AVICENNA ALLIANCE

Avicenna Alliance
Association for Predictive Medicine

Avicenna Alliance Position Paper

Ensuring the Quality of *in silico* Evidence:
Application to Medical Devices

Contributions

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I. About the Avicenna Alliance

The Avicenna Alliance is an association of industry, academia, and healthcare organizations who have a commercial or research interest in the development of *in silico* medicine.

The Alliance, established in 2016, has its origins in the Virtual Physiological Human Initiative, a European Commission endorsed research area on computer modelling and simulation applied to medicine. Tasked by the European Commission with developing a "Roadmap for *in silico* medicine", the Alliance now seeks to put this roadmap into policy and ensure the development of a well-functioning framework for the *in silico* medicine ecosystem.

This Alliance bridges the gap between the scientific community, industry and policymakers by advocating for policy changes that take scientific and market developments into account.

II. Preface

The objective of this white paper is to inform industry, academic researchers and regulators in competent authorities about a pathway for the broader acceptance of *in silico* (computational) evidence in the regulatory decision-making process for medical devices. As the medical device industry mostly serves a global population, harmonization of the guidance for acceptance of *in silico* evidence by individual regulatory authorities around the world is of great importance. At this point in time, the maturity of the *in silico* evidence presented by industry to the regulatory agencies, as well as the ability of regulators to conduct a timely and appropriate review, differs significantly between jurisdictions. As it is generally accepted that *in silico* evidence accelerates medical device innovation without negatively impacting safety and efficacy, broader and more predictable acceptance of *in silico* evidence is a commonly expressed goal.

This document describes the benefits of *in silico* methods, defines essential terms, and outlines a risk-based framework for establishing that a model has sufficient credibility for decision-making. Additional considerations on model reporting, simulation lifecycle, and health technology assessment are also summarized. To highlight the need for a globally consistent framework, the paper concludes with a comparison of documents published by various global regulatory authorities and standards bodies that focus on the predictable and consistent use of *in silico* evidence in submissions. The core elements of the paper are based on foundational documents developed by industry, regulatory agencies, and academic researchers [1-3], whose work has led to a common terminology and harmonized understanding of the credible development and utilization of *in silico* evidence.

This white paper is structured in a manner similar to the series of three documents published by the International Medical Device Regulators Forum (IMDRF) [4-6], which provide global regulators with a risk-based framework for the evaluation of Software as a Medical Device (SaMD). This white paper can provide essential background information and input for the creation of a similar document.

It should also be noted that a group of experts and stakeholders (*InSilico* World, [7]) has initiated a consensus process for the development of a Good Simulation Practice (GSP) document to complement existing Good Clinical Practice (GCP, (ICH E6(R2) [8]), Good Laboratory Practice (GLP, [9]), and Good Manufacturing Practice (GMP, [10]) documents. In contrast to this paper, the GSP document will provide more detail regarding the best practices for implementing and utilizing GSP.

III. Introduction

Medical device manufacturers have traditionally relied on bench testing, animal testing and clinical trials (*i.e.*, human testing) 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 increasingly relying on computational modeling and simulation throughout the product life cycle to accelerate development and provide additional assurance of performance and safety. Their efforts range from models that support early design decisions to models that guide and refine bench

testing to models of devices interacting with human anatomy or physiology. This latter class of models is an individualized virtual test of a medical device or other treatment and is commonly referred to as an *in silico* trial (see the ***Special Feature*** for additional details and examples). One of the primary benefits of an *in silico* trial is that the model predicts the safety or efficacy of an intervention by increasing confidence in the new therapy prior to exposing human subjects. And in contrast to other approaches, *in silico* trials can also provide a physical explanation for the success or failure of a therapy. This is not only a safety benefit, but can shorten development time as well.

