SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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Executive summary

The project presentation is a document illustrating the project including its *rationale, mission and objectives, consortium composition and role of partners, implementation and expected impacts*, in a common language and in the form of a high-level summary, to serve in project communication and dissemination. The document will constitute the base for all project communication and dissemination materials in the following months, including project website, brochure(s), poster(s), press releases, newsletters and more.

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Acronyms

Acronym	Full name
AVD	Aortic valve disease
CHA	Charité – Universitätsmedizin Berlin
BIO	Biotronik SE & Co. KG
ECRIN-ERIC	European Clinical Research Infrastructure Network
EU	European Union
HF	Heart failure
ICT	Information and communication technologies
IHS	Institut für Höhere Studien – Institute for Advanced Studies
IIB	Institut für ImplantatTechnologie und Biomaterialien e.V.
LYN	Lynkeus
PAPS	Pulmonary artery pressure sensors
PC	Project Coordinator
PHI	Philips Electronics Netherlands B.V.
R&D	Research and development
SME	Small and medium-sized enterprise
SOP	Standard operating procedure
TAVI	Aortic valve implantation
TUE	Eindhoven University of Technology
TUG	Graz University of Technology
UCL	University College of London
UTBV	Universitatea Transilvania Din Brașov
V&V	Verification and validation
VPH/VPHi	Virtual Physiological Human Institute for Integrative Biomedical Research VZW

VRE	Virtual research environment
WP	Work package

Abstract

The growing standards for clinical safety and performance of medical devices and the complexity and speed of technological innovation, with increasingly short product cycles, create a huge demand for innovative, computer-based solutions, standards and guidelines for a statistically robust, repeatable and efficient validation of biomedical devices, to become closer to the market and the clinics. SIMCor will address this challenge by providing manufacturers of cardiovascular implantable devices with an open, reusable, cloud-based platform for in-silico testing to accelerate development, validation and regulatory approval of their products. The platform will support device verification and validation along the whole research and development pipeline: from initial modelling and in-vitro experiments, to animal studies, device implantation and effect simulation on human cohorts. In particular, SIMCor's 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, also including extensive paediatric populations, meeting the critical need of testing devices in young patients. A standardized multi-level validation process and sensitivity analysis will guarantee statistical credibility for in-silico tests and the platform as a whole, proving solid experimental ground for regulatory authorities, thus accelerating approval and time to market for new products, reducing the burden of human and animal studies and boosting innovation at large. 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). Based on proof-of-validation results and regulatory approval for these use cases, SIMCor will define *standard operational procedures* (SOPs) and a generalised technical framework for the in-silico testing, validation and regulatory approval of cardiovascular devices, to be put at the service of researchers, medical device manufacturers and regulatory bodies.

Reference information

SIMCor is a 3-year (1 January 2021 - 31 December 2023), 7.2 M€ Research and Innovation Action (RIA) funded under the topic SC1-DTH-06-2020 (*Accelerating the uptake of computer simulations for testing medicines and medical devices*) of the call H2020-SC1-DTH-2018-2020 (*Digital transformation in Health and Care*), in the Health, Demographic Change and Wellbeing area of the Horizon 2020 Framework Programme.

Rationale

Verification and validation: an open issue in medical device development

Cardiovascular implantable medical devices are among the most sophisticated, used and life-sustaining implants in medicine. According to the Regulatory Affairs Professionals Society, *verification and validation* (V&V) are amongst the most critical activities in their development lifecycle, and inadequate validation processes is one of the most common issues leading to warnings from the US Food and Drug Administration and recalls which can cost millions of dollars, ruin reputation and directly affect share price.

In-silico methodologies: a promising solution for enhanced device implementation

In-silico methodologies for medical device testing and validation, such as virtual cohorts of animal and human patients and computer modelling solutions, represent a promising opportunity for enhancing the quality of medical devices released into the market, increasing their efficacy and safety, meanwhile reducing costs and time-to-market, allowing for a wider accessibility of treatments, and minimising the need for live testing on animal and human subjects.

However, the complexity and speed of technological innovation strongly demands the establishment of agreed protocols, standards and shared resources between device manufacturers, authorities and regulatory bodies, allowing for a standardised, reliable and integrated use of in-silico methodologies into the entire product cycle of medical device development, validation and regulatory approval.

