SIMCor

In-silico testing and validation of Cardiovascular IMplantable devices

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Executive summary

The purpose of the document is to provide recommendations on the formatting, organization, and content of reports describing in-silico modelling and results in the field of *computational fluid dynamics* (CFD) and *finite element analysis* (FEA) for medical device regulatory submissions. Besides that, those recommendations also aim at helping clear and transparent communication about computational studies in interdisciplinary teams and at improving reproducibility of studies.

This document has been built on published recommendations of various organizations concerned with modelling and simulations and V&V activities for health products, such as the Committee on Credible Practice of Modelling & Simulation in Healthcare, V&V sub-Committees of the *American Society of Mechanical Engineers* (ASME), the *Food and Drug Administration* (FDA), the *European Medicines Agency* (EMA) and the *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use* (ICH). In addition, even though they are not specific to human health and health products, recommendations from NASA have also been accounted for as they provide a high-quality framework for CM&S in potentially high-risk applications[1],[2]. The structure of the document has been built on the FDA guidance for reporting computational modeling studies in medical device submissions[3], mainly.

[1] NASA-STD-7009, NASA Standard for Models and Evaluation (2017), https://standards.nasa.gov/standard/nasa/nasa-std-7009 .

[2] NASA handbook for models and simulations: an implementation guide for NASA-STD-7009. *NASA-HDBK-7009a* (2017), https://standards.nasa.gov/standard/nasa/nasa-hdbk-7009

[3] FDA, Reporting of Computational Modeling Studies in Medical Device Submissions - Guidance for Industry and Food and Drug Administration Staff. (2016). U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and

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Acronyms

Acronym	Full name
ASME	American Society of Mechanical Engineers
AWT	Accelerated Wear Testing
CAD	Computer Aided Design
CFD	Computational Fluid Dynamics
CM&S	Computational Modeling and Simulations
COU	Context Of Use (R-COU: reality-COU; M-COU: model-COU)
EMA	European Medicines Agency
EOA	Effective Orifice Area
FDA	Food and Drug Administration
FEA	Finite Element Analysis
FSI	Fluid-Structure Interaction
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IFU	Instructions For Use
OSI	Oscillatory Shear Index
PAPS	Pulmonary Artery Pressure Sensor
QOI	Question Of Interest
RANS	Reynolds-Averaged Navier-Stokes-Equations
RoI	Reality of Interest
TAVI	Transcatheter Aortic Valve Implantation (also known as TAVR for Transcatheter Aortic Valve Replacement)
TAWSS	Time Average Wall Shear Stress
V&V	Validation and Verification

Introduction

Reporting computational fluid dynamics and mass transport simulations

In continuum mechanics, differential equations are used to represent physical or biological laws that underlie the process to be simulated. The microscopic structure of matter, e.g., the lattice structure of crystalline solids and the molecular structure of liquids, is ignored and the object of investigation is approached as a continuum.

Numerical methods, such as *computational fluid dynamics* (CFD), *finite element analysis* (FEA) or *fluid structure interaction* (FSI) and computational models, which solve problems of continuum mechanics, have been used for medical device development. Within this guideline, the process is called *computational modelling and simulation* (CM&S).

The purpose of the document is to provide guidance on the formatting, organization, and content of reports for CFD, FEA and FSI cases in order to perform simulation studies for medical device regulatory submissions. Furthermore, the order of the chapters could also be used as a template for reporting.

We see very high potential in standardized scientific / technical documentation with regard to the reproducibility and comparability of numerical studies.

Furthermore, the SIMCor consortium sees the relevance of such a guideline also in supporting communication of interdisciplinary teams working together on new medical devices. Due to interdisciplinary working groups in the field of medical research and medical device development, communication is one key aspect of understanding opportunities and limitations of CM&S. Program and project management in collaboration with the Technical Authority have the responsibility to identify and document the critical decisions to be addressed with CM&S and to determine which CM&S are in scope, based upon the criticality of the situation addressed by the proposed use of the CM&S[1]. Therefore, the complete and clear communication of the credibility of CM&S results can reduce the risks associated with CM&S-influenced decisions as stated by NASA-STD-7009A[1]. As an example, for clear communication the factors leading to CM&S credibility should be more apparent as proposed by NASA and ASME V&V40 subcommittee[4].

We are convinced that transparent communication, consisting of full description and clear understanding, will contribute to CM&S credibility. The given guideline for reporting focused therefore on aspects which leverage the deeper understanding of CM&S to better evaluate the results of the simulation for decision makers.

This report has been built on published contributions from many other organizations concerned with CM&S and health products or Verification and Validation (V&V). Worth noting is the FDA guidance “Reporting of Computational Modelling Studies in Medical Device Submissions”[3]. The FDA guidance was structured and complemented by the consortium's expertise in the field of cardiovascular implant testing and development.

The following chapters are to assist researchers and developers in preparing technical reports on numerical studies in the field of biomedical engineering.

[4] ASME V&V 40-2018: Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices.

Executive report summary

The report should start with an *"Executive Report Summary"*. The executive summary provides an overview of the information relevant to the decision on one to two pages. Not only the most important results should be presented, but also key statements from the motivation till conclusion.

The most important information includes:

1. Brief summary of the *context of use* (COU): describe the use case in the real environment and which decisions are derived from the results of the analysis. Briefly summarize the rationale for choosing the computer modelling approach (M-COU: *computer model and simulation used for COU decision making / COU question*). Also, justify why other approaches (e.g., further numerical methods or even experimental methods) were not used. Describe if the numerical method used is supported by other methods, e.g., for validation purposes (references to further reports).

2. Briefly describe the nature and scope of the analyses performed. In this context, describe whether the analysis code/software is commercially available, e.g., ISO 9001:2008 certified, open source, and/or user developed. In this context, comment on the validation (describe the computational model and simulations used for validation: M-VAL and describe the physical experimental setting: R-VAL) and explain how it is suitable to support the use of the CM&S study in the *context of application* (COU).

3. Briefly summarize the model, including geometry, material properties, boundary/starting conditions, and contact conditions. If the device has multiple sizes and/or configurations, provide a rationale for the sizes and configurations of the evaluated and unevaluated device system and reference standards (e.g., ISO 5840), if available.

4. Discuss the simulation results, the variables of interest, and their impact on the safety and effectiveness of the product. Summarize the limitations as well as the main conclusions.

The modeler may use a table to shortly summarize that information and the model informed decision. For instance, the structure of the credibility matrix proposed for regulatory evaluation of in-silico models in drug development may be used for that purpose[5]. The so-called credibility matrix consists of the subsections presented in *Table 1*, which can help to structure the executive summary.

