SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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SOPs for validation of in silico models

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Executive summary

This SOP guides on how to apply the ASME V&V 40 standard for in-silico model validation, with examples of the clinical endpoints device perforation, device migration, thrombosis for the pulmonary artery pressure sensor as well as thrombosis, paravalvular leakage and durability for the transcatheter aortic valve. Emphasis is placed on the application of a tiered validation approach of the in-silico models, consisting of a low-fidelity validation to gain trust in the engineering metrics output in bench tests, ex-vivo experiments and acute animal trials, as well as high-fidelity validation steps in chronic animal trials and (retrospective) clinical trials supported by tests in virtual cohorts. The results are subjected to an applicability analysis. The validation and applicability assessment steps are derived from the applicable standards, extended where necessary, and applied to the specific use cases. Detailed examples for both use cases can be found in the two appendices.

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Acronyms

Acronym	Full name
ASME	American Society of Mechanical Engineers
BIO	BIOTRONIK
APT	Axial pull test
CFD	Computational fluid mechanics
CHA	Charité - Universitätsmedizin Berlin
CM&S	Computational modelling and simulation
CU	Context of Use
CT	Computed tomography
EV	Ex-vivo
FDA	Food and Drug Administration
FEA	Finite element analysis
FSI	Fluid structure interaction
HALT	Hypo attenuated leaflet thickening
HF	Heart failure
IIB	Institute for Implantable Technologies and Biomaterials
ISCT	In-silico clinical trials
ISO	International Organization for Standardization
IV	In-vivo
IVT	In-vitro
LYN	Lynkeus
MIGR	Migration
MRI	Magnetic resonance imaging
OSI	Oscillatory shear index
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PAPS	Pulmonary artery pressure sensor
PERF	Perforation
PIV	Particle image velocimetry
PVL	Paravalvular leakage
QoI	Questions of Interest
RFT	Radial force test
SA	Sensitivity analysis
SM	Solid mechanics
SOP	Standard operating procedure
TAVI	Transcatheter aortic valve implantation
THRO	Thrombosis
V&V	Validation and verification
VDT	Vessel deformation test
WSS	Wall shear stress

Cover page of the SOP D4.6

SIMCor responsible partner	BIOTRONIK (BIO)				
Short Title, ID	SOP-SIMCor-4.6	Page	1	of	48
Title	SOPs for validation of in-silico models				
Version	1.0	Created on	27/12/2023		
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Purpose and field of application:

Guidance of how to apply the ASME V&V 40 standard for in-silico model validation, with the examples of the clinical endpoints device perforation, device migration, thrombosis for the pulmonary artery pressure sensor as well as thrombosis, paravalvular leakage and durability for the transcatheter aortic valve. Emphasis is placed on the application of a tiered validation approach of the in-silico models consisting in a low-fidelity validation to gain trust in the engineering metrics output in bench tests, ex-vivo experiments and acute animal trials, as well as high-fidelity validation steps in chronic animal trials and (retrospective) clinical trials supported by tests in virtual cohorts.

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Introduction

Validation activities are an essential step for assessing the credibility of computational models. The methodology for development, *verification, and validation* (V&V), as well as documentation of computational models in SIMCor follows established standards and guidelines where applicable. The developed framework for modelling and simulation of two cardiovascular devices - *pulmonary artery pressure sensors* (PAPS) and *transcatheter aortic valve implants* (TAVI) - shall serve as an example for further exploitation by the in-silico modelling community. For this purpose, a set of SOPs has been developed describing the process of model development (*D4.4 - Guidelines for documentation (IIB, M12)*[1]), model verification and benchtop validation (*D4.5 - SOP for in-silico analysis of TAVI (IIB, M24)*[2]) as well as this SOP on comprehensive model validation.

The SOP on hand is to be understood as an illustrative example on the application of parts of the risk-informed credibility assessment framework provided in the *American Society of Mechanical Engineers* (ASME) V&V 40 "Assessing credibility of computational modelling through verification and validation: application to medical devices"[3]. The SOP contextualises the validation work performed for both use cases within the V&V 40 standard and provides best practices on planning, conduction, assessment, and documentation of validation activities. A special focus will be the so-called high-fidelity validation of the numerical models with respect to clinical endpoints. The steps described in the SOP are meant to be generic; specific examples concerning SIMCor will be highlighted in the main text of the document.

Whenever a specific standard is referenced, we list corresponding text from the official document, if deemed relevant. For distinction, such texts are highlighted in a blue-coloured boxes, as follows (example reference to ASME V&V 40 text on "*Question of Interest* (QoI)").

QoI (ASME VV 40 - 2018)
"...The **question of interest** describes the specific question, ..."

Likewise, to highlight the use case specific text relating to the standard, the following colour-coded box is used for use cases, i.e., for "PAPS" or "TAVI" use cases.

QoIs (PAPS) – migration, perforation
QoI 1: migration, perforation …Can the fixation of the PAPS anchor the device...?

[1] Stiehm, M., Brüning, J., Lesage, R., Czypionka, T., Oldenburg, J., Huberts, W., Rolf-Pissarczyk, M., Luther; Torsten, Staumont, B., & Geris, L. (2021). SIMCor. Deliverable 4.4: Guidelines for documentation (IIB, M12). Zenodo. https://doi.org/10.5281/zenodo.6150905

[2] To be made publicly available in Zenodo by June 20204.

[3] V&V 40, A. S. M. E. (2018). Assessing credibility of computational modeling through verification and validation: application to medical devices. *The American Society of Mechanical Engineers*.

Published standards and guidelines on in-silico model validation

In general, mechanical in-silico modelling for medical devices encompasses computational *structural (or solid) mechanics* (SM), *computational fluid dynamics* (CFD) and thermodynamics (heat transfer). While domain-specific standards are available for computational SM (ASME V&V 10[4]) and for CFD and heat transfer (ASME V&V 20[5]), their application to medical devices is standardised in the ASME V&V 40. V&V 40 builds upon several preceding modelling standards, V&V 10 and V&V 20 being among them. As an extension of the framework provided in the V&V 40, the *U.S. Food and Drug Administration* (FDA) has issued the guidance for "Assessing the credibility of computational modelling and simulation in medical submissions"[6] for situations where classical V&V work is not feasible to provide evidence on model credibility. Subsequently the concepts of both standards are briefly outlined.

ASME V&V 40

The framework laid out in this standard "centres on establishing that model credibility is commensurate with the risk associated with the decisions influenced by the computational model". "This Standard provides a risk-informed credibility assessment framework to empower the medical device industry to determine and justify the appropriate level of credibility for using a computational model to inform a decision" (Figure 1).

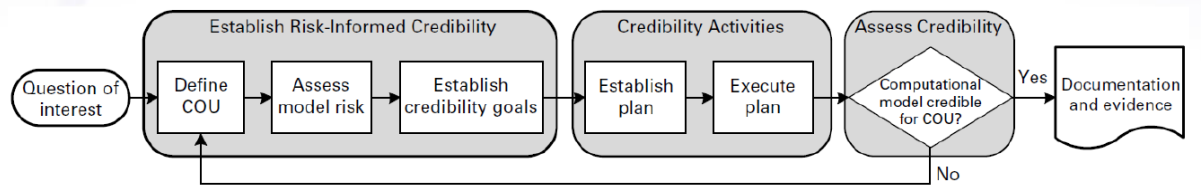


Figure 1: Process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

"The risk-informed credibility assessment framework begins with identifying a question of interest, which describes the specific question, decision, or concern that is being addressed. The next step is to define the *context of use* (COU), which is a statement that describes the role and scope of the computational model used to inform that decision in relation to other evidence. Then, model risk is assessed for the COU, which considers the role of the computational model to inform the decision and the potential consequence of an incorrect decision. Model risk is then used to establish the goals for each credibility factor. The credibility factors are elements of the process used to establish the credibility of the computational model for a COU; the factors include verification, validation, and applicability. The goals for the credibility factors are used to plan the activities that establish credibility. Once the activities are defined, the plan is executed. After the credibility activities are completed, an assessment is performed to determine if the computational model is credible for the COU. If sufficient credibility is not achieved, then the risk-informed credibility portion of the framework can be revisited, as indicated by the return arrow in Figure 1. [...] If sufficient credibility is achieved for the COU, then the computational model can be used to inform the decision. Finally, the credibility activities and findings should be summarised."

[4] V&V10, A. S. M. E. (2006). *Guide for Verification and Validation in Computational Solid Mechanics. The American Society of Mechanical Engineers.*

[5] V&V20, A. S. M. E. (2009). Standard for Verification and Validation in Computational Fluid Dynamics and Heat Transfer. *The American Society of Mechanical Engineers*.

[6] Guidance for Industry and Food and Drug Administration Staff; Docket Number: FDA-2021-D-0980; Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

Model validation is a key activity within the frame of credibility assessment. Validation provides the evidence that the computational model and the simulation results properly reflect the reality of interest. For model validation, V&V 40 requires the comparison of the model predictions with results from a comparator which can be a combination of bench tests, preclinical tests, and clinical studies.

FDA Guidance "Assessing the credibility of computational modelling and simulation in medical device submissions"

This guidance document complements the ASME V&V 40 by considering additional sources of evidence to support model credibility, such as results from clinical studies, robust model calibration results, or population-level validation results. Thus, it provides a more generalised framework for assessing *computational modelling and simulation* (CM&S) credibility in medical device regulatory submissions. The draft guidance provides a generalised framework for model credibility assessment consisting of multiple steps. These steps are categorised in different phases, such as initial steps, credibility assessment planning, adequacy assessment, FDA interaction, and study execution (for more details see Figure 1, page 14 of the FDA guidance document).

Overall, these steps resemble the framework provided in the ASME V&V 40 but allow for more flexibility in providing the credibility evidence. However, key aspects of the framework, such as the initial definition of QoI, COU, and model risk assessment are similar. Furthermore, the document refers to more categories of credibility evidence than the V&V 40. Overall, the document refers to 8 categories of credibility evidence, of which only three are explicitly within the scope of the ASME V&V 40. These 3 categories are code results from code verification, bench test validation, as well as in-vivo validation. Other categories include results from population-based validation studies, model plausibility and model calibration.

SIMCor strategy on in-silico model validation for implantable cardiovascular devices

In general, SIMCor closely adheres to the ASME and FDA guidance documents described in the previous section and uses the credibility assessment framework provided in the ASME V&V 40 as foundation for its validation activities. However, a tailored approach for the step of establishing credibility goals that accounts for the specific requirements of the two example use cases is presented (Figure 2). To facilitate a concise and clear description of this approach, its individual steps have been labelled. Furthermore, aspects that closely adhere to official guidance documents will be kept succinct, while emphasis is put on the SIMCor-specific approach.

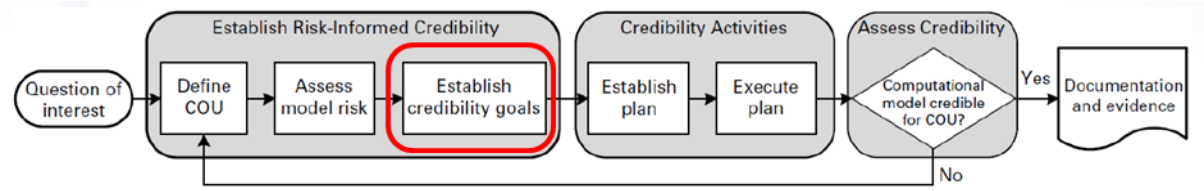


Figure 2: Validation activities are part of the risk-informed credibility assessment framework provided by ASME V&V 40.

The first three steps of the approach (see Figure 3) are the same preliminary steps as in the V&V 40 and relate to defining the *Question of Interest* (QoI) and COU for the models to be evaluated, as well as assessing the model risk. The fourth step, focusing on establishing credibility goals, is where the SIMCor-based approach adds to the V&V 40 framework. This step consists of three different activities of verification, validation, and applicability analysis, which are labelled steps 4A to 4C, accordingly. The step 4A on verification activities is not altered either and therefore not within the scope of this SOP. Instead, we will focus on the activities for model validation (red box in Figure 3 - Step 4B), followed by the applicability analysis (Step 4C).

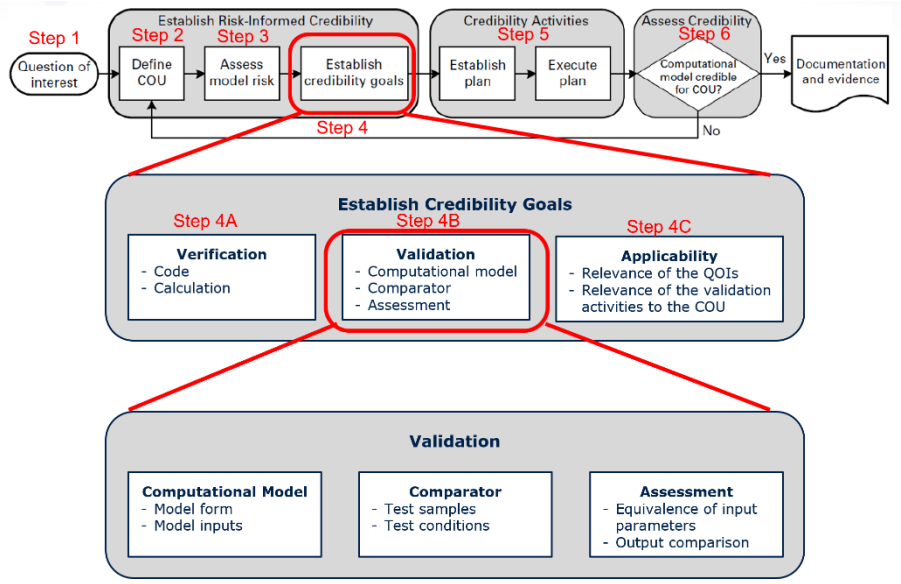


Figure 3: Activities comprising the validation step of the ASME V&V 40 framework.

In general, model validation is to be performed by comparing model predictions with results from tests with the comparator which can be in-vitro, ex-vivo or in-vivo tests. But, prior to designing validation experiments with comparators, the credibility of the computational model with regard to model form and inputs must be established. These activities include assessing the sensitivities and

uncertainties of the computational model and are covered in previous deliverables *D4.5 - SOPs for in-silico analysis of TAVI (IIB, M24)*[7], *D8.2 - PAPS model (BIO, M12)*[8], *D8.1 - TAVI model (IIB, M12)*[9] and *D9.2 – device specific models (IIB, M24)*[10]. They will not be covered in detail in this SOP and can instead be found in the respective deliverables.

Therefore, the focus of the current SOP will be on Step 4B, which pertains to the definition, planning execution and assessment of validation activities for the comparison of the model predictions with comparator studies of different levels. These levels are:

1. Low-fidelity validation with respect to engineering metrics;
2. High-fidelity validation with respect to clinical endpoints.