Mission and objectives

Our mission

SIMCor aims to establish a computational platform for in-silico development, validation and regulatory approval of cardiovascular implantable devices as an open resource for collaborative R&D among device manufacturers, researchers, medical authorities and regulatory bodies. The platform will support in-silico devices testing along the entire value chain: from in-silico modelling and in-vitro experiments to virtual animal and clinical studies to integration of these models with traditional R&D methodologies, to the quantified assessment of their clinical, societal and economic value.

Objectives

SIMCor will pursue a number of strategic goals, detailed below.

O1. Provide proof-of-validation for virtual cohorts and computer-based simulation of cardiovascular device implantation and performance.

SIMCor will define a methodology for the generation of virtual cohorts in replacement of in-vitro and preclinical test in animals 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 will also elaborate a framework for the virtual implantation of medical devices on bench test environments, animal and patient cohorts, as well as for the assessment of device performance in regard to safety, efficacy and usability, based on device, vessel and device-specific effect models. SIMCor will implement and apply a standardised, multi-level validation and refinement process based on the use of preclinical, clinical and synthetic data, to demonstrate robustness and reliability of in-silico testing methodologies for the evaluation and regulatory approval of cardiovascular devices.

O2. Develop standards and protocols for in-silico testing and validation of cardiovascular devices.

The process chain of SIMCor will be exemplarily applied to two representative use cases, *transcatheter aortic valve implantation* (TAVI) and *pulmonary artery pressure sensors* (PAPS), based on their large potential socio-economic impact, the wide range of pathophysiologic conditions and biomechanical properties involved. Based on proof-of-validation results for TAVI and PAPS, SIMCor aims to extrapolate best practices, standards and guidelines for development, validation and regulatory approval of any type of cardiovascular device. Through a strict collaboration with regulatory authorities, clinicians and industry developers, these will be translated into *standard operating procedures* (SOPs) at the service of the entire cardiovascular device manufacturing community.

O3. Quantify the benefits of in-silico testing for healthcare, industry and society as a whole.

SIMCor will define and apply a framework for assessing the impact of the integration of virtual cohorts and computer-based models in traditional clinical trials. Leveraging proof-of-validation results, literature, databases and interviews with relevant stakeholders, SIMCor will evaluate and quantify envisaged benefits of the use of virtual cohorts and computer simulations on the clinical research workflow, the industrial development cycle and the market, as well as on a broader societal perspective. Expected benefits include increased treatment efficacy and patient safety through reduction in device failure and adverse events, improved clinical indications, implantation strategies and device designs, reduced use of animal and human testing, device development costs and time-to-market, decreased costs and wider accessibility of device-based treatments, boosting of innovation and creation of economic added value.

O4. Accelerate the integration of in-silico testing into the medical device regulatory approval process, the market and the clinics.

SIMCor will work to accelerate the adoption and integration of virtual cohorts and simulation models into the development, testing and regulatory approval process of medical devices in cardiology as a complement or substitution of traditional clinical trials, as well as the translation of in-silico validated devices into the market and the clinics. To do so, SIMCor will leverage its developed resources, proof-of-validation and impact assessment results and widely disseminate them among researchers, manufacturers, healthcare professionals and patients, to increase trust towards in-silico solutions, address needs, expectations and concerns, making them an active part of the innovation process and fostering the creation of a community of interest. SIMCor will work in close cooperation with regulatory authorities through the VPH Institute and the Avicenna Alliance, a collaborative ecosystem of patients, clinicians, academics, industries, policy makers, regulators and payers with the goal of making in-silico medicine standard practice in healthcare.

O5. Contribute to the European Open Science Cloud with data, virtual cohorts, simulation models, methodologies, standards and guidelines.

SIMCor will implement a *virtual research environment* (VRE) as a computational infrastructure that will integrate available preclinical, clinical and synthetic data resources, virtual cohorts, simulation models, methods, guidelines and SOPs developed in the course of the project, to serve as unique, digitised, personalised testing environment at the service of researchers, manufacturers and regulatory bodies.

Clinical focus: TAVI and PAPS

Transcatheter aortic valve replacement (TAVI): a less invasive therapy for severe aortic stenosis

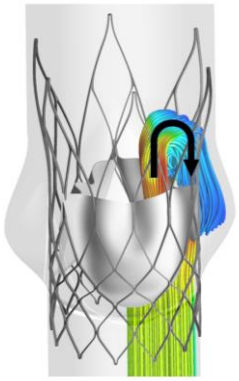

Figure 1: Transcatheter aortic valve implantation (TAVI) model. Photo credits: Institut für ImplantatTechnologie und Biomaterialien e.V.

