SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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Executive summary

SIMCor is an ambitious H2020 research project that focuses on the development of an open, reusable, cloud-based platform for in-silico testing to accelerate the development and regulatory approval of products of manufacturers of cardiovascular implantable devices.

In this deliverable we define the technical requirements for adapting and extending the UTBV cloud-based infrastructure to integrate collected data and computational tools to facilitate the in-silico clinical trial workflow. First, the system requirements specification methodology is defined, including scope, commitments and purpose. The system requirements process is unfolded in two phases: (i) initial system requirements gathering, and (ii) platform system requirements specification and refinement. Templates have been defined both for the use cases and the requirements. Overall, four use cases have been defined for each of the two medical use cases of SIMCor, i.e., *pulmonary artery pressure sensor* (PAPS) and *transcatheter aortic valve implantation* (TAVI). The use cases pertaining to a medical use case are linked together: (i) the first use case generates a virtual population of PAPS/TAVI cases, (ii) the second use case addresses a structural simulation (fixation of sensor/replacement valve deployment), (iii) the third use case addresses blood flow simulations, and (iv) the fourth use case allows for data analysis (statistics computation). Subsequent use cases may receive input from preceding use cases.

Next, system requirements are detailed, describing the functions the system needs to do. These are divided into: (i) functional requirements and (ii) non-functional requirements. The formers determine the goals that users want to reach and the tasks they intend to perform. The important point to note is that WHAT is wanted is specified, and not HOW it will be delivered. The non-functional requirements determine the restrictions on the types of solutions that will meet the functional requirements. Specification of non-functional requirements includes performance aspects, security, privacy, and general criteria that judge the operation of the system. One of the main goals of SIMCor is to contribute to the *European Open Science Cloud* (EOSC) initiative by becoming a provider, offering services and resources to researchers.

Table of contents

List of figures

List of tables

List of acronyms

Acronym	Full name
AU	Authorized users
EOSC	European Open Science Cloud
ESC	European Society of Cardiology
FAIR	Findability, Accessibility, Interoperability, and Reusability
GB	Gigabyte
GDPR	General Data Protection Regulation
IPR	Intellectual Property
IT	Information Technology
MB	Megabyte
OA	Open Access
PAPS	Pulmonary artery pressure sensors
PHI	Philips Electronics Netherlands B.V.
R&D	Research and Development
SIMCor	In-Silico testing and validation of Cardiovascular IMplantable devices
SOP	Standard operating procedure
TAVI	Transcatheter aortic valve implantation
TB	Terabyte
TUE	Eindhoven University of Technology
UCL	University College of London
UR	Upon Registration
UTBV	Universitatea Transilvania Din Brașov
VPH	Virtual Physiological Human
VRE	Virtual research environment
WP	Work Package

Introduction

SIMCor is an ambitious H2020 research project that focuses on the development of an open, reusable, cloud-based platform for in-silico testing to accelerate the development and regulatory approval of cardiovascular implantable devices. The platform will support device validation along the whole R&D pipeline: from initial modelling and in-vitro experiments to animal studies as well as device implantation and effect simulation on human cohorts. In particular, SIMCor innovative virtual cohort technology will allow to generate and expose new or existing devices to a range of clinically realistic and diversified anatomies and (patho)physiological conditions, meeting the critical need of testing devices in young patients. High-priority safety, efficacy, and usability endpoints will be investigated, focusing on device implantation and effect simulations in two representative areas: *transcatheter aortic valve implantation* (TAVI) and *pulmonary artery pressure sensors* (PAPS).

Moreover, SIMCor exploitation plan aims at creating synergies rather than appearing as a competitor to existing solutions. This way, the benefits of SIMCor will spread to all the potential medical device providers. All key points of the SIMCor *virtual research environment* (VRE), described above, will play an important role in addressing the complexity and speed of technological innovation, which creates a huge demand for standardized best practices to apply in-silico validation methods in a statistically robust, repeatable, and efficient way.

The SIMCor system requirements that have been specified in this deliverable will set the basis for the VRE implementation.

System requirements specification methodology

The approach taken in specifying the requirements was determined by a number of factors: scope, constraints, and purpose.

Scope

The scope of the present deliverable is to be understood in the context of the overall SIMCor work plan. SIMCor aims to establish a standardized platform for in silico development, validation, and regulatory approval of cardiovascular implantable devices as an open resource for collaborative R&D for cardiovascular device manufacturers, medical authorities, and regulatory bodies.
The platform will support cardiovascular device manufacturers to perform, in a standardized way, quality approved in-silico tests for accelerating research and the development process and the regulatory evaluation of device safety, efficacy, and usability endpoints at the preclinical and clinical trial level. The virtual cohort technology to be developed in SIMCor will allow exposing new devices to a vast number of clinically realistic and relevant geometries and pathophysiologic conditions.

The need for integrated IT services to share data, computational resources, and knowledge has been largely acknowledged by the VPH community, including the VPH-Share initiative[1], where several consortium partners (PHI, TUE, UCL) have been involved. SIMCor embraces this concept by adapting the cloud-based infrastructure available at UTBV and creating a VRE (WP3) where it will be possible to share data acquired from different sources (WP5), statistical shape models, computational resources (WP8-9), workflows, guidelines, standards, and protocols (WP4) for collaborative R&D, in-silico testing, validation, and regulatory approval of cardiovascular devices (storage space > 10TB). The platform will be designed to have two different domains of R&D: (a) a domain for the generation and validation of virtual cohorts and (b) a domain for the actual in-silico testing and validation of device effects according to safety, efficacy, and usability endpoints.

WP3 - Virtual research environment implementation focuses specifically on the platform, i.e., it will create, based on the cloud-based infrastructure available at UTBV, a VRE where to integrate preclinical, clinical, and synthetic data, acquired in the context of WP5, as well as virtual cohorts, simulation models and other computational tools, developed and validated in WP7, WP8, and WP9. Besides serving as a data repository for project resources, the infrastructure will represent a working environment for collaborative simulation, testing, and validation. Most importantly, the infrastructure will support the SIMCor contribution to the *European Open Science Cloud* (EOSC) with reusable data, tools, methods, guidelines, and *standard operating procedures* (SOPs) developed in the course of the action. More specifically, the activity is structured along with the following objectives:

1. Define technical requirements to adapt and extend the UTBV cloud-based infrastructure into the VRE;
2. Integrate data sources, virtual cohorts, models, methods, and guidelines into the defined VRE;
3. Develop user interfaces, data visualization tools, and user profiles for different kinds of user groups.

Task 3.1 defines the technical requirements for adapting and extending the UTBV cloud-based infrastructure to integrate collected data and computational tools to facilitate the in-silico clinical trial workflow. The input and output format of each element is defined along with the requirements for the exchange of data between partners and between workflow elements. FAIR principles are followed for the management of the prospective and retrospective data collected within WP5. Specifically, requirements will be aligned with the EOSC initiative guidelines. The task also defines differential future accessibility profiles for platform resources, including *Open Access* (OA, publicly available with

[1] http://www.vph-share.eu/

no registration), *available upon registration* (UR), and for *authorized users only* (AU), based on the IPR set by the producer. Finally, to promote a safe, homogeneous, and controllable quality process for software development and infrastructure management, a set of quality criteria are being collectively identified.

Project commitments

In the following we briefly mention relevant project commitments:

- SIMCor exemplarily addresses two representative cardiovascular device use cases, (1) TAVI and (2) PAPS, based on their large potential socio-economic impact, the wide range of pathophysiologic conditions and biomechanical properties involved.
- SIMCor defines a methodology for the generation of virtual cohorts to be used for in-silico tests in replacement of in vitro and preclinical tests in animals (i.e., porcine and ovine models) as well as of clinical I-III stage human trials in adults and children, reproducing a variety of geometries, pathophysiologic conditions, and clinical features.
- SIMCor elaborates a standardized framework for the virtual implantation of medical devices on bench test environments, animal, and patient cohorts, based on TAVI and PAPS device and vessel models and generalizable for other cardiovascular devices and clinical use cases.
- SIMCor leverages an existing consortium cloud-based infrastructure for the development of a VRE for development and innovation, for the benefit of the medical device manufacturing, in-silico medicine research and other stakeholder communities. The VRE will integrate available preclinical, clinical, and synthetic data resources, virtual cohorts, simulation models, methods, guidelines, and SOPs developed in the course of the project, and serve as a working environment for collaborative simulation, testing and validation.