This differentiation is necessary as the in-silico models to be validated in SIMCor aim at facilitating development, testing, and regulatory approval of medical devices. These aspects result in different requirements for the model outputs and predictions. For some aspects, this requires the prediction of engineering metrics such as mechanical stresses and strains in the tissue and the device, and blood flow velocities. Comparators for validation of these engineering metrics can often be measured well in in-vitro and ex-vivo testing conditions. Measuring them in-vivo is often only possible in acute settings, if at all. Especially for internal devices, such as implantable cardiovascular devices PAPS and TAVI, in-vivo measurement of engineering metrics is encumbered. For assessing aspects such as device safety and efficacy, clinical endpoints that are usually used in clinical trials, such as thrombosis or device migration, must be estimated in-silico models as well. A comparator of these clinical endpoints for model validation often cannot be measured in in-vitro and ex-vivo settings, or only in settings strongly varying from the real clinical application. Therefore, chronic animal experiments or even human studies are required to obtain sufficient comparator information.

Therefore, comparators for both engineering metrics and clinical endpoints can usually not be acquired within the same validation experiment, which results in a gap within the credibility assessment framework. For this reason, SIMCor proposes a tiered validation strategy including dedicated validation steps for engineering metrics as well as clinical endpoints.

[7] This deliverable will become publicly available in Zenodo by June 2024.
[8] This deliverable is confidential, thus not publicly available, but can be requested to Jan Romberg (Jan.Romberg@biotronik.com).
[9] This deliverable is confidential, thus not publicly available, but can be requested to Michael Stiehm (michael.stiehm@uni-rostock.de).
[10] This deliverable is confidential, thus not publicly available, but can be requested to Michael Stiehm (michael.stiehm@uni-rostock.de).

SOP on validation of in-silico models for implantable cardiovascular devices

In the following sections, the methodology of planning, executing, and evaluating model validation activities is outlined, using the PAPS use case as an example. After a brief introduction of the clinical need and the description of the device, the step-by-step procedure for model credibility assessment will be reported to an extent that is required to plan validation activities. Special emphasis is then placed on the validation activities.

Exemplary use case - PAPS

PAPS are used to infer cardiac filling pressures in *heart failure* (HF) patients to facilitate their medical management. HF patients suffer from excessive fluid accumulation (hypervolemia), which causes first hemodynamic and then clinical pulmonary and/or systemic congestion and presents a major risk to HF patients. It has been shown that measurement of cardiac filling pressures, or related pulmonary pressures, can reduce the rate of cardiac decompensations and hospital admissions.

PAPS are implantable devices which are deployed into the pulmonary artery of the patient by means of a minimally invasive catheter procedure. After deployment, the device performs measurement of the *pulmonary artery pressure* (PAP) either automatically or triggered by the patient and transmits the measured signal to a device external to the patient.

It is necessary that the implanted PAPS device does not cause adverse events like migration, vessel perforation or rupture, inflammation, or thrombosis. In this context, SIMCor focuses on in-silico testing and validation of implantable devices like PAPS. Thus, it strives to establish validation methods and workflows to determine the safety, efficacy, and performance of the medical device under investigation using in-silico models.

Preliminary steps based on ASME V&V 40

Step 1: define QoI

QoI (ASME VV 40 - 2018)

"The question of interest describes the specific question, decision, or concern that is being addressed by each computational model developed for a specific medical device. There might be just one model to address one or more questions of interest or there might be several models, possibly in different domains to answer a set of questions of interest."

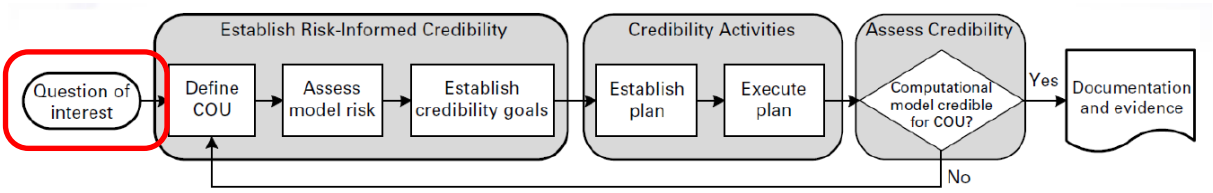


Figure 4: Highlighting of the current step QoI within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Note: For simplicity, only a single QoI is presented here, while multiple QoIs have been identified for the PAPS use case (for details see Appendix 1).

QoIs (PAPS) – migration, perforation
QoI 1: migration, perforation Can the fixation of the PAPS anchor the device in the pulmonary artery in such a way that the implant stays safely attached to the targeted implant site selected by the physician without causing: a. Device migration b. Vessel perforation in the entire patient population indicated for implantation of the sensor over the entire remaining life span of the patients?

Step 2: define the COU

COU (ASME VV 40 - 2018)
… "*the COU defines the specific role and scope of the computational model(s) used to address the question(s) of interest. It should include a detailed statement of what will be modelled and how the outputs from the computational model(s) will be used to answer or inform the question(s) of interest. To establish the scope of the computational model, the COU should include a description of other supporting evidence, such as data from in-vitro and/or in-vivo studies or other forms of analysis, in its description of the relative contribution of the computational model.*"

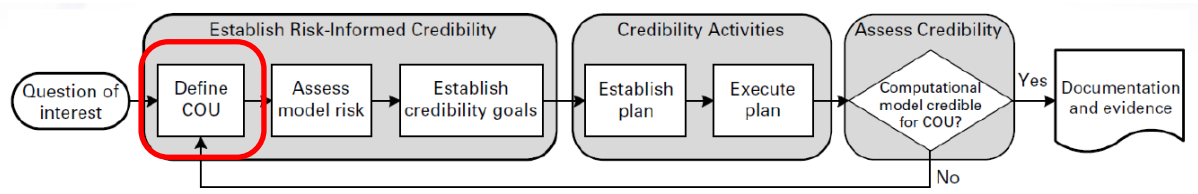


Figure 5: Highlighting of the current step "Definition of the COU" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

COU (PAPS – QoI 1 migration, perforation)[11]
COU 1.1 The *finite element* (FE) model will support the design process of the device, e.g., finding the optimal geometry of the fixation elements as well as the optimal material and manufacturing parameters. The model predictions will be partly validated through in-vitro and ex-vivo experiments where radial forces, vessel deformation, and axial forces are measured.
COU 1.3 The FE model will be used to demonstrate the absence of adverse events, i.e., device migration and vessel perforation, in clinical use through an *in-silico clinical trial* (ISCT) using a virtual human cohort. The final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Ideally, the clinical feasibility study, i.e., the first in human study, can enrol patients faster when safety data from the ISCT are available.

[11] For simplicity, only two COU pertaining to the first QoI are presented here. In actual practice, multiple COU were identified for each QoI.

Step 3: assess model risk

The following section describes the necessary elements of model risk assessment according to V&V40.

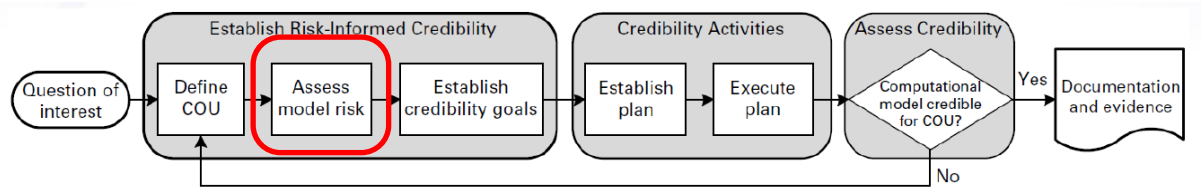


Figure 6: Highlighting of the current step "Assess model risk" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Model risk (ASME VV 40 - 2018)

… "**Model risk** is the possibility that the use of the computational model leads to a decision that results in patient harm and/or other undesirable impacts". "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).":

Model risk = model influence x decision consequence

If a classification system for model influence and decision consequence exists in the Quality Management System of the device manufacturer, it must be applied. If such a classification system does not exist, the classification of the decision consequence shall follow the classification system for medical device risk management according to ISO 14971, which is mandatory for every device manufacturer. For the sake of illustration, we will choose three-staged scales for model influence and decision consequence for both use cases.

Model influence (ASME VV 40 - 2018)

"**Model influence** is the contribution of the computational model relative to other contributing evidence in making a decision."

These other contributing factors can be in-vitro or in-vivo testing or experiences with a predicate device.

Model influence

Minor: simulation outputs from the computational model are a minor factor in the decision for the respective COU. There will be comprehensive evidence to support the decision like in-vitro or in-vivo testing or experiences with a predicate device.

Moderate: simulation outputs from the computational model are a moderate factor in the decision for the respective COU. There will be additional, though not comprehensive, evidence to support the decision like in-vitro or in-vivo testing for the same or a different COU or experiences with a predicate device.

Significant: simulation outputs from the computational model are a significant factor in the decision for the respective COU. There will be NO additional evidence to support the decision.

Decision consequence (ASME VV 40 - 2018)

"**Decision consequence** is the significance of an adverse outcome resulting from an incorrect decision."

The decision consequence must be rated regardless of mitigation measures which might reduce the model influence.

Decision consequence

Low: an incorrect decision would not adversely affect patient safety or health but might result in a nuisance to the physician or have other minor impacts like increased development time and costs.

Medium: an incorrect decision could result in minor patient injury or the need for physician intervention or have other moderate impacts like additional design iterations.

High: an incorrect decision could result in severe patient injury or death or have other significant impacts, like a need for major redesign or repetition of preclinical or clinical studies.

Exemplarily, for the two COUs that were introduced for the PAPS use case, the following risk for model-based decision consequences are estimated. In both cases the model influence is judged to be medium, whereas decision consequences were judged to be medium and high respectively, resulting in different overall risk evaluation for both COUs.

Model risk assessment (PAPS – QoI 1 migration, perforation)

COU 1.1:
Model influence: model influence is *moderate.* In-vitro and in-vivo experimental results will verify the decisions based upon the model predictions. However, some model outputs cannot be completely verified in-vivo such as peak contact stress.

Decision consequence: Decision consequence is *medium* because a wrong decision could lead to device failures in animal experiments which in turn would trigger a design iteration.

Model risk: 3

COU 1.3:
Model influence: model influence is *moderate* as the final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Animal tests are, however, limited in sample size and do not faithfully resemble human anatomy and physiology.

Decision consequence: decision consequence is *high* because a wrong decision could lead to adverse events i.e., device migration and vessel perforation in clinical use. These adverse events might cause serious injury to the patient.

Model risk: 4a

Risk graph

This model risk assessment based on both aspects of model influence and decision consequence are combined in a risk graph resulting in 5 risk grades, which is shown in Figure 7, including the two exemplary PAPS COU.

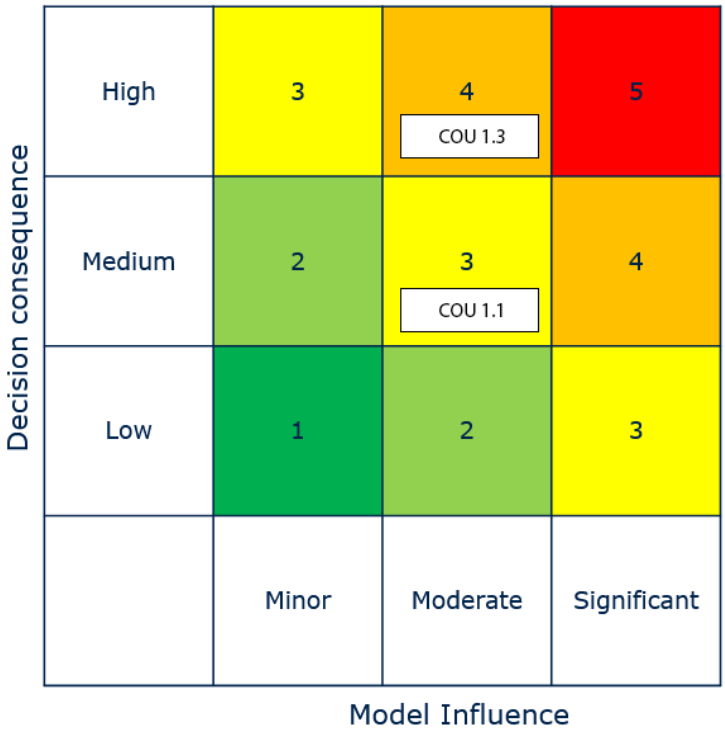


Figure 7: Risk graph to map model influence and decision consequence to a risk class according to the V&V 40 standard[12], as applied to PAPS use case.

Step 4: establish model credibility goals

Activities to establish model credibility comprise verification, validation, and applicability analysis (Figure 8). As mentioned before, this step is where the SIMCor approach adds to the V&V 40 framework. This framework foresees the following sub-steps.

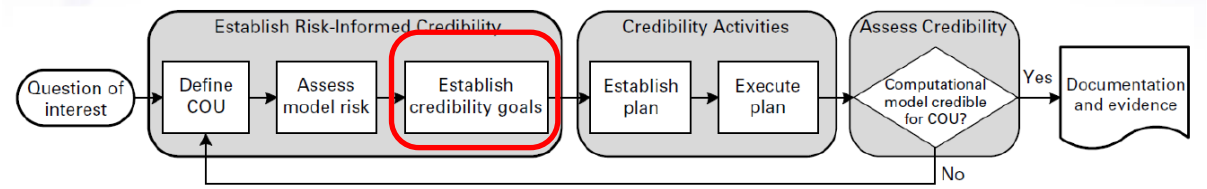


Figure 8: Highlighting of the current step "Establishing credibility goals" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Credibility goals (ASME VV 40 - 2018)
"Model **credibility** refers to the trust in the predictive capability of a computational model for the COU. Trust can be established through the collection of evidence from credibility activities."

[12] Assessing Credibility of Computational Modelling through Verification and Validation: Application to Medical Devices, V&V 40 - 2018, ISBN: 9780791872048

Step 4A: determine verification activities

Verification comprises code and calculation verification. Verification activities are not within the scope of this SOP. Please refer to the V&V 40 standard for general information on verification activities and to *D9.2* for SIMCor-specific information.

Verification (ASME VV 40 - 2018)
"The objective of **verification** is to ensure that the mathematical model is implemented correctly and then accurately solved."

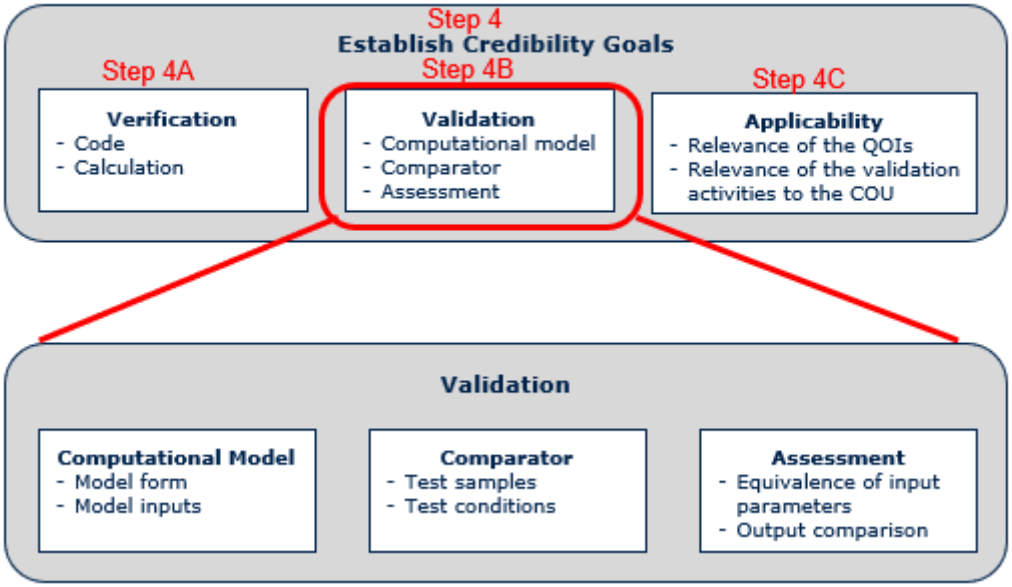


Figure 9: Highlighting of the current step "Validation" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Step 4B: determine validation activities

Validation comprises the comparison of model predictions with experimental results using appropriate comparators (Figure 9). Thus, even during development of the numerical model including engineering metrics, validation should be considered with regard to feasible comparators. Finally, an applicability analysis will check the relevance of the V&V activities to support the use of the computational models for the respective COUs. In the following, we will assign a gradation to these credibility factors commensurate with the model risk.

