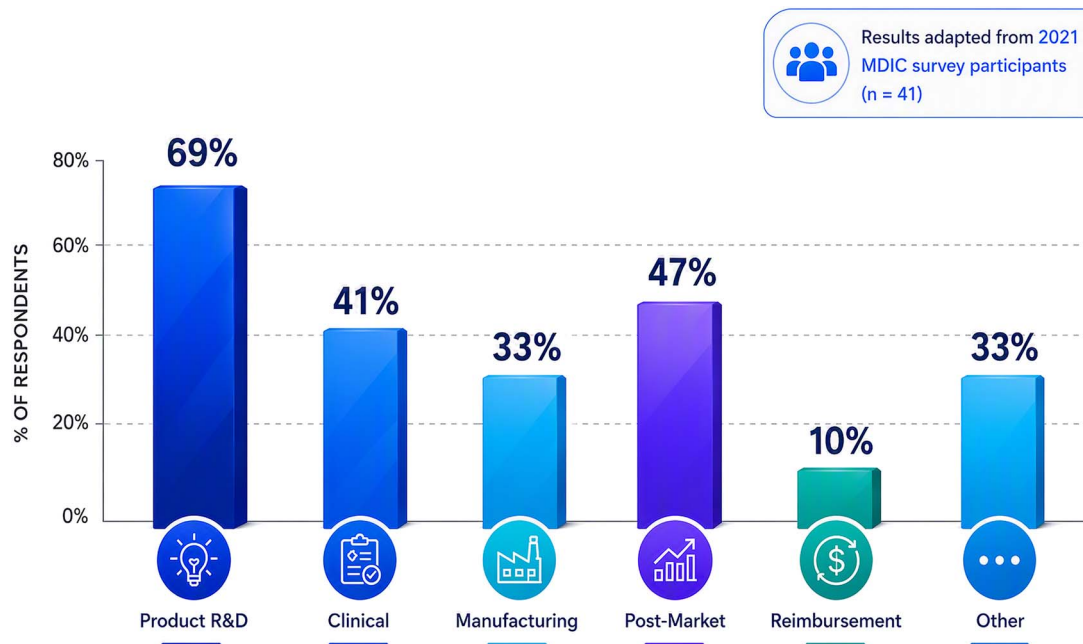


Figure 1 Results of a 2021 MDIC survey regarding the use of CM&S to support the development of medical devices throughout the total product life cycle.

used in the early stages of product development and for post-market activities. Another observation was the $2.2\times$ increase in the use of CM&S for clinical evaluations since their 2014 survey. This is likely a reflection of industry trends towards identifying alternatives to animal models as well as the use of *in silico* clinical trials to virtually predict device evaluation in patients. Over time, as the confidence in modelling results increases and global regulatory pathways become well established, it is expected that there will be increased use of *in silico* evidence as part of the regulatory submission process (Fig. 2). The objective being to reduce, refine, or replace conventional evidence without jeopardising safety, efficacy, or effectiveness of the device.

Morrison et al. [14] provide a comprehensive overview of how computational modelling is being used in the research, development, and regulatory approval of medical devices, from simulating a device to simulating physiology to simulation as a medical device to simulating clinical trials. Many examples of the benefits of *in silico* evidence are available in the peer-reviewed literature. Focusing on the more advanced example of *in silico* to support clinical trials, Faris and Shuren [18] discussed how the duration of a clinical trial and/or the number of enrolled patients can be reduced by substituting a clinical endpoint with a computational model. This article included a real-world used case where Medtronic was able to utilize a computational model, combined with bench and animal testing, to support MRI safety labelling of a new lead design. Haddad et al. [19, 20] outlined a Bayesian statistical approach that combined the results from a human clinical trial and an *in silico* clinical trial to refine the study design and to reduce the number of clinical trial participants. These workflows highlight the role of statistical bioinformatics methods in integrating heterogeneous evidence sources to improve inference and decision-making. The VICTRE trial replicated a human trial that was conducted to evaluate the diagnostic equivalence of digital breast tomosynthesis and digital mammography [21]. A computational pipeline was developed to simulate image acquisition and interpretation for both imaging

modalities using virtual patients (Fig. 3). This study demonstrated how a human imaging trial could be replaced with an *in silico* clinical trial, potentially eliminating the need for human subjects when evaluating new imaging technologies. From a bioinformatics perspective, this workflow highlights the integration of imaging data, anatomical modelling, and computational simulation into a reproducible digital evidence pipeline.

Terminology

This section provides definitions for terminology related to *in silico* methods that are used in this briefing. Most are sourced from ASME VVUQ standards [22–24] and the Avicenna Alliance Glossary, which was developed through a consensus process of alliance members [25]. Citations are included for definitions taken from other sources.

Medical device

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used alone or in combination with humans for one or more of the following specified medical purposes:

- 1) The diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of a disease or other condition;
- 2) The investigation, replacement or modification of the anatomy or of a physiological or pathological process or state;
- 3) The delivery of information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations.

A medical device does not achieve its primary intended action through pharmacological, immunological, or metabolic means, or chemical action in or on the human body.

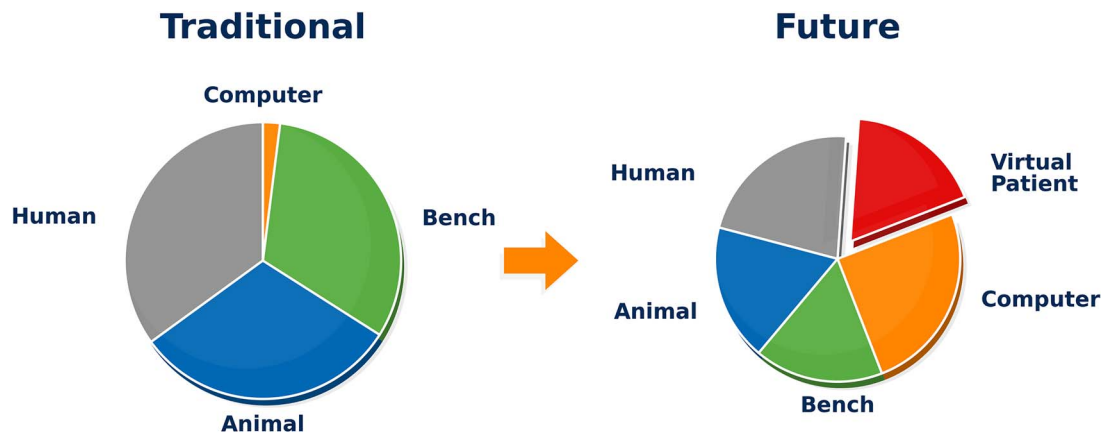


Figure 2 It is expected that increasing the portion of *in silico* evidence relative to bench experiments, animal investigations, and human clinical trials will reduce the overall burden of evidence generation. This pie chart also highlights the concept of virtual patients, which are a special form of computational model that represent the anatomy or physiology of a human subject in a way that is relevant for the interaction with the medical device of interest. (Figure adapted from “Advancing Regulatory Science with Modeling and Simulation at FDA”, T.M. Morrison, FDA Grand Rounds, August 9, 2018).

