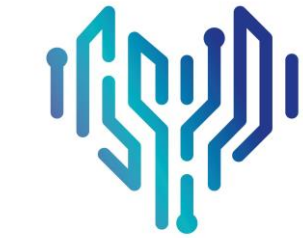

SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

Call: H2020-SC1-DTH-2018-2020 (*Digital transformation in Health and Care*)

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Deliverable 10.1

In-silico trial impact assessment framework

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Executive summary

The objective of this deliverable is to define and develop a framework for estimating the impact of in-silico methods and technologies on clinical and preclinical trials, laying the basis for the assessment of broader effects on patient safety, animal welfare and industry workflow. In the introductory part a status view on this area is given. The document starts with basic terminology and definitions related to in-silico approaches. Thereafter, existing standards, guidelines and frameworks relevant for in-silico trials are referenced. Examples and use cases of published in-silico trials are presented as well as existing tools to support in-silico trials described. The introductory part of the deliverable closes with a selection of projects and programs dedicated to in-silico approaches and relevant for SIMCor.

The approach for executing an in-silico trial in SIMCor will be based on the methodology provided by Bodner and Kaul (Proceedings of the ASME 2021 Verification and Validation Symposium, V001T02A0012021) for in-silico clinical trials for medical devices. This framework heavily relies on ideas already developed for model verification, validation, and uncertainty quantification. The process starts with the computational model, which is developed upstream of the in-silico trial. The next step is to establish baseline credibility evidence with the goal that the model is ready to use for the in-silico trial. After this step, clinical trial planning starts with developing the in-silico trial protocol. Thereafter, the in-silico trial is designed as follows: a virtual cohort following the specifications of the human cohort is generated and a final model validation will be performed using human data. If the model is adequate the model predictions to the target population can be performed and the clinical endpoints can be evaluated. An important aspect in applying in-silico trials is the transfer from engineering outputs to clinical endpoints. To support this process, transfer functions based upon available data will be considered in SIMCor.

The impact assessment framework, describing the in-silico trial workflow will be embedded in three infrastructures: The virtual cohort generator, the analysis environment and the *virtual research environment* (VRE). The clinical trial design is specified within the analysis environment and then communicated to the virtual cohort generator, which produces a trial-specific cohort. The data generated are transferred to the analysis environment, where the in-silico trial is run according to the defined design. The in-silico trial datasets produced by the virtual cohort generator will be archived in the VRE. This is also done for information generated in the analysis environment, covering the in-silico trial specification, the scripts for the analysis and the results from the analysis. This process is cyclic and repeated as often as there is a need to do so. If all necessary results have been achieved, the process is closed and the results are explored and a decision is taken. This process is considered as the bare minimum to give transparency and to allow repeatability of trial results. If adequate clinical trial data are available, it is foreseen to validate the results of the in-silico trials against these data. For that reason, a search has been performed, identifying randomised TAVI trials with the intention to share data for secondary research.

Based on the conceptual framework, the clinical impact of in-silico trials will be assessed, and benefits allowed by in-silico device testing technologies along several outcome dimensions will be estimated. The results achieved by the in-silico trials will be injected into the quantitative assessment of socioeconomic effects.

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Acronyms

Acronym	Full name
ABM	Agent-Based Modelling
AHRQ	Agency for Healthcare research and Quality (AHRQ)
ASME	American Society of Medical Engineers
CoU	Context of Use
FD-PASS	Flow Diverter Performance Assessment
IAM	Identity and Access Management
IPD	Individual Participant Data
ISW	In Silico World
MIDD	Model-Informed Drug Development
MISTIR	Multicentric In-Silico Trials in Radiotherapy
ML	Machine Learning
NSCLC	Non Small Cell Lung Cancer
IPD	Individual Participant Data
PAPS	Pulmonary Artery Pressure Sensor
PDBK	Physiologically Based Pharmacokinetic Analyses
ROCOCO	Radiology Oncology Collaborative Comparison
TAVI	Transcatheter Aortic Valve Implantation
UISS	Universal Immune System Simulator
VICTRE	Virtual Imaging Clinical Trial for Regulatory Evaluation
VRE	Virtual Research Environment
VVUQ	Verification, validation, Uncertainty Quantification

Introduction

The objective of this deliverable is to define and develop a framework for estimating the impact of in-silico methods and technologies on clinical and preclinical trials, laying the basis for the assessment of broader effects on patient safety, animal welfare and industry workflow. The document covers an overview on the status of in-silico trials in the literature, defines the methodological approach used in SIMCor and provides the impact assessment framework.

The deliverable has been aligned with the Research strategy plan (Deliverable 1.1), the Data management plan (Deliverable 3.2), the Definition of the model output (Deliverable 7.1) and the Protocol for clinical data collection (Deliverable 5.1). It is based upon internal ECRIN workshops, discussions from the virtual cohort working group (VC WG) and the general assembly and additional meetings between WP3, WP7 and WP10.

Status in the literature

Terminology and definitions

The term "in-silico" is increasingly used in the context of computer modelling and simulation. In-silico means carried out by the computer, which is in contrast to *in vitro* (on the bench), *ex vivo* (outside the body), or *in vivo* (inside the body)[1]. In-silico trials can be preclinical or clinical studies or linked to benchtop testing and animal studies. An in-silico clinical trial refers to the use of individualised computer simulations in a cohort of patients during the development or regulatory evaluation of a medicinal product, medical device, or medical intervention. Another definition is: If predictive technologies are used in the development and assessment of new biomedical products (whether drugs, biologicals, medical devices or combination products) or in the management of biomedical product life cycles, they are called in-silico clinical trials[2]. A set of basic definitions related to in-silico is given in [1].

Different modelling and simulation methodologies can be used in in-silico trials. Some rely on pure computer science techniques (i.e., *agent-based modelling* (ABM) and *machine learning* (ML)), others are rather mathematical approaches (i.e., differential equations, finite elements and regression analyses). In addition, both techniques are combined in hybrid approaches. In [2] a taxonomic approach to this complex territory is offered. These can be divided into two broad fields: models that predict only the average behaviour of populations (population-specific) or models that predict the behaviour of each individual in a population (subject-specific). Subject-specific approaches cover clinical decision support, self-care decision support, policy decision support and development of biomedical products.