The aortic valve is a valve placed between the left heart ventricle and the aorta and opens when blood is pumped from the heart to the rest of the body. *Aortic valve diseases* (AVD), such as aortic stenosis or aortic regurgitation, are conditions where the aortic valve cannot open and close properly, putting an extra strain on the heart and possibly resulting in breathlessness, swollen ankles, chest pain, dizziness and, sometimes, blackouts. When untreated, AVD progresses rapidly, resulting in an increased mortality.

The usual treatment for aortic stenosis is surgical replacement of the diseases valve using a prosthesis, but open heart surgery is considered too risky for people who are too weak or have concurrent conditions. A safer and less invasive alternative is *transcatheter aortic valve replacement* (TAVI or TAVR), a procedure to implant an aortic valve using a long narrow tube (catheter), that is inserted into a large blood vessel in the groin or through a small incision in the chest.

Transcatheter aortic valves are made of natural (cow or pig) tissue, that is re-engineered and attached to a flexible expanding mesh frame. The valve is implanted into the heart by squeezing it around or inside a catheter, that is and inserted and guided to the aortic valve. Once the new valve is implanted within the existing one, the catheter is removed, and the new valve starts working.

Pulmonary artery pressure sensors (PAPS): a wireless system for blood dynamics and cardiac pressure monitoring

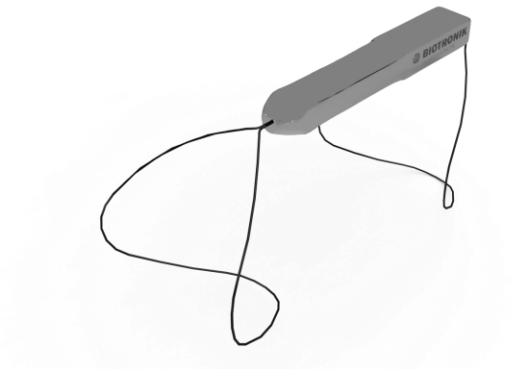

Figure 2: Pulmonary artery pressure sensors (PAPS) model. Photo credits: Biotronik SE & Co. KG.

Heart failure (HF), also known as congestive heart failure, is a medical condition where the heart muscle is unable to pump blood around the body properly, as it has become too weak or stiff due to narrowed arteries, high blood pressure, diabetes, obesity or other damaging conditions. Common symptoms include breathlessness after activity or at rest, fatigue, swollen ankles and legs.

Treatment for heart failure is aimed to control the symptoms as long as possible and slow down disease progression, and includes lifestyle changes (healthy diet, regular exercise, interruption of smoking), drug therapy, surgery (bypass operation), heart transplant, and heart rhythm monitoring devices.

Pulmonary artery pressure sensors (PAPS) are implantable, wireless monitoring systems able to transmit information on the patient's blood flow dynamics and intra-cardiac pressure to caregivers. By enabling earlier intervention, PAPS have been shown to reduce hospitalisation and improve patients' quality of life.

Consortium

The Consortium consists of 12 partners from 8 countries, including clinical centres, academia, industry and small and medium-sized enterprises (SMEs):

1. Charité - Universitätsmedizin Berlin (CHA), Germany (*Coordinator*)
2. Lynkeus (LYN), Italy
3. Biotronik (BIO), Germany
4. European Clinical Research Infrastructure Network (ECRIN), France
5. Institut für Höhere Studien – Institute for Advanced Studies (IHS), Austria
6. Institut für ImplantatTechnologie und Biomaterialien e.V. (IIB), Germany
7. Philips Electronics Netherlands B.V. (PHI), Netherlands
8. Eindhoven University of Technology (TUE), Netherlands
9. Graz University of Technology (TUG), Austria
10. Universitatea Transilvania Din Braşov (UTBV), Romania
11. University College of London (UCL), United Kingdom
12. Virtual Physiological Human Institute for Integrative Biomedical Research VZW (VPH), Belgium