The requirements reflect the above fundamental commitments. These include:

- Security requirements that reinforce the privacy of data and trustworthiness of the SIMCor platform;
- Functional requirements that take into account the two representative cardiovascular devices use cases;
- Non-functional requirements.

Purpose of platform requirements

The scope of the VRE is to integrate available preclinical, clinical, and synthetic data resources, virtual cohorts, simulation models, methods, guidelines and SOPs developed in the course of the project, and serve as a working environment for collaborative simulation, testing and validation.

System requirements specification process

The requirements specification process was focused, with known targets, known constraints, and a well-understood scope. Setting the aforementioned parameters was non-trivial, but the consensus was built between partners in the course of reaching a common understanding of the project's objectives and the ways its benefits could be demonstrated in the two medical use cases.

The SIMCor platform requirements specification process unfolded in two phases:

Phase I (end M1 to mid M4): Initial system requirements gathering.
The first phase of the requirements specification process was initiated at the kick-off meeting in January 2021. It covered both general SIMCor platform requirements and use case-specific requirements concurrently, with most progress, inevitably, made on the former (general SIMCor platform requirements) as the latter (SIMCor use case-specific requirements) required significantly more deliberation with partners.

Initial requirements gathering took place over the course of approximately two months, including several online discussions.

Key achievements and outcomes included:

- An understanding of the commitments the SIMCor Consortium has undertaken.
- An understanding of:
  - the kinds and amounts of data that will be made available;
  - the level of functionality that can be made available at different times in the project given the expected availability of data to enable said functionality.
- An understanding of the scope of D3.1.
- An initial understanding of who the users of SIMCor will be:
  - Technical partners of the projects
  - Medical device manufacturers
  - IT System Administrators.
- An initial understanding of
  - Basic functional requirements among all partners and
  - Basic security requirements
  - Basic performance requirements.

Phase II (M4-M6): SIMCor platform system requirements specification and refinements.
In Phase II, specification of system requirements began with decisions about how the requirements are to be recorded and organized and decisions about whether use cases and scenarios are to be used. The following decisions were taken:

- It was decided that use cases will be used as the basis for functional and, where appropriate, non-functional requirements and that these use cases would be generic, addressing the functionality provided by the platform.
- It was decided to use structured natural language for recording the requirements, using the templates described below.
- The overall structure of use cases, functional and non-functional requirements was, provisionally, finalized.

Two core tracks need to be supported by the VRE platform:

a. *Virtual cohort generator*. The virtual cohort generator will constitute a core module of the SIMCor in-silico platform: it will support the generation of virtual cohorts for SIMCor use cases (i.e., TAVI, PAPS) and provide a generalized methodology for the generation and validation of virtual animal and patient cohorts. The core of the tool will consist of a module allowing for state-of-the-art uncertainty and sensitivity analysis. The uncertainty analysis quantifies the uncertainty in model predictions caused by uncertainties in the model parameters and boundary conditions (i.e., model inputs). The sensitivity analysis is used to attribute each fraction of the total output uncertainty to uncertainties in the different parameters of the model input. By doing this, sensitivity analysis helps decide which input data are relevant to assess patient-specific features and determine which model inputs are mostly responsible for output realizations within the predefined range, and therefore relevant for virtual cohort generation. In SIMCor these tools will be used for the first time to quantify uncertainties and relevant inputs on a cohort level and will be adapted to the specific use cases.

b. *Device effect simulation*. The platform will allow the simulation of device effects by generic and subject-specific patient and animal models for assessing device performance, including mechanisms of device failure, with the possibility to conduct design optimization between simulation iterations. The computational domain for device effect simulation will contain two components: (1) for virtual implantation, where devices are implanted and fitted through finite element models for detailed, subject-specific modelling, and through reduced-order

models for larger numbers in virtual cohorts; (2) for actual simulation of device effects in regard to safety, efficacy, and usability endpoints, based on structural and fluid mechanics models. For PAPS, the assessment focus will be on device migration, perforation, or thrombosis; in TAVI it will be on thrombosis, paravalvular leakage and durability. To facilitate the seamless and standardised application of the SIMCor methodological framework for in-silico trials according to the defined SOPs, the platform will also be equipped with a user interface that will guide the user step-by-step through the complete in-silico trial process, including the upload of data templates, definition of output and input ranges, generation of virtual cohorts, execution of simulation models.

The requirements gathering process focused on collecting input from all technical partners. The first version of the SIMCor platform system requirements specification was created over the course of approximately four weeks (4 – 30 April 2021) of collaborative effort on the basis of Phase I results and the Phase II preparatory work mentioned above. The results of this work were presented and discussed in a dedicated meeting on 27 April, where all partners discussed the first version of the SIMCor platform system requirements specification after having reviewed it in its entirety. This was an important milestone as it completed the move from the Phase I efforts to achieve a shared understanding of SIMCor platform requirements to a concrete SIMCor platform systems specification which could be evaluated (across a number of criteria, such as completeness, lack of ambiguity, usefulness, achievability, and correctness of prioritization) and refined where appropriate. Subsequent versions of the SIMCor platform system requirements were created in the following weeks, as part of the corresponding versions of the present deliverable.

System requirements testing process

Testing is an important part of any product development, especially to guarantee the quality of the product. Testing can be performed manually and automatically. Our scope is to automate the testing process as much as possible. By automating our testing process, we are saving time and delivering a higher quality product.

The purpose of system requirements testing is to evaluate the end-to-end system specifications. System requirements testing must be conducted on a complete integrated system to evaluate the system's compliance with its functional requirements, non-functional requirements, or both.

For testing system requirements we are proposing the following categories of test cases:

- **Use-case test cases** (for testing functional requirements): ensure that certain business functionality (use case) is delivered by the system as a whole. This type of tests usually implements a sequence of steps imitating user interaction, and checks for the result in the closest possible way to the real scenario.
- **Non-functional test cases:** ensure that particular non-functional characteristics (qualities) are fulfilled. This usually implements a sequence of steps, but unlike use-case tests during assertion focuses on measuring system health, required resources, required time, etc. It may also involve code to stress the system, e.g., pumping extensive amounts of data to test performance or deliberately killing service instances to test system availability.

In addition to software testing that will be automatically run on every new version of the VRE, we plan to validate the implementation of the system requirements with all consortium members, by organizing regular feedback sessions, so that we can improve and adapt the development of software requirements based on that feedback.

System requirements update process

In modern software development, the improvement and adaptation of system requirements, to fulfil the project needs, should be a continuous process. If the project will require certain adaptations that were not considered during the definition of the system requirements, the consortium will have the possibility to update system requirements, based on a common agreement.

Use cases and requirements specification templates

We have defined templates for use case scenarios and requirements to have a harmonized structure and enforce a standard layout and look across all the collected scenarios and requirements. The templates provide the framework that brings together common elements, gives a unique reference ID to every scenario and requirement to facilitate the linkage between them and encourages repeatability and efficiency.

The above templates for requirements and scenarios give textual descriptions inspired by a standardized formal language. We often highlight in block letters SHALL, SHOULD and COULD/MAY. These should however not be confused with the similar keywords that we use for the priority of accomplishment of a requirement, i.e., “Shall have”, “Should have”, “Could have”.