Validation (ASME VV 40 - 2018)
"**Validation** is the process of assessing the degree to which the computational model is an appropriate representation of the reality of interest."

Step 4C: Determine applicability

Applicability (ASME VV 40 - 2018)
"**Applicability** is the relevance of the validation activities to support the use of the computational model for a COU".

Tailoring V&V 40: a tiered validation approach for cardiovascular implantable devices

Why do we need a tailored validation approach? In applications where models shall predict not only engineering metrics but also clinical outcome it is advisable to apply a tiered, two-fidelity-level validation strategy, where the process is separated into a low-fidelity validation track for subject-specific (in-vitro, ex-vivo, and animal) studies with the aim to validate model predictions of engineering metrics and a high-fidelity validation track for both subject-specific or population-based validation of the model predictions regarding clinical endpoints.

Low-fidelity validation of modelling tools

The **Low-fidelity validation** is based on the comparison of in-silico results with measurements from

- Conventional bench tests
- Ex-vivo tests
- Acute animal studies.

In these tests the fidelity of the model will be validated by measurement of engineering properties (e.g., deformation, flow profile). The term “low-fidelity” means that the validation setting is relatively different from the clinical setting but selected in a way that the measurement of all quantities of interest is possible (such as measurement of forces and strains, which are not accessible during clinical use or chronic animal studies). The prefix “low” contains no statement of the quality of experimental measurements. The rigour of validation must consider the risk classification of the model.

Low-fidelity validation for PAPS (PAPS – QoI 1 migration, perforation)
COU 1.1 will require a low-fidelity validation scheme. The engineering metrics used for assessing the device performance and safety are radial forces, vessel deformation and axial forces. Radial forces can be measured in bench tests, whereas axial forces and vessel deformation can be measured in in-vivo and ex-vivo tests.

High-fidelity validation of device simulations by chronic animal studies

The **high-fidelity validation** consists of comparative simulations of endpoints based on

- Long-term animal studies
- Post-hoc clinical studies
- Prospective clinical studies.

Using these study designs, clinical endpoints can be observed but engineering metrics can usually not be measured in detail. The term “high-fidelity” means that the validation setting is similar to the clinical setting. High-fidelity validation can be either performed through chronic preclinical studies or post-hoc use of clinical studies. Preclinical testing offers the possibility to test devices currently under development and still invasively measure parameters of interest and even to use test samples representing worst-case conditions. Subject-specific analysis is possible. Clinical trials, however, will be limited to population-based comparison of simulation results with clinical results obtained with predicate devices but usually offer a large sample size within the target population. Finally, prospective clinical trials can be performed, but for this the maturity of the device must already be advanced, meaning that this approach is not suitable for generating evidence for the model safety. Still, the approach can be beneficial as models validated using this approach can still be employed during subsequent design iterations or even other devices requiring similar models.

High-fidelity validation for PAPS (PAPS – QoI 1 migration, perforation)

For COU 1.3 a high-fidelity validation scheme is necessary. To validate the model predictions of the endpoints migration and perforation, these adverse events must be observed in the validation studies, which is not possible in acute animal experiments or bench tests. Therefore, a chronic animal trial is necessary to provide the relevant data.

- Migration of the device can be assessed using recurrent computed tomography scans from which the device position on the pulmonary artery can be assessed.
- To assess the perforation endpoint, histology examination after explantation of the device is performed.

Tailored Step 4: low-fidelity validation

Step 4A focussing on model verification is not part of the scope of this document and is therefore omitted in this description. In addition, the order or activities in the substeps 4A to 4C is not strongly affected by the tiered validation scheme. Therefore, only the specific aspects for the low-fidelity validation scheme are mentioned in this section in addition to examples from the PAPS use case. All PAPS-specific examples will focus on COU 1.1.

Step 4B: Validation

In the low-fidelity validation scheme, the focus is on validation of in-silico models' capabilities to predict engineering metrics. This scheme adheres closely to common validation strategies and activities, as engineering metrics are the common outputs of in-silico models. A specific focus should lie on engineering metrics associated with the clinical endpoints. These engineering metrics can either be derived by previous experiments, literature, or causation.

Low-fidelity validation for PAPS (PAPS – QoI 1 migration, perforation)

Device migration and device perforation are related to the forces, stresses, and strains of the sensor fixation and the pulmonary artery wall. Low contact stresses will result in low axial retention forces and therefore increase the risk of device migration. High contact stresses will increase the risk of tissue damage and therefore device perforation.

Step 4B-1 - model form and input: the tiered validation scheme adds no specific requirements for the definition of model form and input.

Low-fidelity validation for PAPS - model form

Stresses and strains in the fixation as well as the vessel wall are calculated using a finite element model implemented in ANSYS Mechanical (Ansys, Inc., USA). A detailed description of the model used as well as its inputs is provided in D9.2 as well as appendix 1.

Step 4B-2 - comparator: based on the engineering metrics of interest, suitable validation experiments and measurements must be identified and designed. Here, emphasis of the design should lie on accurate measurement of engineering metrics. The test setting will deviate from the clinical setting in which the evaluated medical device will be used. However, this deviation can often not be avoided due to measurement techniques not being applicable in in-vivo settings or not even in acute animal experiments.

Low-fidelity validation for PAPS - comparator (axial retention force)
Axial retention forces will be measured in an in-vitro setting using a tensile tester. The device is implanted in a silicon tube with known mechanical properties. In addition, ex-vivo measurements are performed using explanted porcine pulmonary arteries. In-silico models of both setups are generated using models of the silicone tubes as well as 3D scans of the porcine pulmonary arteries, allowing direct comparison of simulated and measured axial retention forces.

Step 4B-3 - assessment: in this step the equivalency of input and output parameters must be evaluated. According to ASME V&V 40, this refers to the "Equivalency between the type and range of the input / output parameters of the computational model and those of the comparator". Within the low-fidelity validation scheme, equivalency should be high for both.

Low-fidelity validation for PAPS - assessment (axial retention force)
For low-fidelity validation, the types and ranges of all input parameters were equivalent. Known properties and geometries of the silicone tubes were used. For the ex-vivo tests, species-specific material properties and animal-specific anatomical information was used. The axial retention force was the evaluated output in all validation tests, as well as for the in-silico model.

Step 4C: applicability

in this step, the relevance of the quantities of interest and the validation activities must be compared and evaluated against the context of use.

Low-fidelity validation for PAPS - applicability (migration, perforation)
For the low-fidelity validation, the quantities of interest were closely related to COU 1.1, which focussed on assessing mechanical properties for evaluation of the device design and performance. However, quantities of interest are weakly related to the other COUs that focussed on prediction of clinical endpoints.

Tailored Step 4: high-fidelity validation

As neither the order nor activities in the sub-steps 4A to 4C are strongly affected by the tiered validation scheme, only the specific aspects for the high-fidelity validation scheme are mentioned in this section, along with examples from the PAPS use case. All PAPS-specific examples will focus on COU 1.3.

Step 4B: validation

In the high-fidelity validation scheme, the main focus lies on validation of the in-silico models' capabilities of predicting clinical endpoints. This scheme can deviate largely compared to common validation strategies and activities, in-silico models are usually not directly capable of estimating clinical endpoints unless those are directly related to engineering metrics.

High-fidelity validation for PAPS (PAPS – QoI 1, migration, perforation)
Device migration and device perforation are related to the forces, stresses, and strains of the sensor fixation and the pulmonary artery wall. However, for the high-fidelity validation, acceptance criteria must be defined for these parameters to assess: • Whether a device will either migrate due to too loose fixation or

- Whether a device and or fixation will cause vessel perforation due to too large contact stresses or strains.

Step 4B-1 - model form and input: the tiered validation scheme adds no specific requirements for the definition of model form and input.

High-fidelity validation for PAPS - model form
The same in-silico model was used for validation of stresses and strains in the fixation as well as the vessel wall are calculated using a finite element model implemented in ANSYS Mechanical (ANSYS Inc., USA). A detailed description of the model used as well as its inputs is provided in D9.2 and Appendix 1.

Step 4B-2 - comparator: the choice of the comparator is heavily influenced by the high-fidelity validation scheme. Validation experiments must be identified and designed to closely match the clinical setting in which the evaluated medical device will be used. Furthermore, these experiments must allow for observation of the clinical endpoints to be predicted by the model. In many scenarios this requires continuous observations as many clinical endpoints of interest, such as thrombosis and device migration, do often not occur immediately after device implantation, rather over a long period of time.

High-fidelity validation for PAPS - Comparator (occurence of migration)
The PAPS device will be implanted in a porcine pulmonary artery and the occurrence of device migration is observed over a duration of up to three months. • At fixed time points, a computed tomography scan of the porcine pulmonary artery is performed to assess the device position and any changes to it. • The axial retention force necessary to dislodge the sensor is calculated using a reconstruction of the animal-specific pulmonary artery, with the sensor being implanted exactly at the position as observed in-vivo. • Axial retention forces between sensors for which migration was observed and those that remained in position are compared.

Step 4B-3 - assessment: in this step, the equivalency of input and output parameters must be evaluated. Within the high-fidelity validation scheme, high equivalency cannot always be achieved.

High-fidelity validation for PAPS - assessment (occurence of migration)
For the high-fidelity validation, there is no overlap in output parameters of the model and the comparator validation experiments. Occurrence of migration was compared against axial retention forces.

Step 4C: applicability

In this step, the relevance of the quantities of interest and the validation activities must be compared and evaluated against the context of use.

High-fidelity validation for PAPS - applicability (migration, perforation)
For the high-fidelity validation, the quantities of interest calculated using the in-silico model were related to COU 1.3 but differed markedly.

Post-validation steps based on ASME V&V 40

Step 5: validation activities & results

After establishing the model credibility goals, appropriate activities and acceptable results are defined to assess the credibility of the computational model. A comparative overview of the computational model and experimental design and a short summary of the outcome for the different experiments are provided in this step.

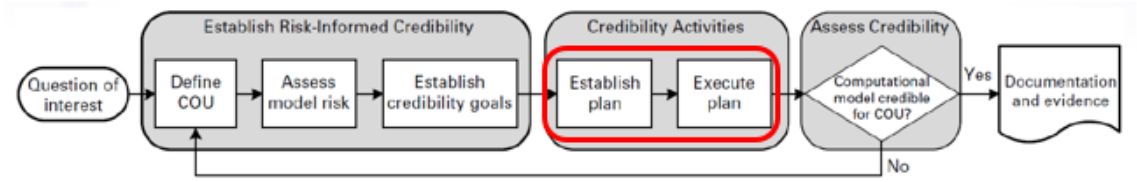


Figure 10: Highlighting of the current step "Credibility Activities" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Step 6: assess credibility

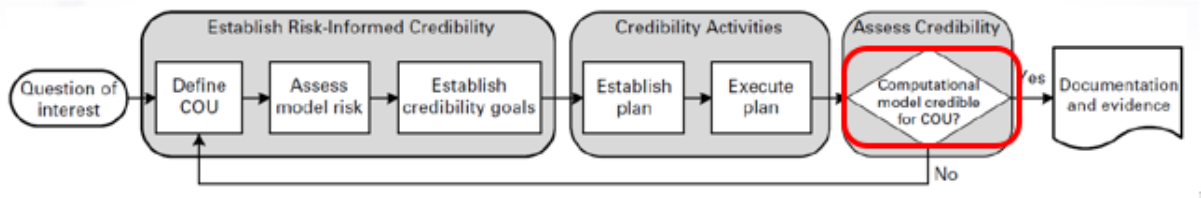


Figure 11: Highlighting of the current step "assess credibility" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Based on the results of the validation activities, the credibility of the computational model for the COU is determined. To this end, the COU, model risk, credibility goals, and V&V outcome are reviewed. At the end, there are three different outcomes possible:

1. The credibility activities and results are sufficient to establish credibility for the COU.
2. The computational model is changed, additional credibility activities are performed, or the COU is modified, and the resulting credibility activities are reviewed again.
3. The computational model is abandoned, and the credibility activities and results are insufficient to establish credibility for the COU.

Outlook

In conclusion, the overall structure of the ASME V&V 40 is found to be feasible to guide through the process of assessing credibility for cardiovascular implants such as PAPS and TAVI. Due to the broad range of engineering metrics, clinical quantities and model types there is a huge variety in credibility evidence. The FDA guidance for "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions" helps to categorise and structure the different types of credibility evidence. Both documents were found to be very helpful to deal with the challenge of proving model credibility.

This document additionally presents complex examples which were neither highlighted within V&V 40 nor the FDA guidance. This includes dealing with multiple questions of interest and COUs, that complicate the validation schemes. Using the tiered validation approach (low-fidelity, high-fidelity), we presented a strategy to go a step further towards validation of in-silico models predicting clinical endpoints.

This tiered validation strategy is not entirely sufficient to bridge the gap between the engineering metrics (a common and easily interpretable output of in-silico models), and the clinical endpoints (actual quantities of interest, necessary to assess safety and efficacy of medical devices). Nonetheless, the tiered validation approach provides evidence of both aspects individually, allowing the high-fidelity validation to be based on the sound foundation of the low-fidelity validation's results.

Overview of appendix

The two appendices of this document provide detailed examples of the validation activities performed for the PAPS (appendix 1) and TAVI (appendix 2) use case within SIMCor.

Appendix 1 – In-silico validation for PAPS

In this appendix, the methodology of planning, executing and evaluating model validation activities as embedded in the model credibility assessment, is documented using the example of an implantable cardiovascular device PAPS. After a brief introduction of the clinical need and the description of the device, the step-by-step procedure for model credibility assessment will be reported to an extent that is required to plan validation activities. Special emphasis is then placed on the validation activities.

Clinical need: heart failure patients

PAPS are used to measure cardiac filling pressures in HF patients to facilitate their medical management. HF patients suffer from hypervolemia caused by mal-adapted compensatory mechanisms. Hypervolemia causes first hemodynamic and then clinical pulmonary and/or systemic congestion and presents a major risk to patients. Patients receive guideline-directed medical therapy to prevent and revert fluid accumulation. Titration of these drugs is challenging relying on signs and symptoms only. It has been shown that measurement of cardiac filling pressures or related pulmonary pressures like PAP can significantly reduce the rate of cardiac decompensations and hospital admissions.