	Credibility matrix
Investigational product	
Type of model	
Scientific Question(s) of interest (QOI)	
Context of use	
Acceptability criteria	
Regulatory impact	
Risk based analysis of decision consequence	
Credibility activities results	
Model informed decision	

Table 1: Template of the credibility matrix for executive report summary. Adapted from F.T. Musuamba et al.[5].

In addition, when using a document management system, it may be helpful to include keywords.

Keywords – examples: biofluid mechanics, *fluid structure interaction* (FSI), *transcatheter aortic valve replacement* (TAVR), drug delivery, blood flow, transport, finite volume method, finite element method, pump, non-Newtonian flow, transient and pulsatile flow, washout, residence time, radial force.

[5] F. T. Musuamba, I. Skottheim Rusten, R. Lesage, G. Russo, R. Bursi, L. Emili, G. Wangorsch, E. Manolis, K. E. Karlsson, A. Kulesza, E. Courcelles, J. P. Boissel, C. F. Rousseau, E. M. Voisin, R. Alessandrello, N. Curado, E. Dall'ara, B. Rodriguez, F. Pappalardo, L. Geris, Scientific and regulatory evaluation of mechanistic *in-silico* drug and disease models in drug development: Building model credibility. *CPT Pharmacometrics Syst. Pharmacol.* (2021), doi:10.1002/psp4.12669

Introduction and scope / background / purpose

The investigator should provide a brief description of the device, along with its intended use environment and deployment/implantation procedure. The details provided in this section should correspond to the objectives of the analysis, which should be outlined in the COU statement.

One of the key aspects for preparation of CM&S study is to define the purpose of this study. To do so, the question of interest (QOI) and the COU must be defined, the specific reason you decided to write your report must be identified and the specific focus on the document needs to be clarified, see ASME V&V 10[6], 20[7] and 40[4].

Possible questions, which should be answered are the following:

- *Which specific process do you address?*
- *Which goal of the simulation is possible?*
- *Which question is to be answered?*
- *Which quantities are to be calculated and what acceptance criteria is used?*
- *Which conclusions are you going to draw from the simulation?*
- *What is the required precision of your calculation?*
- *Do you need an estimate or a precise number?*

This will determine the relevant details necessary for review and the level of credibility activities necessary in relation with the perceived risk. NASA proposed a criticality assessment matrix as fundamental for communicating the criticality of the decision, which is derived from CM&S results[1]. This can be used as a tool to justify the V&V activities. Five levels of CM&S result influence as well as decision consequences were introduced. The philosophy of this approach was also used in the development of the ASME V&V 40-2018 risk-informed credibility assessment framework, which provides a workflow for V&V activities. According to NASA and ASME V&V40 the level of rigor of the V&V is driven by model risk, which is defined as: "the possibility that using the computational model to inform a decision can result in undesirable effects, such as patient harm"[8]. Similarly, the use of a credibility matrix has been proposed and tested by European regulators as a tool in the context of in-silico model regulatory evaluation[5].

In this introductory section we recommend positioning the study on the *model influence* vs. *decision consequence* scale, following the risk-based approach recommended by the ASME V&V40-2018 in order to justify the relevance and adequacy of the V&V activities that will be described later. This provides the initial basis of development and feeds into the concepts of "accepted use" at the end of development and "proposed use" at the beginning of CM&S use[1].

It is also important to define the acceptance criteria and range of application for the computational study. Furthermore, the report shall document the permissible uses of the CM&S, which is defined by NASA as "the purposes for which a M&S is formally allowed"[1]. What aspects or metric of CM&S results were used to make decisions? For example, that could be hemodynamic metrics such as shear rate, *time average wall shear stress* (TAWSS) or *oscillatory shear index* (OSI).

[6] Standard for Verification and Validation in Computational Solid Mechanics. VV10 – 2019. https://www.asme.org/codes-standards/find-codes-standards/v-v-10-standard-verification-validation-computational-solid-mechanics

[7] Standard for Verification and Validation in Computational Fluid Dynamics and Heat Transfer. VV20 - 2009(R2021). https://www.asme.org/codes-standards/find-codes-standards/v-v-20-standard-verification-validation-computational-fluid-dynamics-heat-transfer

[8] B. Parvinian, P. Pathmanathan, C. Daluwatte, F. Yaghouby, R. A. Gray, S. Weininger, T. M. Morrison, C. G. Scully, Credibility evidence for computational patient models used in the development of physiological closed-loop controlled devices for critical care medicine. *Front. Physiol.* **10**, 220 (2019)

Roles and responsibilities

When conducting CM&S studies and more particularly in case of an in-silico trial, the roles, tasks and responsibilities should be clear and documented appropriately, similarly to what is recommended in guidelines for regular clinical trials by the *International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use* (ICH)[9].

Responsibilities and tasks should be agreed between the sponsor/ initiator of the in-silico study and the investigators who carry the CM&S activities and the credibility activities (V&V) at the beginning of the project through a documented agreement.

When reporting CM&S activities it may be appropriate to state the training profile and responsibilities of specialized staff (e.g., developers, operators, and analysts), who are involved in the CM&S process and writing the report. When CM&S tasks have been delegated to third parties (e.g., clinicians) this should also be documented.

As proposed by NASA possible training topics for developers, operators, and analysts of CM&S may or should include the following aspects:

- The limits of operation for CM&S, with implications and rationale.
- CM requirements.
- Documentation requirements and recommendations
- How to recognize unrealistic results from simulations.
- Feedback processes to improve CM&S processes and results, including providing feedback for results that are not credible, are unrealistic, or defy explanation.
- Sensitivity analysis.
- Uncertainty characterization.
- Verification and validation.
- How to report simulation results to decision makers.
- Statistics and probability.

In addition, we recommend a profound knowledge of biomechanics, as we are active in the field of implant development.

However, given the diversity of profiles involved in the conduct of CM&S activities for health products no specific degree or certificate can be requested or would even be sufficient to cover all aspects of the in-silico study. The profiles represented in the team of responsible investigators should be appropriate for the CM&S activities, V&V activities and results described in the report.

[9] ICH-E6(R3) EWG - Good Clinical Practice (GCP), https://database.ich.org/sites/default/files/ICH_E6-R3_GCP-Principles_Draft_2021_0419.pdf

Simulation plan / workflow

Building a computational model requires sequential steps and iterations (e.g., model conceptualization, data processing, parameter estimation, verification, evaluation, etc..). A validated model is subsequently used to simulate scenarios, make predictions and eventually help decision making. The modeler should provide a comprehensive description of the modeling and simulation process that has been employed. We recommend a schematic workflow as a general overview of the simulation project. *Figure 1* shows an example workflow.