Computational modelling and simulation, computational model, simulation

- Computational modelling and simulation: The use of mathematics, physics and computer science to create numerical representations of real-world (or conceptual) systems that can be used for example, to reduce, refine or replace experimental and clinical research.
- Computational model: A numerical representation of a mathematical model such that it can be executed on a computer.
- Simulation: The act of executing the model for a specific set of input parameters.

Mechanistic models and empirical models

- Mechanistic (knowledge-based or physics-based) models: Models that describe causal relationships of a system based on scientific laws, e.g. mass and energy balances, or other equations that describe the behaviour of a system or specific phenomena, e.g. blood flow in the heart, orthopaedic implant performance, and protein folding. This is in contrast to empirical (data-based) models.
- Empirical (data-based or phenomenological) models: Models built exclusively on statistical analysis of (real-world) observation data that describe relationships between variables without necessarily understanding the underlying processes driving those relationships.

NOTE: In practice, many regulatory-relevant models combine mechanistic and data-driven components, requiring integration of bioinformatics pipelines for data preprocessing, parameter estimation, and model calibration. These are referred to as hybrid models.

In silico

In silico means carried out in the computer (i.e. in the silica), which is analogous to *in vitro* (in the glass), *ex vivo* (outside the living organism), or *in vivo* (inside the living organism).

In silico methods

In silico methods (ISMs) are procedures to conduct experiments, evaluations or analyses, using computer-based tools. *in silico* methods may

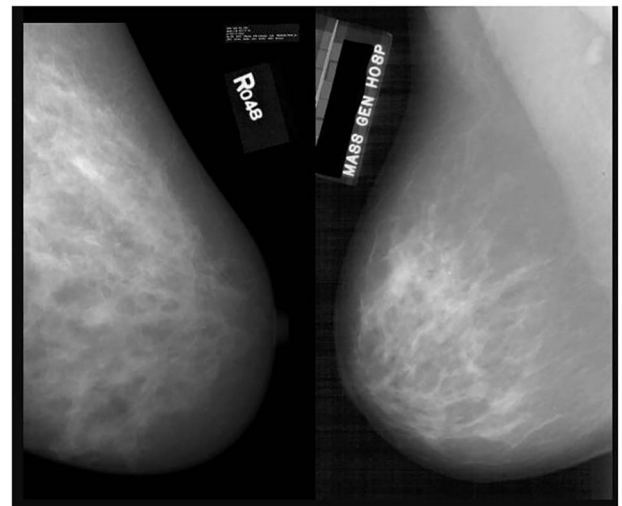


Figure 3 A real full-field digital mammogram of a patient (right) next to a computational model of the human anatomy (left). Image from the FDA VICTRE website.

utilise mechanistic, empirical, or hybrid models. The three subtypes of *in silico* evaluation methodologies considered here are:

- *in silico* medicine refers to the use of individualised (i.e. patient-specific) computational modelling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.
- *in silico* trials (ISTs) refer to the use of CM&S for testing medical interventions, including drugs and medical devices, in both preclinical and clinical contexts. ISTs aim to provide digital evidence under well-defined conditions, ideally described in standards, thus supporting drug/device development including for regulatory approval processes (Note that ISTs applied to clinical deployments involve the development and execution of individualised computer simulations that mimic *in vivo* testing in patient cohorts.).
- *in silico* clinical trials (ISCTs) refer to the use of CM&S to mimic the human experimentation required in the regulatory evaluation process of a medicinal (including medical devices) product or intervention, under well-defined conditions using verified and

validated models. It requires the definition of virtual patients or virtual populations of patients.

In silico (digital) evidence

CM&S outputs that are included in a regulatory dossier/submission to support the evaluation of a medical product (i.e. a medical device, drug, or combination product).

Real-world data

Real-world data (RWD) are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, e.g. electronic health records, claims and billing activities, and product and disease registries [18].

Real-world evidence

Real-world evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD [18].

Question of interest

A question of interest describes the specific question, decision or concern that is being addressed (at least in part) based on the results of a computational model [22].

Context of use

A statement that defines the specific role and scope of the computational model used to address the question of interest [22]. It should include a detailed description of what will be modeled and how the outputs from the computational model will be used to answer or inform the question of interest. It is important to note that the COU is distinct from the ‘indications for use’ or ‘intended use’ of a medical device, which are descriptions of how a device is intended to be used in clinical practice. Viceconti et al recently compiled an extensive list of COUs that are classified according to their ability to reduce, refine, or replace nonclinical and clinical experimentation [26].

Model risk

The possibility that the use of a computational model could lead to a decision that results in patient harm and/or other undesirable impacts. It reflects the risk the decision-maker incurs when using a computational model to support a decision. As shown in Fig. 4, model risk is the combination of the influence of the computational model (model influence) and the consequence(s) of an adverse outcome resulting from an incorrect decision (decision consequence).

- *Model influence* is the contribution of the computational model relative to other contributing evidence in making a decision.
- *Decision consequence* is the significance of an adverse outcome resulting from an incorrect decision.

Consequences are typically considered in the context of potential harm to the patient. However, non-patient-related impacts may also be considered, such as delayed patient access to medical devices, impact on the clinician, financial loss, or increased time to market.

Model credibility

Model credibility refers to the trust in the predictive capability of a computational model for the COU [22]. Trust can be established

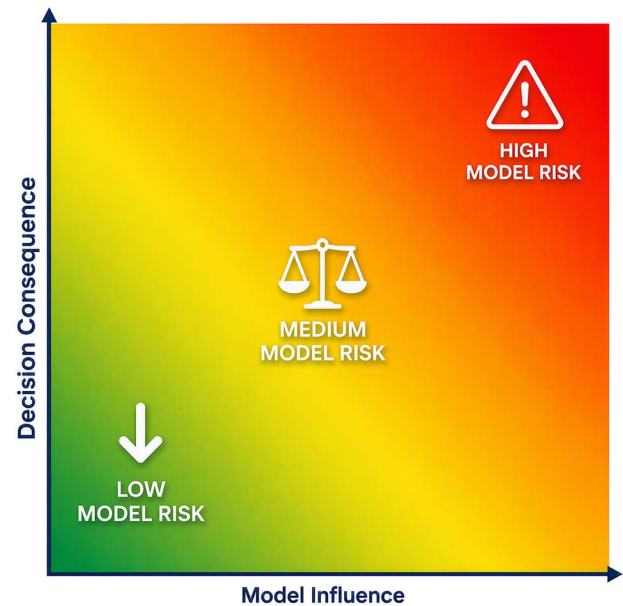


Figure 4 Schematic of how model influence and decision consequence determine model risk Adapted from ASME V&V 40–2018.

through the collection of evidence from credibility activities, which includes performing verification, validation, and uncertainty quantification (VUUQ) and then demonstrating the applicability of the VUUQ evidence to support the use of the computational model for the COU.