The use case scenarios template

The defined use case scenario template is as follows:

ID	***A unique ID distinguishing this use case from any other. To form use case IDs the following scheme should be used:*** ***<Prefix>.<number>*** ***where*** ***<Prefix> := PAPS | TAVI*** ***The use of the one of the above prefixes should indicate the corresponding medical use case:*** ● ***PAPS: Pulmonary Artery Pressure Sensor*** ● ***TAVI: Transcatheter Aortic Valve Implantation***
Name	*A short string indicating the meaning of the use case*
Description	*A brief summary outlining the overall purpose of the use case and the interaction taking place with the SIMCor platform*
Input Data	*[Optional] Input data to be used for the use case. May refer to data origin, boundary conditions, input parameters, geometry, mesh, time resolution*
Initial conditions	*[Optional] Initial conditions of the models employed by the use case*
Model parameters	*[Optional] Parameters of the models employed by the use case*
Filtering parameters	*[Optional] Parameters that can be employed for filtering the input data*
Output Data	*Output data of interest obtained as a result of performing the main steps described below*
Main steps	*The typical sequence of steps that should be taken to realize the interaction between the SIMCor platform and the use case actors that this use case describes. The steps should be listed in the exact sequence in which they occur and be numbered in a way that indicates this sequence (i.e., 1. (for the first step), 2. (for the second step) etc.) Steps should be atomic (i.e., a step should be a single action that is taken by either the external actor or the system as part of the interaction) and indicate with clarity who is responsible for taking the step (i.e., the system or an external actor).*
Visualization requirements	*[Optional] Specifications regarding the approaches for visualizing the data related to the use case (e.g. input / output data)*
Data import	*File types used when importing data*
Data export	*File types used when exporting data*

Table 1: SIMCor use-case scenarios template.

The requirements template

The requirements template is as follows:

ID	*A unique ID for this requirement/assumption*
Name	*A title/short name for this requirement/assumption*
Priority of accomplishment	*One of the following: **Shall have**: The system shall implement this requirement to be accepted. **Should have**: The system should implement this requirement: some deviation from the requirement as stated may be acceptable. **Could have**: The system should implement this requirement but may be accepted without it.*
Description	*Specify the intention of the requirement/assumption*
Rationale	*If the description is not descriptive enough, this entry gives a justification of the requirement/assumption. Otherwise, this entry will be filled with N/A.*
Supporting materials	*If applicable, give a pointer to documents that illustrate and explain this requirement/assumption. Otherwise, this entry will be filled with N/A.*

Table 2: SIMCor requirements template.

Use cases

Use case overview

Figure 1 displays an overview of the use cases detailed in this chapter. Overall, four use cases have been defined for each of the two medical use cases of SIMCor (PAPS and TAVI). The use cases pertaining to a medical use case are linked together:

- The first use case generates a virtual population of PAPS / TAVI cases;
- The second use case addresses a structural simulation (fixation of sensor/replacement valve deployment);
- The third use case addresses a blood flow simulation;
- The fourth use case allows for data analysis (statistics computation).

As can be observed in *Figure 1*, subsequent use cases may receive input from preceding use cases. Finally, one use case has also been defined for SOPs. All use cases are described in detail in the following sections, based on the template introduced in the previous chapter.

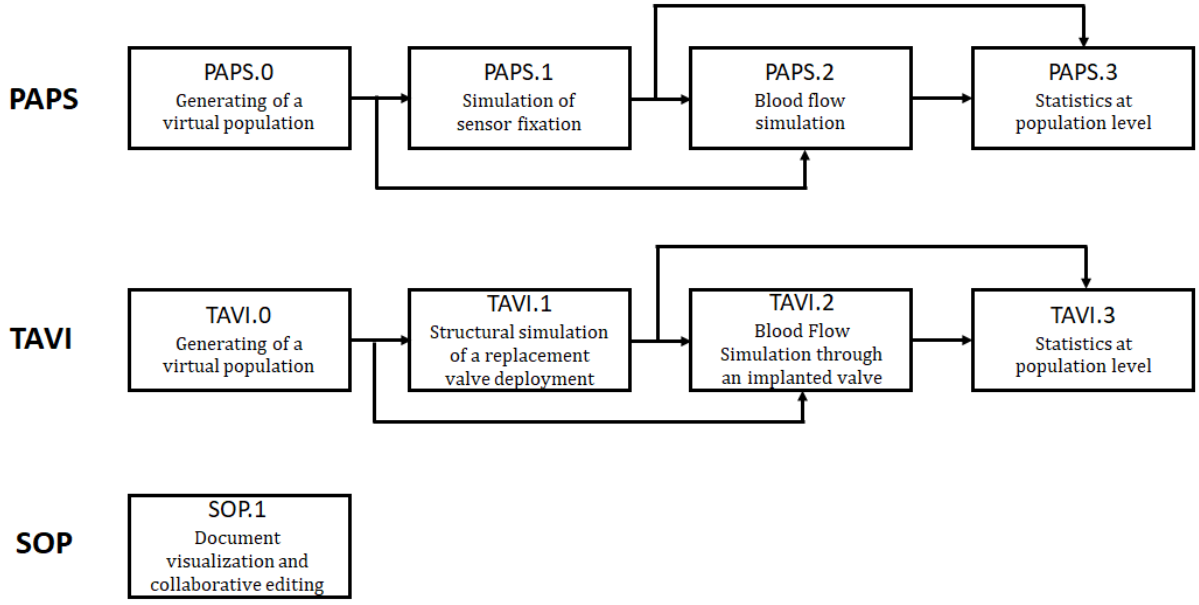

Figure 1: Use case overview.

Pulmonary artery pressure sensors use cases

Use Case PAPS.0 - Generating a virtual cohort of synthetic geometries for PAPS simulation

ID	PAPS.0
Name	Generating a virtual cohort of synthetic geometries for PAPS simulation
Description	This use case focuses on generating synthetic patients / cases which are similar to real patients considered for the PAPS medical use case
Input Data	Data origin: patient-specific models Ranges of input parameters related to: ● geometry ● boundary conditions ● material properties Ranges for output parameters: ● pressure ● flow ● compliance
Model parameters	Reduced order model for generating virtual cohort
Filtering parameters	All input and output parameters listed above
Output Data	Virtual PAPS cohort
Main steps	1. User selects a set of patient geometries to be used as a starting point for generating a virtual cohort 2. User sets the parameters (input, output) configuring the virtual cohort generation. 3. The algorithm for generating a virtual cohort is run and the synthetic geometries are obtained. 4. Statistics and characteristics of synthetic geometries in the virtual cohort are computed. 5. User filters the virtual cohort based on the filtering parameters. 6. Statistics and characteristics of the filtered synthetic geometries in the virtual cohort are computed (steps 1 to 5 may be run iteratively) 7. User visualizes individual synthetic geometries
Visualization requirements	Tabular visualization of patient and synthetic geometry characteristics 3D visualization of the 3D PA surface including MPA, LPA and RPA
Data import	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)
Data export	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)

Table 3: Use Case PAPS.0 - Generating a virtual cohort of synthetic geometries for PAPS simulation.

Use Case PAPS.1 – Patient Specific Simulation of Sensor fixation

ID	PAPS.1
Name	Patient Specific Simulation of Sensor fixation
Description	This use case focuses on modelling the fixation of the PAPS in the pulmonary artery for supporting the evaluation of following endpoints: perforation and migration
Input Data	Data origin: ● Patient ● Animal ● Synthetic sample
	Boundary conditions: ● Initial deformation of fixation wires ● Contact definition ● PA wall boundary conditions
	Input parameters: ● Geometric parameters via geometry of PA each for M (main PA), R (right PA) proximal and distal and interlobar, L (left PA) proximal and distal and interlobar ● material models and parameters
	Pulmonary artery geometry: 3D PA surface including MPA, LPA and RPA
	PAPS Geometry: 3D PAPS surface with fixation wires
	Mesh
	Time resolution
Initial conditions	● PAPS with wires preloaded in protector cup ● Position for placement of PAPS in PA ● Orientation for placement of PAPS in PA
Model parameters	● Size of PA section ● Compliance of PA wall ● Friction coefficient between fixation wires and PA wall ● PAPS geometry
Output Data	Perforation: ● contact length of fixation ● peak contact stress ● contact force ● contact force modulation (systolic/diastolic) ● parameter for cell reformation Migration: ● axial retention force (systolic/diastolic)
Main steps	1. User selects a patient for which the PAPS fixation should be simulated 2. User selects / modifies boundary conditions (starting from pre-specified values) 3. User selects PAPS geometry 4. User sets PAPS position 5. User sets time resolution 6. Simulation model is run (online/offline) 7. User visualizes output data
Visualization requirements	Tabular visualization of boundary conditions and time resolution 3D visualization of PA and PAPS input geometry 3D visualization of perforation output data
Postprocessing requirements	-
Data import	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)
Data export	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)

Table 4: Use Case PAPS.1 – Patient Specific Simulation of Sensor fixation.