Various regulatory agencies have taken steps to ensure the rigorous application and implementation of *in silico* evidence as part of their decision-making processes [1, 11-13]). The European Union Regulation (EU) 2017/745 explicitly mentions "computer modeling" as an allowable form of pre-clinical evidence [14]. In the United States, 21 CFR 860.7 lists the accepted forms of scientific evidence without explicitly mentioning computational modeling and simulation [15]. Several documents published by the FDA [2, 16-18] list bench testing, animal testing, human testing (clinical trials), and computational modeling as four forms of accepted science-based regulatory evidence. However, current regulatory frameworks regarding modeling and simulation may not always translate across geographies, address the unique public health risks posed by the use of *in silico* trials, or ensure an appropriate balance between patient/consumer protection and the promotion of public health by facilitating innovation.

Successful utilization of *in silico* evidence as part of the market authorization process requires primary legislation that recognizes the use of *in silico* evidence or regulations/guidance/standards describing how to develop, employ, report, and assess computer simulations. To address the latter requirement, this document aims to provide a common framework for regulators to incorporate a harmonized approach into their regulatory processes for evaluating *in silico* testing and *in silico* trials. This document also aims to provide regulators with supporting information when relying on *in silico* evidence during regulatory decision-making.

Special Feature: Use of *in silico* evidence in the medical device development lifecycle

Conventionally, nonclinical investigations, investigations using laboratory animals, or investigations involving human subjects represented the accepted forms of evidence for demonstrating the safety and effectiveness of a medical device [15]. In the past decade, *in silico* evidence has been introduced as an additional form of evidence, which can be used in lieu of or in conjunction with conventional evidence. In 2014, the Medical Device Innovation Consortium (MDIC) surveyed 35 medical device companies about their use of computational modeling and simulation (CM&S) in the product life cycle (**Figure 1**). The chart shows that CM&S is more often used in the early stages of product development or post product launch, but rarely to simulate the interaction of the device with a laboratory animal or a patient. Over time, the confidence in modeling results has increased and the regulatory pathway has become more established, supporting increased use of *in silico* evidence as part of the regulatory submission process (**Figure 2**). The objective being to reduce, refine, or replace conventional evidence without jeopardizing safety, efficacy, or effectiveness of the device.

The paper by Morrison et al. provides a comprehensive overview of how computational modeling is being used in the research, development, and regulatory approval of medical devices [18]. Additional examples of the benefits of *in silico* evidence are also available in the peer-reviewed literature. Faris and Shuren showed how the duration of a clinical trial or the number of enrolled patients can be reduced by substituting a clinical endpoint with a computational model [19]. Haddad *et al.* outlined a Bayesian statistical approach that combined the results from a human clinical trial and an *in silico* trial to refine the study design and to reduce the number of clinical trial participants [20]. The VICTRE trial [21] demonstrated that a full-field digital mammogram of a patient and a computational model of the human anatomy are interpreted consistently within the context of the trial (Figure 3). The human clinical trial was replaced with an *in silico* trial, i.e. no human subjects were part of the evidence generation in this example. The Avicenna Alliance also collected member case studies demonstrating the value of *in silico* medicine for both devices and drugs [22].

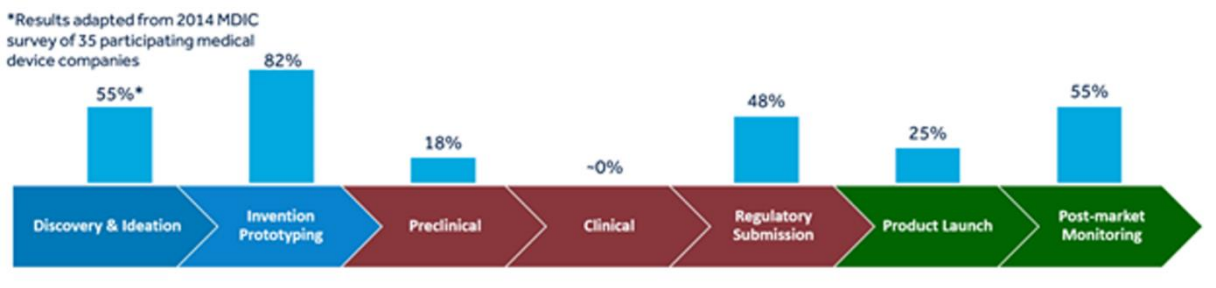

Figure 1: Computational modeling and simulation is being used to support the development of medical devices throughout the total product life cycle. According to a 2014 survey conducted by the Medical Device Innovation Consortium (MDIC), the utilization of CM&S differs significantly between the stages.