Standards, guidelines and frameworks

Guidelines for in-silico approaches have been defined by regulatory bodies and international organisations. In 2016, FDA has provided guidance on "Reporting of computational studies in medical device submissions", with the purpose to provide recommendations to industry on the formatting, organisation, and content of computational model and simulation studies that are used to support medical device submissions[3]. This was followed in 2018 by the publication of the *American Society of Mechanical Engineers* (ASME) V&V 40-2018 technical standard "Assessing Credibility of Computational Modelling through Verification and Validation: Application to Medical Devices", introducing a risk-informed credibility assessment framework[4]. This standard provides a framework for assessing the relevance and adequacy of completed verification and validation activities that establish credibility of a computational model. The activities to establish credibility should be commensurate with the degree to which the computational model is relied on as evidence of device performance, functional characteristic, and/or safety to support a decision, and the consequences of that decision being incorrect. The applicability of the ASME V&V40 standard in the field of drug development and evaluation was recently discussed in a white paper[5], in which the framework is applied to three use cases using a credibility matrix as a tool tested by European regulators.

[1] Horner et al., Avicenna Alliance Position Paper. Ensuring the quality of in silico evidence: Application to medical devices. 2021 (Avicenna_Alliance_Position_paper_Global_Harmonization.pdf (avicenna-alliance.com)

[2] Pappalardo et al., In silico clinical trials: concepts and early adoptions. Brief Bioinform. 2019; 20: 1699.

[3] FDA: Guidance for Industry and Food and Drug Administration Staff. Reporting of Computational Modeling Studies in Medical Device Submissions. September 21, 2016

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

[5] Musuamba et al., Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility. CPT Pharmacometrics Syst Pharmacol. 2021; 10: 804

The *European Medicines Agency* (EMA) has founded a Modelling and Simulation Working Party, providing support to EMA's scientific committees[6] and working parties on modelling and simulation relating to medicines. In 2020, EMA Regulatory Science to 2025 – strategic reflection was published, recognising the importance of emerging technologies in general and modelling and simulation, also known as in-silico methods[7]. Unfortunately, however, the document tends to stress the value of in-silico methods almost exclusively in connection with the reduction of animal experimentation. EMA has also issued guidelines for reporting of *physiologically based pharmacokinetic* (PDBK) modelling and simulation[8] and guidelines on reporting the results of population pharmacokinetic analyses[9].

The Avicenna Alliance (Association for Predictive Medicine), an association of industry and renowned academia/healthcare organizations, who have a commercial or research interest in the development of in-silico medicine, was established in 2015. It has its origins in the Virtual Physiological Human Initiative and an EC Coordination Support Action, providing an international and technological research and development roadmap for in-silico clinical trials[10]. In 2021, a position paper was endorsed by Avicenna Alliance, entitled "Ensuring the quality of in-silico evidence. Application to medical devices"[11]. The Avicenna Alliance[12] Good Simulation Practice Task Force is expected to produce a Position Paper on future "Good Simulation Practice"[13]. In close collaboration with the Avicenna Alliance, the In Silico World community of practice hosts the consensus process to develop the so-called Good Simulation Practice. *In Silico World* (ISW) is an EU-funded project that aims at accelerating the uptake of modelling and simulation technologies for the development and regulatory assessment of all kinds of medical products[14]. Eventually, the idea is to develop a document equivalent to the Good Clinical Practice[15] defined by the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use[16].

In 2016, the *Agency for Healthcare Research and Quality* (AHRQ), an agency within the US Department of Health and Human Services, presented general guidance for modelling and simulation in the context of health technology assessment[17]. The guidance aims to encourage the use of good modelling and reporting practices in conjunction with systematic reviews and describes how systematic reviews can increase the transparency of the modelling process and contribute to the development of useful models. A year later, this was complemented by a review of existing guidance, future research needs, and validity assessment[18].

Other regulatory documents and workshop reports of the various authorities around the world that are related to this topic, are summarised on the ISW webpage[19]:

- ISO 14155, 2020 – Revision of Clinical investigation of medical devices for human subjects — Good clinical practice[20]

[6] https://www.ema.europa.eu/en/committees-working-parties-other-groups
[7] EMA Regulatory Science to 2025 Strategic reflection. 2020
[8] EMA: Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation. December, 2018
[9] EMA: Guideline for reporting the results of population pharmocokinetic analyses. June, 2007
[10] Viceconti et al. In: In silico clinical trials. How computer simulation will transform biomedical industry. Chapter V: In silico clinical trials: Use cases for medical devices. International Journal of Clinical Trials. 2016; 3: 37
[11] Horner et al., Avicenna Alliance Position Paper. Ensuring the quality of in silico evidence: Application to medical devices. 2021
[12]https://avicenna-alliance.com/latest-news/news/towards-good-simulation-practice-an-interview-of-luca-emili-and-prof-marco-viceconti/
[13] In silico talks: Towards good simulation practice. 2021
[14] https://insilico.world/
[15] https://en.wikipedia.org/wiki/Good_clinical_practice
[16] https://www.ich.org/
[17] Dahabreh et al. AHRQ. Guidance for the Conduct and Reporting of Modeling and Simulation Studies in the Context of Health Technology Assessment. Methods Guide for comparative Effectiveness Reviews, 2016
[18] Dahabreh et al. AHRQ. Methods for Effective health Care. In: Modeling and Simulation in the Context of Health Technology Assessment: Review of Existing Guidance, Future Research Needs, and Validity Assessment, 2017
[19] https://insilico.world/community/good-simulation-practice-gsp-document-collection/
[20] https://www.iso.org/standard/45557.html

- European Commission, 2020 – Guideline. MDCG 2020-1 Guidance on Clinical Evaluation (MDR) / Performance Evaluation (IVDR) of Medical Device Software[21]
- EMA, 2019 – Presentation. Optimise capabilities in modelling, simulation and extrapolation[22]
- IMDRF, 2019 – Guideline. Guidance on Clinical Evaluation (.docx)
- IMDRF, 2019 – Guideline. Clinical Evidence – Key Definitions and Concepts (.docx)
- IMDRF, 2019 – Guideline. Clinical Investigation (.docx)
- FDA, 2019 – Guidance Document. Clinical Decision Support Software[23]
- ASME, 2018 – Technical Standard VV-40 2018 – Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices[24]
- University of Bath, 2018 – Clinical Trial validation. ToKa HTO Versus Generic HTO Virtual Clinical Trial[25]
- FDA, 2018 – Presentation. How Simulation Can Transform Regulatory Pathways[26]
- FDA, 2018 – Pilot Program. Model-Informed Drug Development Pilot Program[27]
- IMDRF, 2018 – Optimizing Standards for Regulatory Use (.docx)
- EMA, 2017 – Guideline. Reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation[28].
- IMDRF, 2017 – Software as a Medical Device (SaDM): Clinical Evaluation (.docx)
- EMA, 2016 – Workshop. Workshop on qualification and reporting of physiologically-based pharmacokinetic (PBPK) modelling and simulation[29]
- FDA, 2016 – Guideline. Reporting of Computational Modeling Studies in Medical Device Submissions[30]
- IMDRF, 2014 – "Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations (.docx)