Use Case PAPS.2 – Patient Specific Blood Flow Simulation

ID	PAPS.2
Name	Patient Specific Blood Flow Simulation
Description	This use case focuses on modelling and simulating blood flow in the pulmonary artery with PAPS for supporting the evaluation of the following endpoints: migration and thrombosis
Input Data	Data origin: ● Patient ● Animal ● Synthetic sample
	Boundary conditions: ● Inlet Flow Rate: mean flow rate, peak systole flow rate, heart cycle period, Fourier series flow rates (100) ● Inlet Turbulence (e.g. constant turbulence intensity of 5%) ● Outlet flow rates division (e.g. following Murray's law) OR constant pressure ● Walls (Rigid, no-slip)
	Input parameters ● Geometric parameters via geometry of PA each for M (main PA), R (right PA) proximal and distal and interlobar, L (left PA) proximal and distal and interlobar ● Hemodynamic parameters ● Material parameters
	Pulmonary artery geometry: 3D PA surface including MPA, LPA and RPA
	PAPS Geometry: 3D PAPS surface with fixation wires
	PAPS position and orientation
	Mesh
	Time resolution
Initial conditions	- PAPS deployed in PA
Model parameters	● Size of PA section ● Rheological parameters Geometrical shape of PAPS
Output Data	Thrombosis: ● Oscillating shear index (OSI) ● Wall shear stress (WSS) ● Shear rate ● Recirculation zone volume
	Migration: ● ● Force applying on sensor though blood flow
Main steps	1. User selects a patient for which the blood flow simulation should be run 2. User selects / modifies boundary conditions (starting from pre-specified values) 3. User selects PAPS geometry 4. User sets PAPS position 5. User sets time resolution 6. Simulation model is run (online/offline) 7. User visualizes output data
Visualization requirements	Tabular visualization of boundary conditions and time resolution 3D visualization of PA and PAPS input geometry 3D visualization of output data (velocity, pressure, WSS, OSI, pressure and friction force acting on PAPS)
Postprocessing requirements	-
Data import	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)
Data export	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)

Table 5:Use Case PAPS.2 – Patient Specific Blood Flow Simulation.

Use Case PAPS.3 – Statistics at population level

ID	PAPS.3
Name	Statistics at population level
Description	This use case focuses on computing statistics on a cohort of PAPS patients (real or virtual)
Input Data	PAPS input data: ● Geometric parameters via geometry of PA each for M (main PA), R (right PA) proximal and distal and interlobar, L (left PA) proximal and distal and interlobar ● hemodynamic parameters ● material parameters PAPS output data for each clinical endpoint (see PAPS.1): ● Perforation ● Migration ● Thrombus formation PAPS patient data (see D5.1 for extensive parameter list): ● Demographics: Age, Gender, BMI, BSA, Primary diagnosis, NT-proBNP ● Material: friction parameters, PA Young's modulus ● Anatomy: Pulmonary artery: min Diameter at branch entry, Pulmonary artery: min Diameter at exit, Pulmonary artery: diameter change syst. / diastolic ratio mean value, Pulmonary artery: elliptical shape: ratio min/max axis (mean value for whole branch), Pulmonary artery: curvature (radius), Pulmonary artery: tissue thickness, Pulmonary artery: length, Pulmonary artery branches: existence of branch 1...n, Pulmonary artery branch 1...n: distance of branches from entry, Pulmonary artery branch 1...n: rotary angle to main branch axis, Pulmonary artery branch 1...n: angle difference main branch to branch, Pulmonary artery branch 1...n: orientation in space or to gravity vector ● Hemodynamic: mean flow rate, maximum flow rate, heart rate, CVP, RVP, PAP, PAWP, mean velocity, maximum velocity, PA flow profile ● Perforation: contact length, peak contact stress, contact force, contact force modulation (ratio syst/diast)
Output Data - Statistics	Histograms, mean, median, quartile ranges, standard deviation Classification performance: accuracy, F1 score, precision of the positive class, recall of the positive class, precision of the negative class, recall of the negative class, macro-averaged precision, and macro-averaged recall. Bland-Altman plots, scatter plots
Main steps	1. User selects a set of patients using filters applied on input and output data 2. User selects statistics to be computed on the dataset selected at point 1 3. User visualizes statistics and individual data sets
Visualization requirements	Tabular visualization of numerical statistics 2D/3D plots
Data import	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)
Data export	File-based (.stl,.txt,.csv,.xlsx, STEP, IGES)

Table 6:Use Case PAPS.3 – Statistics at population level.

Transcatheter aortic valve implantation use cases

Use Case TAVI.0 - Generating a virtual cohort of synthetic geometries for replacement valve simulations.

ID	TAVI.0
Name	Generating a virtual population representative for the TAVI medical use case
Description	This use case focuses on generating synthetic patients / cases which are similar to real patients considered for the TAVI medical use case
Input Data	Data origin: patient-specific models Ranges for input parameters: ● geometry ● boundary conditions ● material properties Ranges for output parameters: ● paravalvular leakage ● thrombosis
Model	Reduced order model for generating virtual cohort
Filtering parameters	All input and output parameters listed above
Output Data	Virtual TAVI cohort
Main steps	1. User selects a set of patient geometries to be used as a starting point for generating a virtual cohort 2. User sets the parameters (input, output) configuring the virtual cohort generation. 3. The algorithm for generating a virtual cohort is run and the synthetic geometries are obtained. 4. Statistics and characteristics of synthetic geometries in the virtual cohort are computed. 5. User filters the virtual cohort based on the filtering parameters. 6. Statistics and characteristics of the filtered synthetic geometries in the virtual cohort are computed (steps 1 to 5 may be run iteratively) 7. User visualizes individual synthetic geometries
Visualization requirements	Tabular visualization of patient and synthetic geometry characteristics 3D visualization of aorta and aortic valve geometries
Data import	File-based (.stl,.txt,.csv,.xlsx)
Data export	File-based (.stl,.txt,.csv,.xlsx)

Table 7: Use Case TAVI.0 - Generating a virtual cohort of synthetic geometries for replacement valve simulations.

Use Case TAVI.1 - Patient Specific Simulation of a replacement valve implantation

ID	TAVI.1
Name	Patient Specific Simulation of a replacement valve implantation
Description	This use case focuses on modelling and simulating a replacement valve: determining the deformation of the aorta and of the aortic valve after the placement of the valve
Input Data	Data origin: ● Patient ● Synthetic sample ● Animal
	Boundary Conditions: ● (Initial) load ● Prescribed displacement ● Contact definition
	Replacement valve: ● Additional information for alignment / insertion in aortic valve: local coordinate systems, size after expansion
	Mesh: ● Mesh of aorta (calcification present or not) ● Mesh of replacement valve
	Modelling Hypothesis: elasticity models
	Time resolution
Initial conditions	Aortic valve state (e.g. open) Replacement valve: ● Size during insertion ● Position / trajectory for replacement valve insertion ● Orientation for replacement valve insertion
Model parameters	Parameters for normal / calcified tissue: ● Compliance ● Distance constraint weight ● Pre-Stress distance constraints ● Bending constraint weight ● Area conservation constraint weight ● Volume conservation constraint weight ● Collision distance
	Rigid body parameters: ● Centre of inertia ● Inertia tensor
	Mass
Output Data	Aorta deformation and aortic valve geometry: ● Displacement from initial position ● Orientation change from initial placement ● Stress map
	Positioning of device in aortic valve
	Durability-fatigue assessment
Main steps	1. User selects a patient for which the replacement valve simulation should be run 2. User selects / modifies boundary conditions (starting from pre-specified values) 3. User selects / modifies model parameters (starting from pre-specified values) 4. User selects / modifies initial conditions (starting from pre-specified values) 5. User selects aorta / aortic valve geometry 6. User selects replacement valve geometry 7. User sets time resolution 1. Simulation model is run (online/offline) 2. User visualizes output data
Visualization requirements	Tabular visualization of boundary conditions, model parameters, initial conditions, and time resolution 3D visualization of aorta, aortic valve, and replacement valve input geometry 3D visualization of output data (aorta deformation, aortic valve geometry, positioning of device in aortic valve)

	Assessment of leakage / thrombosis / durability-fatigue
Data import	File-based (.stl,.txt,.csv,.xlsx)
Data export	File-based (.stl,.txt,.csv,.xlsx)

Table 8: Use Case TAVI.0 - Generating a virtual cohort of synthetic geometries for replacement valve simulations.