The workflow should provide information about the application context and be representative of the specific model and simulations being reported. It should also show how the physical system is constrained. The workflow should show in a simple way which steps were performed in the simulation and which steps were omitted. This overview helps the reader to quickly understand the simulation project.

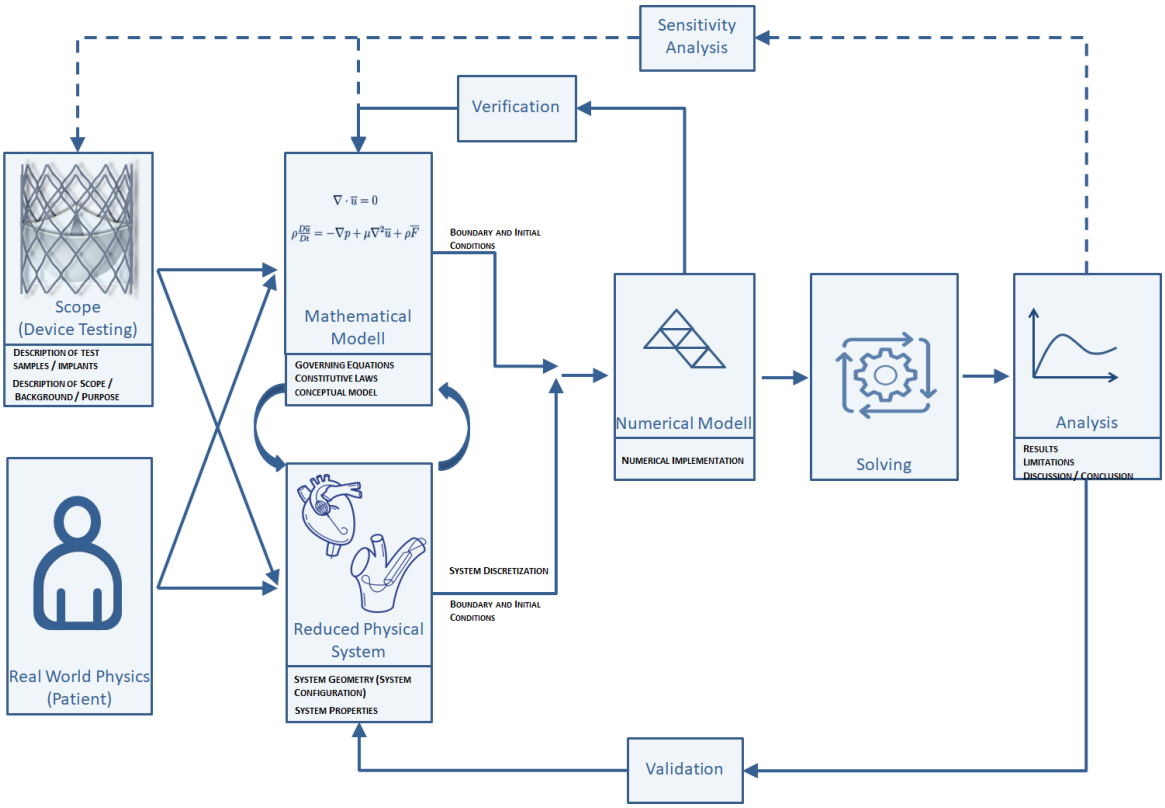

Figure 1: Exemplary simulation workflow to provide an overview of the following simulation steps: physical problem, modelling, running the simulation, and analysing the results.

In addition to the model development, detailed information must be provided regarding the design of the in-silico study carried with the model. For instance, the modeler should describe the conditions applied to the system (e.g., boundary and initial conditions), the experimental setup and information such as characteristics of the virtual population (e.g., number of individuals) or the length of the study, as advised for CM&S reporting by both FDA[3] [10] and EMA[11]. Here again a graphical representation may be used, if appropriate.

[10] A. Erdemir, T. M. Guess, J. Halloran, S. C. Tadepalli, T. M. Morrison, Considerations for reporting finite element analysis studies in biomechanics. J. Biomech. 45 (2012), pp. 625–633

[11] EMA, Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation | European Medicines Agency (2018), https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation

Data certificate of birth

The data used in the model, whether for its construction or its validation, must be trustworthy. Hence, the report should evidence the good quality of the data and its relevance to the COU by presenting the type of data, including the format and form of data (e.g., deterministic, range of values, average with spread, image, etc.), as well as all relevant metadata (e.g., the source, method to obtain the measurement, number of replicates, sex and age of individuals, etc.). This is referred to as the "certificate of birth"[5] of the data or "data pedigree"[1,2] in different guidelines and standards. The NASA standard also proposes to include in that pedigree some traceability information such as the processing, storage and transmission of the data. While part of that information might be missing for some historical or retrospective data, the level and type of detail needed to demonstrate the quality and relevance of the data depends on the COU and the risk associated with the CM&S-based decision.

System geometry (system configuration)

The technical objects to be simulated, such as TAVI and PAPS, and the simulation environment, such as vessel sections, are often complex in their geometry. Therefore, special attention should be paid to the exact description of the system components.

Often the anatomical characteristics are described by a generic model, which has a representative character. These assumptions and simplifications must be described and justified.

If your system consists of different sections or regions, e.g., tissue layers, which will be defined with different system properties, the derivation of the system structure has to be described. This also includes interfaces between system components. It is recommended to describe the differences between the real situation and the computational domain.

In addition, it is often advisable to model an inlet and outlet section for fluid mechanical analyses. The geometry of the inlet and outlet sections must be described and justified.

Another important aspect is the surface topology, in particular when considering friction or contact problems. Sufficient information must be provided.

Often only sections of the vessel are modelled or even further assumptions like symmetries are made. Describe the selection of the vessel section as well as assumptions to be made.

In addition to the geometric description, information should also be provided on the software and imaging methods and measurement procedures used and on the procedure for creating the computational domain. A suitable visual representation is recommended, e.g., by photos, illustrations (CAD data, etc.) and schematics.

Details for TAVI

For the TAVI use case, anatomical information of the aortic root, including the left ventricular outflow tract, the aortic annulus, the aortic bulbus and the proximal part of the ascending aorta is usually required. This information can be derived using either magnetic resonance imaging, echocardiography, or computed tomography. However, for visualization of the device landing zone, computed tomography data is preferred due to its superior contrast and resolution. From this data also other aspects such as the aortic valve's leaflet geometry, the position of the coronary ostia and localization of plaques can be discerned, which might be required depending on the CoU.