Verification

Verification is the process of determining that a computational model accurately represents the underlying mathematical model and its solution [23]. Verification is composed of two activities: code verification (ensuring code reliability) and calculation verification (estimating/quantifying numerical errors, e.g. discretization error).

Validation

Validation is the process of assessing the degree to which the computational model is an accurate representation of the reality of interest [23]. Therefore, validation activities are principally concerned with demonstrating the correctness of the underlying model assumptions and the degree to which sensitivities and uncertainties of the computational model and the associated comparator(s) are understood. Validation is generally demonstrated by comparing the computational model predictions with the results from the comparator(s), which might be *in vitro* or *in vivo* data. Therefore, appropriate validation activities require attention to both the computational model and the comparator.

Note that the terms verification and validation can have a variety of meanings outside the CM&S community, for example:

- Verification and validation of a product design ensures that the final design meets the internally specified and customer requirements, respectively.
- Verification and validation of software refers to consistency and correctness of the software and whether the software meets the user requirements, respectively.

A theme that appears in all these definitions is that verification refers to whether or not a product accurately meets the specified

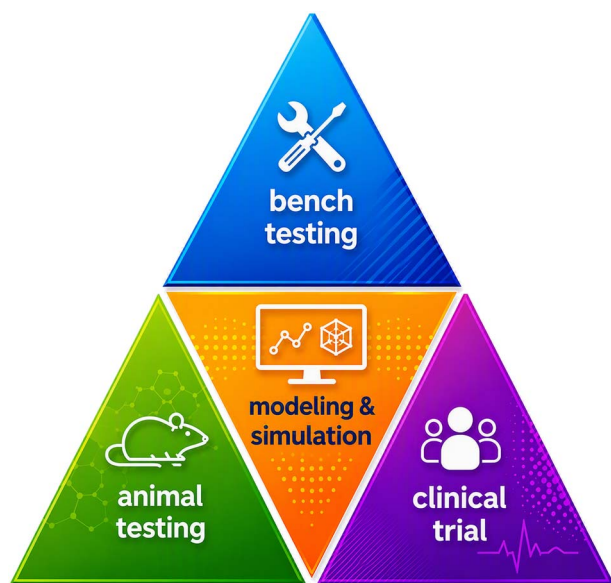


Figure 5 *In silico* supports product development either as a stand-alone form of evidence or by complementing the already accepted forms of evidence.

requirements and validation refers to how well the product meets the end user's needs. Put another way, verification asks the question 'was it built correctly?' and validation asks the question 'was the correct thing built?'

The role of *in silico* methods in medical device development

In silico methods are instrumental to enhancing our understanding of the *ex vivo* and *in vivo* performance of devices throughout development, manufacture, and use in the field. In the latter case, *in silico* methods can support post-market activities through virtual clinical trials running alongside clinical observation, providing additional insights into real-world data regarding performance outcomes. Digital evidence offers robust support throughout the product development lifecycle, serving as either a stand-alone form of evidence or acting in tandem with established methods such as bench testing, animal testing, and clinical trials. In this way, computational modelling may potentially reduce, refine, or replace reliance on the three traditional sources of evidence or act as a bridge between the various sources (Fig. 5). As such, digital evidence is increasingly being incorporated into regulatory decision-making processes. The subsequent sections of this document outline some of the essential considerations for the development and application of computational modeling and simulation across the entire lifecycle of medical devices, with a focus on enabling the use of *in silico* results as part of regulatory activities.

The importance of risk in model development and regulatory review

Device manufacturers base a variety of decisions on computational models during the design and development of new products and manufacturing processes. There is a broad spectrum of model COUs, and each is associated with an inherent risk that may carry through to the utilisation of the device. Therefore, the various sources of risk should

be considered at the start of the modelling activity and then used to establish model credibility requirements. This permits organizations to estimate the resources required to generate models with sufficient credibility before incorporating into a product development roadmap.

The connection between risk and model credibility has been established by a number of harmonised guidance documents and standards [5, 22, 27–29]. Articles from the peer-reviewed literature also highlight the importance of this connection [30, 31]. Two common themes in these documents are that the use of the model is categorized as low, medium or high risk, and that risk is the primary consideration when establishing model credibility requirements.

In addition to the risk associated with using a computational model to support internal or product development decisions (i.e. model risk as defined by ASME V&V40), an additional layer of regulatory risk should also be considered when planning to incorporate CM&S results into regulatory submissions. Regulatory risk refers to the risk of adverse regulatory or business outcomes arising from how *in silico* evidence is interpreted, weighted, or accepted by regulatory authorities, even when the model itself has been developed and assessed as credible for its defined COU. Regulatory risk does not replace or redefine model risk; rather, it emerges at the submission level and depends on factors such as the degree of reliance on *in silico* evidence within the overall weight of evidence, the availability of supporting nonclinical or clinical data, regulator familiarity with the modelling approach, and alignment with established standards and best practices. To manage this risk, sponsors should integrate the *in silico* evidence strategy—including its intended regulatory role, assumptions, limitations, credibility rationale, and supporting documentation—into the product's broader risk management and quality systems (e.g. submission planning, FMEA, and regulatory interaction strategies). Alignment with Good Simulation Practices and recognized model credibility frameworks can reduce uncertainty, support regulatory confidence, and facilitate a transparent weight-of-evidence assessment by regulators [16, 32].

Assessing the credibility of *in silico* evidence

As discussed in the previous section, the concept of a risk-informed credibility assessment is applicable to a broad variety of scientific, technical, and regulatory questions. The ASME V&V 40 standard provides a risk-informed credibility assessment framework that was developed for computational models that are used to support medical device development and regulatory review [22]. This standard was developed with the intent of augmenting the verification, validation, and uncertainty quantification frameworks provided by ASME V&V 10 [23] and ASME V&V 20 [33]. This section provides a high-level overview of the ASME V&V 40 standard. The reader is referred to the ASME V&V 40 standard for a detailed explanation and examples.