Use Case TAVI.2 - Patient Specific Blood Flow Simulation through an Implanted Valve

ID	**TAVI.2**
Name	Patient Specific Blood Flow Simulation through an Implanted Valve
Description	This use case focuses on simulating the blood flow through an implanted aortic replacement valve: determining leakage and thrombosis
Input Data	Data origin: ● Patient ● Synthetic sample ● Animal
	Boundary conditions: ● symmetry ● wall boundary conditions ● inlet flow rate ● pressure loss during diastole ● contact properties (friction)
	Mesh of aorta / implanted aortic valve
	Modelling Hypothesis: ● turbulent/laminar ● steady/unsteady ● viscosity
	Time resolution
Initial conditions	● deformed aortic model ● position of the prosthesis (implantation height) ● deformed prosthesis model
Model parameters	Material properties: ● material properties of aorta, stent and native leaflets ● rheological parameters
Output Data	Leakage: ● Regurgitation / paravalvular leakage volume during diastole ● paravalvular leakage velocity field
	Thrombosis: ● Blood residence time ● platelet activation
Main steps	1. User selects a patient for which the blood flow simulation should be run 2. User selects / modifies boundary conditions (starting from pre-specified values) 3. User selects / modifies model parameters (starting from pre-specified values) 4. User selects / modifies initial conditions (starting from pre-specified values) 5. User selects geometry containing native aorta and implanted valve 6. User sets time resolution 7. Blood flow simulation model is run (online/offline) 8. User visualizes output data
Visualization requirements	Tabular visualization of boundary conditions, model parameters, initial conditions, and time resolution 3D visualization of aorta, aortic valve, and replacement valve input geometry 3D visualization of output data (leakage, thrombosis) Visualization of video clip / screenshots exported from the simulation tool
Data import	File-based (.stl,.txt,.csv,.xlsx)
Data export	File-based (.stl,.txt,.csv,.xlsx)

Table 9: Use Case TAVI.2 - Patient Specific Blood Flow Simulation through an Implanted Valve.

Use Case TAVI.3 - Statistics at population level

ID	TAVI.3
Name	Statistics at population level
Description	This use case focuses on computing statistics on a cohort of TAVI patients (real or virtual)
Input Data	TAVI input data: ● Boundary conditions ● Aorta / aortic valve geometry ● Replacement valve geometry ● Model parameters ● Initial conditions TAVI output data: ● Aorta deformation and aortic valve geometry ● Positioning of device in aortic valve ● Leakage / thrombosis / durability-fatigue assessment TAVI patient data (see D5.1 for extensive parameter list): ● Demographics: Age, Gender, BMI, Body surface area, STS operative risk score, New York Heart Association class, Geriatric assessment frailty score, Previous history, Primary diagnosis, Death (Yes/No), Time laps of death after intervention (if happened) ● Pre-surgery: CT measured systolic annular area, Peak aortic velocity, Peak pressure gradient, Mean pressure gradient, Aortic valve area, indexed aortic valve area, Energy loss index, LVED diameter, LVES diameter, LV mass index, LV hypertrophy, LV EF, LV SV (all echocardiography based) ● Medical device: Brand, Model, Size, Delivery, Self-expandible, Deployed successfully (y/n), Positioning (fluoroscopy) ● Immediate Post-surgery: Complication (bleeding, stroke, …), Death prior to discharge (Yes/No), Paravalvular aortic regurgitation, Total aortic regurgitation, Peak aortic velocity, Peak pressure gradient, Mean pressure gradient, Aortic valve area, Indexed aortic valve area, Energy loss index, moderate paravalvular aortic regurgitation, moderate total aortic regurgitation, LVED diameter, LVES diameter, LV mass index, LV hypertrophy, LV EF, LV SV ● Post-surgery: Paravalvular aortic regurgitation, Total aortic regurgitation, Peak aortic velocity, Peak pressure gradient, Mean pressure gradient, Aortic valve area, Indexed aortic valve area, Energy loss index, moderate paravalvular aortic regurgitation, moderate total aortic regurgitation, LVED diameter, LVES diameter, LV mass index, LV hypertrophy, LV EF, LV SV
Output data - Statistics	Histograms, mean, median, quartile ranges, standard deviation Classification performance: accuracy, F1 score, precision of the positive class, recall of the positive class, precision of the negative class, recall of the negative class, macro-averaged precision, and macro-averaged recall. Bland-Altman plots, scatter plots
Main steps	1. User selects a set of patients using filters applied on input and output data 2. User selects statistics to be computed on the dataset selected at point 1 3. User visualizes statistics and individual data sets
Visualization requirements	Tabular visualization of numerical statistics 2D/3D plots
Data import	File-based (.stl,.txt,.csv,.xlsx)
Data export	File-based (.stl,.txt,.csv,.xlsx)

Table 10: Use Case TAVI.3 - Statistics at population level.

Standard operating procedures

Use Case SOP.1 - SOP document visualization and collaborative editing

ID	SOP.1
Name	SOP document visualization and collaborative editing
Description	This use case focuses on the preparation of the SOPs
Main steps	1. User uploads a document (e.g., word) or starts a blank document. 2. User edits SOP document 3. User saves SOP document
Visualization requirements	Web visualization of document in MS Office formats.
Data import	File-based
Data export	File-based

Table 11: Use Case SOP.1 - SOP document visualization and collaborative editing.

System requirements

The SIMCor VRE infrastructure will have a significant computational power to allow the execution of different algorithms (e.g., statistical shape models for the creation of geometries) or advanced physics-based simulation models. To improve the runtime of computationally demanding models, advanced state-of-the-art metamodeling (i.e., reduced order) techniques will be integrated into the infrastructure. Since many of the above-mentioned tools are run on massively parallel processors (i.e., *graphical processing units*, GPUs) UTBV will employ the methodology for GPU instance orchestration on the UTBV private cloud (*Figure 2*).

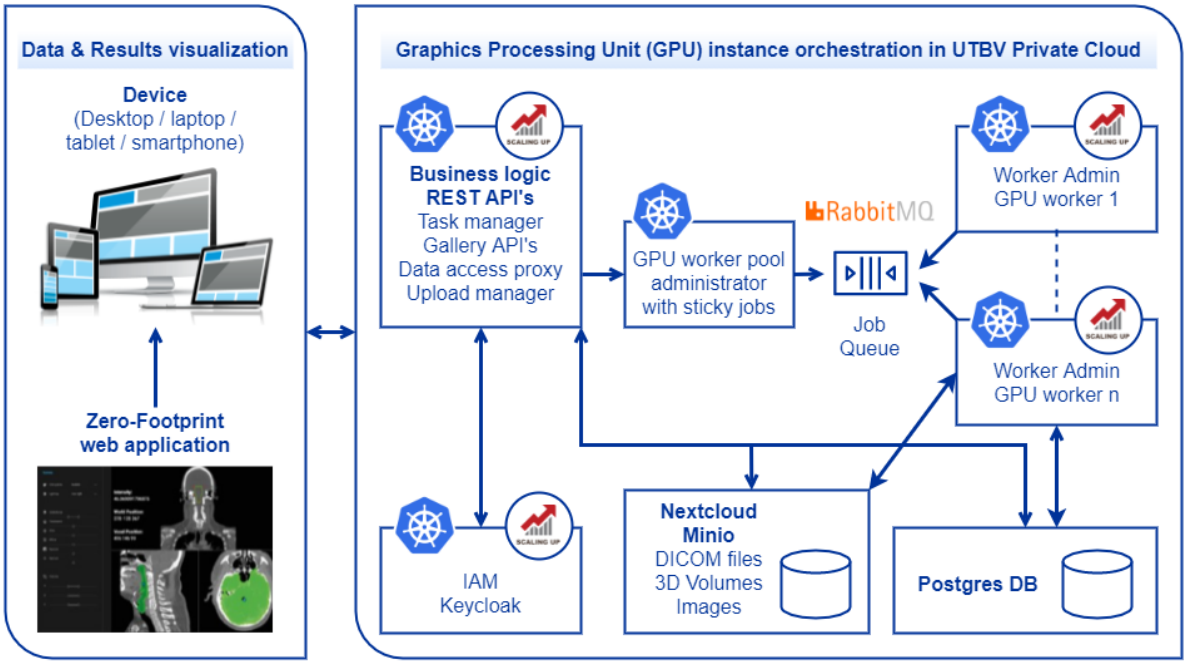

Figure 2: GPU instance orchestration in the UTBV private cloud solution for the SIMCor virtual research environment. Since many of the advanced analytics tools are run on massively parallel processors (graphics cards) a methodology for GPU instance orchestration in the UTBV private cloud solution will be employed. Data and results can be visualized using zero-footprint apps from different devices: desktop, laptop, tablet, smartphone.