In addition to the patient-specific anatomical information, information of the device, including the stent design and the leaflet configuration are required.

Details for PAPS

For the PAPS use case, anatomical information of the pulmonary artery during systole and diastole are required. This information is derived from computed tomography data, ideally using a contrast agent. Depending on the sensor position within the vessel, the proximal parts as well as branching vessels of the left and right pulmonary artery must also be included.

Governing equations and system properties

The governing equations are the key element of a numerical simulation. Therefore, be specific about the governing equations and/or constitutive laws that you used to perform the simulation.

We recommend to name in this chapter also the physical properties used for constitutive laws (e.g., in fluid mechanics: viscosity, diffusion and reaction coefficients, permeability and porosity, temperature) as well as the used variables together with their units.

In addition to stating the system of equations or constitutive laws, the underlying assumptions must also be included.

The EMA guideline for reporting PBPK model and simulations[11] recommends presenting the data in a structured way (e.g., tabular form), possibly in annexe of the main report. For clear communication, the distinction could be made between the physiological system's properties, and the medical device model properties. In accordance with the EMA guideline for reporting PBPK model and simulations[11] you should describe and provide rationale for the assumptions and simplifications used to determine the system properties (model parameters). Furthermore, identify the sources of the physical properties and coefficients adopted (e.g., literature, in-vivo, ex-vivo, in-vitro testing, and manufacturer's data). If literature data are cited, discuss their applicability to the specific conditions. If testing is conducted to determine the parameters, then provide appropriate details regarding the test. If applicable, discuss any relevant aspects related to the tissue physiology used (e.g., young versus mature, healthy versus diseased).

Uncertainty in system properties: when different sources provide different values for a parameter, the choice should be justified in the report, the dependence of the model on such parameter described and the consequences discussed[11]. Both EMA and FDA guidelines on reporting CM&S recommend contextualizing the possible effect of a wrong assumption on the simulation results, for instance via sensitivity analysis or testing of alternative values [11,3]. In some cases, unknown parameters may be estimated (through data fitting), in that case, the method and data employed should be described. When this concerns more than one parameter and that identifiability issues are suspected, the EMA suggests considering additional data, including in vitro data, to increase the certainty [11].

Finally, the assumptions must be described in detail in the "Limitations" section. Here, examples for fluid mechanics will be provided, as those are most relevant for the project. Models targeting structural mechanics, pharmacokinetics, metabolism modelling or electrophysiology will have their own set of governing equations and assumptions.

Fluid mechanics example: the most prominent and most relevant governing equations for fluid mechanics are the Navier Stokes Equations, a set of partial differential equations describing the conservation of mass and momentum for Newtonian fluids.

Commonly, additional governing equations for the conservation of energy, for example if thermal processes are considered, are also required.

The detailed description of those equations varies strongly depending on the relevant assumptions. For example, the Navier-Stokes-Equations are only valid for Newtonian fluids. However, blood has a

distinct non-Newtonian, shear-thinning behaviour. In case of a non-Newtonian fluid, the conservation of momentum is described using the Cauchy momentum equation. Therefore, the description and rationale of the used viscosity model is important.

Other aspects that will affect the governing equations is whether turbulent effects are expected and will be modelled. If the flow is laminar or the whole turbulent spectrum is to be modelled the Navier-Stokes-Equations are valid. However, modelling all turbulent scales is associated with very high computational expenses and is often not possible for real applications as very small time and spatial scales must be modelled (see Discretization section). In those cases, turbulence models will be used. Here, the most common approach is using *Reynolds-Averaged Navier-Stokes-Equations* (RANS). Here, the Navier-Stokes-Equations are averaged over a small timeframe (ensemble average). This averaging introduces new terms to the RANS equations that are resolved using various assumptions and models (e.g., 2-equation turbulence models as k-epsilon and k-omega). Finally, whether the process that is to be simulated is transient or stationary will also affect the governing equations, as temporal derivatives can be neglected in stationary problems.

Various non-dimensional numbers provide insights regarding whether specific assumptions are valid. Examples for those numbers and their respective assumptions are:

- Reynolds number - this number is, among others, used to determine whether turbulence must be considered;
- Strouhal or Womersley number - these numbers provide insight, whether pulsatility of the flow must be considered or whether quasi-steady assumptions might be valid as well;
- Mach number - provides insight whether compressible effects must be considered;
- Peclet or Sherwood number (diffusion/convection);
- Dean number (curved flow).

If applicable, these non-dimensional numbers should be stated, and the decisions derived from them should be described.

Boundary and initial conditions (system conditions)

Boundary and initial conditions are essential for running an in-silico model. While some boundary conditions are directly resulting from the model specifications covered in the previous sections, others are vital for parametrization of in-silico models towards specific patients or investigations. For example, if elasticity of vascular walls is modelled, patient-specific properties of the tissue might be required. However, if vascular vessels are modelled as rigid, a no-slip boundary condition, meaning that the velocity at each stationary wall equals zero, will be applied independently of the patient. The boundary and initial conditions that were imposed on the system must be provided. These might include, but are not limited to, the boundary and loading conditions, initial conditions, and other constraints that control the system.

A. Details

All boundary conditions and initial conditions that are required to run the in-silico model are to be described. Ideally, this description should differentiate between constant boundary conditions which are invariant to the patient-specific parameterization of the model and those boundary conditions that will change depending on the specific patient or investigation that is to be evaluated. The following list is not exhaustive but provides an overview over commonly used boundary conditions.

- Hemodynamic modelling
    - Pressure boundary conditions: if pressures at the inlets and outlets of the computational domain are known or can be modelled using literature or assumptions, they can be specified as boundary conditions. Please state the type of boundary condition, e.g., Neumann, Dirichlet, etc.
    - Velocity boundary conditions: velocity boundary conditions or similar boundary conditions as for example the specification of a given mass flow are common. Here, inlet and outlet velocities can be specified. A common velocity boundary condition is the no-slip condition specifying that the relative velocity at a wall is zero. Please state the type of boundary condition, e.g., Neumann, Dirichlet, etc. If the velocity boundary condition is inhomogeneous, as used for Hagen-Poiseuille or Womersley flow, please describe the spatial velocity distribution.
    - Lumped parameter model boundary conditions: in particular for hemodynamic modelling, lumped parameter models are commonly used to model the physiological behaviour at inlets and outlets of the computational domain. While these are numerical models on their own, the specific parameters (e.g., resistance, compliance and impedance of a three-element Windkessel model) should be specified. Ideally, the method used to identify or quantify these parameters is documented as well.
    - Turbulence: depending on the turbulence model chosen, the appropriate boundary conditions as for example the initial turbulent kinetic energy or dissipation rate should be specified.
- Mechanical modelling
    - Mechanical properties of tissues and devices: depending on the constitutive models used for describing biological tissues and artificial material (e.g., bare metal stents) different parameters that are required to parametrize those models must be specified.
    - Prescribed motion: another common approach for modelling of deformations is prescribing a motion that was measured, for example using transient medical imaging, as boundary condition.