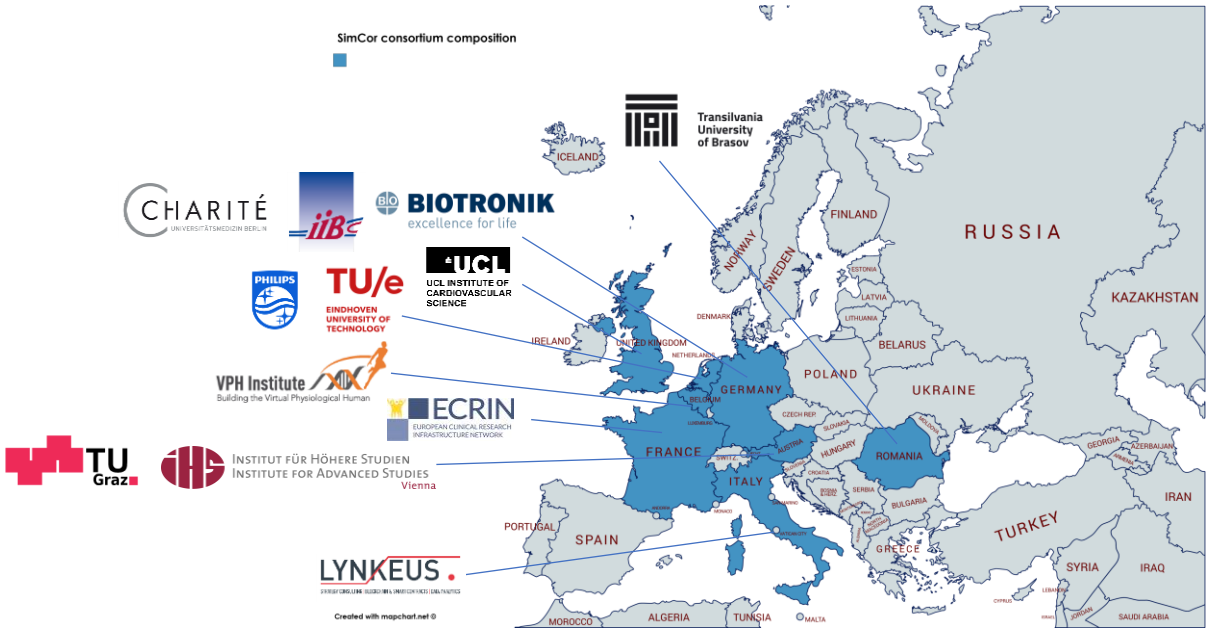

Figure 3: Geographical distribution of SIMCor consortium partners across Europe (EU and United Kingdom).

P1 - Charité – Universitätsmedizin Berlin (CHA) – Coordinator

Extended over 4 campuses and 17 clinical centres, CHA is one of the largest university hospitals in Europe, which is internationally renowned for its excellence in clinical care, teaching and training. At CHA, approximately 3,700 researchers are actively engaged in the development of pioneering innovations in the field of medicine across 1,000 projects, working groups and national as well as international collaborative projects for the benefit of clinicians, patients, and society.

As coordinating institution, CHA is responsible for project scientific and clinical supervision, besides leading the processing of imaging and sensor data from bench tests, preclinical and clinical studies as input for the generation of virtual cohorts and simulation modelling. CHA will also carry out preclinical tests as well as simulations and validations of blood flow modelling for PAPS, in cooperation with BIO.

P2 - Lynkeus (LYN)

Lynkeus is an independent research and consultancy firm specialized in the design and implementation of advanced IT solutions in healthcare and the biomedical sciences. Its team of IT and biomedical scientists, lawyers and experts in public administration delivers GDPR-compliant and scalable medical data sharing systems leveraging privacy-preserving solutions from blockchain to synthetic data. Founded in 2000, Lynkeus develops solutions at the intersection of ethics, law and medical technologies.

Lynkeus is supporting the Coordinator as Project Manager and is chief responsible of scientific communication, dissemination and exploitation of project results. LYN is also conducting the assessment of data management procedures for privacy, security and GDPR compliance and will contribute to the conception of operating procedures and guidelines.

P3 – BIOTRONIK (BIO)

Founded in 1963, Biotronik is a leading global medical device company with products and services that save and improve the lives of patients suffering from cardiovascular and endovascular diseases, ranging from cardiac rhythm management, electrophysiology to vascular intervention solutions. Key products include pacemakers, implantable defibrillators and leads, external remote monitoring systems for patients with cardiac arrhythmias, catheters, stents, balloon catheters and guide wires.

Biotronik will be the project lead responsible for computer simulations for the evaluation of device safety, efficacy and usability. It will also contribute to the development of device models, modelling of vessel-device interaction during and after device implantation, validation of modelling tools and will support the approval of in-silico testing strategies by regulatory authorities.