Implantation of PAPS

PAPS are devices which are implanted into the pulmonary artery of the patient by means of a minimally invasive catheter procedure. They are in the market or in development from different medical device manufacturers, e.g. Abbott[13]. They consist of a rigid housing which contains the pressure transducer, active or passive electronics and optionally an energy source, such as a battery. The rigid housing is made from titanium, glass or similar biocompatible and biostable materials. Fixation elements are attached to the sensor housing to attach the device to the wall of the pulmonary artery. These fixation elements are made from shape memory alloys like Nitinol which allows crimping onto or into the implantation catheter and to revert to their original shape once the device is deployed and released from the catheter.

After deployment the device performs measurement of the PAP either automatically or triggered by the patient and transmits the measured signal to an external device. As the sensor will permanently stay implanted in the patients, it must not cause any adverse events like migration, vessel perforation or rupture, inflammation or thrombosis for long implantation periods exceeding 10 years.

Preliminary steps based on ASME V&V 40

Step 1: define QoI

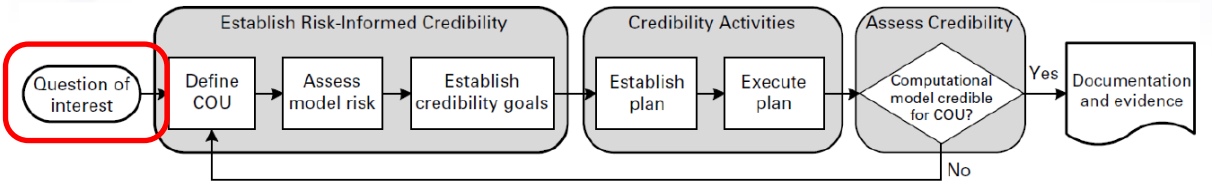


Figure 12: Highlighting of the current step "QoI" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

[13]Radhoe, Sumant P, and Jasper J Brugts. "CardioMEMS™: a tool for remote hemodynamic monitoring of chronic heart failure patients." *Future cardiology* vol. 18,3 (2022): 173-183. doi:10.2217/fca-2021-0076

Question(s) of interest (PAPS) – migration, perforation, thrombosis
QoI 1: migration, perforation Can the fixation of the PAPS anchor the device in the pulmonary artery in such a way that the implant stays safely attached to the targeted implant site selected by the physician without causing: 1. Device migration 2. Vessel perforation in the entire patient population indicated for implantation of the sensor over the entire remaining life span of the patients. **QoI 2: Thrombosis** Can the PAPS be implanted in the *pulmonary artery* (PA) in such a way that blood flow alteration would not lead to thrombosis and finally pulmonary embolism in the entire patient population indicated for implantation of the sensor over the entire remaining life span of the patients?

Step 2: Define of COU

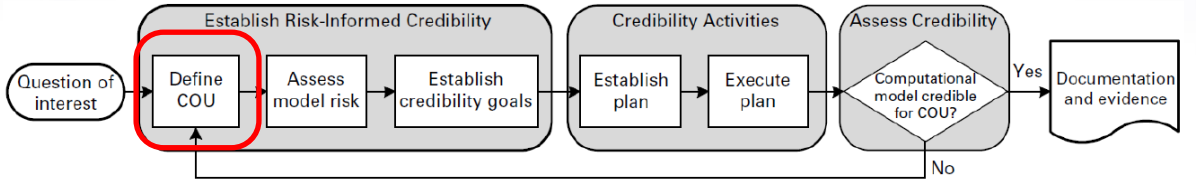


Figure 13: Highlighting of the current step "Definition of the COU" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

For QoI 1 addressing **migration and perforation**, a FE structural mechanics model, comprising the pulmonary artery and the PAPS device, will be used to determine the interaction between device and pulmonary artery. The pulmonary artery is modelled as an elastic body using both generic and animal-specific geometries and material parameters. Appropriate pressure boundary conditions are applied. The device fixation is modelled using a super elastic beam model.

COU (PAPS – QoI 1; migration, perforation)
COU 1.1: The FE model will support the design process of the device, e.g., finding the optimal geometry of the fixation elements as well as the optimal material and manufacturing parameters. The model predictions will be partly validated through in-vitro and ex-vivo experiments where radial forces, vessel deformation, and axial forces are measured.
COU 1.2: The FE model will be used to determine loading conditions for durability estimation, e.g., determine pre-strain and maximum cyclic strain rates and locations. This information will then be used together with load-cycle curves to predict the durability of the fixation. The result will be verified by in-vitro durability testing of the final design.
COU 1.3: The FE model will be used to demonstrate the absence of adverse events i.e. device migration and vessel perforation in clinical use through an ISCT using a virtual human cohort. The final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Ideally, the clinical feasibility study, i.e., the first in human study, can enrol patients faster when safety data from the ISCT are available.

For QoI 2 on **thrombosis**, a finite volume CFD model, comprising a rigid-wall pulmonary artery and the PAPS device, will be used to determine the influence of the PAPS on the pulmonary arterial blood flow and vice versa. The implant is modelled as a rigid body neglecting the thin fixation elements.

COU (PAPS – QoI 2; thrombosis)
COU 2.1: The CFD model will support the design process of the device, e.g., finding the optimal geometry of the implant housing, especially the leading and trailing edges of the housing. The model predictions will be partly validated through in-vitro experiments where the 3D velocity field is measured using 4D Flow MRI.
COU 2.2: The CFD model will be used to determine fluid forces acting on the sensor body. These forces will be considered during the migration analysis (see COU 1.3). The result will not be verified by in-vitro testing.
COU 2.3: The CFD model will be used to demonstrate the absence of adverse events, i.e., thrombosis and pulmonary embolism in clinical use through an ISCT using a virtual human cohort. The final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Ideally, the clinical feasibility study (aka first in human study) can enrol patients faster when safety data from the ISCT are available than without ISCT data.

Step 3: assess model risk

In this step, we will assign a risk class to the different COUs according to their model influence and decision consequence.

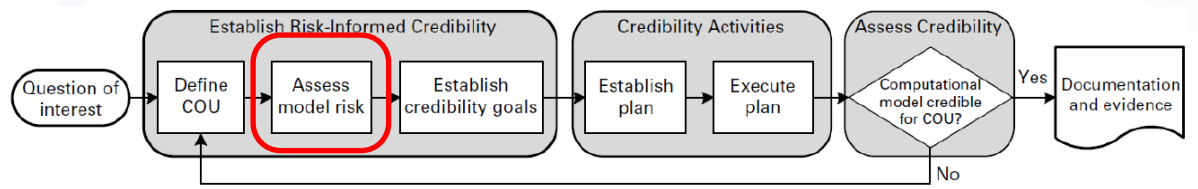


Figure 14: Highlighting of the current step "assess model risk" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

When the quality of the model is assessed at the end of the validation process, the context of how significant deviations from the model are for patient safety is important. This should be determined in the definition phase to avoid bias.

Model risk assessment (PAPS – QoI 1 migration, perforation)
COU 1.1 *Model influence*: model influence is *moderate.* In vitro and in-vivo experimental results will verify the decisions based upon the model predictions. However, some model outputs cannot be completely verified in-vivo such as peak contact stress. *Decision consequence*: decision consequence is *medium* because a wrong decision could lead to device failures in animal experiments which in turn would trigger a design iteration. *Model risk*: 3

COU 1.2

Model influence: model influence is *minor* as in-vitro durability tests with the final design under physiologic loading conditions will demonstrate durability.

Decision consequence: decision consequence is *medium* because a wrong decision could lead to device failures in the in-vitro durability test which in turn would trigger a design iteration and the repetition of the long-term durability test. A longer development time is the consequence.

Model risk: 2

COU 1.3:

Model influence: model influence is *moderate* as the final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Animal tests are, however, limited in sample size and do not faithfully resemble human anatomy and physiology.

Decision consequence: decision consequence is *high* because a wrong decision could lead to adverse events, i.e., device migration and vessel perforation in clinical use. These adverse events might cause serious injury to the patient.

Model risk: 4

The risk of the model is the sum of the assessment of the model influence on the decisions and the consequences of the decisions themselves. For the mechanical questions to PAPS, the model influence was rated as low to medium, and the consequences were assessed as medium to high.

Model risk assessment (PAPS – QoI 2 thrombosis)

COU 2.1

Model influence: model influence is *moderate.* In-vitro experimental results will verify the decisions based upon the model predictions.

Decision consequence: decision consequence is *medium* because a wrong decision could lead to device failures in animal experiments which in turn would trigger a design iteration.

Model risk: 3

COU 2.2

Model influence: model influence is *significant* as no in-vitro tests will be conducted to verify the model predictions.

Decision consequence: decision consequence is *medium* because a wrong decision could lead to an over or underestimation of the fluid forces. As the fluid force is an order of magnitude lower than the gravitational forces acting on the implant the impact of a wrong decision is moderate.

Model risk: 4

COU 2.3

Model influence: model influence is *moderate* as the final design will also be tested in a chronic animal trial before starting the clinical feasibility study. Animal tests are, however, limited in sample size and do not faithfully resemble human anatomy and physiology, especially the coagulation system and platelet function.

Decision consequence: decision consequence is *high* because a wrong decision could lead to adverse events, i.e., thrombus formation and pulmonary embolism in clinical use. These adverse events might cause serious injury to the patient.

Model risk: 4

For PAPS thrombosis, the model influence was rated as medium to high, and the consequences were assessed as low to medium.

Summary of risk assessment for PAPS device

The risk assessment for the 6 COUs identified before is summarised in the risk chart in Figure 15.

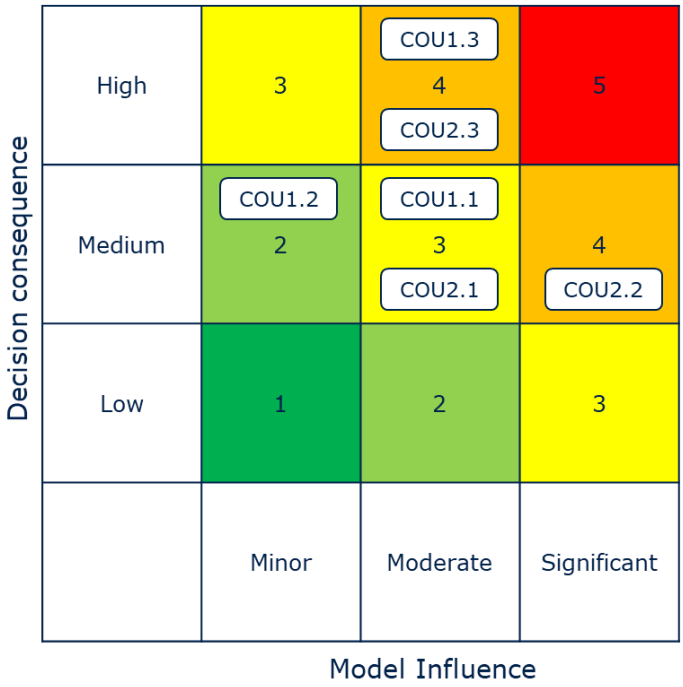


Figure 15: Assignment of the COUs defined for the PAPS use case to the different risk classes.

Step 4: establish model credibility goals / factors – verification, validation, applicability

Activities to establish model credibility comprise verification, validation, and applicability analysis (Figure 16).

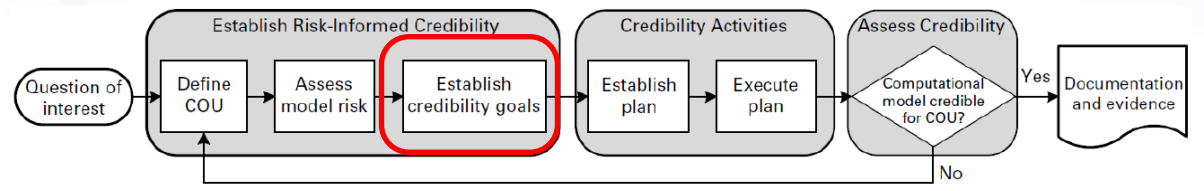


Figure 16: Highlighting of the current step "establishing credibility goals" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40. Step 4A: verification.

Verification comprises code and calculation verification. Verification activities are not within the scope of this SOP. Please refer to *D9.2* for information on verification activities. The gradation of the credibility factors must be commensurate with the model risk.

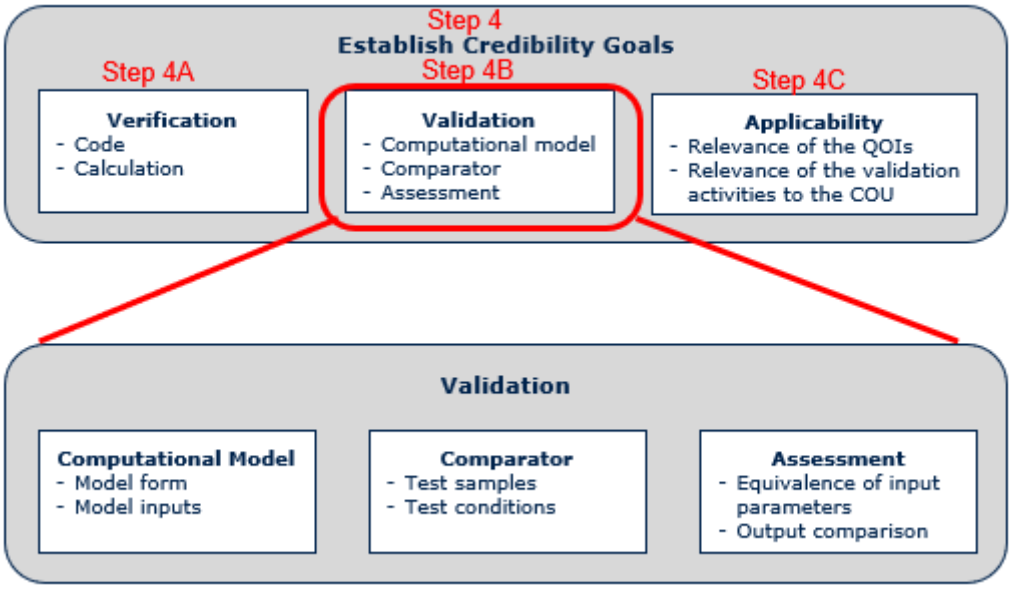


Figure 17: Highlighting of the current step "Validation" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Step 4B: validation

For both the low and high-fidelity validation scheme the same numerical models and similar model inputs were used. Therefore, these common aspects are described jointly before providing the details on the respective validation schemes.

Step 4B-1: model form and input

Model form CFD

A commercial finite volume solver (STAR-CCM+, Siemens PLM, USA) was used for the CFD model. The underlying governing equations were the Reynolds-averaged Navier-Stokes equations, as a k-omega two-equation turbulence model was used. An implicit scheme was used for temporal discretization. Details of the model used are provided in D9.2 as well as a recent publication[14].

Model form SM

The software tools and the model for the implant have been describe in D8.1 and the material model in D9.2.

Figure 18 provides an example of the mesh of the fixation elements. The mesh consists of hexahedral elements with an element length of 0.1 mm in longitudinal and 24 elements in circumferential direction. The discretisation achieves a maximum aspect ratio of 4.2 (best value 1, values greater than 1000 can be critical), a maximum parallel deviation of 45° (best value 0°, values greater than 70 are critical)[15] and a maximum corner angle 138° (best value 90° for Quadrilaterals, values greater than 165° are critical)[16].