System requirements are detailed specifications describing the functions the system needs to do and are divided into:

- **Functional requirements**
  Functional requirements determine the goals that users want to reach and the tasks they intend to perform. By eliciting the functional requirements, we understand why the user performs certain activities, what are his/her constraints and preferences, and how the user would trade-off between different software capabilities. The important point to note is that WHAT is wanted is specified, and not HOW it will be delivered.
- **Non-functional requirements**
  Non-functional requirements determine the restrictions on the types of solutions that will meet the functional requirements. Specification of non-functional requirements includes performance aspects, security, privacy, and general criteria that judge the operation of the system.

Functional requirements

As SIMCor VRE is meant as a tool for researchers and the majority of functional requirements stem from the relevant use cases. What is described below are SIMCor VRE-specific requirements that ensure implementation of those use cases.

Functional Requirement FUNC01

ID	FUNC01
Name	Generation of synthetic patients (virtual cohorts) / cases of the pulmonary artery for modelling and simulating interaction with PAPS.
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to generate synthetic patients (virtual cohorts) of the pulmonary artery that will be used to simulate interaction with PAPS.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2 & PAPS.3
Supporting materials	N/A.

Table 12: Functional Requirement FUNC01.

Functional Requirement FUNC02

ID	FUNC02
Name	Simulate and model the fixation of the PAPS in the pulmonary artery
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to model and simulate the fixation of the PAPS in the pulmonary artery for supporting the evaluation of the following endpoints: perforation and migration.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2 & PAPS.3
Supporting materials	N/A.

Table 13: Functional Requirement FUNC02.

Functional Requirement FUNC03

ID	FUNC03
Name	Simulate and model the blood flow in the pulmonary artery with PAPS
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to model and simulate the blood flow in the pulmonary artery with PAPS for supporting the evaluation of the following endpoints: thrombosis and migration.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2 & PAPS.3
Supporting materials	N/A.

Table 14:Functional Requirement FUNC03.

Functional Requirement FUNC04

ID	FUNC04
Name	Compute statistics on a cohort of PAPS patients (real or virtual)
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to compute statistics on a cohort of PAPS patients (real or virtual).
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2 & PAPS.3
Supporting materials	N/A.

Table 15: Functional Requirement FUNC04.

Functional Requirement FUNC05

ID	FUNC05
Name	Generate a virtual cohort of synthetic geometries for replacement valve simulations
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to generate synthetic patients/cases for simulating a replacement valve: setting up a virtual cohort resembling a real population.
Rationale	Supporting TAVI.0, TAVI.1, TAVI.2 & TAVI.3
Supporting materials	N/A.

Table 16: Functional Requirement FUNC05.

Functional Requirement FUNC06

ID	FUNC06
Name	Simulate and model a replacement valve implantation on specific patients
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to simulate and model a replacement valve implantation on specific patients, determining the deformation of the aorta and of the aortic valve after the placement of the valve.
Rationale	Supporting TAVI.0, TAVI.1, TAVI.2 & TAVI.3
Supporting materials	N/A.

Table 17: Functional Requirement FUNC06.

Functional Requirement FUNC07

ID	FUNC07
Name	Simulate the blood flow through an implanted aortic replacement valve
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to simulate the blood flow through an implanted aortic replacement valve, determining leakage and thrombosis.
Rationale	Supporting TAVI.0, TAVI.1, TAVI.2 & TAVI.3
Supporting materials	N/A.

Table 18: Functional Requirement FUNC07.

Functional Requirement FUNC08

ID	FUNC08
Name	Compute statistics on a cohort of TAVI patients (real or virtual)
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should be able to compute statistics on a cohort of TAVI patients (real or virtual).
Rationale	Supporting TAVI.0, TAVI.1, TAVI.2 & TAVI.3
Supporting materials	N/A.

Table 19: Functional Requirement FUNC07.

Functional Requirement FUNC09

ID	FUNC09
Name	SOP document visualization and collaborative editing
Priority of accomplishment	**Shall have**
Description	The SIMCor virtual research environment should allow to upload, share, visualize and collaboratively edit the SOP documents.
Rationale	Supporting SOP.1
Supporting materials	N/A.

Table 20: Functional Requirement FUNC09.

Non-functional requirements

This section gives an overview of the non-functional requirements for the system. These are requirements on aspects of quality of the SIMCor that will be essential in satisfying the user requirements and help make SIMCor integration an attractive value proposition for researchers**.**

European Open Science Cloud

One of the main goals of SIMCor is to *"Contribute to the EOSC with data, virtual cohorts, simulation models, methodologies, standards, and guidelines"*.

The EOSC will be Europe's virtual environment for all researchers to store, manage, analyse and re-use data for research, innovation, and educational purposes. EOSC is intended to set off the ground by federating existing scientific data infrastructures and digital infrastructures for data exploitation that are now spread across disciplines and EU member states. This will make access to scientific data and other scientific outputs easier and more efficient.[2]

Services and resources of the EOSC Portal are provided and maintained by different providers under a variety of licenses. To become a provider is required that:

- The service is accessible to users outside its original community.
- The service is described through a common template focused on value proposition and functional capabilities.
- At least one service instance is running in a production environment available to the user community.
- Publish research data, which is Findable, Accessible, Interoperable and Reusable (FAIR).
- Release notes and sufficient documentation are available.
- Helpdesk channels are available for support, bug reporting and requirements gathering.

One of the most important criteria for becoming an EOSC provider is to ensure that the research data we are publishing in the course of the project is *findable, accessible, interoperable, and reusable* (FAIR).

In 2016, the 'FAIR Guiding Principles for scientific data management and stewardship'[3] were published in Scientific Data. The authors intended to provide guidelines to improve the Findability, Accessibility, Interoperability, and Reuse of digital assets. The principles emphasize machine-actionability (i.e., the capacity of computational systems to find, access, interoperate, and reuse data with none or minimal human intervention) because humans increasingly rely on computational support to deal with data as a result of the increase in volume, complexity, and creation speed of data. The FAIR principles refer to three types of entities: data (or any digital object), metadata (information about that digital object), and infrastructure.[4]

In order to achieve the **F**indability, **A**ccessibility, **I**nteroperability, and **R**eusability of SIMCor digital assets, we should consider the following steps:

- The first step in (re)using data is to find them. Metadata and data should be easy to find for both humans and computers. Machine-readable metadata are essential for automatic discovery of datasets and services, so this is an essential component of the FAIRification process.
- Once the user finds the required data, she/he/they need to know how they can be accessed, possibly including authentication and authorisation.

[2] EOSC Portal, For Providers. Available at: https://eosc-portal.eu/for-providers

[3] Wilkinson, M. D., Dumontier, M., Aalbersberg, I. J., Appleton, G., Axton, M., Baak, A., ... & Mons, B. (2016). The FAIR Guiding Principles for scientific data management and stewardship. Scientific data, 3(1), 1-9. Available at https://www.nature.com/articles/sdata201618

[4] *FAIR Principles - GO FAIR*. (n.d.). Retrieved from FAIR Principles - GO FAIR: https://www.go-fair.org/fair-principles/

- The data usually needs to be integrated with other data. In addition, the data needs to interoperate with applications or workflows for analysis, storage, and processing.
- The ultimate goal of FAIR is to optimise the reuse of data. To achieve this, metadata and data should be well-described so that they can be replicated and/or combined in different settings.