Examples and use cases of in-silico trials

So far only a limited number of in-silico trials has been performed and published, some of them not under the denomination of in-silico. The majority of them are dealing with medicinal products or radiological treatment. Examples are:

a) *Flow diverter performance assessment* (FD-Pass) in-silico trial, investigating treatment of intracranial aneurysms with a flow-diverting stent, using computational fluid dynamics to quantify post-treatment flow reduction[31]
b) Virtual trial to evaluate the robustness of cementless femoral stems to patient and surgical variation[32]

[21] https://ec.europa.eu/docsroom/documents/40323?locale=en
[22] https://www.ema.europa.eu/en/documents/presentation/presentation-ema-regulatory-science-2025-optimise-capabilities-modelling-simulation-extrapolation_en.pdf
[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-decision-support-software
[24]https://www.asme.org/codes-standards/find-codes-standards/v-v-40-assessing-credibility-computational-modeling-verification-validation-application-medical-devices
[25] https://clinicaltrials.gov/ct2/show/NCT03419598
[26] https://www.fda.gov/science-research/about-science-research-fda/how-simulation-can-transform-regulatory-pathways
[27] https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program
[28] https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation
[29]https://www.ema.europa.eu/en/events/workshop-qualification-reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation
[30]https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions
[31] Sarrami-Foroushani et al., In-silico trial of intracranial flow diverters replicates and expands insights from conventional clinical trials. Nat Commun. 2021; 2: 3861
[32] Al-Dirini et al., Virtual trial to evaluate the robustness of cementless femoral stems to patient and surgical variation, Journal of Biomechanics. 2019; 82: 346

c) In-silico trial with the university of Virginia/Padova type 1 diabetes simulator to explore the potential benefit of different dosing regimens of inhaled human insulin on postprandial glucose[33]
d) Clinical Trial Simulations to Identify and Individualize Optimal Isoniazid Doses in Children with Tuberculosis[34]
e) In-silico trial based upon a systems pharmacology model to explore anti-CTLA-4 and anti-PD-L1 immunotherapies in metastatic breast cancer[35]
f) VICTRE (*Virtual Imaging Clinical Trial for Regulatory Evaluation*) in-silico clinical imaging trial evaluating digital breast tomosynthesis (DBT) as a replacement for digital mammography (DM)[36]
g) ROCOCO (*Radiology Oncology Collaborative Comparison*) trial, emulating a real clinical trial comparing photon, proton, and C-ion therapy for cancer patients (*non small cell lung cancer*, NSCLC) using the collaborative *multicentric in-silico trials in radiotherap*y (MISTIR) framework[37]
h) In-silico clinical trial using high performance computational modelling of a virtual human cardiac population to assess drug-induced arrhythmic risk[38]
i) Predicting the artificial immunity induced by RUTI® vaccine against tuberculosis using *universal immune system simulator* (UISS)[39]
j) In-silico pre-clinical trials for implantable cardioverter defibrillators

Use cases for in-silico clinical trials for medical devices, spanning the range from design use via preclinical to clinical assessment have been outlined in [10].

A number of case studies of successful applications of in-silico medicine have been summarised in a document by the Avicenna alliance[40], covering:

a) Using Modeling and Simulation to Establish Safety of the Metallic Passive Implants in MRI Scanners (DePuy Synthes Spine, Johnson & Johnson)
b) Enabling early approval through a smarter approach to generating robust clinical evidence and Identifying the best overall strategy for study designs and drug development pathways (Exploristics)
c) Modeling and simulation platform (Mimesis)
d) In-silico disease model of chronic HBV patients (Novadiscovery)
e) CT-based patient-specific model to predict the risk of hip fracture (Rizzoli Orthopaedic Institute)

[33] Visentin et al., Improving Efficacy of Inhaled Technosphere Insulin (Afrezza) by Postmeal Dosing: In-silico Clinical Trial with the University of Virginia/Padova Type 1 Diabetes Simulator. Diabetes Technol Ther. 2016;18:574
[34] Jeena et al. In Silico Children and the Glass Mouse Model: Clinical Trial Simulations to Identify and Individualize Optimal Isoniazid Doses in Children with Tuberculosis 2011. Antimicrob Agents Chemother. 2011; 55: 539
[35] Wang et al., In silico simulation of a clinical trial with anti-CTLA-4 and anti-PD-L1 immunotherapies in metastatic breast cancer using a systems pharmacology model. R. Soc. Open Sci. 2019; 6
[36] Badano A. In silico imaging clinical trials: cheaper, faster, better, safer, and more scalable. Trials. 2021; 22: 64
[37] Roelofs et al., Results of a Multicentric In Silico Clinical Trial (ROCOCO): Comparing Radiotherapy with Photons and Protons for Non-small Cell Lung Cancer. Journal of Thoracic Oncology. 2012; 7: 165
[38] Aguado Sierra et al., In-silico clinical trial using high performance computational modeling of a virtual human cardiac population to assess drug-induced arrhythmic risk. medRxiv 2021
[39] Pennisi et al., Predicting the artificial immunity induced by RUTI® vaccine against tuberculosis using universal immune system simulator (UISS). BMC Bioinformatics.2019; 20: 504
[40] Avicenna Alliance: Avicenna Alliance Members Case Studies on in silico medicine. April 2020

Tools and computing environments

Several toolboxes and platforms are offered to manage in-silico trials. For an in-silico platform to be efficient, models need to be effectively developed and executed. Key features are therefore multi-functionality, adequate software and hardware architecture, and high levels of automation[41]. The majority is for simulations related to medicinal products.

Some of them are commercial, an example is the **InSilico trial platform**[42]. It enables users to input parameters of choice into the model. For a model from the digital library, parameters choices are guided by best practice ranges. Simulations are launched and run on protected and secured Microsoft Azure Cloud computing resources. The platform enables users to view and analyse the modelling and simulation results and to optimize modelling and simulation scenarios depending on objectives.
Others are open and (partially) freely available, such as:

The **QSP (*quantitative systems pharmacology*) Toolbox** is designed to support QSP workflows, including calibrating the model using experimental data, defining and generating virtual patients, exploring model variability by the unweighted cohort of virtual patients and weighted virtual populations, and predicting new experimental/trial outcomes[43]. Although the QSP Toolbox is freely available, other associated software costs or preference for another scripting language may be disadvantages for some users.