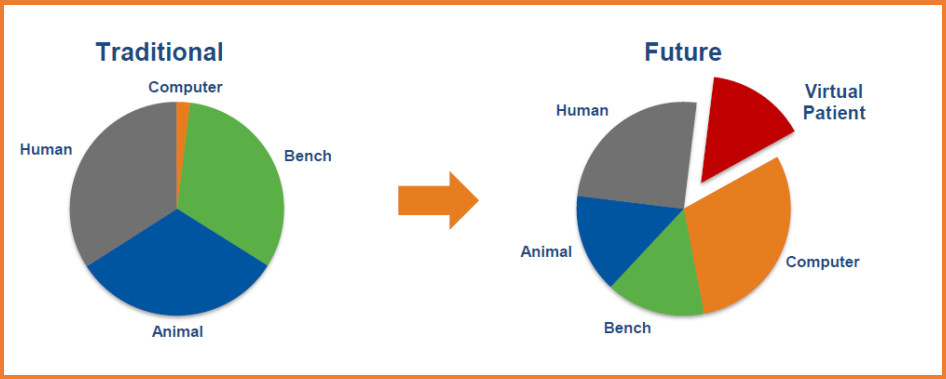

Figure 2: The goal is to reduce the overall burden of evidence generation by growing the evidence that is generated with computational modeling in a way that is able to reduce the contribution of results from bench experiments, animal investigations, and human clinical trials. The pie chart on the right highlights the concept of virtual patients, which are a special form of computational models 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.

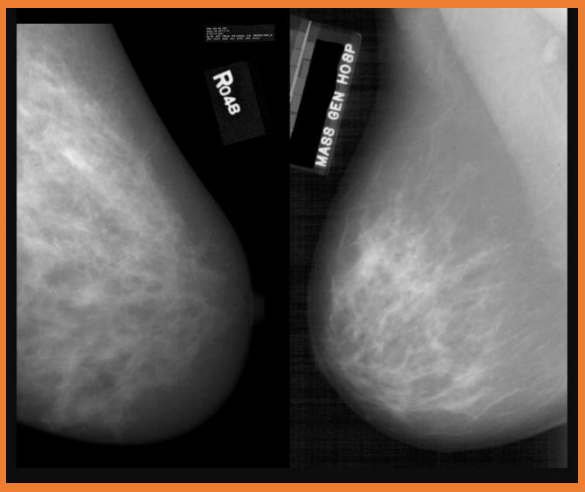

Figure 3: A real full-field digital mammogram of a patient (right) next to a computational model of the human anatomy (left). Image from the FDA VICTRE website[1].

[1] https://wayback.archive-it.org/7993/20190424090307/https:/www.fda.gov/MedicalDevices/ScienceandResearch/ResearchPrograms/ucm477418.htm

IV. Definitions

Medical device

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used alone or in combination in humans for one or more of the following specified medical purposes: diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of a disease or condition, or to effect an anatomical structure or physiology in any other form. Both European Medical Device Regulation [14] and US FDA [23] definitions state that 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.

Computational modeling, Computational model, Simulation

- Computational modeling is the use of computers to simulate and study real-world systems using mathematics, physics and computer science [24].
- A computational model is a numerical implementation of the mathematical model used to capture the relevant behavior of a physical system.
- A simulation is the result of running a computational model for a specific set of model input parameters. Simulation, therefore, is the process of running a computational model.

Mechanistic model and phenomenological model

Computational models that are based on cause-and-effect relationships are called mechanistic models [25, 26]. Models that develop a predictor without making any causal assumptions are called phenomenological models. In practice, there is a continuum between mechanistic and phenomenological models. In this context, models utilizing artificial intelligence (AI), machine learning (ML), and deep learning are considered phenomenological models.

In silico

in silico means carried out in the computer, which is in contrast to *in vitro* (on the bench), *ex vivo* (outside the body), or *in vivo* (inside the body).