P4 – European Clinical Research Infrastructure Network (ECRIN)

ECRIN is a sustainable, not-for profit, distributed European Research Infrastructure Consortium that provides support for the planning and implementation of multinational clinical research projects in Europe. ECRIN includes a Core Team based in Paris, France and European Correspondents working in each of its 12 Member and Observer Countries hosted by the national scientific partners/networks of academic clinical trial units.

ECRIN will be responsible for assessing and quantifying the benefits of the use of in-silico solutions on clinical trials and the healthcare sector at large. It will evaluate the potential reduction in the size and duration of human trials and the use of animal testing, as well as in terms of enhanced device testing efficacy and reliability, improved patient outcomes and reduced adverse events.

P5 - Institute für Höhere Studien – Institute for Advanced Studies (IHS)

IHS is an independent, non-profit research institute that brings together high-level expertise from various disciplines (economics, sociology and political science among others) to address fundamental economic and social problems and policy choices. Through the combination of basic academic research, applied research and policy advice on topics such as health, labour market, European integration, and education under one roof it has a unique position in the Austrian scientific landscape.

IHS will lead the assessment and quantification of healthcare, industrial and socioeconomic impacts. Specifically, it will conduct analyses on the impact of using virtual cohorts on the industry and market on the one hand, and the healthcare system and society as a whole on the other, through the analysis of literature, interviews and project-generated data.

P6 - Institut für Implantat Technologie und Biomaterialien e.V. (IIB)

The IIB was founded in 1996 and is an affiliated institute of the University of Rostock in the legal form of a non-university, non-profit institute. The institute focuses on basic and industrial research in the fields of biomaterial testing, implant development, biomechanics and sensor technology, especially on cardiovascular implants such as vascular stents, transcatheter valve prostheses and other transcatheter-based implant technologies. Prof. Schmitz, director and founder of the IIB e.V., is member of the German Academy of Science and Engineering.

IIB will develop and optimise device-specific in-silico models predicting transcatheter aortic valve prosthesis performance related to safety, efficacy and usability, focussing on risk of thrombosis, leakage rate and durability, through bench tests and virtual cohorts. Additionally, IIB will take part in the developing of standard operating procedures.

P7 - Philips Electronics Netherlands B.V. (PHI)

PHI is a leading health technology company focused on improving people's health and enabling better outcomes from healthy living and prevention to diagnosis, treatment and home care. Philips leverages advanced technology and deep clinical and consumer insights to deliver integrated solutions. Headquartered in the Netherlands, the company is a leader in diagnostic imaging, image-guided therapy, patient monitoring and health informatics, as well as in consumer health and home care.

PHI will lead the virtual device implantation activity, that will develop 3D high-fidelity and reduced order finite element models to describe the device and its interaction with the recipient's tissue. It will also support the development of virtual cohorts and simulation of device effects, and the development of standard operating procedures.

P8 - Eindhoven University of Technology (TUE)

TUE is a research university specialised in engineering, science and technology. With over 11,000 students, 2,000 research staff and 1,500 PhD students, TU/e is one of the largest universities in Europe and includes a Department of Biomedical Engineering with a dedicated undergraduate and graduate program. Here, the Cardiovascular Biomechanics group focuses on numerical and experimental modelling of the cardiovascular system to develop diagnostic methods, model-based decision support systems and therapeutic protocols.

The main role of TUE is the development and validation of virtual cohorts for TAVI and PAPS simulation for in-silico clinical trials, based on image, sensor and laboratory patient data from aortic valve stenosis and heart failure, as well as a small virtual cohort of animals for in-silico preclinical studies. TUE will also contribute to virtual device implantation, device and device tissue interaction modelling.

P9 - Graz University of Technology (TUG)

The quality of the education and training at TUG is due to its knowledge-oriented and applied research. TUG has over 2.000 staff, 12.000 undergraduate and 1.180 PhD students, and a Biomedical Engineering program with around 200 new students every year. BioTechMed-Graz, a cooperation and networking initiative between the University of Graz, the Medical University of Graz and Graz University of Technology, works at the interface of biomedical basics, technological developments and medical implementation.

TUG will lead the development of constitutive models for the deployment of devices in the cardiovascular system and the simulation of device-specific effects in regard to safety, efficacy and usability. Particularly, TUG will study the structure of the vessel wall, develop and validate sophisticated models describing its material behaviour and incorporating tissue-device interaction effects.