- Fixations: the fixations used in a mechanical model should be specified.

The above-mentioned boundary conditions are only to be seen as an example. Also, they can vary in their complexity with respect to transient or spatial description. For example, a constant velocity can be specified as inlet boundary condition. However, also a patient-specific velocity inlet profile or transient velocity information for the whole heart cycle can be used. Similarly, tissue properties might vary at different locations (e.g., stiff calcifications). This information should be described as well, and for complex information (e.g., tables containing spatiotemporally resolved boundary conditions) the location of the appropriate files should be documented.

In general, most transient boundary conditions in cardiovascular modelling are of periodic nature. Here, the information for one heart cycle is usually sufficient. However, information on the number of heart cycles calculated to damp out initial transient effects (e.g., if the fluid's initial condition was stationary) should be specified.

B. Assumptions, simplifications and rationale

Describe and provide rationale for the assumptions and simplifications used to determine the conditions applied on the system. Provide appropriate documentation of the system conditions (e.g., literature, test reports, clinical data, medical imaging data).

In particular, you should describe any differences or simplifications between the simulation environment and the actual environment, such as:

- A description of how the natural development and physical character of the flow was unaffected by the boundaries of the simulation;
- Operating conditions of the simulation, especially if the simulation did not cover the expected range of use of the device;
- Other simplifications (e.g., use of symmetry, use of rotating frame of reference instead of unsteady simulation for centrifugal pump).

System discretization

Provide information regarding the discretization and refinement techniques utilized during the numerical solution as outlined below.

A. Details

Details of the discretization used for the respective models should always be described sufficiently to allow replication of the in-silico study. In the following section we assume mesh-based methods to be used. However, most aspects will also be relevant for the specification of meshless methods, as for example Smooth Particle Hydrodynamics. The following aspects regarding spatial and temporal discretization are of special interest:

- Which pre-processing steps were performed to generate the final geometries that are used in the in-silico study. For example, if the geometries were smoothed the software as well as the appropriate settings used for this procedure should be documented.
- Which software (name, manufacturer, version) was used for mesh generation?
- Which type of mesh was used with respect to Lagrangian or Eulerian approaches? Is the resulting mesh structured or unstructured?
- Which element types, as for example tetrahedral, hexahedral or polyhedral cells (e.g., *Figure 2*), were used for mesh generation in general?
- If an FEA analysis is performed, which element order was chosen for the meshes (e.g., linear, quadratic or polynomial)?
- Which quality metrics were evaluated throughout the mesh generation procedure and which thresholds were set for the respective quality metrics as for example the aspect ratio? Which general metrics as for example the target element size or edge length were set during mesh generation?
- In addition to the general parameter used for mesh generation, also specifics, such as local mesh refinement in areas of interest (areas of high shear stress, recirculation zones, critical concentrations, interactions between the device and the body), should be specified (*Figure 2*).

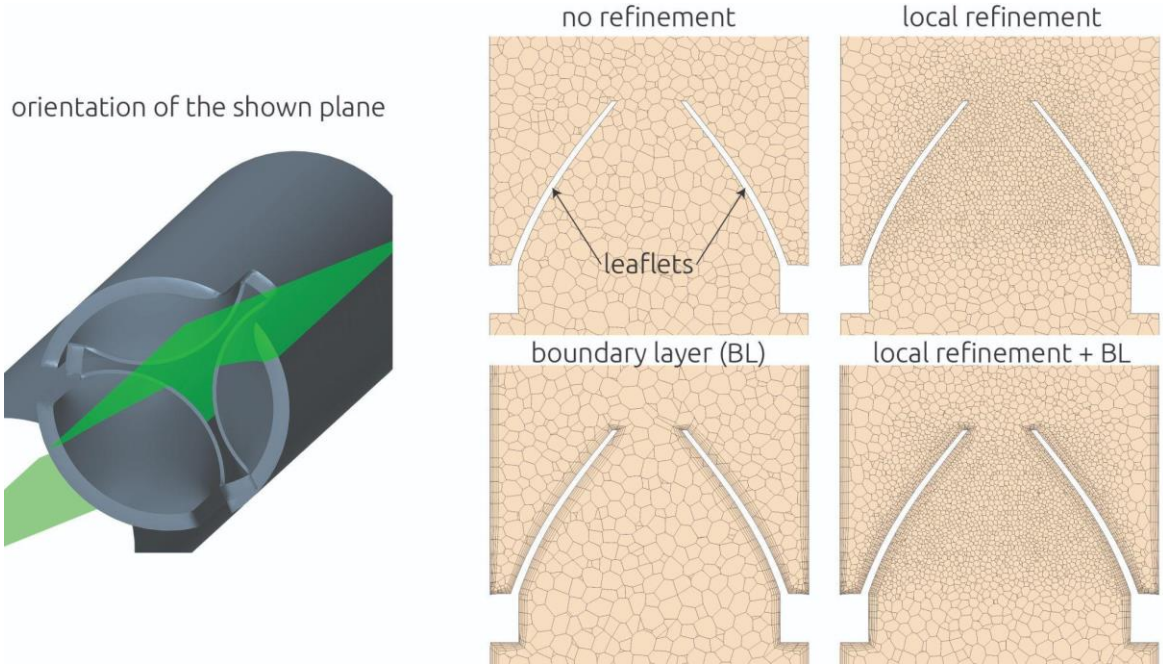

Figure 2: Visualization of different mesh refinement strategies for a finite volume mesh of a biological valve prosthesis within a tube. The geometry to be meshed is shown in the left panel together with a plane (green) in which the mesh is visualized. The right panel shows four different polyhedral meshes using local refinement at the leaflets, boundary layers at all surfaces, a combination of both approaches as well as a baseline mesh without refinement.