***In silico* methods**

in silico methods comprise mechanistic and phenomenological models. The three types of *in silico* evaluation methodologies considered here are:

- *in silico* test (or experiment or study) refers to the execution of an *in vitro* or *ex vivo* experiment in the computational environment [3] (Chapter I, page 11).
- *in silico* medicine refers to the use of individualized computational modeling in all aspects of the prevention, diagnosis, prognostic assessment, and treatment of diseases.
- *in silico* trial refers to the use of individualized computer simulations in a cohort of patients during the development or regulatory evaluation of a medicinal product, medical device, or medical intervention. An *in silico* trial can be preclinical or clinical studies [27].

***In silico* evidence**

in silico evidence is the result from *in silico* methods applied in the regulatory approval process and encompasses *in silico* trials and *in silico* tests.

Real-world data (RWD)

Real-world data 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 [28].

Real-world evidence (RWE)

Real-world evidence is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD [28].

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 [1].

Context of Use

Context of use (COU) defines the specific role and scope of the computational model used to address the question of interest [1]. It should include a detailed statement 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 (submitted) recently compiled an extensive list of COUs that are classified according to their ability to reduce, refine, or replace nonclinical and clinical experimentation [29].

Model risk

Model risk is the possibility that the use of a computational model leads to a decision that results in patient harm and/or other undesirable impacts [1]. It reflects the risk the decision-maker incurs when using a computational model to support a decision. Model risk is the combination of the influence of the computational model (model influence) and the consequence of an adverse outcome resulting from an incorrect decision (decision consequence) (**Figure 4**).

- 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.

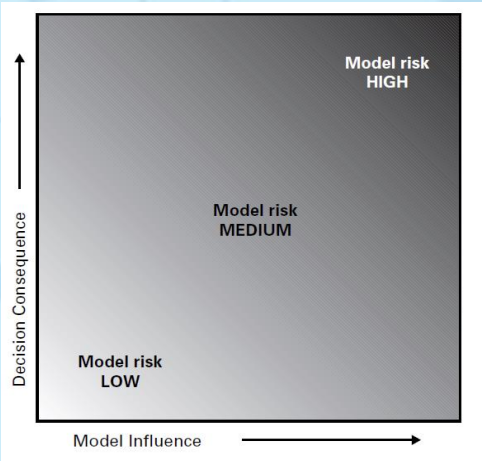

Figure 4. Schematic of how model influence and decision consequence determine model risk [1]. Reprinted from ASME V&V 40-2018, by permission of The American Society of Mechanical Engineers. All rights reserved". No further copies can be made without written permission from ASME. Permission is for this edition only.

Model credibility

Model credibility refers to the trust in the predictive capability of a computational model for the COU [1]. Trust can be established through the collection of evidence from credibility activities, which includes performing verification & validation (V&V) and then demonstrating the applicability of the V&V 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 [30]. Verification is composed of two activities: code verification and calculation verification.

Validation

Validation is the process of assessing the degree to which the computational model is an accurate representation of the reality of interest [30]. 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.

Please note that the terms verification and validation can have a variety of meanings outside the space of computational modeling and simulation, 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 embedded 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 requirements and validation refers to how well the product meets the user's need. Put another way, verification asks the question "did I build it right?" and validation asks the question "did I build the right thing?"

V. Role of *in silico* Testing and *in silico* Trials in Medical Device Development

Computational models are used throughout the development and manufacture of a medical device to enhance understanding of *ex vivo* or *in vivo* performance. Computational modeling has the ability to support product development as either a stand-alone form of evidence or in conjunction with already accepted forms of evidence (bench testing, animal testing, and clinical trials). In this way, computational modeling may reduce, refine, or replace the three traditional sources of evidence or act as a bridge between these various sources (**Figure 5**). Models may also be used as part of the regulatory decision-making process. The remainder of this document outlines key considerations when developing and deploying models throughout the lifecycle of a medical device.