P10 - Universitatea Transilvania Din Brașov (UTBV)

UTBV is a public academic institution with over 800 full-time scientists and professors and around 20,000 undergraduate and PhD students. The University has 16 faculties, eight of which focused on engineering areas. The Department of Automation and Information Technology, within the Faculty of Electrical Engineering and Computer Sciences, has carried out numerous biomedical engineering research projects at national and EU level, with a strong know-how in mathematical and machine-learning based modelling and cloud computing.

UTBV is responsible for the implementation of the virtual research environment of the SIMCor research platform, supporting data collection and sharing, virtual cohort validation, execution of device effect simulations and virtual clinical trials, and contributing to the European Open Science Cloud. UTBV will also contribute to virtual patient cohort generation, device modelling and validation.

P11 - University College London (UCL)

UCL is London's leading multidisciplinary university, with more than 13,000 staff and 38,000 students from 150 different countries. UCL has a global reputation for excellence in research and is committed to delivering impact and innovations that enhance the lives of people in the UK, across Europe and around the world. UCL was identified by the UK Research Excellence Framework as the top university in the UK for research strength and UCL is consistently placed in the global top 20 across a wide range of university rankings (currently joint 7th in the QS World University Ranking).

UCL will bring clinical and modelling expertise to the project, leading data acquisition for TAVI and PAPS population, reviewing and reporting retrospective data quality and creating synthetic data. Also, UCL will contribute to the processing imaging data and creation of anatomical models and boundary conditions for the simulations, as well as the definition of standards of practice.

P12 - Virtual Physiological Human Institute for Integrative Biomedical Research VZW (VPHi)

VPHi is an international non-profit organisation whose mission is to ensure that the in-silico medicine paradigm is fully realised and universally adopted in research and clinics, by integrating quantitative biological knowledge from molecular to cell, tissue, organ and whole-body scales, and translating it into clinical practice. VPHi acts as a catalyst to bring together a variety of stakeholders (policy makers, science funding bodies, regulatory agencies, clinical organisations, industry) to maximise the benefit of in-silico medicine approaches for industry and public good.

VPHi will lead the development of standard operating procedures and guidelines for the in-silico testing of cardiovascular devices, in collaboration with clinical, academic and industry partners and external advisory boards, as well as strongly support dissemination activities leveraging its broad network of research centres and industries active in in-silico medicine and communication channels.

Implementation

Workplan and work packages

SIMCor will be implemented through 10 *work packages* (WPs), listed below along with leading partner and main goals.

- **WP1 - Coordination and management (CHA):** scientific coordination (clinical strategy, research lines and objectives) and operational management of project activities (monitoring and reporting, quality and risk control, financial and administrative management).
- **WP2 - Engagement, communication, dissemination and exploitation (LYN):** engagement with project stakeholders (researchers, manufacturers, regulatory authorities, clinicians and patients), dissemination and exploitation of project results and broader communication.
- **WP3 - Virtual device environment implementation (UTBV)**: creation of the virtual research environment where to integrate data, virtual cohorts, simulation models, methodologies, standards and guidelines.
- **WP4 - Definition of standard operating procedures (VPH)**: establishment of standard operating procedures (SOPs), best practices and documentation guidelines in collaboration with regulatory authorities and representatives from clinics, academia and industry.
- **WP5 - Preclinical and clinical data acquisition (UCL)**: collection of preclinical and clinical data, conduction of preclinical studies, creation of synthetic data.
- **WP6 - Data processing for anatomy and function (CHA)**: postprocessing and statistical analysis of data to derive a library of data models for cohort generation and modelling, including anatomical geometries (heart chambers, heart valves, large vessels), functional information (haemodynamics, ventricular function) and material properties (anatomical distribution of strains, compliance/distensibility).
- **WP7 - Virtual cohort generation and validation (TUE)**: generation and validation of virtual cohorts for in-silico testing and simulation modelling, including aortic valve disease and heart failure adult and children patient populations, and health pig population.
- **WP8 - Virtual device implantation (PHI)**: elaboration of a framework for the virtual implantation of PAPS and TAVI on bench test environments, animal and patient cohorts.
- **WP9 - Device effect simulation (BIO)**: elaboration of a methodology for the development and validation of computational models to target device safety, efficacy and usability.
- **WP10 - Quantification of healthcare, industry and socioeconomic effects (IHS)**: quantitative assessment of the integration of in-silico solutions in traditional clinical trials, evaluating its benefits on the healthcare system, industry and market, and society at large.