NonFuncEOSC01 - Findability

ID	NonFuncEOSC01
Name	Findability
Priority of accomplishment	**Shall have**
Description	SIMCor aims to support the Findability of digital assets.
Rationale	The first step in (re)using data is to find them. Metadata and data should be easy to find for both humans and computers. Machine-readable metadata are essential for automatic discovery of datasets and services, so this is an essential component of the FAIRification process (FAIR Principles - GO FAIR, n.d.). Objectives: ● F1. (Meta)data are assigned a globally unique and persistent identifier. ● F2. Data are described with rich metadata (defined by R1 below) ● F3. Metadata clearly and explicitly include the identifier of the data they describe. ● F4. (Meta)data are registered or indexed in a searchable resource Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	FAIR Principles - GO FAIR

Table 21: NonFuncEOSC01 - Findability.

NonFuncEOSC02 - Accessibility

ID	NonFuncEOSC02
Name	Accessibility
Priority of accomplishment	**Shall have**
Description	SIMCor aims to support the Accessibility of digital assets.
Rationale	Once the user finds the required data, she/he needs to know how they can be accessed, possibly including authentication and authorisation (FAIR Principles - GO FAIR, n.d.). Objectives: ● A1. (Meta)data are retrievable by their identifier using a standardised communications protocol: ○ A1.1 The protocol is open, free, and universally implementable ○ A1.2 The protocol allows for an authentication and authorisation procedure, where necessary ● A2. Metadata are accessible, even when the data are no longer available Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	FAIR Principles - GO FAIR.

Table 22: NonFuncEOSC02 - Accessibility.

NonFuncEOSC03 - Interoperability

ID	NonFuncEOSC03
Name	Interoperability
Priority of accomplishment	**Shall have**
Description	SIMCor aims to support the Interoperability of digital assets.
Rationale	The data usually needs to be integrated with other data. In addition, the data needs to interoperate with applications or workflows for analysis, storage, and processing (FAIR Principles - GO FAIR, n.d.). Objectives: ● I1. (Meta)data uses a formal, accessible, shared, and broadly applicable language for knowledge representation. ● I2. (Meta)data use vocabularies that follow FAIR principles. ● I3. (Meta)data include qualified references to other (meta)data. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1

Supporting materials	FAIR Principles - GO FAIR

Table 23: NonFuncEOSC03 – Interoperability.

NonFuncEOSC04 - Reusability

ID	NonFuncEOSC04
Name	Reusability
Priority of accomplishment	**Shall have**
Description	SIMCor aims to support the Reusability of digital assets.
Rationale	The ultimate goal of FAIR is to optimise the reuse of data. To achieve this, metadata and data should be well-described so that they can be replicated and/or combined in different settings. The principles refer to three types of entities: data (or any digital object), metadata (information about that digital object), and infrastructure. For instance, principle F4 defines that both metadata and data are registered or indexed in a searchable resource (the infrastructure component) (FAIR Principles - GO FAIR, n.d.). Objectives: ● R1. (Meta)data are richly described with a plurality of accurate and relevant attributes: ○ R1.1. (Meta)data are released with a clear and accessible data usage license ○ R1.2. (Meta)data are associated with detailed provenance ○ R1.3. (Meta)data meet domain-relevant community standards Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	FAIR Principles - GO FAIR

Table 24: NonFuncEOSC04 - Reusability.

NonFuncEOSC05 - Functional and flexible operation

ID	NonFuncEOSC05
Name	Functional and flexible operation
Priority of accomplishment	**Should have**
Description	The SIMCor platform must be able to support the functional, flexible, and efficient operation in a distributed cloud infrastructure.
Rationale	The operational compatibility of the SIMCor platform is a crucial quality characteristic for the platform's operation and reusability. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	ISO/IEC 25010:2011. (2007)[5]

Table 25: NonFuncEOSC05 - Functional and flexible operation.

NonFuncEOSC06 – High availability

ID	NonFuncEOSC06
Name	High availability
Priority of accomplishment	**Should have**
Description	The SIMCor framework should remain operational under adverse conditions and must protect its ability to recover operation even under extreme conditions.
Rationale	Meeting this generic requirement involves preparing to face a number of issues, ranging from hardware failure to malicious actions targeting the integrity of the system and its data or its ability to service legitimate requests. Non-disruption of service is important, but the ability to restore service is crucial. The main means of satisfying this requirement is redundancy (e.g., local backups and remote backups) and either over-provisioning or highly efficient on-demand provisioning to avoid non-malicious threats to availability due to demand peaks, as well as specialised additional measures to thwart malicious distributed denial-of-service (DDOS) attacks. The interoperability of the SIMCor platform is a crucial quality characteristic for the platform's compatibility, extensibility, and exploitation potentials. The SIMCor platform should be able to ensure high availability of the system and the stored information.

[5] ISO/IEC 25010:2011. (2007). Retrieved from https://www.iso.org/standard/35733.html

	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 26: NonFuncEOSC06 – High availability.

NonFuncEOSC07 - Recovery and Fault-tolerance

ID	**NonFuncEOSC07**
Name	Recovery and Fault-tolerance
Priority of accomplishment	**Should have**
Description	The SIMCor platform must be able to recover from system failure conditions and effectively handle software failure conditions without affecting the platform's overall functional operation.
Rationale	The recoverability and fault-tolerance of the SIMCor platform is a crucial quality characteristic for the platform's reliability. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	ISO/IEC 25010:2011. (2007)

Table 27: NonFuncEOSC07 - Recovery and Fault-tolerance.

NonFuncEOSC08 - Modularity

ID	**NonFuncEOSC08**
Name	Modularity
Priority of accomplishment	**Should have**
Description	The SIMCor platform should be composed of independent components that have well defined interfaces and are replaceable with minimum impact and effort.
Rationale	The evolution of SIMCor efficient deployment of the SIMCor platform, as well as the efficient replacement of the components of the platform if needed is a crucial quality characteristic for the platform's portability. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	ISO/IEC 25010:2011. (2007)

Table 28: NonFuncEOSC07 - Recovery and Fault-tolerance.

Security

SIMCor needs to know the identity of entities that attempt actions on data, to categorize them by means of a roles system in order to systematize access control rules, to have a system that enforces those access rules, and a system for recording access to resources and various parts of the system at a reasonable and suitable granularity level (see *'Data accessibility'* section).

To do that, SIMCor VRE will have an *Identity and Access Management* (IAM) system which will be defining and managing the roles and access privileges of individual network entities (users and devices) to SIMCor VRE applications and data assets. Users can include consortium partners or external partners; devices can include computers, smartphones or tablets. The core objective of IAM systems is one digital identity per individual or item. Once the digital identity has been established, it must be maintained, modified and monitored throughout each user's or device's access lifecycle.

The integrity of SIMCor's executables, configuration files and data (including models) must be protected at rest and in transit; only authorised entities (users, software components etc.) must be allowed to make changes and only in the ways allowed. For ensuring data protection in-transit, the SIMCor VRE will use end-to-end SSL/TLS encrypted connections. The SIMCor VRE will store data on encrypted volumes to ensure data protection at rest. Also, the SIMCor VRE will provide data safety by using a RAID system for data storage.

NonFuncSEC01 - Authentication, Authorisation, and Accounting

ID	NonFuncSEC01
Name	Authentication, Authorisation, and Accounting
Priority of accomplishment	**Shall have**
Description	SIMCor must support: ● trustworthy mechanisms for the authentication of third-party entities ● trustworthy mechanisms for the authorisation of entities and the enforcement of access control policies ● trustworthy mechanisms for accounting i.e., keeping audit logs of actions and usage of resources
Rationale	SIMCor needs to know the identity of entities that attempt actions, to categorize them by means of a roles system in order to systematize access control rules, to have a system that enforces those access rules and a system for recording access to resources and various parts of the system at a reasonable and suitable granularity level. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 29: NonFuncSEC01 - Authentication, Authorisation, and Accounting.