If the mesh refinement was based on hemodynamic parameters this procedure should also be described, as for example if local mesh refinement required for large eddy simulations is based on local flow properties calculated in RANS simulations:

- Any special elements/cells used if a turbulence model (or any other numerical method requiring special elements/cells) was used.
- In case of complex models combining different regions and or tissues, the mesh in all regions of the computational domain should be described as well as the interface between them. For example, if an FSI analysis is performed, not only should the mesh of the structural part (e.g., the vessel wall or an implanted device) and the mesh of the fluid domain (e.g., the vessel lumen) be described, but also the method that was used to link the interface between both domains.
- Also, if specific techniques are used for interaction between device and body meshes, as for example immersed boundary methods or overset mesh, their specific parameters of interest should be described.
- Not only the spatial but also the temporal discretization scheme should be described properly, including time step width and whether explicit or implicit temporal discretization schemes are used (*Figure 3*). If adaptive methods are used for time step width estimation, these methods are to be described as well as their target metrics (e.g., the target Courant-Friedrichs-Lewy number).

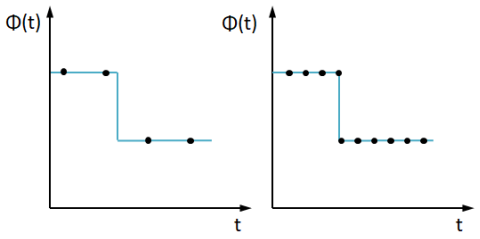

Figure 3: Example of timestep for temporal discretization.

B. Assumptions, simplifications, and rationale

The spatiotemporal discretization described above must be justified by means of mesh independency analyses. The aim of a mesh independency analysis is to assess the discretization error in a systematic manner. This is usually achieved by stepwise reduction of the grid size and simultaneous evaluation of the metrics of interest. In theory, only the parameters that are to be evaluated using the model must be investigated during a mesh independency analysis. For example, an in-silico model for calculation of the pressure drop across aortic stenosis must not necessarily be performed on a mesh that also provides mesh-independent solutions for other independent parameters. However, the mesh size effect on other parameters should still be investigated and documented if possible.

Also, it might not be possible to identify a mesh size for which the solution is completely mesh independent. Furthermore, the required accuracy should be weighed against the computational costs associated with a respective mesh size. However, in those cases, the bias introduced by the spatial discretization must be quantified and documented.

The rationale and following details regarding the mesh refinement study that supports the spatiotemporal discretization should be provided:

- The methods of the mesh refinement study;
- Mesh characteristic, such as y+-values and other quantifications for partial mesh refinement;
- The hemodynamic / structural mechanic metrics (e.g., shear rates, concentration gradients, stresses) chosen to establish the mesh density.

Numerical implementation

Numerical implementation is used to transfer the mathematical model to a computational model. Numerical methods are used to solve the governing equations.

This chapter is closely related to the section “Verification” of the chapter “Verification and Validation (V&V) and uncertainty characterization”. In the context of verification, it is recommended to provide justifications about the assumptions and simplifications of the selected solution methodology and associated parameters.

The following aspects can help to describe and rationalize the numerical implementation in detail[3]:

- Type of software (e.g., commercial, open-source, user-developed);
- Numerical method used (e.g., finite element, finite volume, finite difference);
- Temporal discretization, if any (e.g., explicit, implicit, semi-implicit);
- Spatial discretization (i.e., interpolation of field variables between grid points);
- Method for interpolating from face to nodes or vice versa (e.g., upwind, power law).

Verification and validation (V&V) and uncertainty characterization

The topic of *verification and validation* (V&V) is essential for the model building process and very complex. Therefore, V&V should be addressed in a separate V&V report, to which reference must be made.

Basic features of a V&V analysis should nevertheless be called out in every report. Model credibility, which can be reached through V&V process, is the topic of the ASME V&V 40 Subcommittee[4]. In addition to the ASME V&V 40 document, we refer to the NASA-STD-7009 standard[1].

General advice: if you modify your model significantly (because you build up a complicated model in steps, have to correct errors or add more complex material behaviour to get agreement with experimental results etc.), you should again check the model.

The rigor of the V&V activities is based on the credibility level and therefore on the risk associated with decision consequences due to model prediction failure. The credibility level and the derived V&V activities should be stated.

It is important to define and justify the acceptance criteria. These can be, for example, hemodynamic metrics such as shear rate, TAWSS, or OSI. These acceptance criteria should be considered in the subsequent V&V process.

Verification helps to see if the mathematical model is implemented correctly, and the equations are solved correctly. The purpose is to prove that the model has been correctly specified and actually does what it was created to do (loads, boundary conditions, material behaviour, etc., are correct). Numerically obtained results are often compared with analytical benchmark solutions (starting with Hagen-Poiseuille and Womersley flow in straight cylindrical tubes). This could be done by monitoring physically relevant quantities at a probe point or surface location. Additionally, a monitoring of the residual reduction of physical quantities, such as velocity and pressure, as well as continuity residuals to prove the compliance of basic conservation laws should be provided.

According to ASME V&V 40 the verification process can be divided into:

1. Code verification

Describe the process of how errors in the source code and numerical algorithm were detected and removed. This can be done by *Software Quality Assurance* (SQA), which asks: Is the software implemented correctly and are the results reproducible? and by *Numerical Code Verification* (NCV), which concentrates on numerical schemes (first order, second order, higher order, under relaxation, etc.) and their effect on the simulation result. You may reference available documentation and verification results from the software developer.

2. Calculation verification

Describe the process of error evaluation due to spatial and time discretization. Please give details and rationale about grid and time step convergence study as well as selection for solver parameters. Provide rationale to support the selection of the numerical settings, either default or modified. What convergence criteria were used (e.g., 1E-6 vs 1E-7)).

Validation means to check the model by making an independent prediction (i.e., a prediction that was not used in specifying or calibrating the model) and checking this prediction in some other way (for example, experimentally):

- assessing the degree to which the computational model is an appropriate representation of the reality of interest,
- comparing prediction from computational model with results from comparator (*in vitro* experiment or *in vivo* study).

We recommend that you provide information regarding the method(s) employed to validate the computational model[3]. We recommend the following format for presenting that information.

According to ASME V&V 40 the validation can be subdivided into three aspects: computational model (1), comparator (2) and assessment of the accuracy (3).

Computational model (1)

In general, the computational model used for the numerical study can be differentiated from the computational model used for the V&V process. If differences occur, they must be made clear. In this case, it should also be evaluated how the differences affect the prediction of the computational result in the COU.

Comparator (2)

Important aspects of the comparator are the methodology, test samples, and test conditions.