The ***Universal Immune System Simulator*** **(UISS)** in-silico platform is potentially ready to be used as an in-silico trial platform to predict the outcome of vaccination strategy against SARS-CoV-2[44].

Simulo is a user-friendly clinical trial simulator developed by SGS Exprimo[45]. It uses Monte Carlo simulations and R code to assess study designs and compare different dosing strategies using mixed-effects models. This will help in the optimization of the clinical trials steps and in the prediction of probability of success, the optimal dose, the cost effectiveness and finally the go or no go decisions. There are two available versions of the software, basic free version and expert version.

In addition, there are also clinical trial simulators, which may be of value for the conception of in-silico trials, such as:

Highly Efficient Clinical Trials Simulator **(HECT)** is a web based clinical trial simulator for planning of adaptive trials (a type of trials that is more flexible than conventional clinical trials), written with statistical software R, with friendly user graphical interface[44]. This simulator allows the user to set multiple clinical trial parameters and investigate different settings such as varying treatment effects, control response and adherence. It is an opensource tool and it is most useful for clinical trial investigators who don't have specialized statistical capacity or an access to a commercial trial simulator. An important note here is that the simulation code in this software has been validated against six clinical trials designed by the designer of the software[46].

The existing software tools and services do not perfectly fit SIMCor. The requirements for virtual cohort generation and in-silico trials defined by the project can only be partly fulfilled. In order to

[41] Favre P, Maquer, G, Henderson, A. *et al. In Silico* Clinical Trials in the Orthopedic Device Industry: From Fantasy to Reality? Annals Biomed Eng. 2021
[42] https://insilicotrials.com/platform/
[43] Cheng et al. QSP Toolbox: Computational Implementation of Integrated Workflow Components for Deploying Multi-Scale Mechanistic Models. AAPS J. 2017; 19: 1002
[44] Russo G, Pennisi, M, Fichera, E *et al.* In silico trial to test COVID-19 candidate vaccines: a case study with UISS platform. BMC Bioinformatics 202; 21**:** 527
[45] Abdelrahman et al., Exploring the Power and Promise of In Silico Clinical Trials with Applications in COVID-19 Infection. Sudan Journal of Medical Sciences. 2021; 16: 355
[46] https://mtek.shinyapps.io/hect/

cover the full development cycle of SIMCor, a necessity was seen to develop and implement a specific software environment.

Projects and programs

Several other projects and programs dealing with in-silico trials have been launched recently and are of relevance for SIMCor, all described below.

In Silico World (EU H2020, 1 January 2021 to 31 December 2024)

In Silico World is dedicated to lowering barriers to ubiquitous adoption of in-silico trials[47]. In Silico World aims at accelerating the uptake of modelling and simulation technologies used for the development and regulatory assessment of medicines and medical devices, by lowering seven identified barriers: development, validation, accreditation, optimisation, exploitation, information, and training.

SimInSitu (EU H2020, 1 January 2021 – 31 December 2024)[48]

Valvular heart disease requires valve replacement or repair. Advances in tissue engineering offer the opportunity to develop a new class of heart valve replacements: synthetic biodegradable heart valves. To accelerate the development of these devices, the EU-funded SimInSitu project is proposing an in-silico model capable of predicting the device's short- and long-term safety and performance. It will incorporate tissue-remodelling-algorithms, patient-specific-modelling, and device-modelling. All relevant components and processes will undergo an extensive verification, validation and uncertainty quantification programme to generate the necessary credibility and trustworthiness. The development of the in-silico model can facilitate the development of biodegradable devices, shorten the time to market, and contribute to development of a regulatory framework of in-silico methods.

SimCardioTest (EU H2020, 1 January 2021 – 31 December 2024)[49]

Computer modelling and simulation have the power to increase speed and reduce costs in most product development pipelines. SimCardioTest aims to implement computer modelling, simulation and artificial intelligence to design and test cardiac drugs and medical devices. Scientists will establish a platform for running in-silico trials and obtaining scientific evidence based on controlled investigations. The simulation of disease conditions and cohort characteristics has the potential to overcome clinical trial limitations, such as under-representation of groups. It also reduces the size and duration of human clinical trials as well as animal testing, and offers robust, personalised information. Leveraging in-silico technology in healthcare will expedite product and drug certification and offer patients the best possible care.

INSIST (EU H2020, 1 November 2017 – 30 April 2022)[50]

The main goal of INSIST is to advance treatments of ischemic stroke and its introduction in clinical practice by realizing in-silico clinical stroke trials in which stroke and treatment are modelled. INSIST will generate virtual populations of stroke patients, generate and validate in-silico models for intra-arterial thrombectomy, thrombosis and thrombolysis, and microvascular perfusion and neurological deterioration after stroke, and integrate the in-silico models to realize an in-silico clinical stroke trial.

[47] https://insilico.world/
[48] http://www.siminsitu.eu/
[49] https://digital-strategy.ec.europa.eu/en/news/simcardiotest-eu-funded-project-develops-new-predictive-tools-cardiac-pathologies
[50] Konduri et al. In-silico trials for treatment of acute stroke. Front. Neurol. 2020

FDA: *Model-Informed Drug Development Pilot Program* (MIDD)

As displayed in the Federal Register[51] notice on April 16, 2018, the FDA is conducting a *Model-Informed Drug Development* (MIDD) Pilot Program to facilitate the development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources, referred to as MIDD approaches. MIDD approaches use a variety of quantitative methods to help balance the risks and benefits of drug products in development.

It would be an enormous advantage to discuss the in-silico trial impact assessment framework developed in SIMCor together with the other EU H2020-funded projects on in-silico research. Therefore, it is suggested to perform a workshop in 2022 to discuss overlaps and synergies and to explore a common approach between the different projects.

[51] https://www.federalregister.gov/documents/2018/04/17/2018-08010/pilot-meetings-program-for-model-informed-drug-development-approaches

Objectives of the deliverable

The objective of the deliverable is to define a framework for estimating the impact of in-silico methods and technologies on clinical and preclinical trials, laying the basis for the assessment of broader effects on patient safety, animal welfare and industry workflow. The framework will envision two phases. First, based on initial assumptions about the predictive value of in-silico models, hypotheses about potential impact on clinical trials will be derived (e.g., effect on sample size, shortening of trials), exploring different scenarios for prospective clinical trials. Second, effects of constructing the virtual cohort (population) will be assessed by selecting which protocols to compare and specifying trial parameters (e.g., outcome) on sample size and duration of trial. The methodological approach of the second phase lies in the systematic variation, comparison and optimisation of key trial parameters with respect to the simulated trial outcome. Currently there is no standard methodology available to deal with this innovative approach. We will look into the different methodological approaches applicable to the scenario (e.g., Bayesian approaches, multivariate techniques), choose the most appropriate methodology based on predefined criteria, and apply it to the data.