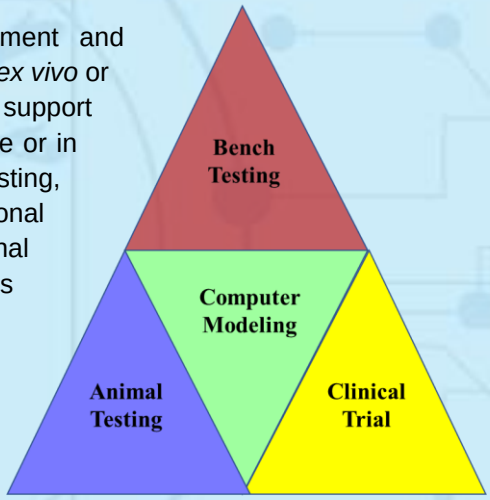

Figure 5. Computational modeling has the ability to support product development as a stand-alone form of evidence or in conjunction with already accepted forms of evidence.

VI. The Importance of Risk in Model Development

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 models that may be developed, and each is associated with an inherent risk that may carry through to the application of the device. Therefore, the various sources of risk should be considered at the start of any modeling activity and then used to establish the model credibility requirements. This permits organizations to estimate the resources required to generate models with sufficient credibility.

The connection between risk and model credibility has been established by a number of harmonized guidance documents and standards [1, 5, 31] Two common themes in these documents are that models are 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 utilizing the results of a model to support internal decision-making, a regulatory risk must be evaluated. Regulatory risk in this context refers to the risk associated with regulatory decisions supported by *in silico* evidence. The regulatory risk is currently perceived as higher if the decision relies only on *in silico* evidence as the primary source of evidence to support a safety and efficacy assessment, compared to a product assessment supported primarily by traditional nonclinical and clinical data.

VII. Assessing the Credibility of *in silico* Evidence

The ASME V&V 40 Standard introduces a risk-informed credibility assessment framework that has been developed for computational models supporting medical device development and regulatory review (**Figure 6**) [1]. This standard augments the verification, validation, and uncertainty quantification frameworks provided by ASME V&V 10 and ASME V&V 20 [30, 32]. The concept of a risk-informed credibility assessment is applicable to a broad variety of scientific, technical, and regulatory questions. This section outlines these concepts and provides a high-level overview. Please refer to the ASME V&V 40 Standard for a detailed explanation and examples [1].

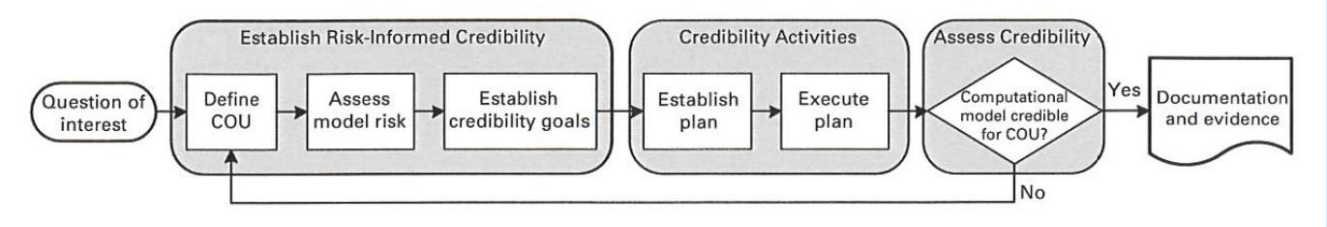

Figure 6. Process diagram for the risk-informed credibility assessment framework. Note: after assessing credibility, it may be necessary to go back to one of the previous steps (defining COU, assessing the model risk or establishing the credibility goals) [1]. Reprinted from ASME V&V 40-2018, by permission of The American Society of Mechanical Engineers. All rights reserved". No further copies can be made without written permission from ASME. Permission is for this edition only.

The process begins with identifying the *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 *context of use* (*COU*), which describes the role and scope of the model and how it is going to be used in relation to other forms of evidence. The *model risk* is then assessed for the specific COU. Model risk takes into account the potential consequences of an incorrect model output and the strength of the modeling 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, business, or regulator) when basing a decision (at least in part) on a model. The risk associated with each of these two factors is assessed independently before determining the overall model risk. The model credibility requirements are established based on the 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 model risk versus a scenario where the diagnosis relies solely on the computational model. The lack of supporting evidence means that the model credibility requirements are greater for this latter case.