[14] Brüning, Jan et al. "In-silico enhanced animal study of pulmonary artery pressure sensors: assessing hemodynamics using computational fluid dynamics." *Frontiers in cardiovascular medicine* vol. 10 1193209. 7 Sep. 2023, doi:10.3389/fcvm.2023.1193209

[15] www.cae-wiki.info/wikiplus/index.php/Netzqualtiät

[16] Ansys Mechanical APDL Theory Reference, Release 2021 R2, 2021

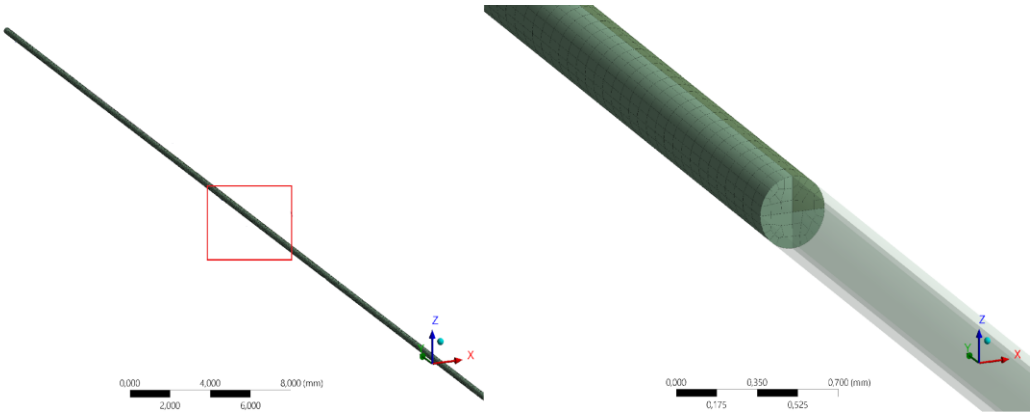


Figure 18: Mesh of the ANSYS Mechanical model for the fixation element.

Boundary conditions and loads are used equivalent to the explicit simulation. The quality of the simulation model is checked by the evaluation of the difference of nodal stress values between neighbouring elements and between averaged and unaveraged nodal values, which should be below 10%.

Tailored step 4: low-fidelity validation

Model risk for both PAPS models (CFD, FE) has been identified to range between medium to high. For the respective COUs the rigour of validation activities should be medium to high as well to achieve a medium/high credibility level for both models.

Step 4B-2: comparator

Figure 19 provides a matrix of tests which are performed to validate different aspects of the *finite element analysis* (FEA) and CFD models corresponding to the questions of interest and the COUs. Overall, 3 different testing strategies, in-vitro, ex-vivo and in-vivo were utilised for the low-fidelity validation scheme. All in-vivo measurements were performed within the setting of an acute animal trial.

In total, the following 6 comparator test designs were defined. In the subsequent tables they will be referred to using the following abbreviations.

1. **IVT-RFT**: In vitro radial force test
2. **IVT-APT**: In vitro axial pull test
3. **EV-APT**: Ex vivo axial pull test
4. **IV-VDT**: In vivo vessel deformation test
5. **IV-APT**: In vivo axial pull test
6. **IV-MRI**: In vivo *magnetic resonance imaging* (MRI) test

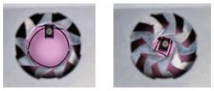
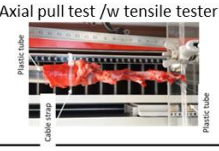
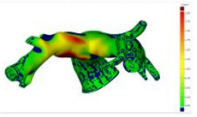
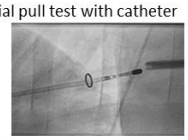
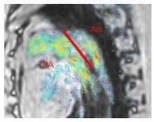
Validation step	Clinical endpoint	Perforation	Migration	Thrombosis
	Related engineering metrics to be validated	- Peak contact stress - Radial force - Vessel deformation	- Axial retention force - Implant alignment - Contact length	- WSS, OSI - Recirculation area - Residence time
	Model type / **Experiment setup**	Structural mechanics FE model with pressure boundary conditions		CFD model for transient simulations with rigid vessel
In vitro	- Silicone mock vessel - 3D printed pulm. artery - Tensile tester - Radial force tester - PIV or MRI flow visualisation	Radial force bracket tester 	Axial pull test /w tensile tester 	
Ex vivo	- Harvested or slaughter house pulmonary artery - Tensile tester - 3D scanner		Axial pull test /w tensile tester 	
In vivo	- Acute animal experiment in domestic pigs - Cardiac CT - Cardiac cine MRI - Segmentation tools	Vessel deformation validation 	Axial pull test with catheter 	MRI Flow field validation 

Figure 19: Overview of low-fidelity validations experiments for the PAPS use case.

Test samples: quantities, range of characteristics, measurements and uncertainty quantification of measurements are selected such that a medium to high level of credibility will be achieved. In particular, a statistically relevant sample size shall be used, a wide range of sample characteristics (e.g., PA vessel diameters) shall be used, all key characteristics shall be measured, and the uncertainty analysis shall include instrument uncertainty and repeatability. An overview of the design of test samples is provided in **Error! Reference source not found.**. Test conditions are specified in Table 2.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Quantities	n=7	N=3x2x2=12	N=1	N=1-6	N=1-3	N=2
Range of characteristics	1 wire size	2 wire sizes	2 wire sizes	2 device types, 3 wire sizes (4 combinations)	2 wire sizes	2 wire sizes
Measure-ments (all quantitative)	wire diameter, geometry in relaxed state	wire diameter, geometry in relaxed state	wire diameter, geometry in relaxed state	wire diameter, geometry in relaxed state, sensor body dimensions	wire diameter, geometry in relaxed state	spatiotemporally resolves velocities
Measurement uncertainties	instrument uncertainty of calliper and microscope					MRI accuracy

Table 1: Overview of the test samples for the low-fidelity validation of the PAPS use case.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Quantities	1	1	1	1	1	1
Range of conditions	continuous vessel diameters (min to max)	1 retraction velocity	1 retraction velocity	Target PA diameter in 5 pigs	Target PA diameter in 5 pigs	target diameter in 2 pigs
Measurement of conditions via key characteristics	radial force, temperature, diameter	diameter, shore hardness	retraction velocity, temperature	body weight, vessel diameter	body weight, vessel diameter	body weight, vessel diameter, heart rate
Measurement uncertainties	instrument accuracy	instrument accuracy	instrument accuracy	instrument accuracy; image analysis	instrument accuracy, position estimation; catheter movement	instrument accuracy; image analysis;

Table 2: Overview of the test conditions for the low-fidelity validation of the PAPS use case.

Step 4B-3: assessment

Table 3 provides an overview of the assessment of similarity of input and output parameters for the low-fidelity validation experiments.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Equivalency of input parameters	The types and ranges of all inputs were equivalent.					
Output comparison	Multiple outputs were compared. Types of outputs were equivalent.					Single output was compared. Type of output was equivalent.

Table 3: Overview of the assessment for the low-fidelity validation of the PAPS use case.

Step 4C: applicability

Table 4 provides an overview of the applicability of the low-fidelity validation experiments, assessing the relevance of quantities of interest and the relevance of the validation activities to the COU.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Relevance of quantities of interest	Quantities from the validation activities were related though not identical to those for the COU					
	Device migration and vessel perforation can be both characterised using radial forces	Device migration can be characterised using axial forces	Device migration can be characterised using axial forces	Vessel perforation can be characterised using contact stress	Device migration can be characterised using axial forces	Thrombosis can be estimated using parameters calculated from velocities
Relevance of the validation activities to the COU	Partial overlap of validation points and COU.					

Table 4: Overview of the applicability for the low-fidelity validation of the PAPS use case.

Summary of credibility factors

Based on the test design, the levels of rigour for the different experiments can be estimated. A detailed description of the different levels of rigour can be found in ASME V&V 40 (pages 10, 26-28). The levels of rigour for the low-fidelity validation of the PAPS use case are specified in **Error! Reference source not found.**. Based on the levels of rigour, an overall model credibility can be determined, which commensurate with the model risks (see Table 5: Overview of the levels of rigour for the low-fidelity validation of the PAPS use case.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Test samples - Measurements and measurement uncertainty	Medium (B)	Medium (B)	Medium (B)	Medium (B)	Medium (B)	Medium (B)
Test conditions - Measurements	Low (A)	Medium (B)	High (C)	High (C)	High (C)	Medium (B)
Test conditions - Measurement uncertainty	Medium (B)	High (C)	Medium (B)	Medium (B)	Medium (B)	Medium (B)
Assessment – Equivalency of input parameters	High (C)	High (C)	High (C)	High (C)	High (C)	High (C)
Assessment – output comparison	High (C)	High (C)	Medium-high (B)	High (C)	Medium-high (B)	Medium (B)
Applicability - Relevance of QOIs	High (C)	High (C)	High (C)	High (C)	High (C)	Medium (B)
Applicability – Relevance of the Validation Activities to the COU	High (C)	Medium (B)	Medium (B)	Medium (B)	Medium (B)	Medium (B)

Table 5: Overview of the levels of rigour for the low-fidelity validation of the PAPS use case.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Credibility level	Medium-high	Medium-high	Medium	Medium-high	Medium	Medium
Model risk	Minor / medium	Moderate / medium	Moderate / medium	Minor / medium	Moderate / medium	Moderate / high

Table 6: Overview of the credibility factors for the low-fidelity validation of the PAPS use case.

Tailored step 4: high-fidelity validation

The low-fidelity validation allows validation for the prediction of occurrence of clinically relevant events. The high-fidelity validation closes this gap by calibrating the metrics with the clinical endpoints (Figure 20).

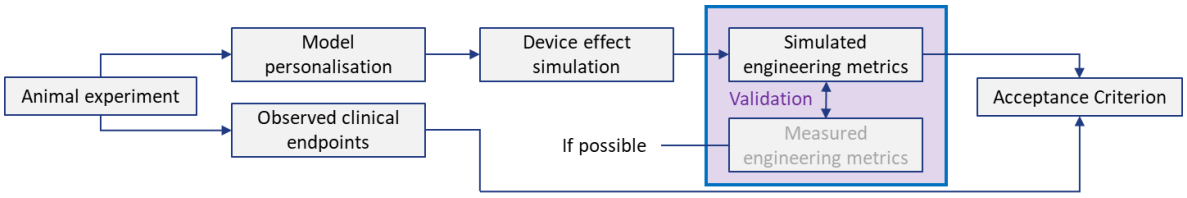


Figure 20: Model calibration with preclinical data.

Step 4B-2: comparator

The high-fidelity validation consists of different tests, which are all performed using the same chronic animal experiments. For assessing the credibility factors of these tests, the following abbreviations are used.

1. IV-MIGR: Occurrence of migration vs. simulated retraction force
2. IV-PERF: Occurrence of perforation vs. simulated contact stress
3. IV-THRO:Occurrence of thrombosis vs. simulated hemodynamic parameters

Test samples: quantities, range of characteristics, measurements and uncertainty quantification of measurements are selected such that a medium to high level of credibility will be achieved. In particular, a statistically relevant sample size shall be used, a wide range of sample characteristics (e.g., pulmonary artery vessel diameters) shall be used, all key characteristics shall be measured and the uncertainty analysis shall include instrument uncertainty and repeatability. An overview of the design of test samples is provided in Table 7. Test conditions are specified in Table 8.

	IV-MIGR	IV-PERF	IV-THR
Quantities	20 implanted sensors, each 2 per animal		
Range of characteristics	2 wire sizes; 1 implant size		
Measurements	wire diameter; geometry in relaxed state	wire diameter; geometry in relaxed state	sensor body position
Uncertainties of measurement	Instrument uncertainty of caliper and microscope; CT image resolution	Instrument uncertainty of caliper and microscope; CT image resolution	CT image resolution

Table 7: Overview of the test samples for the high-fidelity validation of the PAPS use case.

	IV-MIGR	IV-PERF	IV-THR
Quantities	2	2	2
Range of conditions	10 pigs with comparable weight and vessel diameter		
Measurement of conditions	body weight and vessel diameter at multiple time points	body weight and vessel diameter at multiple time points	body weight and vessel diameter at multiple time points; heart rate
Uncertainty of measurement	instrument accuracy; growth of animal during test period	instrument accuracy only	instrument accuracy; inter-observer variability in surface reconstruction

Table 8: Overview of the test conditions for the low-fidelity validation of the PAPS use case.

Step 4B-3: assessment

Table 9 provides an overview of the assessment of similarity of input and output parameters for the high-fidelity validation experiments.

	IV-MIGR	IV-PERF	IV-THR
Equivalency of input parameters	There is no overlap between the ranges of the validation points and the COU		
	Occurence of migration vs. simulated retraction force	Occurence of vessel perforation vs. simulated contact stress	Occurence of thrombus formation vs. simulated hemodynamic parameters (wall shear stress, oscillatory shear index)
Output comparison	A single output was compared. Types of outputs were dissimilar.	A single output was compared. Types of outputs were dissimilar.	Two outputs were compared. Types of outputs were dissimilar.

Table 9: Overview of the assessment for the high-fidelity validation of the PAPS use case.

Step 4C: applicability

Table 10 provides an overview of the applicability of the high-fidelity validation experiments, assessing the relevance of quantities of interest and the relevance of the validation activities to the COU.

	IV-MIGR	IV-PERF	IV-THR
Relevance of quantities of interest	Quantities from the validation activities were related, though not identical, to those for the COU.		
Relevance of the Validation Activities to the COU	Partial overlap of validation points and COU. Partial overlap of validation points and COU. There was partial overlap between the ranges of the validation points and the COU.		

Table 10: Overview of the applicability for the high-fidelity validation of the PAPS use case.

Summary of credibility factors

Based on the test design, the levels of rigour for the different experiments can be estimated. The levels of rigour for the high-fidelity validation of the PAPS use case are specified in Table 11. Based on the levels of rigour, an overall model credibility can be determined, which commensurate with the model risks (see Table 11: Overview of the levels of rigour for the high-fidelity validation of the PAPS use case.

).

	IV-MIGR	IV-PERF	IV-THR
Test samples - Measurements and measurement uncertainty	Medium (B)	Medium (B)	Medium (B)
Test conditions - Measurements	Medium (B)	Medium (B)	Medium (B)
Test conditions - Measurement uncertainty	Low (A) - Medium (B)	Low (A) - Medium (B)	Low (A)
Assessment – Equivalency of input parameters	Low (A)	Low (A)	Low (A)
Assessment – output comparison	Medium (B)	Medium (B)	Low (A)
Applicability - Relevance of QOIs	Low (A)	Low (A)	Low (A)
Applicability – Relevance of the Validation Activities to the COU	Medium (B)	Medium (B)	Medium (B)

Table 11: Overview of the levels of rigour for the high-fidelity validation of the PAPS use case.

	IV-MIGR	IV-PERF	IV-THR
Credibility level	Low/medium	Low/medium	Low/medium
Model risk	Moderate/medium	Minor/medium	Moderate/high

Table 12: Overview of the credibility factors for the high-fidelity validation of the PAPS use case.