As shown in Fig. 6, the risk-informed credibility process begins with identifying a *question of interest*, which describes the specific question, decision or concern that is being addressed (at least in part) by a computational model. The next step is to define the COU, which describes the role and scope of the model and how it is going to be used to answer the question of interest in relation to other forms of evidence. *Model risk* is then assessed for the specified COU, which accounts for the potential consequences of an incorrect model output and the strength of the modelling results in the decision-making process. The two primary factors that impact model risk are the influence of the model on the decision and the consequence (on the patient,

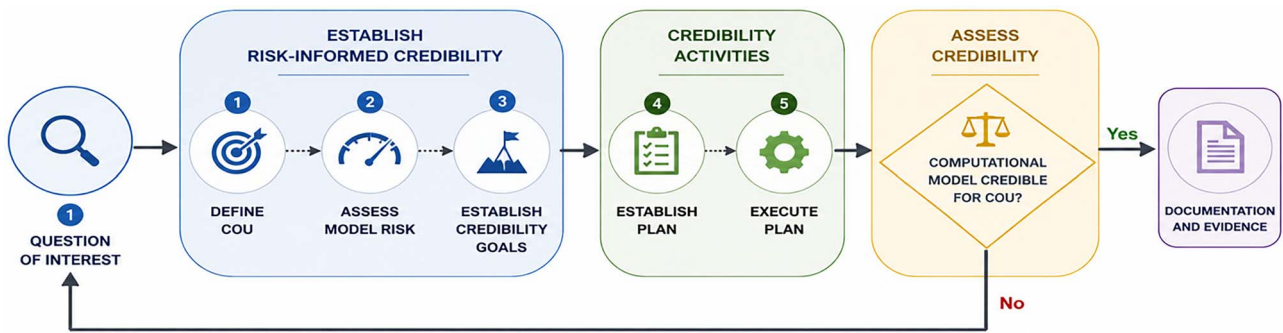


Figure 6 Process diagram for the risk-informed credibility assessment framework. Figure adapted from the ASME V&V 40–2018 standard.

business, or regulator) when basing an incorrect decision (at least in part) on a model. These two factors are assessed independently before determining the overall model risk. The model credibility requirements are then established based on the model risk assessment. This is accomplished by using model risk to determine the required degrees of model verification, validation, and applicability such that the model has sufficient credibility for the COU.

As an example of how the COU drives risk-informed credibility, a computational model that is used for a diagnosis that is also supported by medical imaging and clinical assessment would have lower overall model risk versus a scenario where the diagnosis relies solely on the results of a computational model. The lack of supporting evidence when making a decision means that the model credibility requirements are greater for the latter case.

After risk assessment, the next step is the development and assessment of the model form as well as the collection and preparation of the model inputs, such as part geometry, medical imaging data, material properties, boundary conditions, and initial conditions. As defined by ASME V&V 40, model input assessment is divided into sensitivity analysis and uncertainty quantification. Sensitivity analysis evaluates the relative impact of the various model input parameters on the outputs. This guides the identification of which input parameters to include in the uncertainty analysis, which is typically more computationally intensive. Uncertainty quantification helps estimate uncertainties in the model output based on known or assumed uncertainties in the model inputs. When framed in this way, it should be clear that the quality of the model inputs directly influences the quality of the model outputs. In some scenarios, the collection of model inputs is the limiting factor in the credibility assessment. However, the same is true for all evidence that is collected by designed experiments or observations.

Principles of simulation governance, which are discussed below, are applied during model creation and execution. These company-specific protocols are managed in the company's quality management system (QMS) and followed for all computational models which will become regulatory evidence.

The evaluation of the simulation outputs against a *comparator* is an essential part of the validation exercise. Acceptable forms of validation comparators include *in vitro*, *ex vivo* or *in vivo* studies. These studies may be performed as part of the validation process or based upon historical data (e.g. nonclinical, clinical trial) or real-world evidence. The comparator should be relevant for the defined COU and cover a sufficient sample size as well as the desired range of inputs.

Applicability is the relevance of the validation activities to support the use of the computational model for the COU. Applicability is highest

when the simulation outputs and measured quantities are identical and the application domain of the comparator overlaps the model validation domain. Note that a more rigorous verification and validation exercise may be required when there are differences between the quantities of interest and the application domain.

Once the credibility assessment is completed, it needs to be determined if the model is sufficiently credible for the COU. The ASME V&V 40 standard [22] and the FDA guidance on 'Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions' [5] both emphasize the iterative nature of the evaluation process. These documents also discuss options for refining and improving the model if it does not meet the required level of credibility. This continuous improvement cycle may involve: (i) iterative testing and model enhancements/refinements, (ii) incorporating new data or evidence as it becomes available, or (iii) revising the COU and associated credibility activities. Additionally, the FDA guidance emphasizes the need for providing a detailed justification for model credibility that considers all the results and any other relevant information, in a stage defined as 'Adequacy Assessment'.

A comprehensive summary of the computational model, model results, and conclusions must be documented and archived upon conclusion of the modelling project. According to FDA guidance [5, 34], the documentation should clearly describe the model and summarize the VVUQ activities along with their results and interpretations. This includes recording all assumptions, limitations, and a rationale for why these do not diminish confidence in the model's credibility. The following section outlines the reports that may be developed at different points in the computational model lifecycle.

Reporting

Computational modelling represents a complex development effort that builds upon a wide variety of information and data types. From a bioinformatics perspective, this reporting structure should be interpreted as the documentation of a full computational pipeline. This includes not only the model formulation and simulation outputs, but also data provenance, preprocessing steps, parameter derivation, software environment, and post-processing workflows. Transparent reporting of these elements is essential to ensure reproducibility, traceability, and regulatory trust in *in silico* evidence.

At a certain level of abstraction, a computational modelling activity requires identification of a numerical software platform, governing equations and their associated input parameters (geometry, material properties, boundary conditions), numerical settings, and post-processing activities used to summarize the results. Depending on the

COU, associated model validation activities (*in vitro* or other tests) may also be required to establish sufficient trust in the predictive capability of a model. This last point is especially important since regulators may shoulder some level of risk when relying on the outputs of a computational model as part of a regulatory decision regarding device safety and efficacy. Therefore, it is necessary to summarize all relevant information regarding the details of model generation, execution, and results extraction, as well as evidence and conclusions supporting model credibility. Clear and comprehensive documentation not only supports regulatory review, but also ensures transparency.