The next step is the collection and preparation of the model inputs such as part geometry, medical imaging, material parameters, boundary conditions, and initial conditions. The quality of the model inputs directly influences the quality of the model outputs. The assessment of the model inputs can be divided into two parts. The quantification of sensitivities is concerned with how variations in input parameters propagate through the simulation and affect the output. The quantification of uncertainties addresses how known or assumed uncertainties in the model inputs are propagated to uncertainties in the model results. 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 observation.

Principles of simulation governance, which are discussed in **Section IX a**, shall be applied to model creation and execution. These principles should be defined in company-specific protocols and be followed for all computational models which will become regulatory evidence.

The evaluation of the modeling results against a c*omparator* is an essential part of the validation exercise. Acceptable forms of validation experiments 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 (RWE). The comparator needs to be relevant for the defined COU and needs to cover a sufficient sample size as well as the desired range of inputs. More than one comparator may be required to validate a model framework.

Applicability is the relevance of the validation activities to support the use of the computational model for the COU. Applicability is highest when the measured quantities and the application domain of the comparator and the model are identical. The validity of the model can only be inferred if the quantities of interest and the application domain are not identical, therefore requiring a more rigorous verification and validation exercise.

Once the credibility assessment is completed, it needs to be determined if the model is sufficiently credible for the COU. Note that the COU can be modified, and the credibility assessment repeated if the model fails the credibility assessment. Alternatively, the model itself, or the credibility activities, can be revisited and improved to reach the required level of model credibility.

A comprehensive summary of the computational model, model results and conclusions must be documented and archived upon conclusion of the modeling project. **Section VIII** outlines the structure of a computational modeling and simulation report for use with internal decision-makers and external stakeholders.

VIII. Reporting

Computational modeling represents a complex development effort that builds upon a wide variety of information and data types. At a certain level of abstraction, a computational modeling activity requires identification of a numerical software platform, governing equations and their associated input parameters (geometry, material properties, boundary conditions), numerical settings, and post-treatment procedures used to summarize the results. Depending on the context of use, 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 provide a summary report that contains all relevant information regarding the details of model generation, execution, and results extraction, as well as evidence supporting model credibility.

This section reviews the structure of a modeling and simulation report that addresses the aforementioned concerns. The report outline generally follows the FDA guidance on “Reporting of Computational Modeling

Studies in Medical Device Submissions" [2], which describes the format and contents of reports summarizing the *in silico* testing included as valid scientific evidence in regulatory submissions. The specific elements of the report are as follows:

- Overview: a summary of the computational modeling activity, including the question of interest that is being addressed by the model, a description of the context of use, 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 a computational model to justify the safety or effectiveness of one or more elements of a medical device;
- 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;
- System Configuration: a description of the computational domain being investigated, typically the geometry of the device and surrounding physiological milieu;
- 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 context of use;
- 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 addresses these elements facilitates consistency and predictability in the regulatory review of *in silico* evidence because a complete and thorough description of the modeling activity has been provided.

IX. The Lifycycle of Computational Models

a. Simulation Governance

Simulation governance is the management of organizational modeling and simulation capabilities as a corporate competence [33]. It is concerned with all aspects of modeling 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 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 modeling 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 modeling activities are met.

b. Data Integrity

Data integrity is of utmost importance as it pertains to critical safety and efficacy endpoints analysis in classical clinical trials. It should therefore be of paramount concern when considering *in silico* testing or trials.

In silico methods can be applied to a variety of points in the total product life cycle of a medical device (**Figure 7**), ranging from early ideation to invention and prototyping to animal or human trials, during regulatory review, and post-market. A high proportion of the data generated during *in silico* testing may not impact the final design, especially data generated during the design and ideation phases when researchers are scoping out a new design. However, *in silico* evidence included in regulatory submissions must meet stringent data integrity requirements [34-37].