Post-validation steps based on ASME V&V 40

Step 5: validation activities & results

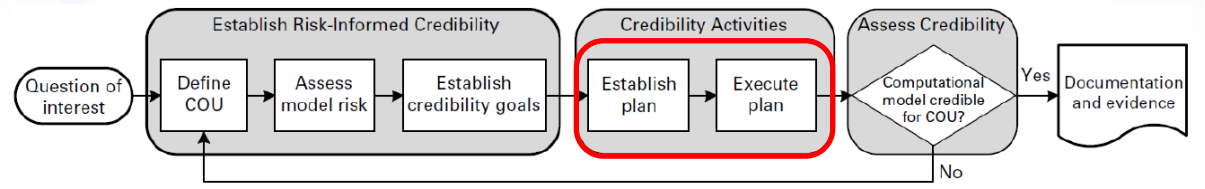


Figure 21: Highlighting of the current step "Credibility activities" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Low-fidelity validation results with respect to engineering metrics

Table 13 summarises the validation results of the low-fidelity validation. A detailed description of the results would exceed the scope of this document.

	IVT-RFT	IVT-APT	EV-APT	IV-VDT	IV-APT	IV-MRI
Purpose	Vessel perforation and migration	Device migration	Device migration	Vessel perforation	Device migration	Thrombosis
Conceptual model	Which radial forces are applied by the device?	Which axial force causes a dislocation of the device?	Which axial force causes a dislocation of the device?	Which radial forces result in which deformation of the vessel?	Which axial force causes a dislocation of the device?	What is the effect of the device on the intra-arterial hemodynamics
Physical model	Compressing the fixation from open position radially and measuring the resulting compression and opening force	Pulling the PAPS implanted into a silicone tube and measuring the resulting axial retention force	Pulling the PAPS implanted into a pulmonary artery (ex-vivo) and measuring the resulting axial retention force	Measuring the vessel shape before and after implantation	Pulling the PAPS implanted into an pulmonary artery (in-vivo) and measuring the resulting axial retention force	Measuring of spatio-temporal velocity field after implantation using 4D flow MRI.
Computational model	Measuring bore: Exact model of the iris diaphragm test bench. PAPS: simplified sensor body with different fixation diameters	Silicone tube: Cylindrical 3D model of the silicone tube PAPS: sensor body with different fixation diameters	Pulmonary artery: 3D scanned model. PAPS: sensor body with different fixation diameters	Pulmonary artery: CT scan from porcine PA PAPS: sensor body with different fixation diameters	Pulmonary artery: CT scan from porcine PA PAPS: sensor body with different fixation diameters	Pulmonary artery: CT scan from porcine PA PAPS: sensor body without fixation elements
Experimental design	Measuring bore: iris diaphragm test bench to measure chronic outward force PAPS: sensor body with fixation loops	Pulmonary artery: silicone tube PAPS: sensor body with different fixation diameters	Pulmonary artery: porcine pulmonary artery (explant) PAPS: sensor body with different fixation diameters	Pulmonary artery: porcine pulmonary artery PAPS: sensor body with different fixation diameters	Pulmonary artery: porcine pulmonary artery PAPS: sensor body with different fixation diameters	Pulmonary artery: porcine pulmonary artery PAPS: sensor body with different fixation diameters
Simulation results	force-diameter-diagram of fixation elements	minimum principal stress; force-distance-diagrams	deformation and stress of PA; force-distance diagram	deformation of PA, Mises equivalent stress; contact stress	Deformation and stress of PA, force-distance diagram	velocity vector field over time
Experimental data	Compression and opening force for different conditions	force-distance diagram	3D geometry of pulmonary artery; force-distance diagram	deformation of PA measured using CT data	3D geometry of pulmonary artery; force-distance diagram	volume flow rates in left and right PA; velocity vector field
Simulation outcomes vs. experimental outcomes	Good agreement of force-diameter diagrams	Good agreement of force-distance diagrams	Similar shape of force-distance diagrams and force plateau values; different initial force peak values	Good agreement of deformation regarding shape, position, and magnitude	failure of measuring axial retention force in-vivo	Moderate to good agreement of velocity fields; good agreement of volume flow rates in left and right PA

Degree of agreement	Sufficient	Sufficient	Insufficient	Sufficient	Insufficient	Insufficient
Next step	None	None	Improve agreement of orientation of PAPS in PA for experiment and simulation	None	Improve agreement of orientation of PAPS in PA for experiment and simulation	Optimise MRI protocols

Table 13: Overview of the results of the low-fidelity validation of the PAPS use case.

High-fidelity validation results with respect to clinical endpoints

Table 14 summarises the validation results of the low-fidelity validation. A detailed description of the results would exceed the scope of this document.

	IV-MIGR	IV-PERF	IV-THR
Purpose of credibility activity	Calibration of engineering metric to clinical outcome: retraction force to implant migration	Calibration of engineering metric to clinical outcome: contact stress to vessel perforation	Calibration of engineering metric to clinical outcome: *wall shear stress* (WSS) and *oscillating shear index* (OSI) to thrombus formation
Conceptual model (abstracted)	Which axial force causes device migration?	Which contact stress causes vessel perforation?	Which thresholds of OSI and WSS cause thrombus formation?
Description of computational model	Virtual implantation of PAPS with matching fixation diameters into pre-interventional 3D reconstruction of the animal-specific PA.	Virtual implantation of PAPS with matching fixation diameters into pre-interventional 3D reconstruction of the animal-specific PA.	Virtual implantation of PAPS without fixation elements into pre-interventional 3D reconstruction of the animal-specific PA.
Description of physical model	Chronical animal experiment (2-3 months), CT scans pre and post implantation and after 2-3 months follow-up. Observation of device migration using the CT images.	Chronical animal experiment (2-3 months), CT scans pre and post implantation and after 2-3 months follow-up. Observation of device perforation using the CT images and histo-pathological examination of the explanted PA.	Chronical animal experiment (2-3 months), CT scans pre and post implantation and after 2-3 months follow-up. Observation of device thrombosis using histo-pathological examination of the explanted PA.
Computational model	Pulmonary artery: CT scan from porcine PA before implantation PAPS: sensor body at exact position as after one month	Pulmonary artery: CT scan from porcine PA before implantation PAPS: sensor body at exact position as after one month	Pulmonary artery: CT scan from porcine PA at implantation PAPS: sensor body at exact position as after one month
Experiment design	Animal: pigs PAPS: sensor with different fixation diameters Imaging: CT scans	Animal: pigs PAPS: sensor with different fixation diameters Imaging: CT scans Histology: postmortem examination and report	Animal: pigs PAPS: sensor with different fixation diameters Histology: postmortem examination and report
Simulation results	Contact stresses and axial retention force.	Contact pressures and stresses in the fixation and tissue.	WSS, OSI, pressure gradients, velocity vector field
Experimental data	Sensor position before and after migration. Migration occurred in 3 animals	CT scans of vessel perforation; CT-based diameter measurements; histological examination	Histological examination of the lungs and the pulmonary artery
Simulation outcomes vs. experimental outcomes	Moderate agreement; migrated sensors have lower retraction force in the simulation but virtual implantation results in different fixation configuration compared to CT scans	Good agreement; perforated implant has slightly higher contact stress; vessel deformation in CT scans and simulation agrees well	Moderate agreement; slightly elevated WSS and lower OSI for devices featuring thrombosis. No significant differences between groups. No embolism observed in any animal.
Degree of agreement	Sufficient	Sufficient	Insufficient
Next steps	For a valid prediction the model needs to be refined by measuring personalised acceleration and disturbance forces acting on the device.	More *in-vivo* data needed, only one perforation occurred in the chronic animal trial.	More in-vivo data needed, however, embolism rate in existing PAPS studies is reported below 1%.

Table 14: Overview of the results of the low-fidelity validation of the PAPS use case.

Step 6: assess credibility

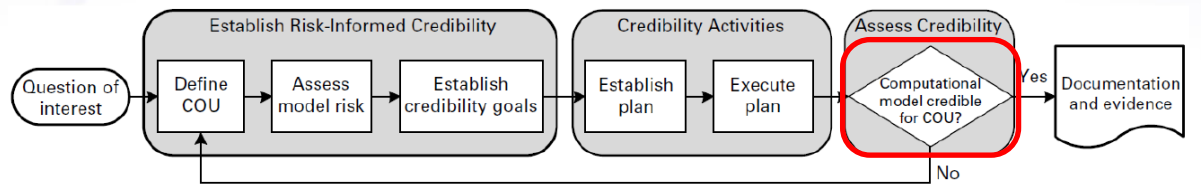


Figure 22: Highlighting of the current step "Assess Credibility" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

As device migration, vessel perforation, and thrombosis formation cannot be measured, related validation activities were conducted. To this end, two strategies were applied: (1) low-fidelity and (2) high-fidelity validation. The credibility activities for the low-fidelity validation demonstrated that the computational models, especially for the in-vitro experiments, were credible for the COU. With increasing complexity of the experiment, it was difficult to reach a good agreement between experimental and simulation outcomes. It was, for example, not possible to measure the axial force in-vivo as effects such as breathing, and movement superimposed the force. Comparing the simulation and experimental outcomes for the EV-APT, some good agreement could be observed, and some unexpected effects could be clarified. Additionally, the deformation of the fixation wires could be visualised and the resulting deformation of the PA as well as the stress could be determined. However, it was also seen that the orientation of the sensor in the PA plays a major role. Therefore, further work is needed to improve the agreement of sensor orientation in the experiments and in the simulations to match more the resulting axial forces. Overall, credibility factors of the low-fidelity validation were matching the risk factors estimated based on the context of use.

For the high-fidelity validation, it was possible to establish a calibration of engineering metrics and clinical endpoints. Furthermore, a good agreement between the simulation and the experiment was achieved. However, even though the experimental design anticipated the need for different designs that are vulnerable to migration and perforation to different extents, it remained an issue that device migration, vessel perforation, and thrombosis formation within chronic animal experiments were only occurring in very few cases, resulting in insufficient data for statistical comparison and proper model calibration was available. Therefore, the credibility activities had to be conducted with a small sample number. Considering the low to moderate model risk for device migration and device perforation, these activities are sufficient to establish credibility for the COU. Only for device thrombosis, additional credibility activities are needed as the decision consequence is high and a wrong decision could lead to adverse events.

Outlook

In conclusion, the overall structure of the ASME V&V 40 is found to be feasible to guide through the process of assessing credibility for cardiovascular implants such as PAPS and TAVI. Due to the broad range of engineering metrics, clinical quantities and model types there is a huge variety in credibility evidence. The FDA guidance for "Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions" helps to categorise and structure the different types of credibility evidence. Both documents were found to be very helpful to deal with the challenge of proving model credibility.

The tiered validation scheme proposed in this work, allowed initial assessment of the model credibility using the low-fidelity validation scheme. Here, well-posed in-vitro, ex-vivo, and to a given extent also in-vivo, experiments which had high levels of credibility facilitated direct comparison of outcomes of simulations and validation experiments. However, those experiments deviated from the intended clinical application of the device and did not allow assessing the risk of occurrence for any of the clinical endpoints. For this, dedicated validation experiments were conducted in the high-fidelity

validation scheme. Here, the credibility assessment of the models was markedly lower, as these experiments differed strongly from the numerical models. However, those experiments closely matched the intended clinical application of the device and allowed direct measurement and observation of clinical endpoints. Through combination of these two strategies, the strengths and weaknesses of the different approaches can complement each other and add further evidence for device evaluation.

Appendix 2 – In-silico validation for TAVI

In this appendix, the methodology of planning, executing and evaluating model validation activities will be embedded in the model credibility assessment on the examples of an implantable cardiovascular device, TAVI. After a brief introduction of the pathology and the device, the step-by-step procedure of model credibility assessment will be reported to an extent that is required to plan validation activities. Special emphasis is then placed on the validation activities.

Clinical need: aortic valve stenosis

TAVI, also known as a transcatheter aortic valve replacement, is a device used to treat a severe condition called aortic stenosis. Aortic stenosis is a narrowing of the aortic heart valve, which obstructs the blood flow into the aorta, and subsequently to the rest of the body. This narrowing can lead to reduced blood flow, increased ventricular pressures and therefore stress on the heart, as well as various cardiac symptoms.

Implantation of transcatheter aortic valve

TAVI devices are designed to replace the diseased or narrowed aortic valve without the need for open-heart surgery and have different designs and mechanisms for deployment, such as self-expanding or balloon-expandable valves. This minimally invasive procedure is often recommended for patients who are at high risk for traditional open-heart surgery due to age or underlying health conditions. It has improved the treatment of aortic stenosis by offering a less invasive and faster recovery option for eligible patients, ultimately improving their quality of life and prognosis.

Components of TAVI

The foundational component of a TAVI device is a frame or stent. This frame is typically made of metal alloys, such as nitinol or stainless steel. The stent provides structural support and anchors the replacement valve within the native aortic valve. The actual valve of the TAVI device consists of 3 artificial valve leaflets. These leaflets are typically made of xenogen tissue such as porcine or bovine pericardium. The leaflets are designed to mimic the function of natural aortic valve leaflets by opening and closing to regulate blood flow. Surrounding the base of the valve leaflets, there is often a sealing skirt or cuff made of flexible material. The TAVI device is mounted on a specialised delivery catheter, which is a thin, flexible tube.

TAVI devices come in various sizes to accommodate the anatomical differences among patients. The choice of device size is crucial to ensure a proper fit within the patient's native aortic valve.

Preliminary steps based on ASME V&V 40

Step 1: Define QoI

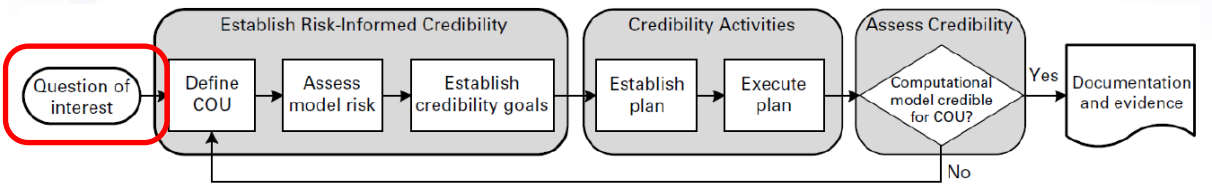


Figure 23: Highlighting of the current step "QoI" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

In SIMCor, we concentrate on three device effects for TAVI: thrombosis, paravalvular leakage and durability. Therefore, there are 3 underlying questions of interest.

Question(s) of interest (TAVI) – thrombosis, paravalvular leakage, durability
Qoi 1: thrombosis Are there any TAVI design features, regarding the leaflets, which affect thrombus formation, and can these features be evaluated by their potential to promote (or inhibit) thrombus formation? The design features of TAVI should be considered in the context of patient anatomic variability.
Qoi 2: Paravalvular leakage Are there any design features of the TAVI, regarding the stent, which affect the sealing of the device, and can these design features be evaluated by their influence on *paravalvular leakage* (PVL). The design features of TAVI should be considered in the context of patient anatomic variability.
Qoi 3: durability Are there any design features of the TAVI, regarding the stent, which affect the durability of the stent, and can these stent design features be evaluated according to their structural robustness concerning durability. The design features of TAVI should be considered in the context of patient anatomic variability.

Step 2: Define COU

For device approval or evaluation of TAVI due to clinical endpoints, the COU must be defined carefully.