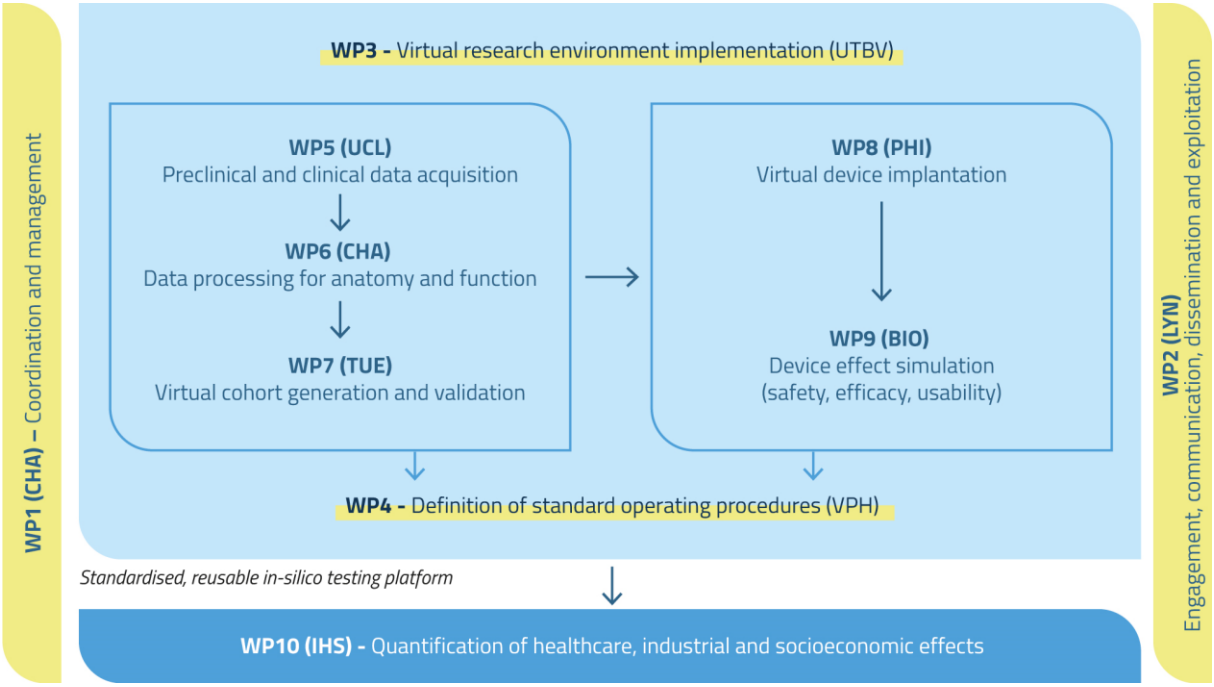

Figure 4: SIMCor implementation workplan and relevant work packages (WPs).

Phases of implementation

The project R&D activities will be articulated into three main phases.

Phase 1 - Requirement specification and resource integration (M1 - M6)

This represents the preparatory phase and will be dedicated to:

- *specification of platform technical requirements, components, workflows and interactions*;
- *acquisition of data resources* from clinical centres (Charité, Great Ormond Street Hospital, Barts Health NHS Trust) and other partners' previous research projects;
- *setup of project management procedures and tools*, such as internal communication tools, self-assessment and quality control criteria, metrics and procedures;
- *conception of the project engagement, communication and dissemination strategy*.

Phase 2 - Development of in-silico modelling resources (M7 - M18).

This phase will be devoted to the development of resources for the in-silico modelling, validation and regulatory approval pipeline, including:

- *processing of clinical data for anatomical and functional modelling*;
- *creation of additional synthetic patient anatomy data*;
- *generation of virtual cohorts of human patients and animal models*;
- *development of TAVI and PAPS device models, vessel models and device effect simulation models*;
- *definition of standard operating procedures and guidelines*;
- *elaboration of the theoretical framework for the evaluation of healthcare, industry and socioeconomic benefits*;
- *engagement of stakeholders* for communication and dissemination of results and feedback gathering.

Phase 3 - Proof-of-concept validation, extension and impact assessment (M19-M36)

This phase is dedicated to the validation, refinement, finalisation and exploitation of project results, particularly:

- *validation of virtual cohorts and device effect simulation models*;
- *refinement and approval of standard operating procedures and guidelines*;
- *assessment of healthcare, industrial and socioeconomic benefits*, based on theoretical and literature-based frameworks, virtual clinical trial results, cost-effectiveness analyses, interviews and focus groups with stakeholders;
- *dissemination and exploitation of project results*.