NonFuncSEC02 - Integrity

ID	NonFuncSEC02
Name	Integrity
Priority of accomplishment	**Shall have**
Description	The integrity of SIMCor' s executables, configuration files and data (including models) must be protected at rest and in transit; only authorised entities (users, software components etc.) must be allowed to make changes and only in the ways allowed.
Rationale	Unless the integrity of SIMCor executables can be guaranteed, SIMCor cannot be trusted to behave in accordance with its specifications and to meet any other security or other requirement. If its configuration files can be tampered with, it may also behave in undesirable ways, possibly even creating significant security loopholes. Finally, if its data can be tampered with, a number of undesirable consequences could ensue including but not limited to, false information about patients being displayed to doctors. The requirement does not prescribe the technological means by which it will be met; these will be determined as part of the detailed design of the SIMCor. These may include among others: basic (e.g. privilege levels) and advanced (e.g. SGX) CPU-based and OS-based access protection measures for executables and data in the filesystem and in RAM, secure hashing for integrity verification, digital signing and verification, and even measures not associated with security but essential in preserving integrity such as atomicity enforcement measures in SIMCor business logic implementations and persistence storage access (to avoid integrity being compromised by authorised entities accidentally interfering with one another while attempting to modify the same resource). An essential prerequisite for the requirement to be non-vacuous or partial is for an exhaustive catalogue of SIMCor assets, how they are allowed to be modified and under what conditions (including by whom). Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 30: NonFuncSEC02 - Integrity.

NonFuncSEC03 - Confidentiality

ID	NonFuncSEC03
Name	Confidentiality
Priority of accomplishment	**Shall have**
Description	The confidentiality constraints for any and all SIMCor assets or parts thereof, such as SIMCor configuration files and data (including models) must be respected and enforced with appropriate technical means at rest and in transit.
Rationale	In a complex system such as SIMCor, overall security relies on secret keys. Additionally, SIMCor components at the healthcare provider's site process sensitive patient data and must protect them from read access. Even parts of code may need to be protected, for IPR or other reasons. As noted also in the Rationale of the Integrity requirement, the exact enforcement mechanisms (access control, private-key or public-key cryptography etc.) will be determined as part of SIMCor' s design; moreover, a catalogue of assets with specific read-access constraints will be necessary to make this requirement concrete and enforceable. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 31: NonFuncSEC03 – Confidentiality.

NonFuncSEC04 – Breach Detection

ID	NonFuncSEC04
Name	Breach Detection
Priority of accomplishment	**Could have**
Description	Any detected security breaches and failures of the system to operate in the prescribed manner, must be recorded. Reasonable effort must be made by the SIMCor to detect such events, notify the relevant system administrators and attempt to self-heal where appropriate.
Rationale	Not all threats and issues can be avoided, but at least when they are discovered, there is a chance, depending on the kind of incident, to minimise their effect, remedy the problem, detect the conditions under which it occurred, and attempt to avoid it reoccurring. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 32: NonFuncSEC04 – Breach Detection.

Privacy

Privacy preservation of data is a crucial requirement in any system and especially in systems that analyse and process personal patients' and other healthcare data. Therefore, patient information shall be treated in a highly confidential manner, hence promoting, and maintaining fundamental medical ethical principles. Once sensitive information about an individual is exposed, it cannot be withdrawn and made secret again, leading to irreparable damages. Thus, issues on privacy preservation are of major importance for SIMCor and will be carefully maintained in all levels of the VRE.

NonFuncP01 - Data privacy inside SIMCor VRE

ID	NonFuncP01
Name	Data privacy inside SIMCor VRE
Priority of accomplishment	**Shall have**
Description	SIMCor Virtual Research Environment must ensure privacy of the data (i.e. datasets, models), protecting it from unauthorized access.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 33: NonFuncP01 - Data privacy inside SIMCor VRE.

NonFuncP02 - GDPR compliancy

ID	NonFuncP02
Name	GDPR compliancy
Priority of accomplishment	**Should have**
Description	SIMCor platform must be compliant with the EU GDPR, as well as the national data protection, privacy and ethical legislation in each participant country.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	European Commission, "EU data protection rules," https://ec.europa.eu/info/law/law-topic/data-protection/eu-data-protection-rules_en, 2018-05-25.

Table 34: NonFuncP02 - GDPR compliancy.

Usability

Usability will be a key factor in the success of SIMCor; researchers need not only be convinced that SIMCor can provide useful results, but also feel comfortable using the relevant SIMCor-powered UI. This UI will need to be cleverly integrated into the UI of the information systems they currently use. These requirements apply to the SIMCor UI where the UI elements will first be incorporated and demonstrated.

NonFuncU01 - Learnability

ID	NonFuncU01
Name	Learnability
Priority of accomplishment	**Should have**
Description	The system should be easy to learn for both inexperienced and experienced users.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 35: NonFuncU01 - Learnability.

NonFuncU02 - Memorability

ID	NonFuncU02
Name	Memorability
Priority of accomplishment	**Should have**
Description	The system should be easy to remember for the casual user.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 36: NonFuncU02 - Memorability.

NonFuncU03 – Error feedback and recovery

ID	NonFuncU03
Name	Error feedback and recovery
Priority of accomplishment	**Should have**
Description	Any errors (of input or otherwise) will be communicated to the user in a straightforward manner, and their impact will be clear, and if applicable, recoverable.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 37: NonFuncU03 – Error feedback and recovery.

NonFuncU04 - Satisfaction

ID	NonFuncU04
Name	Satisfaction
Priority of accomplishment	**Should have**
Description	The user will feel satisfied with the use of the system and will be more likely to recommend it to other patients, than not.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 38: NonFuncU04 - Satisfaction.

NonFuncU05 – Consistent navigation

ID	NonFuncU05
Name	Consistent navigation
Priority of accomplishment	**Should have**
Description	The navigation and content structure must be coherent throughout the system. To this end, i) The same action should produce always the same response, ii) Links, action buttons and objects must be organized coherently, iii) High importance messages should be visible upon login, iv) Response times should be appropriated for each task, and v) Data entries should not be case sensitive and should clearly state which kind of data do they accept.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1.
Supporting materials	N/A.

Table 39: NonFuncU05 – Consistent navigation.

NonFuncU06 – Clear organisation of information

ID	NonFuncU06
Name	Clear organisation of information
Priority of accomplishment	**Should have**
Description	All the information on the system must be well organised.
Rationale	Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 40: NonFuncU06 – Clear organisation of information.

Hardware support requirements

The SIMCor VRE infrastructure will have a large computational power to allow the execution of multiple data (for example, statistical shape models for the creation of geometries) or advanced physics-based simulation models. To accelerate the execution speed of high-demanding models, parallel processors (GPUs) will be integrated into the UTBV private cloud infrastructure. In order to have a balanced system architecture, PAPS, TAVI and SOP can be implemented on different systems, interconnected at application level.

UTBV Private Cloud has a secure communication network with two rows of firewalls, continuously monitored by management and control systems. Installing the platform as a local cloud in the UTBV private VLAN network will provide the system with a high level of security. Three internet providers will ensure the uninterrupted operation of 24/7 data communication.

Minimum requirement for a cloud system communication speed is approximately 40Mbps downstream and 5 Mbps upstream and latency should be consistently less than 80ms.

Memory and storage capacity will be chosen as needed. As a starting point, it is recommended for the servers, part of UTBV Private Cloud, to have 16 GB RAM and 250GB storage capacity. Also, the SIMCor VRE will provide data safety by choosing a RAID system for data storage.

NonFuncH01 - UTBV private cloud x86-64 CPUs support

ID	NonFuncH01
Name	UTBV private cloud x86-64 CPUs support
Priority of accomplishment	**Shall have**
Description	SIMCor cloud components must be capable of running on x86-64 instruction set CPUs.
Rationale	The most widely used server CPUs currently and in the foreseeable future are AMD and Intel 64-bit CPUs supporting the x86-64 instruction set. This requirement does not exclude support for other CPUs either now or in the future but ensures the most widely used ones are supported. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A

Table 41: NonFuncH01 - UTBV private cloud x86-64 CPUs support.

NonFuncH02 - UTBV private cloud GPGPUs support

ID	NonFuncH02
Name	UTBV private cloud GPGPUs support
Priority of accomplishment	**Shall have**
Description	When GPGPUs are available on UTBV private cloud servers, SIMCor should be able to utilise them to provide enhanced performance.
Rationale	GPGPUs can assist in executing computationally intensive tasks, like complex simulations based on virtual cohort models, offering a significant improvement in performance. A decision has not been made about which specific GPGPUs are to be supported. Supporting PAPS.0, PAPS.1, PAPS.2, PAPS.3, TAVI.0, TAVI.1, TAVI.2, TAVI.3 and SOP.1
Supporting materials	N/A.

Table 42: NonFuncH02 - UTBV private cloud GPGPUs support.