"The CoU should concisely describe the role and scope of the model in answering the QoI, briefly describe the data used to build the model and the way the model outcomes will be used."[17] The following COUs describe the academic purpose of the created models within the SIMCor project. Due to the lack of clinical evidence the computational model is not valid to derive clinical relevant decisions such as changing implantation strategy.

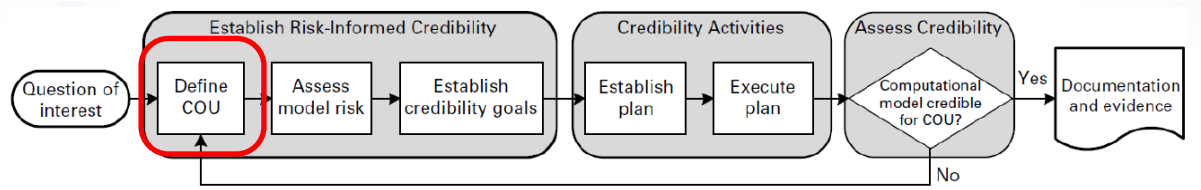


Figure 24: Highlighting of the current step "Definition of the Context of Use" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

COU (TAVI) – thrombosis, paravalvular leakage, durability
CoU1 - QoI 1: thrombosis Numerical models based on *fluid structure interaction* (FSI) have been designed to assess the thrombogenic potential of TAVI devices according to ISO 5840. By comparing different TAVI devices that can be distinguished by certain key design features, the influence of these design features on the hemodynamic situation will be investigated. By mapping hemodynamic and engineering metrics to clinical endpoints the computational model will be adjusted. The numerically obtained flow field as well as leaflet motion is validated against experimental results using high speed camera imaging and *particle image velocimetry* (PIV) measurements.

[17] Aldieri A, Curreli C, Szyszko JA, La Mattina AA, Viceconti M. Credibility assessment of computational models according to ASME V&V40: Application to the Bologna Biomechanical Computed Tomography solution. Computer Methods and Programs in Biomedicine 240 (2023) 107727

CoU - QoI 2: paravalvular leakage
Numerical models based on CFD have been developed to assess the paravalvular leakage of TAVI devices, which were previously virtually implanted in aortic root models. The influence of stent design features on PVL will be tested for different aortic root models. The virtual deployment of the stent inside the aortic root was compared with in-vitro implantation and subsequently micro-CT scanning for a sample case.

CoU2 - QoI 3: durability
FE models have been developed to evaluate the durability of TAVI stents. The mechanical load on the stent is induced by the blood pressure acting on the leaflets. Therefore, the leaflet design is one key element that determines the mechanical load. FEA simulations of the closed valve during diastole (worst case scenario) will be performed to obtain the mechanical load on the stent. Subsequently, FEA simulations of the stent will be carried out using the previously calculated load. Numerous design features such as commissural line and curvature of the leaflet will be compared in different aortic annulus sizes.

Step 3: assess model risk

In this step, we will assign a risk class to the different COUs according to their model influence and decision consequence.

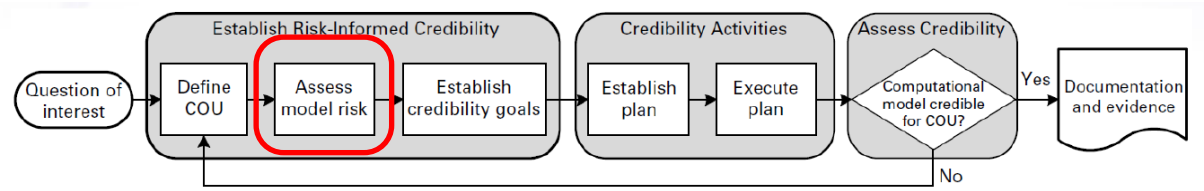


Figure 25: Highlighting of the current step "assess model risk" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Predicting thrombosis: thrombus formation in TAVI is characterised by slowly thickening of the leaflets (*hypo attenuated leaflet thickening*, HALT), which could lead to stiffening of the tissue. Due to stiff leaflet tissue the movement is hindered. Opening and closing of the valve is therefore limited, resulting in a decreased geometric and effective orifice area, increased pressure loss, higher shear flow and reduced washout. These hemodynamic conditions will subsequently promote thrombus formation.

Today, leaflet thrombosis is often declared as subclinical, meaning that the clinical outcome of TAVI procedure is almost not affected by thrombosis. But with TAVI implantation in younger patients, the durability of the valve and so slowly thickening leaflet could lead to major complications in the future. As a consequence, patients should undergo follow ups with clinical imaging to detect HALT and after detecting a nonfunctional TAVI minimal invasive or even surgical treatment options must be discussed.

Predicting PVL: Higher PVL is associated with an increase in mortality rate after TAVI implantation and leakage is an acute complication of today's patient cohort. Thus, a sealed and well-suited TAVI device is one of the goals for manufacturers as well as clinicians.

Numerical simulations of PVL are not required according to ISO 5840 but must be tested by means of pulse duplicator systems. Additionally, in pre-clinical trials as well as clinical trials the detection of PVL is standard.

Predicting fracture of device: Stent fracture could lead to sudden malfunction of the TAVI and therefore would probably cause the death of the patient.

Model risk assessment (TAVI) – thrombosis, paravalvular leakage, durability
CoU1 - QoI 1: thrombosis *Model influence*: accounting that numerical simulations are required according to ISO 5840, but several additional methods are also involved, the *model influence* is declared as “minor”. *Decision consequence*: due to the long-term process of HALT and the resulting possibility of a planned medical treatment, the risk class of *decision consequence* is therefore declared “medium”. *Model risk*: 2 (FSI)
CoU2 - QoI 2: Paravalvular leakage *Model influence*: as there is some additional evidence in addition to the numerical simulations, the risk class of the *model influence* is classified as "low", *Decision consequence*: due to the acuteness of PVL, the risk class of *decision consequences* is declared as “high”. *Model risk*: 3
CoU3-QoI 3: durability *Model influence*: there are several sources of evidence to prove the mechanical integrity and durability of TAVI stents. Among experimental investigations, the FEA is one key methodology to analyse stent durability. The model influence is therefore classified as “moderate”. *Decision consequence*: The consequences resulting from a false decision is classified as “high”, as it would probably cause the death of a patient. *Model risk*: 4

Summary of risk assessment for TAVI device

The risk assessment for the 3 CoUs identified before is summarised in the risk chart in Figure 26.

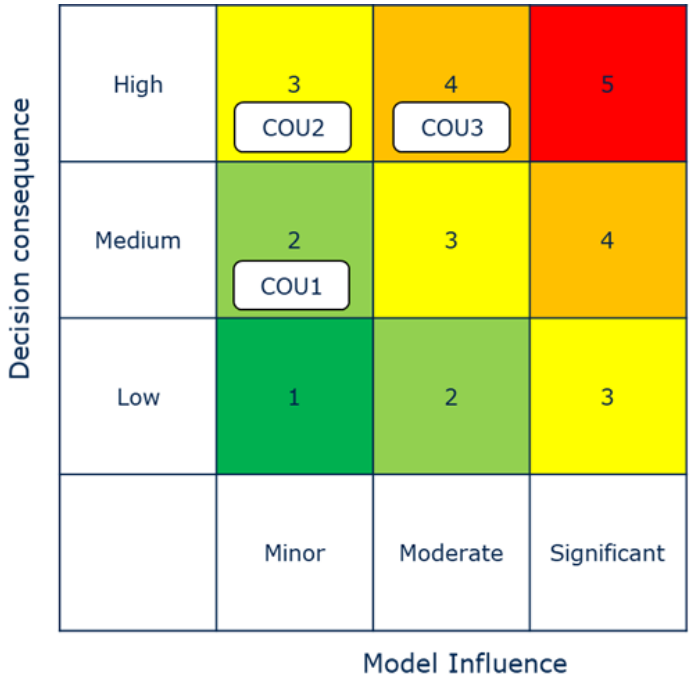


Figure 26: Assignment of the COUs to risk classes for TAVI.

Step 4: Establish model credibility goals / factors – verification, validation, applicability

Activities to establish model credibility comprise verification, validation, and applicability analysis (Figure 27).

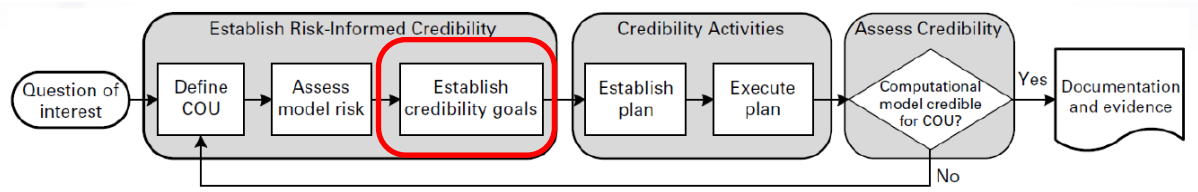


Figure 27: Highlighting of the current step "establishing credibility goals" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Step 4A: verification

Verification: verification comprises code and calculation verification. Verification activities are not within the scope of this SOP. Please refer to *D8.2* and *D9.2* for information on verification activities. The gradation of the credibility factors must be commensurate with the model risk.

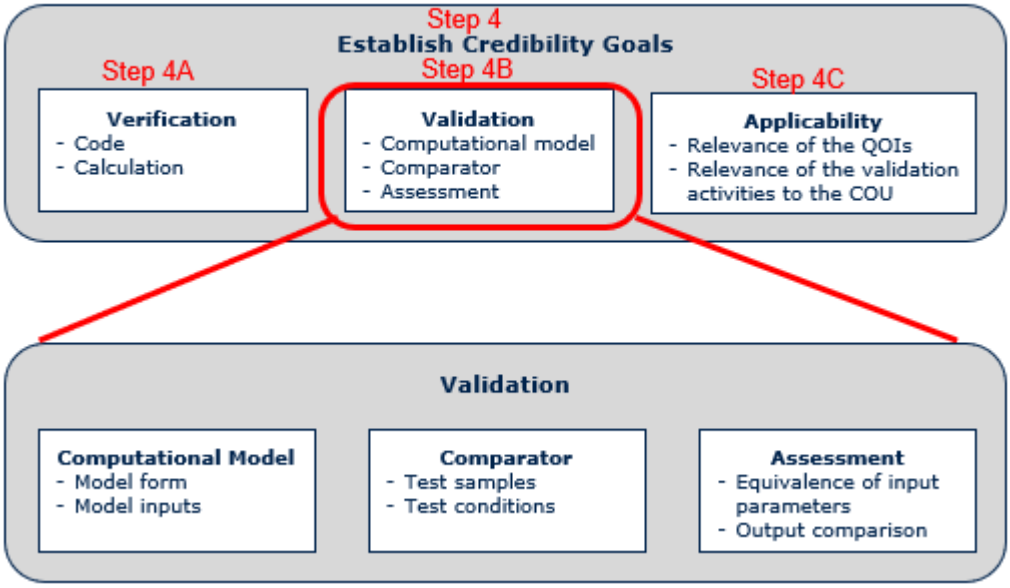


Figure 28: Highlighting of the current step "validation" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Step 4B: validation

Validation comprises the comparison of model predictions with experimental results using appropriate comparators (Figure 28). In applications where models shall predict not only engineering metrics but also clinical outcome it is advisable to apply a tiered, two-fidelity-level validation strategy. The proposed scheme shall be applied for the most relevant safety, efficacy, and usability endpoints like paravalvular leakage and thrombosis for the TAVI example.

Step 4B-1: model form and input

The computational models are described in detail in D8.2 and D9.2. Furthermore, detailed results on the low- and high-fidelity validation are provided in *D9.3 - Low-fidelity validation results (BIO, M30)*[18] and *D9.5 - High-fidelity validation results (BIO, M36)*[19], respectively. The following section will give a short summary of the key aspects regarding model form and model inputs.

Model form

The mathematical description of the 3 device effects is explained in D9.2 (FSI for thrombosis assessment, CFD for PVL and FEA for durability).

Thrombosis	Paravalvular leakage	Durability
Transient Navier-Stokes equations using RANS turbulence model (k-omega SST) for the fluid domain and transient equation of motion for structural components, e.g. leaflet, was applied. The coupling was performed by means of Arbitrary Lagrangian Eulerian approach.	Transient Navier-Stokes equations with RANS turbulence model (k-omega SST), was applied.	The structural analyses were performed as static steady- state analyses in combination with an implicit standard solver. ANSYS (ANSYS Inc., certified according to ISO 9001) was used as FEA software.

Table 15: Mathematical model for device effect simulation of TAVI.

System configurations (geometrical description)

Thrombosis	Paravalvular Leakage	Durability
Generic aortic root model was created in accordance with ISO 5840. The leaflet design models the shape of the TAVI prototype (comparator).	Commercially available TAVI device implanted in a generic aortic root model with calcification under in-vitro conditions. Geometry was obtained by means of microCT scanning.	Computer Aided Design file of the TAVI stent developed by IIB. Aortic root geometry was created according to ISO5840.

Table 16: System configuration for device effect simulation of TAVI.

System properties (material properties of the blood and tissue)

Thrombosis	Paravalvular Leakage	Durability
CFD of the blood with non-Newtonian fluid model according to literature. Structural mechanics for the leaflet with linear-elastic material behaviour according to literature.	CFD with Newtonian fluid model according to ISO5840.	For Finite Element Analysis (FEA) of TAVI stent a super-elastic material law for the shape memory alloy Nitinol with 8 parameters was used.

Table 17: System properties for device effect simulation of TAVI.

System conditions (initial and boundary conditions)

Thrombosis	Paravalvular Leakage	Durability
Hemodynamic boundary and initial conditions based on in-vitro measurements. Initial and boundary conditions of the validation simulation are identical to the comparator.	Hemodynamic boundary and initial conditions based on in-vitro measurements. Initial and boundary conditions of the validation simulation are identical to the comparator.	Initial and boundary conditions of the validation simulation are identical to the comparator. The radial deformation is displacement controlled and the resulting reaction force is calculated

[18] This deliverable is confidential, thus not publicly available, but can be requested to Jan Romberg (Jan.Romberg@biotronik.com).
[19] This deliverable is confidential, thus not publicly available, but can be requested to Jan Romberg (Jan.Romberg@biotronik.com).

Table 18: System conditions for device effect simulation of TAVI.

Tailored step 4: low-fidelity validation

Step 4B-2: comparator

Please note that the presented low-fidelity validation, particularly the used test samples, is not sufficient. Furthermore, the description of the low-fidelity validation is high level and therefore not sufficient to fulfil the required reporting recommendations. For information regarding sample size, range of characteristics of test samples, test conditions, etc. please see ISO 5840. Figure 29 provides a matrix of tests which are performed to validate the three device effects corresponding to the questions of interest and the COUs.

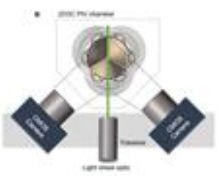
Validation step	Clinical endpoint	Thrombosis	PVL	Durability
	Related engineering metrics to be validated	- Geometric orifice area - Transvalvular pressure difference - Max velocity jet flow and neo sinus	- Leakage volume - Leakage flow rate	- Post deflection
	Model type / Experiment setup	Transient FSI model for systolic phase	Transient CFD model for diastolic phase	Structural mechanics FE model
In vitro		2D3C PIV 	Pulse duplicator leakage testing 	Post deflection testing 

Figure 29: Summary of the validation test that were performed for the device effect simulation of TAVI.