Impact

Given its mission and expected results, SIMCor aims to exercise a substantial impact on the medical device testing, validation and regulatory approval landscape, along with substantial benefits on the healthcare domain, the medical device industry and market, the economy and the society as a whole.

Reduction in the size and duration of human clinical trials and the use of animal testing clinical trials.

Synthetic anatomical and functional heart geometries and virtual cohorts, based on real AVD and HF patients' image, sensor and laboratory data, offer a comprehensive representation of the geometry and (patho)physiology of the human heart, valves and great vessels, while uncertainty and sensitivity analyses enable to assess the variability of physiological parameters at individual patients' level. These tools, jointly with accurate simulations of the devices and their interaction with the patient's anatomy, are able to maximise the efficiency of the validation process and foresee long-term or rare effects undetectable in traditional human trials. This would allow to achieve reduction in the size and duration of trials on cohorts of human patients, as well as minimise the need of assessing the impact of implantation procedures on animal structures and tissues. In addition, the generation of additional animal cohorts of healthy pigs will further contribute to replace the use of live animals for preclinical tests.

The expected reduction in size and duration of clinical trials and animal testing will be quantified by directly comparing key parameters of clinical in-silico and real clinical trials such as sample size, outcome, inclusion/exclusion criteria, effect, duration. SIMCor will identify and analyse specific outcome variables relevant for the reduction of the number of animal or human subjects and their informative power to determine optimal clinical trial designs.

Increased efficacy and patient safety in clinical trials.

The use of virtual cohorts and synthetic data reproducing individual patients' anatomical, functional and (patho)physiological features, accurate device and patient-specific heart, valves and great vessel models, and personalised simulations for device implantation and biomechanical interaction with human tissues, will greatly increase patients' safety and long-term outcomes.

The evaluation of device effects in a staged approach in virtual bench, animal and clinical tests, taking into account structural and functional variabilities at patient-specific level, will allow detection of possible device failure mechanisms and adverse events at early stages, enhancing device safety assessment pre-implantation and thus device implantation success, as well as sensibly reducing the rate of adverse events in the long run. Likewise, in-silico testing will help identify efficacy determinants and refining device design and components accordingly, supporting the generation of devices with higher functional performance, enhanced durability and less risk of device failure.

Given the large and chronic incidence of AVD and HF, the in-silico testing of TAVI and PAPS will benefit a significant number of patients. The SIMCor approach is, however, expected to go far beyond this. SIMCor aims to significantly impact the clinical condition of children with congenital heart defects, commonly treated with heart valves or stents, but affected by the scarcity of devices specifically tested and approved for children, determined by limited availability of patient numbers for clinical trials. By generating a variety of synthetic paediatric anatomies and virtual patient cohorts of HF, SIMCor aims, in the long run, to support device manufacturers in getting easier and faster regulatory approval for PAPS in children, helping to achieve improved treatment outcomes and long-term benefits in the young.

Reduction in development costs and time-to-market for new cardiovascular devices.

SIMCor will assemble an exquisitely efficient process for the development, V&V, regulatory approval of medical devices to achieve a faster, cheaper and higher quality journey of new technologies to market. The increased efficiency of the SIMCor in-silico workflow will be based on the availability of diversified, comprehensive and robust virtual cohorts of animal and patient anatomies, as well as device implantation and effect simulation models, and the adoption of SOPs, defined in collaboration with regulatory bodies and stakeholders in the medical device sector, that will optimise and standardise all phases of design, V&V, towards a faster and seamless regulatory approval and market authorisation.

The testing of new devices based on the use of in-silico tools is substantially faster, less expensive and more comprehensive than conventional testing based on bench and animal tests. Particularly, the testing of anatomical fitting in a large variety of anatomies, with different sizes of implants, allows to evaluate patient-specific devices with individual design features in a timely and cost-efficient manner, enabling new device concepts and designs and leading to optimized products.

The enhanced incorporation of in-silico trials into design and V&V processes allows to assess parameters related to safety, efficacy and usability before conducting real clinical trials, envisaging adverse events and device failure at an early stage and avoiding design changes at a later development phase. In this way, clinical studies can start less cautiously, or even be waived, if the devices under evaluation are similar to already marketed devices and in-silico testing has been completed successfully. Feasibility studies could also be shortened, and pivotal studies for new devices can be better planned, as statistical power calculation will be more informed by prior knowledge from in-silico testing.