The following parameter sets will be analysed and selected for evaluation in the second phase:

a) *Device-related endpoints*: migration, perforation, thrombosis, paravalvular leakage, durability, with impact on device designs and, secondarily, patient safety;

b) *Patient-related parameters*: anatomies, patient features, clinical presentations, to identify study populations where the treatment effect is higher, allowing to recruit less patients and have a higher power trial design.

Methodological approach

The approach for executing an in-silico trial will be based on the methodology provided in[52]. This framework heavily relies on ideas already developed for model verification, validation, and uncertainty quantification.

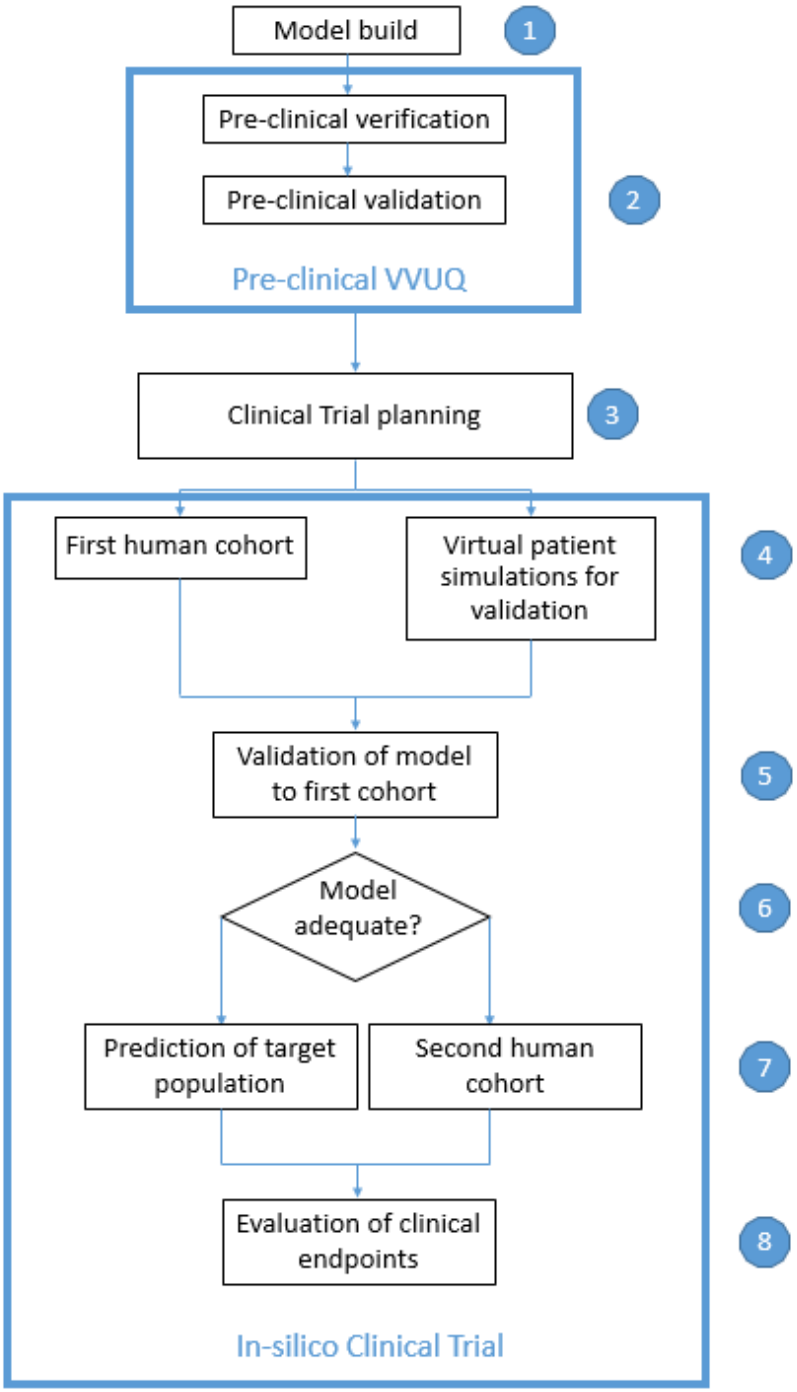

Figure 1: Flowchart of the framework (adapted from 52). VVUQ = Verification, Validation, Uncertainty Quantification.

[52] Bodner J, & Kaul V. "A Framework for *In Silico* Clinical Trials for Medical Devices Using Concepts From Model Verification, Validation, and Uncertainty Quantification (VVUQ)." *Proceedings of the ASME 2021 Verification and Validation Symposium*. *ASME 2021 Verification and Validation Symposium*. Virtual, Online. May 19–20, 2021. V001T02A001. ASME

The process starts with the computational model, which is developed upstream of the in-silico trial (see 1 in the figure). If the model is frozen, the next step is to establish baseline credibility evidence with the goal that the model is ready to use for the in-silico trial. The procedures and best practices for this step are established in the literature and include validation against in vitro models, animal studies and human studies and definition of acceptability criteria before validation (see 2)[4]. After this step, clinical trial planning starts with developing the in-silico trial protocol (see 3). This requires information such as the quantity of interest, the number of patients, the model credibility to inform the clinical endpoints, details for model validation and how to handle post-validation predictions. Thereafter, the in-silico trial is designed as follows: a virtual cohort following the specifications of the human cohort is generated and a final model validation will be performed using human data (see 4). The output of this process is a final assessment of the credibility of the model (see 5). If the model is adequate (see 6), an additional virtual cohort can be generated (optionally) and the model predictions to the target population can be performed (see 7) and the clinical endpoints can be evaluated to complement the regular clinical study and improve the statistical power of the clinical analysis or reducing the sample (see 8). If the in-silico model is ok, then the uncertainty measured upon validation with the first cohort is used to inform / refine the virtual cohort and it is then used to run a new bigger cohort to improve the statistical power of the first human cohort. If the model does not meet the validation criteria, additional information is required and the process has to be repeated with a second human cohort to complement the first cohort (see 7).

Model building in SIMCor

The model building process in SIMcor is detailed in the Grant Agreement - Description of work, and in the deliverables produced in the relevant work packages.