As outlined in the FDA guidance on credibility assessment of CM&S [5], 3 separate reports are suggested at two different phases of the submission process:

- **Prospective Credibility Assessment Report:** This report summarizes the risk-informed credibility requirements of a computational model and is typically created prior to performing final credibility assessment activities. It summarizes the credibility assessment that will be performed as well as the rationale explaining why the planned evidence will be sufficient to support using the model for the COU. In the United States, this prospective report can be submitted to the FDA as part of the Q-submission process for feedback on the planned credibility activities and whether the model would be deemed sufficient if it were to be used as part of the submission process.
- **Simulation Study Report (aka CM&S Report):** This report summarizes the simulation study that was performed to answer the question of interest. It is a technical summary of the data that was collected and is based on the 2016 FDA CM&S reporting guidance [34]. A detailed outline of the expected contents of this report is provided at the end of this section.
- **Credibility Assessment Report:** This report provides full details on the credibility assessment activities, including model risk assessment, verification, validation and uncertainty quantification, and post-study adequacy assessment. The primary goal of this report is to provide justification as to why the model is acceptable for the COU.

In addition, for data-driven and hybrid models, we recommend explicitly documenting: (i) data preprocessing and curation pipelines, (ii) software versioning and computational environment, (iii) training, validation, and testing strategies for AI components, and (iv) procedures for ensuring reproducibility and auditability of results.

Sponsors are asked to supply the Simulation Study Report as well as the Credibility Assessment Report as part of a submission for regulatory approval. The following paragraph summarizes the Simulation Study Report to give the reader some grounding on FDA expectations (the reader is referred to Appendix 2 of the FDA's Credibility Assessment guidance [5] for details on the other reports).

The modelling and simulation report structure shown here generally follows the FDA guidance on 'Reporting of Computational Modeling Studies in Medical Device Submissions' [34]. The specific elements of the report are as follows:

- **Overview:** a summary of the computational modelling activity, including the question of interest that is being addressed by the model, a description of the COU, and the solver type(s) being used to address the question;
- **Risk Analysis:** a description of the risk associated with relying on the results of the computational model to justify the safety or

effectiveness of one or more elements of a medical device (following the ASME V&V 40 model risk assessment);

- **Code Verification:** a description of software quality assurance (SQA) activities of the numerical simulation platform and evidence demonstrating that the code is free of bugs in the source code and numerical algorithms that are relevant to the COU;
- **System Configuration:** a description of the computational domain being investigated, this is typically the geometry of the device and surrounding physiological milieu (as appropriate);
- **Model Form:** a summary of the mathematical relationships representing the governing equations, material properties, and boundary conditions;
- **Model Inputs:** numerical values and associated uncertainties for the geometry, system properties, initial and boundary conditions, externally-imposed conditions, and their provenance;
- **Calculation Verification:** information regarding the computational grid (discretization), including a summary of the grid refinement studies that were performed to ensure a mesh independent solution in space and/or time;
- **Numerical Implementation:** a summary of the numerical simulation platform as well as any solver settings utilized to generate the solution;
- **Validation:** activities that were performed to establish the credibility of the computational model for the COU;
- **Results:** a summary of the quantities of interest and how they were extracted from the model and then compared to the validation data;
- **Limitations:** identification of any assumptions that impose limitations on the predictive capability of the model framework;
- **Conclusions:** describe the final conclusions that were made based on the model.

A report that includes these elements facilitates consistency and predictability in the regulatory review of *in silico* evidence because a complete and thorough description of the modelling activity has been provided.

The lifecycle of computational models

Simulation governance

Simulation governance refers to the management of organizational modelling and simulation capabilities as a corporate competence [35]. It is concerned with all aspects of modelling and simulation development, ranging from the selection and adoption of the best available simulation technology to the formulation of mathematical models to the management of experimental (and other) data and to the revision of mathematical models in light of new information, i.e. continuous improvement. Simulation governance relies on ensuring the repeatability and robustness of an organization's modelling and simulation capabilities to provide assurance of the reliability of information generated by computational models. Each organization should develop a simulation governance plan that ensures the goals of their computational modelling activities are met.

Data integrity

Regulators rely on the availability of reliable and accurate data to protect the public health (*cf* 21 CFR Part 11 (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-11>) and 211 (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-211>)), and [36–39]. For example, data integrity is of the utmost importance



Figure 7 The total product life cycle of a medical device.

when analyzing critical safety and efficacy endpoints in traditional clinical trials. Data should be of a similar paramount concern when considering *in silico* (clinical) trials.

In silico methods can be applied to a variety of points in the total product lifecycle of a medical device (Fig. 7), ranging from early ideation to invention and prototyping to animal or human trials, during regulatory review, and even post-market. A high proportion of the data generated during *in silico* evaluations may not impact the final design, especially data generated during the design and ideation phases when researchers are evaluating new design concepts. However, *in silico* evidence included in regulatory submissions must meet stringent data integrity requirements [40–43]. *In silico* methods can generate significant amounts of electronic data, placing additional importance on data integrity.

Data integrity refers to the completeness, consistency, and accuracy of data throughout the data lifecycle, which includes data creation, modification, maintenance, processing, archival, retrieval, transmission, and disposition [44]. The medical device industry follows the ALCOA+ framework to ensure data integrity, where the ‘ALCOA’ acronym stands for data needing to be Attributable, Legible, Contemporaneously recorded, Original, and Accurate; and the ‘+’ refers to 4 additional data attributes: Complete, Consistent, Enduring, and Available. Data should also be securely stored and backed up and regularly checked for accessibility, readability, and accuracy [45]. Data integrity therefore requires close collaboration between the user of the computerized system and IT and QA departments. Flexible and risk-based strategies can be employed to detect and prevent data integrity issues. Efforts should also be made to ensure a continuously auditable trail throughout the simulation lifecycle.

Health technology assessment

A health technology assessment (HTA) relies on scientific and clinical evidence to determine the value of a health technology, such as clinical effectiveness, expected quality of life for patients, and cost-effectiveness. The assessment helps to inform coverage, reimbursement, and pricing decisions, with the final goal being to ensure an equitable, efficient, and high-quality healthcare system. (<https://htaglossary.net/health-technology-assessment>) An HTA is usually based on systematic review of direct and indirect evidence regarding the device’s performance and overall [44, 46–48]. *In silico*

trials used to reduce, refine, or replace clinical evaluation of high-risk medical devices are also expected to support HTAs [32]. This may occur, for example, when direct experimentation is not possible because of ethical concerns, lack of time, or cost. According to the updated MDR, scientific evidence that is used to assess high-risk medical devices is required to ensure device safety and effectiveness, and this evidence may be based on methodologically robust trials, possibly in combination with other evidence sources such as CM&S [47]. HTA organizations favoured incorporating computational models into the assessment process. However, they vary in the areas for which they provide guidance and recommendations. A guidance prepared for the Agency of Healthcare Research and Quality was published to provide a framework to utilize modelling and simulation in the context of HTA [44]. However, globally harmonized frameworks are needed to move beyond the traditional sources of evidence, such as human trials, systematic reviews, and registry data, to formally include *in silico* evidence as part of HTA assessments.