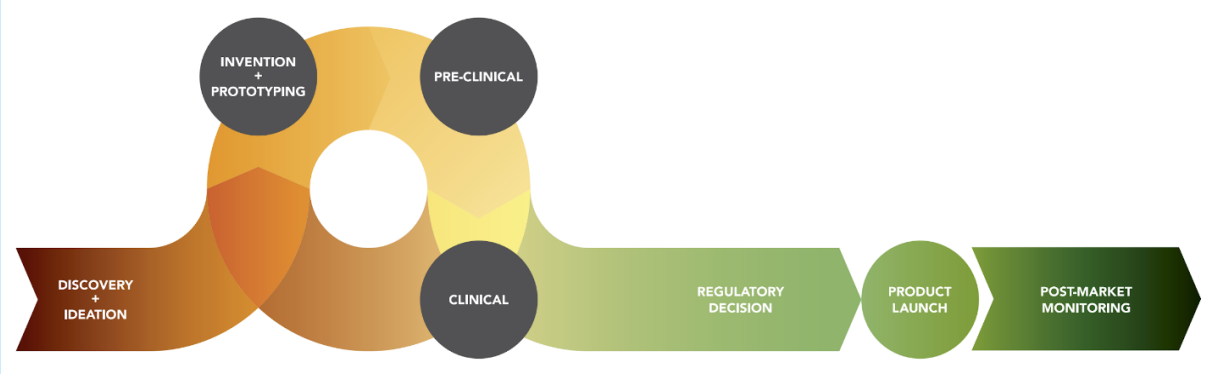

Figure 7: The Total Product Life Cycle of a Medical Device [16].

Data integrity is critical to regulatory compliance and it is industry's responsibility to ensure the safety, efficacy, and quality of their products. Additionally, regulators rely on the availability of reliable and accurate data to protect the public health (refer to 21 CFR Part 210, 211 and 212, [38, 39]), and regulations in other geographies). *In silico* methods 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 life cycle, which includes data creation, modification, maintenance, processing, archival, retrieval, transmission, and disposition [39]. 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 [40]. 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 be made to ensure a continuously auditable trail throughout the simulation lifecycle.

c. Health Technology Assessment

A health technology assessment (HTA) relies on scientific and clinical evidence to determine the various parameters used as part of device approval, such as clinical effectiveness, expected quality of life for patients, cost-effectiveness, *etc*. An HTA is usually based on systematic literature review of direct and indirect evidence [41-44]. When evaluating high-risk medical devices, CM&S can strengthen the scientific evidence. Indeed, the use of CM&S is of heightened interest when direct experimentation is not possible because of ethical concerns, lack of time or even costs. As the European Commission updated the medical device regulations, scientific evidence used to assess high-risk medical devices is required to ensure the evidence quality based on methodologically robust trials, possibly in combination with other evidence sources, such as CM&S [43]. HTA organizations favored incorporating computational models into HTA. However, they vary in the areas for which they provide guidance and recommendations. A guidance

prepared for the Agency of Healthcare Research and Quality has therefore been published to provide a framework to utilize modeling and simulation in the context of HTA [41].

X. Comparison of CM&S Standards/Guidelines

Since 2013, several organizations, ranging from standards bodies and competent authorities (*e.g.*, US FDA) to international regulatory consortia (*e.g.*, IMDRF), have issued relevant documents supporting the use of computational models as regulatory evidence, software as a medical device (SaMD), and artificial intelligence applied to medical devices. With the goal of global harmonization of the acceptance of *in silico* evidence, **Table 1** provides a non-comprehensive listing of the issuing body, applicable jurisdiction, and main objective of the document, among other criteria (the titles are active hyperlinks in the digital version of the document).

XI. 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 computational modelling and simulation can significantly accelerate the introduction of new devices at a lower cost without compromising patient safety. But the lack of harmonized guidance for the acceptance of *in silico* evidence is limiting the utilization of this additional source of evidence. Additionally, the maturity of the *in silico* evidence presented by industry to regulatory agencies varies widely. This white paper outlined a framework establishing the credible use of *in silico* evidence in regulatory submissions. The framework could be adopted in full or adapted to the unique requirements of each competent authority. The Avicenna Alliance is available to review the proposed framework in more detail and can also provide support when developing regional approaches.

HARMONIZED GUIDANCE FOR THE ACCEPTANCE OF *IN SILICO* EVIDENCE BY GLOBAL REGULATORY AUTHORITIES IS CRITICAL TO ENSURING RAPID ACCESS TO SAFE AND EFFECTIVE MEDICAL DEVICES FOR ALL PATIENTS.