In-silico trial planning

In-silico trials refer to the *Context of Use* (CoU), which is a statement that defines the specific role and scope of the computational model used to address the question of interest (V&V40). In-silico trials aim to reduce, refine or replace real clinical trials which needs to be specified in advance. A taxonomy for CoU has been developed in a consensus process that took place within the InSilicoWorld Community of Practice[53]. For SIMCor, the applicable CoUs are still to be defined for each medical question (PAPS and TAVI).

The number and type of patients to be included in the in-silico trial need to be specified. Potential patient risks need to be taken into consideration for the eligibility criteria. Determination of the potential patient risks in scope of an in-silico clinical trial is necessary to ensure the device performance is sufficiently addressed. One proposed approach for identifying the appropriate potential patient risks for inclusion in an in-silico trial could balance (a) the severity and probability of the patient risk (b) the impact of the implant design on the patient risk and (c) the technical feasibility of evaluating the patient risk measure via an in-silico clinical trial[41]. A key limitation to this approach is that it relies heavily on patient risks that have already been identified.

It was agreed that in-silico clinical trial planning should be used as input for the virtual cohort generation (VC-TC, 29.09.2021). The planning of the in-silico trials should be compliant with the principles of simulation studies[54]:

[53] Viceconti et al.. Possible Contexts of Use for In Silico Trials Methodologies: A Consensus-Based Review," in IEEE Journal of Biomedical and Health Informatics. 2021; 25: 3977

[54] Burton et al., The design of simulation studies in medical statistics. Stat Med. 2006. 25: 4279

- Developing a study protocol for the in-silico studies, giving full details how the study is performed.
- This should cover the specific objectives, the choices for the different scenarios, the methods that will be applied, the number of simulations, etc.
- If a random number generator is involved, it must be able to reproduce the identical set of random numbers or at least store the information that was generated using the random number generator.
- Censored data should be taken into consideration in the simulations (drop-out).
- It is essential to plan how the estimates will be stored after each simulation to allow different ways of summarizing the estimate and allow retrospective calculation without the need to repeat the simulations.
- The number of simulations can be based on the accuracy of the estimate of interest.
- After the simulations have been performed, the required estimates stored after each replication and summary measures calculated, it is necessary to consider the criteria for evaluating the performance of the obtained results from the different scenarios or statistical approaches being studied. When judging the performance of different methods, there is a trade-off between the amount of bias and the variability.

The protocol for clinical data collection within SIMCor has been defined in *Deliverable 5.1 - Protocol for clinical data collection (CHA, M3)*. Data will include retrospective collection of demographic information, pre-procedural, peri-procedural and post-procedural imaging assessment, up to at least 1-year follow-up outcomes. For the PAPS use case, follow-up information will only be available for the animal trials. *Deliverable 7.1 - Definition of model output (TUE, M6)* describes the preliminary definition of the physiological outputs that will be used during virtual patient cohort generation of both heart failure and aortic valve disease patients. SIMCor will define clinically measurable outputs that are representative for the patient groups, both before and after, respectively, *transcatheter aortic valve implantation* (TAVI) or insertion of a *pulmonary artery pressure sensor* (PAPS). In addition, clinical targets, related to the clinical performance of the implants, are translated to engineering metrics that can be calculated with physiological models. The targets are paravalvular leakage (TAVI), device migration and vessel perforation (PAPS), and thrombosis (TAVI and PAPS).

Creating a virtual cohort requires the development of a template model for representing each member of the cohort. The template needs to be carefully designed to be able to capture patient variability, physiology, diseases and treatments of interest. In cases where the model is tied to clinical data for specific patients, the model complexity needs to reflect the available clinical data and the time and resources available to create the model[55]. The model template must encode physiologically relevant mechanisms for the virtual cohort application. The level of physiological detail in a model template needs to balance complexity versus the ability to constrain model parameters[55].

In-silico trials can be planned as interventional trials with one or more arms. The trial can be conducted as a fixed sample study without interim analysis or as a group sequential trial. It may follow a fixed or adaptive design. Adaptive designs for clinical trials permit alterations to a study in response to accumulating data in order to make trials more flexible, ethical and efficient.

[55] Niederer et al., Creation and application of virtual patient cohorts of heart models. Philos Trans A Math Phys Eng Sci. 2020; 378: 20190558

Transfer between model engineering outputs and clinical outcomes

Often relevant clinical outcomes cannot be directly measured in in-silico clinical trials. Surrogate measures are needed that can be assessed in an in-silico trial and that correlate with a real clinical endpoint. The transfer function between engineering outputs from a simulation and clinical outcomes can generally be considered part of the model and thus requires independent validation[52].

A typical example is the predictor of hip fracture risk, where models predict strength from CT images and currently available clinical data, and this strength is used as a predictor of the risk of fracture, which may occur even five or ten years later[56].

The transfer function suggested by Bodner and Kaul[52] will be used as a methodological approach to model the transfer between engineering outputs and clinical endpoints.

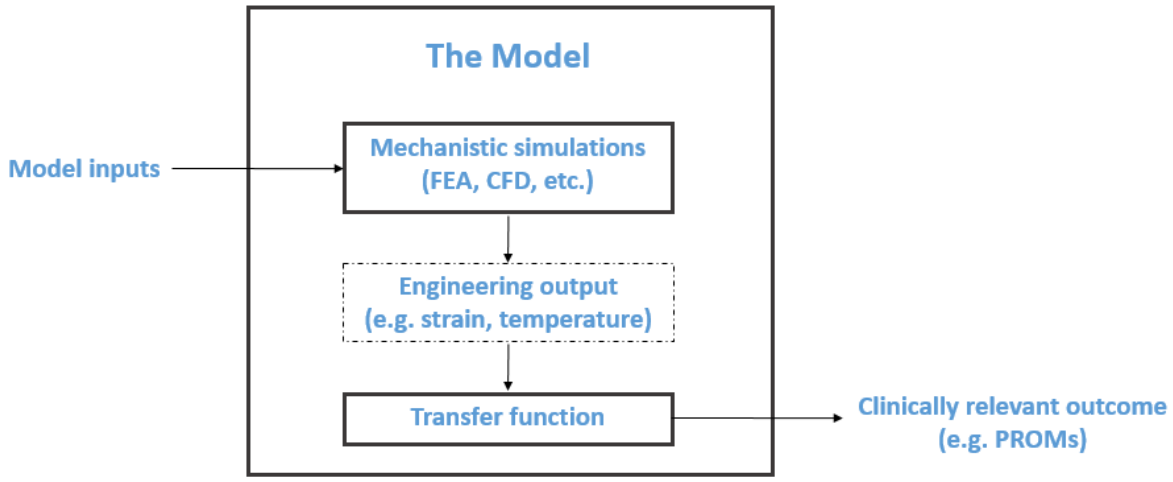

Figure 2: Transfer function between engineering output and clinical outcomes (adapted from 52).