Artificial intelligence

The concepts of simulation governance, data integrity and HTA must also be addressed when using AI systems. ISO/IEC 42001:2023 provides a framework for establishing and maintaining an Artificial Intelligence Management System (AIMS) [49]. The scope of this standard includes continuous learning and ethical considerations such as transparency, human agency and oversight, and fairness and non-discrimination, and provides a structured way to manage risks and opportunities associated with AI, balancing innovation with governance. The criticality of data integrity processes is significantly increasing as the healthcare industry continues to integrate AI into all aspects of the total product lifecycle.

For bioinformatics-oriented applications, AI-based models should be interpreted as components of a broader computational pipeline. Their credibility therefore depends not only on algorithmic performance, but also on dataset representativeness, feature engineering, training-validation-test partitioning, and robustness to distribution shifts. These elements, which are central in bioinformatics and machine learning practice, directly impact the regulatory reliability of AI-enabled *in silico* evidence.

Simulation governance in the context of healthcare AI refers to the frameworks that ensure AI models are credible, validated, and fit for

their intended purpose. This helps to ensure that these models are not only technically sound, but also ethically and clinically appropriate. According to the EU AI Act [10], and supporting documents from the Medical Devices Coordination Group [50], high-risk AI systems (such as those used in medical devices) must undergo rigorous validation using representative, reasonably error-free, and bias-mitigated datasets. An MHRA document goes further, highlighting how data should have sufficient fidelity to the real-world data, represent the full diversity of the intended population, and incorporate transparency by providing a clear explanation of data generation processes, assumptions, and intended use cases [51].

Data integrity is also foundational to regulatory trust. The EU AI Act [10] mandates that training, validation, and testing datasets for high-risk AI systems must be complete, accurate, and traceable. This aligns with traditional regulatory expectations under frameworks like 21 CFR Part 11 (<https://www.ecfr.gov/current/title-21/chapter-I/subchapter-C/part-11>) and ISO 13485 [36] but now extends to AI-generated or AI-processed data. An article on the EU AI Act [52] further emphasizes that data used in AI regulatory sandboxes must remain confidential and cannot be reused outside the sandbox, reinforcing the need for strict data governance.

Comparison of CM&S standards/guidelines

As discussed throughout this document, organizations ranging from standards bodies (e.g. ASME) to competent authorities (e.g. FDA) to international regulatory consortia (e.g. IMDRF) have issued documents supporting the use of computational models as regulatory evidence, software as a medical device, and artificial intelligence applied to medical devices. [Supplementary Tables 1–4](#) provide a non-comprehensive listing of published documents, which includes the issuing body, applicable jurisdiction, and main objective of the document (Note that the titles are active hyperlinks in the digital version of this document.) (see Supplementary Material).

Not included in [Supplementary Table 2](#) is the IEC 63719 standard committee, which was initially formed as an ad hoc working group in 2024 to address limitations in the global acceptance of the ASME V&V 40 standard. This group is therefore tasked with developing an internationally harmonised framework that outlines model development and credibility assessment best practices across the spectrum of physics-based and data-based models. The starting point for this activity is existing standards and thought leadership, which include the ASME V&V 40 risk-based framework and the ISO 9491 series [53].

Examples of *in silico* models that support the regulatory pathway

Credible computational models have been used to support various regulatory activities associated with the development of medical devices, including combination products. The examples in this section cover a wide range of medical sectors and were intentionally selected to represent more advanced uses of CM&S in the regulatory pathway, e.g. models used to replace bench testing or replicate/support clinical trial evaluation of a device. The collection of Avicenna Alliance member case studies provides additional examples that demonstrate the value of *in silico* for both devices and drugs. (<https://www.avicenna-alliance.com/case-studies.html>)

Neurovascular—using existing clinical trial results for *in silico* trial validation (University of Manchester)

Flow diverter devices treat intracranial aneurysms by promoting aneurysmal stabilisation prior to rupture. Sarrami-Foroushi et al. [54] undertook the FD-PASS *in silico* Trial, which replicated a clinical trial by simulating flow diverter performance in 164 virtual patients representing 82 distinct anatomies (Fig. 8). A computational fluid dynamics (CFD) model quantified post-treatment aneurysmal flow reduction under both normotensive and hypertensive conditions. The *in silico* clinical trial predictions matched success rates from three previous trials within 5% accuracy for acute outcomes. Importantly, the study demonstrated that incorporating blood pressure measurements into the model was critical, as normotensive versus hypertensive status resulted in ~15% difference in treatment outcomes. The study also provided evidence of several failure modes that were only anecdotally recorded in the literature and whose safety risks would have been impractical or unethical to ascertain via other regular testing methods.

Extending this work, MacRaidl et al. [55] used *in silico* trials to demonstrate that flow diverter treatment for posterior communicating artery aneurysms is significantly less effective in patients with fetal posterior circulation—a condition more prevalent in Black patients (11.5%) than White patients (4.9%)—highlighting potential racial disparities in treatment outcomes that warrant alternative therapeutic approaches. And in a separate study, MacRaidl et al. [56] concluded that *in silico* trials can credibly replicate clinical outcomes for intracranial aneurysm flow diverters whilst enabling controlled investigation of treatment performance across diverse patient populations and physiological conditions that would be unethical or unfeasible in conventional trials, thereby accelerating device development, reducing patient risk, and promoting equitable healthcare access.

The key conclusions from this study were that *in silico* trials of endovascular medical devices can: (i) replicate observations from conventional clinical trials, and (ii) provide a platform for virtual experimentation that would be challenging or impossible in conventional trials. This enables developers to gain novel insights into treatment failure mechanisms through systematic exploration of different physiological conditions and population subgroups.

Orthopaedics—expanding clinical trial tested configuration with a large *in silico* investigation (Zimmer Biomet)

Zimmer Biomet has commonly utilised *in silico* methods for preclinical device evaluations, running hundreds of finite element analyses (FEA), e.g. to identify worst-case use conditions or device configurations. This information is used to ease the burden on physical testing, saving considerable time and money.

Zimmer Biomet is now exploring the use of *in silico* clinical trials to address limitations of clinical trials. In orthopaedics, these trials provide evidence of safety and/or effectiveness of new products across the broad variation in anatomy (men, women; children, adults, elderly people; people of small stature, tall people; thin or obese persons), use conditions (walking, cycling, carrying loads, physical exercise), and surgical approaches that is encountered in clinical reality (Fig. 9). *In silico* clinical trials are enabling Zimmer Biomet to quickly and cost-effectively evaluate a wide range of clinically-relevant scenarios, providing credible evidence to augment data from clinical trials.