The credibility factors of the following experiments are defined in the following:

1. In-vitro flow field measurement via particle image velocimetry (**IVT-PIV**)
2. In-vitro PVL testing (**IVT-PVL**)
3. In-vitro post deflection testing (**IVT-PD**)

Test samples: quantities, range of characteristics, measurements and uncertainty quantification of measurements are selected such that a medium to high level of credibility will be achieved. In particular, a statistically relevant sample size shall be used, a wide range of sample characteristics shall be used, all key characteristics shall be measured and the uncertainty analysis shall include instrument uncertainty and repeatability. Please note that the TAVI use case presented here is an example of the workflow. Sample size and documentation for device approval must be considerably enlarged.

	IVT-PIV	IVT-PVL	IVT-PD
Quantities	1	3	3
Range of characteristics	Only one size of the valve was used for validation measurements.	Only one size of the valve was used for validation measurements.	Only one size of the valve was used for validation measurements.
Measurement	Valve size was measured using a calliper gauge.	Valve size was measured using a calliper gauge.	Valve size was measured using the prismatic head of the radial force tester.
Uncertainty	The uncertainty of valve size measurements can be neglected for hemodynamic assessment using PIV.	The uncertainty of valve size measurements can be neglected for PVL assessment using pulse duplicator measurements.	The uncertainty of TAVI diameter measurement according to traverse uncertainty.

Table 19: Test samples for the validation experiments for TAVI related device effects.

	IVT-PIV	IVT-PVL	IVT-PD
Quantities	One test conditions were examined	Three test conditions were examined	One test conditions was examined
Range of conditions	The examined test condition falls within the expected condition	Expected range of conditions were examined (worst case, best case, and average conditions of diastolic pressure)	Entire range of conditions was used by measuring the force-displacement hysteresis
Measurement of condition	Pressure, flow rate, refractive index and fluid viscosity was measured. Temperature of the fluid was controlled at the thermal bath.	Pressure, flow rate and fluid viscosity were measured. Temperature of the fluid was controlled at the thermal bath.	Radial force measurement as function of device diameter. Temperature of the prismatic head of the radial force tester was controlled.
Uncertainty of measurement	Uncertainty analysis incorporated a comprehensive quantification of repeatability, calibration of the test machinery, optical distortion, uncertainty of the PIV system and of the pulse duplicator system (flow metre and pressure transducer), uncertainty of the viscosity meter and refractometer. Measurement is aligned with ISO5840 requirements.	Uncertainty analysis incorporated a comprehensive quantification of repeatability, calibration of the test machinery, optical distortion, uncertainty of the pulse duplicator system (flow metre and pressure transducer), uncertainty of the viscosity meter and refractometer. Measurement is aligned with ISO5840 requirements.	Uncertainty analysis incorporated a comprehensive quantification of repeatability, calibration of the test machinery, uncertainty of the load cell (force measurement) and of the position sensor of the traverse.

Table 20: Test conditions of the validation experiments for TAVI related device effects.

Results of the low-fidelity validation are reported in D9.3.

Step 4B-3: assessment

	IVT-PIV	IVT-PVL	IVT-PD
Equivalency of Input Parameters	FSI simulation was performed according to test conditions	CFD simulation was performed according to test conditions	FEA was performed according to test conditions
Output comparison	The numerically obtained velocity was compared to the experimentally resulted velocity field.	The numerically obtained flow rate was compared to the experimentally resulted flow rate depending on the pressure	The numerically obtained force was compared to the experimentally resulted force as a function of TAVI diameter during crimping process

Table 21: Comparison of input and output parameters of the validation experiments for TAVI related device effects.

Step 4C: applicability

	IVT-PIV	IVT-PVL	IVT-PD
Relevance of the quantities of interest	The QOI from the validation activities are related to those of the COU: high shear and high blood residence time can explicitly be derived from the validated velocity field. Both engineering metrics are related to. thrombus formation.	The QOI from the validation activities are identical to those of the COU: flowrate of the leakage.	The QOI from the validation activities are related to those of the COU: force due to stress-strain distribution of the material (in-silico) was validated to further calculate maximum strain for fatigue limit assessment.
Relevance of the validation activities to the COU	High shear and high blood residence time were found to be associated with thrombus formation. Velocity field cannot accurately measured in a clinical setting and thrombus formation is hard to model in an experimental setting. Therefore, there is no direct overlap between the COU and the validation experiment but high shear and high blood residence time can explicitly be derived from the validated velocity field.	The COU encompasses the validation point.	Stent fracture can be detected in a clinical setting. Purpose of the FEA is to detect high strains which exceed fatigue limits (fatigue limits were previously obtained by Pelton et al.). Local strains cannot be measured via radial force test, but the summation of strain results in a radial force which was used as a comparative metric.

Table 22: Table 23: Applicability of the validation experiments for TAVI regarding the CoU.

Step 4: summary of credibility factors

Level of rigor

	IVT-PIV	IVT-PVL	IVT-PD
Test samples - Measurements and measurement uncertainty	Medium (B)	Medium (B)	High (C)
Test conditions - Measurements	Medium (B)	Medium (B)	High (C)
Test conditions - Measurement uncertainty	Medium (B)	Medium (B)	High (C)
Assessment – Equivalency of input parameters	High (C)	High (C)	High (C)
Assessment – output comparison	High (C)	High (C)	Medium-high (B)
Applicability - Relevance of QOIs	low (C)	High (C)	Medium (C)
Applicability – Relevance of the Validation Activities to the COU	Medium (C)	High (B)	Medium (B)

Table 23: Levels of rigor for validation experiments for TAVI related device effects.

Credibility factor

Based on the levels of rigour, an overall model credibility can be determined, which commensurate with the model risks.

	IVT-PIV	IVT-PVL	IVT-PD
Credibility level	Medium	Medium-high	Medium-high
Model risk	Medium	Medium	Medium

Table 24: Comparison of credibility level with model risk of the validation experiments for TAVI related device effects.

Tailored Step 4: high-fidelity validation

Example for paravalvular leakage

For the TAVI use case, our aim was to perform high-fidelity validation through population-based comparison of simulation results with literature results on clinical studies with commercially available TAVI models, see Figure 30.

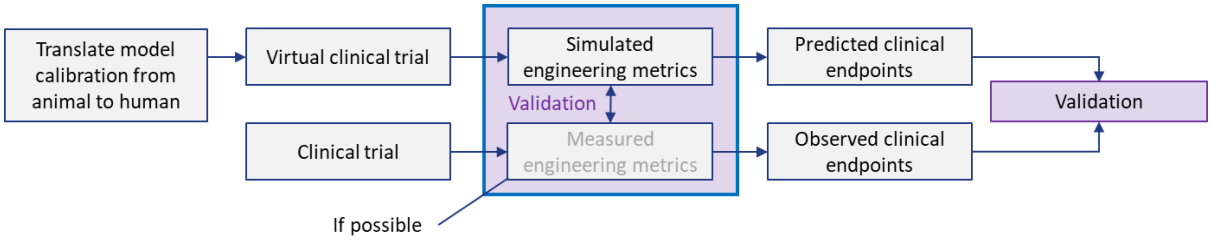


Figure 30: Model validation with clinical data using a virtual cohort.

Within this document we focus on PVL to show an exemplar workflow of the high-fidelity validation. Despite the increasing experience of surgeons and new TAVI designs, PVL remains a significant complication associated with increased mortality. Due to the many other reasons that can lead to a patient's death, we have decided to assess leakage immediately after implantation. PVL is documented in many clinical studies characterised by different degrees of severity (mild, moderate and severe).

As described for low-fidelity validation, CFD analyses were used to assess the leakage rate of virtual patients and so the computational model implemented for high-fidelity validation is equal to the model used for low-fidelity validation.

Post-validation steps based on ASME V&V 40

Step 5: validation activities & results

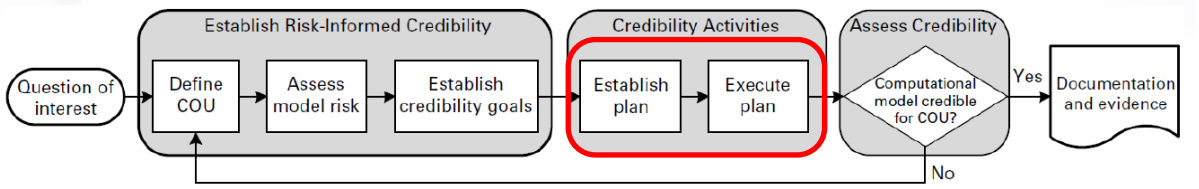


Figure 31: Highlighting of the current step "credibility activities" within the process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

Low-fidelity validation results with respect to engineering metrics

Table 25 summarises the validation results of the low-fidelity validation. Detailed results of the low-fidelity are reported in D9.3.

	IVT-PIV	IVT-PVL	IVT-PD
Purpose of credibility activity	Thrombosis	Paravalvular Leakage	Durability due to stent fracture
Conceptual model (abstracted)	Which hemodynamic condition (high shear and high residence time) is induced by the TAVI?	Which leakage rate can be found after device implantation?	Which strain is induced due to valve closure?
Description of physical model	Flow in the vicinity of the TAVI device could be disturbed. Pathological flow is correlated with thrombus formation.	Paravalvular leakage can occur post-procedural of TAVI implantation due to pathologically altered patients' annulus.	TAVI is mechanically loaded at the attachments in a radial direction due to valve closure.
Computational model	Anatomy is identical to the experimental model, but assumed to be rigid. Leaflet design of TAVI is identical to experimental design. Stent is neglected.	Anatomy is identical to the experimental model, but assumed to be rigid. Stent design is identical to experimental design. Leaflets were modelled in a closed status.	Stents and displacement identical to experimental design.
Experiment design	TAVI device is implantation in silicone mock vessel and incorporated in a pulse duplicator system. Flow is optical detect via particle image velocimetry imaging.	TAVI device is implantation in silicone mock vessel and incorporated in a pulse duplicator system. Leakage is detected via flow metre.	TAVI is mechanically loaded at the attachments in a radial force tester.
Simulation results	Velocity distribution of the flow field distal of the valve for various time steps during diastolic and systolic phase	Transient flow rate during diastolic phase	Force-displacement diagram due to stress-strain- distribution within the material
Experimental data	Velocity distribution of the flow field distal of the valve for various time steps during diastolic and systolic phase	Transient flow rate during diastolic phase	Force-displacement diagram
Simulation outcomes vs. experimental outcomes	Good agreement	Good agreement	Good agreement
Degree of agreement	Sufficient	Sufficient	Sufficient
Next steps	Matching metrics and high-fidelity validation using virtual cohort	Matching metrics and high-fidelity validation using virtual cohort	None

Table 25: Overview of the results of the low-fidelity validation of the TAVI use case.

High-fidelity validation results with respect to clinical endpoints

Data from published clinical studies were used as comparative material. This data was used to create a virtual cohort with the same anatomical characteristics of the aortic root as the clinical study. Subsequently, TAVI models were virtually implanted in these virtual patients and CFD simulations of the closed valve during the diastolic phase were conducted. The resulting leakage rates were compared to population based clinical data. In detail the distribution of severity (no PVL, mild, moderate, severe) of the virtual cohort and the clinical study were compared. In this phase there are several limitations of the methodology:

1. **System configuration**: the calcification nodules were generated according to ISO 5840 and for every patient the position of each calcification nodules was consistent. The positioning of the TAVI device, e.g. commissural alignment, was performed randomly but is consistent for every patient. Implantation depth of the TAVI device was according to the instruction for use.
2. **Test conditions**: the virtual cohort does not include any boundary condition. Furthermore, the clinical studies do not provide information of the diastolic blood pressure of the patient or the cohort. All CFD simulations were carried out by using 70 mmHg for all virtual patients.

Due to these major limitations, we assume a credibility level of low-medium. Further studies need to concentrate on virtual cohort generation including calcification and hemodynamic conditions. Results are reported in D9.5.

Step 6: assess credibility based on validation results

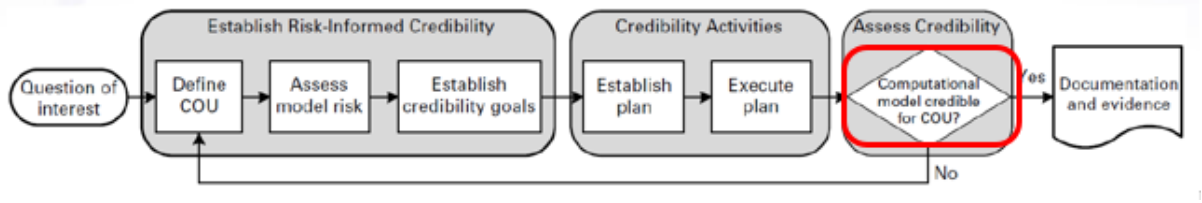


Figure 32: Process diagram of the risk-informed credibility assessment framework provided by ASME V&V 40.

For the TAVI use case, the credibility factor of the low-fidelity validation corresponds to or even exceeds the risk factor of the model. Despite some limitations, which should be documented and evaluated in detail, the overall credibility of the numerical model is given, and further validation steps (high-fidelity validation) could be performed.

As an example, PVL was chosen as a device effect for TAVI to describe the workflow for high-fidelity validation using a population-based approach using virtual cohorts. At this stage, there are several limitations of the methodology due to lack of information about the real cohort such as hemodynamic conditions and implantation position. Therefore, the virtual cohort contains sufficient geometric/anatomical information, but missing information had to be replaced by averaged data or suggestions from the literature. Despite the well-matched results, the virtual cohort generator needs further implementation with regard to hemodynamic conditions to achieve a valid credibility level of in-silico models.

Outlook

In conclusion, the overall structure of the ASME V&V40 is found to be feasible to guide through the process of assessing credibility for cardiovascular implants such as TAVI devices. Due to the broad range of engineering metrics, clinical quantities and model types there is a huge variety in credibility evidence. Thus, the FDA guidance for “Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions” helps to categorise and structure different types of credibility evidence. Both documents were found to be very helpful to deal with the challenge of proving model credibility. Additionally, the documents presented here, including complex examples dealing with different quantities of interest for COU and for validation (thrombus formation as clinical endpoint vs high shear and low blood residence time as engineering metrics), were not highlighted neither within V&V40 nor the FDA guidance. According to the requirements of the ISO 5840:2021, a integrated thrombus and haemolytic potential assessment approach will lead to a broad range of quantities of interest which need to be correlated. We found that the applicability analysis must be moved further into the focus of future guidelines. Therefore, SIMCor will concentrate on the matching of different quantities of interests which come along from bench to bedside.

Additional documents

- ISO 5840-1:2021, *Cardiovascular implants — Cardiac valve prostheses — Part 1: General requirements*
- ISO 5840-2:2021, Cardiovascular implants — Cardiac valve prostheses — Part 2: Surgically implanted heart valve substitutes
- ISO 5840-3:2021, *Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques*
- *ISO 9001:2015, Quality Management Systems*
- *ISO 14971:2019, Medical devices — Application of risk management to medical devices*

Contingencies

None.

Attachments

None.

Publication policy

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