XII. Acknowledgements

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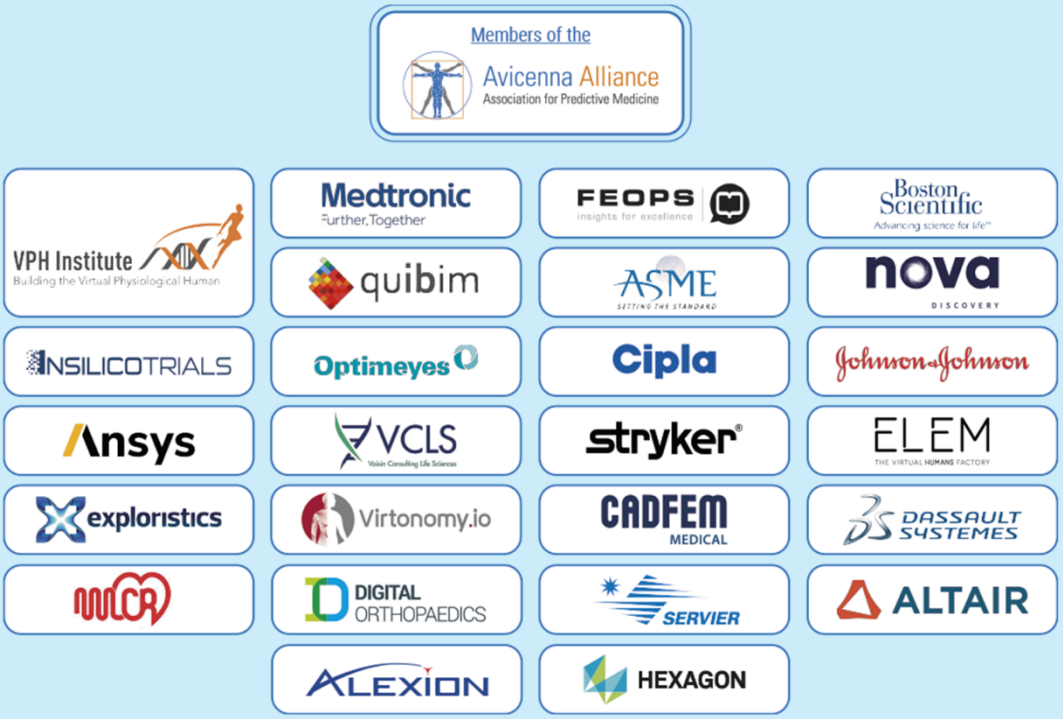
for their kind review of the manuscript.

Table 1: Comparison of various CM&S reference documents

document	**ASME V&V40**	**FDA Model Reporting Guidance**	**IMDRF - SaMD** **3 docs**	**FDA AI Action Plan**	**US AHRQ** [41, 42]	**PMDA Model Informed Drug Development**	**MFDS AI guideline**
primary application	devices	devices	devices	devices	devices and drugs	drugs	devices
issuing body (type of body)	int'l standards organization	regulatory authority	regulatory consortium	regulatory authority	regulatory authority	regulatory representative	regulatory authority
developer	industry, regulators	regulators	regulators, industry, academia	regulator	regulators, industry	regulators, industry, academia	regulators, industry
issue date	2018	2016	2013, 2015, 2017	2021	2016, 2017	2014	2020
applicable jurisdiction	global	US	selected regions	US	US	Japan	South Korea
main objectives	establish framework for determining model credibility requirements	drive consistency and predictability in model reporting and regulatory review	address public health risks associated with SaMD	communicate action plan to establish regulatory framework for AI/ML & SaMD	advance the credibility, transparency, and methodological rigor of modeling	foster model-informed drug development (*e.g.*, PK, PK/PD)	improve transparency of review and approval for big data and AI-based medical devices
intended scope	mechanistic	mechanistic	mechanistic and phenomenological	phenomenological	not specified	phenomenological	phenomenological
intended audience	all CM&S stakeholders (industry, competent authorities, academia)						

This Position Paper is endorsed by the 25 Members of the Avicenna Alliance on Friday 28 May 2021:



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