Describe the methodology of the comparison system, such as the experimental study (e.g., tensile test, particle image velocimetry) or clinical study used for model validation. Discuss their potential limitations with respect to COU. Describe the region in which the validation(s) were performed. You should describe any simplifications for experimental comparators (e.g., use of surrogates when biological information is missing - in this case, demonstrate clinical relevance and validity of the surrogate based on clinical data or the literature). If a biological process was modelled (e.g., haemolysis, platelet injury, binding of the drug in vascular tissue), you should describe how the biological calculations were verified and validated.

The validation experiment can be abstract compared to the case which shall be analysed by the computational model. For example, FDA nozzle benchmark as technical representation of stenosed vessels. Thus, the quantity, range of characteristics as well as measurement including uncertainties of characteristics of the test samples should be provided. Additionally, the validation test geometry should be described.

You should describe the conditions for the validation tests (number and range of test conditions, worst case scenarios). Do the test conditions match the conditions in the COU? Provide details on the main characteristics of the test conditions (e.g., waveform, duration of diastole and systole, etc.) and the uncertainties if an experimental comparison is performed. Instrumentation and calibration should also be described in this context.

Rationale the differences between the operating and boundary conditions of the comparative experiments and simulations, as well as the geometric and dynamic scaling assumptions. Describe any sensitivity analyses performed to determine how the solution changes as a function of unknown parameters (e.g., parameters in turbulence models, boundary conditions, fluid properties).

Assessment (3)

The assessment of the accuracy level is based on the model risk matrix and the derived credibility level, which is necessary to obtain trustworthy predictions in the COU.

Initially, state the acceptance criteria and the degree of precision of the model with respect to the comparator. Describe whether the comparison was quantitative (preferred) or qualitative and what physical quantities were used to evaluate credibility (e.g., velocity, wall shear stress calculations, hydrodynamic pressure drop, crushing forces, deformations).

You should make qualitative comparisons between the QOI of the computational model and the experimental results. For example, images that directly compare model and experimental results (e.g., velocity or shear stress) can provide an overall qualitative assessment of how well the model can capture the relevant behaviour.

For critical areas relevant to the objectives of the study, you should make quantitative comparisons[4,12].

You should discuss the degree of agreement between computational and experimental results.

You should discuss the relevance of your validation experiment to the expected clinical loading conditions, the impact of the model and experimental assumptions on the results, the limits of agreement between the validation model and the experiment, and the extent of predictability for your device or device-tissue model.

If predictions are made about behaviour in domains that are not experimentally accessible, you should provide a measure of confidence, as well as the associated risk and how it affected your decision.

Reporting uncertainty characterization

There are multiple sources or uncertainties in the CM&S process. For instance, they may arise from the conception of the model (e.g., specification of system, abstractions etc..), the modelling and discretization activities, numerical solving, etc. Oberkampf et al.[12] provides an overview of possible sources and types of uncertainties (aleatory and epistemic) in CM&S. Therefore, it is important to characterize that uncertainty and mitigate the risk but also to correctly report the activities and results of the uncertainty characterization

The NASA handbook for models and simulations[2] recommends considering two aspects when documenting uncertainties:

- Explanation of how uncertainties are identified and characterized (rationale and method);
- Description and quantification of the specific uncertainties (what are the sources of uncertainties, impact on the results and decision, etc.).

[12] Oberkampf, W.L., Trucano, T.G., and Hirsch, C., 2004 “Verification, validation, and predictive capability in computational engineering and physics,” Applied Mechanics Reviews, 57, pp. 345–384

Results

General requirements for reporting results are: “reporting accurately, clearly, unambiguously and objectively, and in accordance with any specific instructions [...] or [...] methods.”[13]

The ISO/IEC 17025:2005 stated further that the result “shall include all the information requested by the customer and necessary for the interpretation of the test or calibration results and all information required by the method used.”[13]

The NASA Technical Standard NASA-STD-7009A points out that because of the inexact nature of all modelling activities, the results of a simulation study should provide all needed information for the decision maker to make their own conclusion. Therefore, the result section should also give comments or statements on the uncertainty, credibility and trustworthiness in the results.

We recommend that the results should be arranged in accordance with the variables of interest (hemodynamic / structural mechanic metrics) defined before. The FDA suggests more than one format (e.g., table, graph, plot) for presentation of the results.[3]

[13] General requirements for the competence of testing and calibration laboratories (ISO/IEC 17025:2005)

Limitations

We recommend that you provide details regarding how the assumptions/simplifications described in the previous sections might affect the output of the computational model and simulation, the interpretation of the results, and the relevance to the purpose of the study and COU.

Because assumptions and simplifications are made in the generation of the model device, in the performance of the simulation, and in the interpretation of the analysis, it is important to describe the limitations of the use of the computational model and the interpretation of the results. Therefore, we recommend that you discuss how the assumptions/simplifications might affect the output of the model and simulation and the interpretation of its relevance to device performance and safety.

For example, it is important to know whether the simulation of blood flow through a small gap in a blood pump was based on the nominal dimensions or whether it includes the limits of the manufactured component tolerances. If you believe that your results are significantly dependent on the assumptions and/or simplifications in your model, you should consider performing sensitivity analyses on the computational model parameters associated with the assumptions and simplifications.

Discussion / conclusion

The discussion should evaluate the numerical study with respect to the COU. In addition, the results should be compared and discussed with former numerical and experimental results. Therefore, published studies or own prior results should be included.

Discuss the simulation results, the variables of interest, and their impact on the safety and effectiveness of the product.

If opinions and interpretations are included, they must be clearly marked[13]. Furthermore, according to ISO/IEC 17025:2005 the report shall document the basis upon which the opinions and interpretations have been made. To distinguish between reporting of results and opinions or interpretations, as is often stated in the discussion section, the ISO/IEC 17025:2005 provides a definition.

“Opinions and interpretations included in a test report may comprise, but not be limited to, the following:

- An opinion on the statement of compliance/noncompliance of the results with requirements;
- Fulfilment of contractual requirements;
- Recommendations on how to use the results;
- Guidance to be used for improvements.”

The final conclusion - do the results convey the acceptable performance of the device, product, etc. - must evaluate the credibility of the statements that you have identified. This should be done in accordance with the limitation sections. In addition, the risks associated with accepting the results of the modelling study need to be stated.

Terms and definitions

For the purposes of this document, the following terms and definitions apply. The definitions are quoted from relevant sources being ASME V&V40[4], V&V10[6], FDA[3], ISO 5840-1:2021[15] and NASA[14]

Accreditation: The official certification that a model is acceptable for use for a specific purpose (DOD/DMSO, 1994)[14].