In *Deliverable 1.1 - Research strategy plan (CHA, M6),* an overview is given on the different data types to be considered in the virtual cohort generation. This covers clinical, anatomy and function parameters as well as clinical endpoints.

For the TAVI trials, the following engineering outputs and clinical endpoints have been selected, according to *Table 1* below.

Engineering output	Clinical endpoint
wall shear stresses, oscillatory shear indices, residual times, recirculation regions, washout	thrombosis
cross-sectional area of the regurgitant paravalvular orifice, regurgitant volume flow rate, pressure gradient across the regurgitant orifice	paravalvular leakage
von Mises stresses in stent of the TAVI device	durability

Table 1: Engineering outputs and clinical endpoints for TAVI.

In a first step it should be explored whether surrogate endpoints can already be used to act as substitutes for clinical endpoints and are expected to predict the effect of an intervention. A biomarker can also be used if it acts as a substitute for a clinical endpoint that directly measures clinical benefit. The acceptability of an endpoint as a surrogate endpoint for a specific clinical endpoint is based on its

[56] Viceconti et al., POSITION PAPER: Credibility of In Silico Trial Technologies: A Theoretical Framing. IEEE Journal of Biomedical and Health Informatics. 2020; 24:

biological plausibility and empirical evidence[57]. Surrogate measures or biomarkers are also used in clinical practices and regular clinical trials and there are standards and guidelines for the validation of surrogates by regulators[58]. Sometimes the surrogate measure to the clinical endpoint used in a numerical model may be already commonly accepted in the clinics and validated by experience and clinical literature. If such relations exist for TAVI and PAPS, it should be used to support the transfer function described above.

The transfer between the engineering outputs and the clinical endpoints in SIMCor has been intensively discussed in the virtual cohorts working group (VC-WG) (29.9.2021). It was concluded that this issue is very important, and the transfer function is a crucial step to be achieved in the project. Project partners will try to identify data sources (e.g., clinical trial data, experimental data) that may help to estimate the transfer process from the engineering outputs to the clinical outcomes specified in SIMCor.

Generation and validation of virtual cohort

During this step, data from human studies are selected that are used to perform the validation of the final computational model. If the computational model is found to be adequate, then no additional human results are necessary to meet the complete set of clinical endpoints. All observations needed for all endpoints would thereafter be satisfied by either the clinical observations from the initial cohort or by the computational model[52].

The validation of the virtual cohorts is performed in the context of WP7. If additional individual participant data from TAVI/PAPS trials are available, it is planned to perform further validation of the results of the in-silico trials. A survey has been performed for randomised TAVI trials, identifying trials with a data sharing statement intending to share individual participant data. These trials could be a potential source for further validation.

Assessment of the consequences of the in-silico trial

A model that has been found to be adequate may then be used to generate an additional virtual patient cohort. The sample size for this cohort can be much larger than what is feasible for a traditional clinical trial, owing to the speed and efficiency of the computational model. As the validation has been performed in humans, the applicability of the validation results to the prediction can be done with a high level of confidence.

In the ASME model, the consequences from the in-silico trial are summarised under model treatment decisions[52]. This information will be used as input for the evaluation of the socioeconomic impact. The consequences of in-silico trials may be manifold and provide additional evidence to be complemented by a clinical trial. Examples are shortening of trial duration or a decrease of sample size.

In general, a clear distinction should be drawn between the validation and the prediction activities[52]. In principle, it is possible that there is no difference between the model parameters used for validation and those required for prediction, in which case no further cohorts need to be generated. If a larger sample size is needed, this can be easily achieved with the validated model.

[57]EUNETHA Guideline: Endpoints used in relative effectiveness assessment of pharmaceuticals - Surrogate Endpoints Amended JA1 Guideline. November 2015.
[58] FDA: Surrogate endpoint resources for drug and biologic development. July, 2018.

Variation of in-silico trial design

While a model may generate accurate predictions within one region of parameter space, it may not necessarily extend to producing reliable, or even physiologically plausible, results outside of that region. Confidence in a specific model output should, therefore, reflect its position relative to the regimen in which validation has been undertaken. Furthermore, models will often predict variables that cannot be or were not measured directly, for example stress in cardiac mechanics models. These variables can be of interest for understanding mechanisms underpinning emergent observations. There will be less confidence in these model predictions that cannot be compared against experimental data. However, confidence in the model prediction can be gained if the model is physics based and is validated across a wide range of conditions that alter the unmeasured model output[50].

It may be necessary to explore variants of the in-silico design not included in the validation data (e.g., other inclusion/exclusion criteria, criteria related to the device). In that case a new series of models may be needed with potential consequences related to validation. In SIMCor, a systematic variation of the in-silico trial design will be performed, predictions to the target population will be made and the clinical endpoints will be assessed. This information will provide the basis for the analysis of the socioeconomic impact.

In order to be useful, a model should be able to predict input values that are different from those used to assess its accuracy; but we do not know the predictive accuracy of the model for those new inputs. Considerations on the general regularity of physical quantities, and about the assumption that model accuracy should degrade smoothly in the sense that predictions made for similar inputs should present similar predictive accuracy, allow to assume that a degree of extrapolation is possible, i.e. the model can be considered reliable even when used to predict for inputs different from those observed in the clinical validation cohort (Applicability) [56].

The issue of extrapolation was also discussed in the VC-WG (29.09.2021). It was argued that in the model generation assumptions are made that allow some extrapolation. These assumptions need to be proven before application. One important instrument is sensitivity analysis. For physical functions (e.g., fluid mechanics) extrapolation can be assumed.

Impact assessment framework

Overview

The in-silico trial workflow is embedded in three infrastructures: The virtual cohort generator, the analysis environment and the *virtual research environment* (VRE). The clinical trial design is specified within the analysis environment and then communicated to the virtual cohort generator, which produces a trial-specific cohort. The data generated are transferred to the analysis environment, where the in-silico trial is run according to the defined design and the results are documented. This process is cyclic and repeated as often as there is a need to do so. If all necessary results have been achieved, the process is closed and the results are explored and a decision is taken. The workflow is summarised in the figure below.