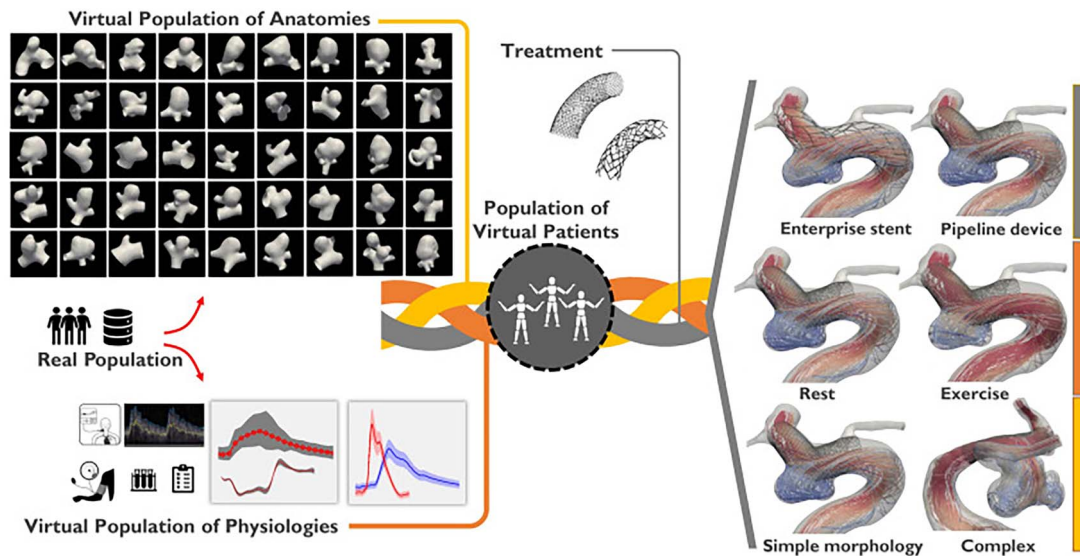


Figure 8 Left: A virtual cohort of patients was developed using CT scan data from 82 patients and used to perform virtual surgeries. Right: Numerical analyses illustrating blood flow trajectories under a variety of anatomical and physiological conditions. NOTE: the FD-PASS study was performed as part of the INSILEX RAEng Chair in Emerging Technologies Programme using data collected during the @neurIST EU Funded project. Figure adapted from [47].

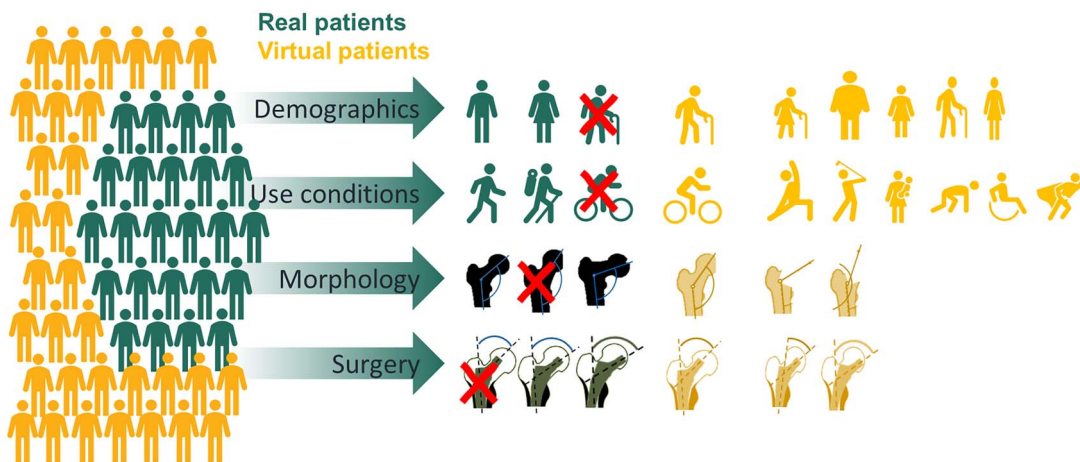


Figure 9 *In silico* clinical trials allow real patient data to be supplemented with virtual patients. Ideally, clinical trials would include real patients (green) representing all types of demographics, use conditions, morphologies and surgeries that the device will experience. However, since clinical trial cohorts are limited in size, time and cost, there will inevitably be some scenarios that may not be tested (red crosses). These gaps can be filled with virtual patients (gold); in addition, ISCTs also allow exploring more conditions and dramatically increasing the sample size (gold). Image courtesy of P. Favre, Zimmer Biomet.

In a recent study of a new shoulder implant, Zimmer Biomet created a large collection of computer models by combining patient specific anatomies, unique surgical interventions and different load cases. Various performance metrics were calculated using this virtual cohort of 3000 *in silico* models, including (i) interfacial micromotion between the implant and the host bone for purposes of assessing implant stability, and (ii) bone stresses for the purposes of evaluating the risk of stress shielding around the implant. This model was developed in accordance with ASME V&V 40 recommendations. The results were found to be in agreement with clinical observations.

For Zimmer Biomet, this *in silico* clinical trial provides valuable information that can be used to refine the next clinical trial. It also reinforces confidence in the value of future *in silico* clinical trials to precede, refine, and possibly reduce clinical trials.

Cardiovascular—incorporating virtual patients into clinical trials (Medtronic)

As early as 2018, Medtronic reported that a complex model of the human heart and an implantable cardiovascular device was presented to the FDA together with clinical evidence. The FDA accepted that additional questions could be addressed by the clinically validated computer model only. This work resulted in ‘one of their products [being] released 2 years earlier than expected, reducing the clinical trials by 256 patients and the estimated cost by \$10 Million US while allowing to treat 10,000 patients during these 2 years.’ Michael Hill former Vice President, Science & Technology and Innovation, Medtronic. (Report of the Avicenna Alliance event at the European Parliament, September 2018.)

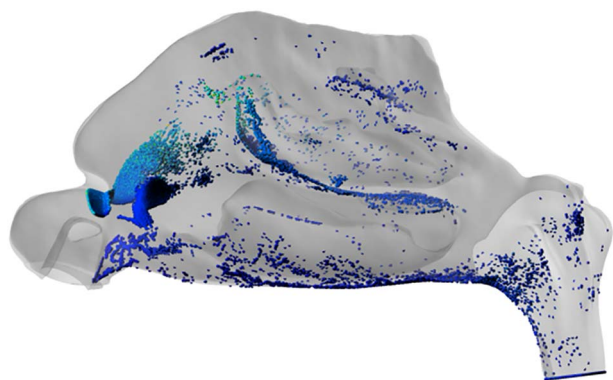


Figure 10 CFD simulations were used to assess regional deposition of intranasal corticosteroid sprays. The predicted nasal dose of the active pharmaceutical ingredient (API) from the CFD model was used as input into a physiologically-based pharmacokinetic (PBPK) model to estimate tissue concentrations and clearance kinetics.