Accuracy: The difference between a parameter, variable or derived quantity (or a set of parameters or variables) within a model, simulation, or experiment and the true value or the assumed true value[3].

Adequacy: The decision that the model fidelity is sufficient for the intended use[3].

Analysis: Any post-processing or interpretation of the individual values, arrays, files of data, or suites of executions resulting from a simulation[4].

Calculation Verification: The process of determining the solution accuracy of a particular calculation[3].

Calibration: The process of adjusting numerical or physical modeling parameters in the computational model for the purpose of improving agreement with experimental data[3].

Calibration Experiment: The experiment performed for the purpose of fitting (calibrating) model parameters[3].

Certification: The written guarantee that a system or component complies with its specified requirements and is acceptable for operational use (IEEE, 1990)[3].

Code: The computer implementation of algorithms developed to facilitate the formulation and approximate solution of a class of models[3].

Code Verification: The process of determining that the numerical algorithms are correctly implemented in the computer code and identifying errors in the software[4].

Comparator: The experimental methodology that is used to perform the validation. The comparator data can be taken from a laboratory bench-test, an animal study, an imaging study, or a clinical study. The selection of the comparator should be based on the context of use[4].

Computational Domain: The spatial and/or temporal domain for which the analysis was conducted. See also System Discretization[4].

Computational Model: The numerical implementation of the mathematical model performed by means of a computer[4].

Computer Model: The numerical implementation of the mathematical model, usually in the form of numerical discretization, solution algorithms, and convergence criteria[3].

Conceptual Model: The collection of assumptions, algorithms, relationships, and data that describe the reality of interest from which the mathematical model and validation experiment can be constructed[3].

Confidence: The probability that a numerical estimate will lie within a specified range[3].

Constitutive Law: An expression which describes the relationship between biological, chemical or physical quantities for a specific material or substance and an external stimuli (e.g., Hooke's Law)[4].

[14] Thacker, B.H.; Doebling, S.W.; Hemez, F.M.; Anderson, M.C.; Pepin, J.E.; Rodriguez, E.A. Concepts of Model Verification and Validation. Los Alamos National Laboratory 2004

Context of Use: The purpose or intent of the computational model and/or simulation study, specifically the role of the CM&S study in the regulatory submission[4]. Or a statement that defines the specific role and scope of the computational model used to address the question of interest[4]

Convergence Analysis: The process of ensuring the solution resolves the physics of interest and the variation of the solution remains within a pre-specified range as the discretization is refined[4].

Decision Consequences: The significance of an adverse outcome resulting from an incorrect decision.

Effective Orifice Area, EOA: The Orifice area that has been derived from flow and pressure or velocity data[15].

Error: A recognizable deficiency in any phase or activity of modeling and simulation that is not due to lack of knowledge[3].

Experiment: The observation and measurement of a physical system to improve fundamental understanding of physical behavior, improve mathematical models, estimate values of model parameters, and assess component or system performance[3].

Experimental Outcomes: The measured observations that reflect both random variability and systematic error[3].

Experiment Revision: The process of changing experimental test design, procedures, or measurements to improve agreement with simulation outcomes[3].

Fidelity: The difference between simulation and experimental outcomes[3].

Field Experiment: The observation of system performance under fielded service conditions[3].

Governing Equation: The mathematical relationship that describes the phenomena of interest[4].

Inference: The drawing conclusions about a population based on knowledge of a sample[3].

Laboratory Experiment: The observation of physical system performance under controlled conditions[3].

Leakage Volume: The portion of the regurgitant volume which is associated with leakage during the closed phase of a valve in a single cycle and is the sum of the transvalvular leakage volume and paravalvular leakage volume[15].

Mathematical Model: The mathematical equations, boundary values, initial conditions, and modeling data needed to describe the conceptual model[3].

Model: A description or representation of a system, entity, phenomena, or process (adapted from Banks, J., ed. (1998). Handbook of Simulation. New York: John Wiley & Sons). Any data that go into a model are considered part of the model. Models may be mathematical, physical, or logical representations of a system, entity, phenomenon, or process. Models can be used by simulation to predict a future state, if so desired[4].

Model Revision: The process of changing the basic assumptions, structure, parameter estimates, boundary values, or initial conditions of a model to improve agreement with experimental outcomes.

Conceptual/mathematical/numerical description of a specific physical scenario, including geometrical, material, initial, and boundary data [3].

Nondeterministic Method: An analysis method that quantifies the effect of uncertainties on the simulation outcomes[3].

[15] ISO, ISO 5840-1:2021(en), Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements (2021)

Performance Model: A computational representation of a model's performance (or failure), based usually on one or more model responses[3].

Prediction: The use of a model to foretell the state of a physical system under conditions for which the model has not been validated[3].

Pretest Calculations: The use of simulation outcomes to help design the validation experiment[3].

Quantity of Interest: The desired output from the computational model. For a particular context of use, there can be multiple quantities of interest. Or the specific question, decision, or concern that is being addressed [4],[3].

Reality of Interest: The particular aspect of the world (unit problem, component problem, subsystem or complete system) to be measured and simulated[3].

Reducible Uncertainty: The potential deficiency that is due to lack of knowledge, e.g., incomplete information, poor understanding of physical process, imprecisely defined or nonspecific description of failure modes, etc[3].

Risk: The probability of failure combined with the consequence of failure[3].

Risk Tolerance: The consequence of failure that one is willing to accept[3].

Sensitivity: The degree to which the output is affected by a particular input[4].

Simulation: The ensemble of models—deterministic, load, boundary, material, performance, and uncertainty—that are exercised to produce a simulation outcome[3].

Simulation Outcome: The output generated by the computer model that reflects both the deterministic and nondeterministic response of the model[3].

System Discretization: The division of the computational domain of the system into discrete parts for numerical implementation.

Uncertainty: A potential deficiency in any phase or activity of the modeling or experimentation process that is due to inherent variability (irreducible uncertainty) or lack of knowledge (reducible uncertainty) [3].

Uncertainty Quantification: The process of characterizing all uncertainties in the model and experiment, and quantifying their effect on the simulation and experimental outcomes[3].

Validation: The process of determining the degree to which a model or a simulation is an accurate representation of the real world from the perspective of the intended uses of the model or the simulation[3].

Validation Experiment: The experiments that are performed to generate high-quality data for the purpose of validating a model[3].

Validation Metric: A measure that defines the level of accuracy and precision of a simulation[3].

Verification: The process of determining that a computational model accurately represents the underlying mathematical model and its solution from the perspective of the intended uses of modelling and simulation[1],[6],[3].