Respiratory drug delivery—establishing credible multi-scale models of inhaled drugs (Applied Research Associates, ARA)

ARA and Ansys collaborated to evaluate the credibility of a multi-scale model of nasal drug delivery following the ASME V&V 40 standard. A combination of CFD (as shown in Fig. 10) and population-based pharmacokinetic (PBPK) models were used to address the question of interest ‘Is the generic nasal spray device bioequivalent to the currently marketed nasal spray device?’. The computational model was used to show that sufficient quantities of the therapeutic drug from the generic nasal spray formulation were reaching the desired sites in nasal tissues while maintaining low systemic concentrations as compared to the already approved product [57]. The authors evaluated various elements of this medium-risk model to develop a comprehensive simulation plan that was able to address the question of interest with sufficient confidence in the model predictions.

Orthopaedics—validated *in silico* equivalent of a bench test (Numalogics)

Numalogics partnered with Sawbones to develop a simulation-as-a-service application that allows orthopedic implant manufacturers to test devices on Sawbones polyurethane foam bone surrogates (polyurethane foam) in a completely virtual environment. This FEA-based application models orthopaedic screw pullout testing according to the ASTM F543–17 standard [58], which is a widely accepted standard for evaluating the mechanical performance of orthopedic screws. Using this application, engineers can now rapidly evaluate new orthopaedic screw designs, reducing or even eliminating device prototyping.

The credibility assessment of this model was conducted based on the ASME V&V 40 framework and on the latest FDA guidance on CM&S credibility assessment and was specifically structured to demonstrate the model’s device-agnostic capabilities, enabling its use across diverse screw types and designs (Fig. 11). The COU of the model stipulates it can be used as a surrogate to physical testing and consequently the model influence was assessed as high. As the significance of an adverse outcome resulting from an incorrect

decision (decision consequence) was medium, the model risk was medium-high.

The credibility assessment covered verification, calibration, validation, and applicability evidence categories, evaluating a total of 25 credibility factors. A high credibility rating was obtained for 19 of the 25 credibility factors and a medium credibility rating was obtained for 6 of the 25 credibility factors. The overall credibility level of the model was assessed to be Medium-High, commensurate with the model’s risk.

The workflow received formal qualification by the US FDA through the MDDT program. (<https://www.fda.gov/media/188766/download>) This represents the first FDA qualification of an *in silico* mechanical test for an orthopedic device, setting a new precedent for virtual testing in regulatory science.

Conclusion

The rising costs of generating the required safety and effectiveness evidence for global regulatory authorities is stifling innovation in the medical device industry. It is recognized that CM&S can significantly accelerate the introduction of new devices at a lower cost without compromising patient safety. But the lack of internationally harmonized guidance and standards guiding the credibility requirements of *in silico* evidence is limiting the utilization of this additional source of evidence. One result is that the maturity of the *in silico* evidence presented by industry to regulatory agencies varies widely. This paper outlined a framework establishing the credible use of *in silico* evidence in regulatory submissions. The risk-based nature of the framework aligns with global regulatory trends for *in silico* technologies and could be adopted in full or adapted to the unique requirements of each competent authority.

Authors’ position regarding the added value of this work

While existing standards and guidelines provide important foundations for the use of computational modelling in regulatory contexts, this paper advances the discussion in several key directions. First, we argue that the credibility of *in silico* evidence should be assessed at the level of the full computational pipeline, rather than at the level of the executable model alone. This includes data provenance, preprocessing, model implementation, and post-processing. Second, we formalize and emphasize the distinction between model risk and regulatory risk, highlighting the need to explicitly consider how *in silico* evidence is interpreted and weighted within regulatory decision-making. Third, we propose that hybrid models require integrated credibility assessment strategies that bridge traditional modelling and bioinformatics practices. Finally, we stress that reproducibility, traceability, and data integrity—core principles in bioinformatics—are essential prerequisites for the regulatory acceptance of digital evidence.

Key Points

- A risk-informed framework grounded in clear definitions of question of interest and context of use is essential to ensure the credible and proportionate regulatory application of *in silico* evidence.

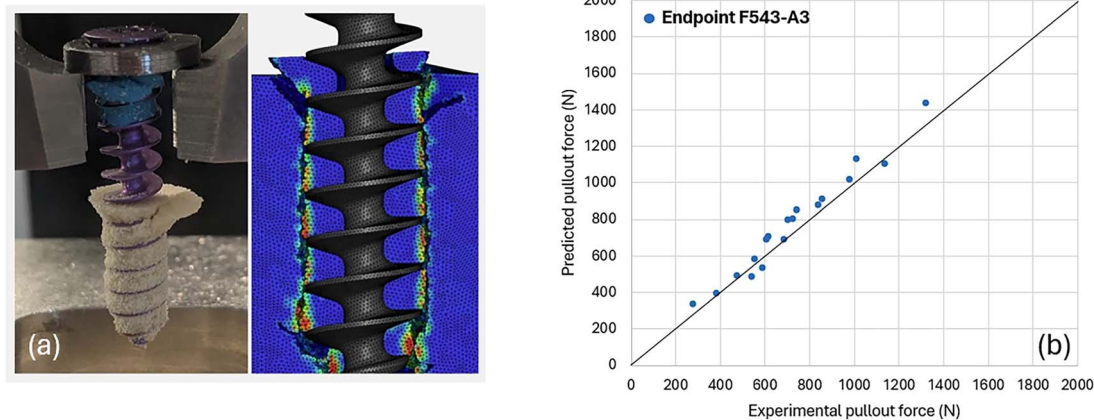


Figure 11 (a) Qualitative and (b) quantitative validation of the ASTM F543–17 simulations of screw pull-out.

- Model credibility must be established through structured verification, validation, and uncertainty quantification (VVUQ), aligned with internationally recognised standards such as ASME V&V 40.
- Regulatory risk, distinct from model risk, should be proactively managed through transparent documentation, simulation governance, and early regulatory engagement.
- Data integrity, simulation governance, and AI lifecycle management are foundational requirements for regulatory acceptance of digital and hybrid models.
- International harmonisation of standards and guidance is urgently needed to enable predictable regulatory pathways and equitable patient access to safe and effective medical products.

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Supplementary material

Supplementary material is available at *Briefings in Bioinformatics* online.

Conflicts of interest

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Data availability

Not applicable.

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