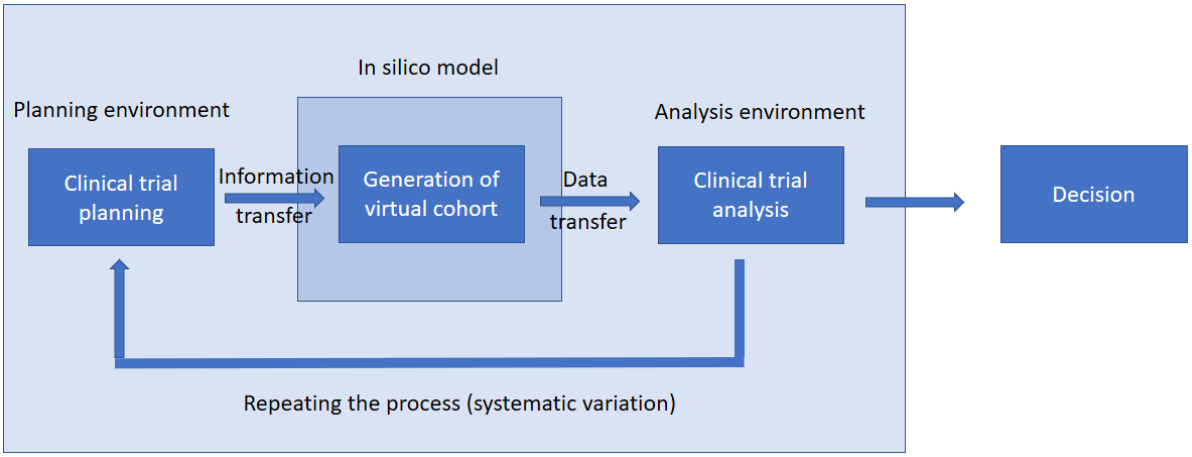

Figure 3: Workflow for an in-silico trial.

The in-silico trial datasets produced by the virtual cohort generator are archived in the VRE. This is also done for information generated in the analysis environment, covering the in-silico trial specification, the scripts for the analysis and the results from the analysis. Thus, the VRE will contain all components of planning, running and analysing an in-silico trial. The interactions between the three infrastructures are summarised in the figure:

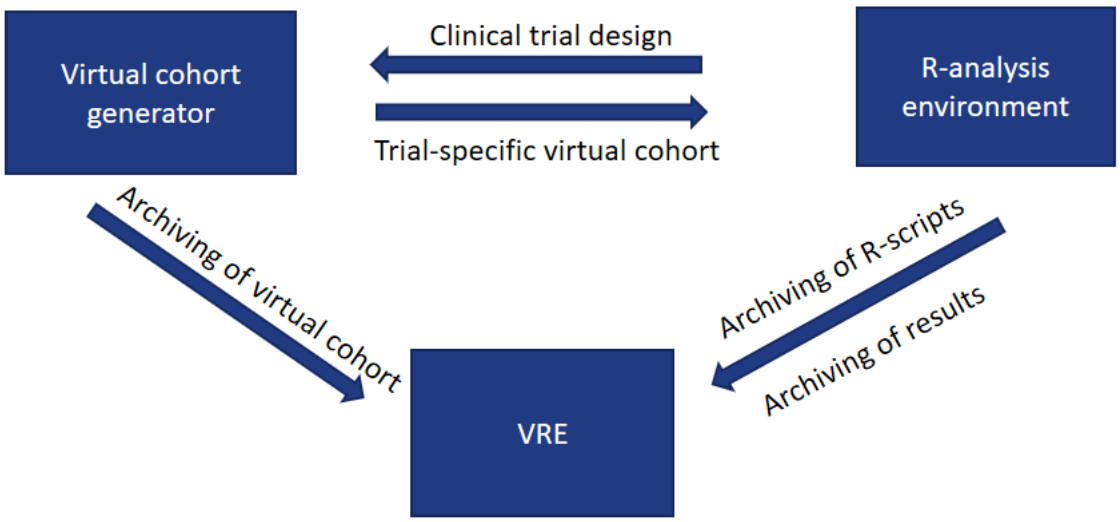

Figure 4: Interaction between virtual cohort generator, analysis environment and VRE.

The storage of these components is considered as the bare minimum to give transparency and to allow repeatability of trial results. To support this, selected use cases will be stored on the VRE, where all components are linked to demonstrate the full workflow related to an in-silico trial. In the course of the project it will be investigated whether this approach could be improved. One option could be to install the virtual cohort generator directly on the VRE.

Following the approach in the EOSC-Life project[59], it was suggested to use a standardised workflow environment for the interaction between the virtual cohort generation environment, the R-analysis environment and the VRE. An example could be Galaxy, a powerful and flexible tool, making it possible to 'inject' R scripts into the workflow and check all input and output parameters. As a partner in the EOSC-Life project, ECRIN will explore whether and how a standardised workflow management in SIMCor can support transparency and repeatability of processes, which is of major relevance for regulators such as EMA.

Planning and analysis environment for in-silico trials

The analysis environment will be implemented within R. It consists of two modules:

a) Clinical trial planning environment
b) Environment for analysing the in-silico trials

For **clinical trial planning**, the following parameters may be of interest:

- Trial design (fixed, Bayesian, adaptive, platform trial)
- Groups (one group, paired, parallel groups, cross-over, hierarchical)
- Analysis methods (superiority, equivalence, non-inferiority, intervals)
- Goals (means/median, proportion, counts, time to event)
- Outcomes (primary, secondary)
- Sample size (fixed, not fixed – sequential)
- Hypothesis (2-tailed, 1-tailed)
- Treatment effect (e.g., effect size)
- Type 1 error, power
- Drop-out rate
- Blinding (open, single, double) (not relevant for SIMCor)
- Randomisation (simple, block, stratified, minimisation, dynamic)
- Interim analysis
- Stop criteria for trial (futility, superiority)
- Analysis (intention to treat, per protocol)

Depending on the requirements defined for an in-silico trial, the applicable parameters are specified in the analysis environment. Those variables relevant for cohort generation (e.g., outcome, sample size) are communicated to the virtual cohort generator.

The sample size assessment is dependent on the type of the trial and follows the usual rules. For the TAVI- and PAPS trials, a power of 80% and an alpha error of 5% is specified (two-sided). An interesting approach could be to use Bayesian methods. The virtual patients can be implemented as prior knowledge in a Bayesian clinical trial. This approach can have benefits of decreased sample size and trial length while minimizing impact to study endpoints, type I error, and type II error[60].

[59] https://www.eosc-life.eu/.

[60] Viceconti et al., In silico assessment of biomedical products: the conundrum of rare but not so rare events in two case studies. Proceedings of the Institution of Mechanical Engineers. Part H: Journal of Engineering in Medicine, 231 (5). pp. 455-466

Of particular importance for an outcome measured in a clinical trial are patient-specific, intervention-related and other relevant risk factors. If possible and covered by the simulation model, major risk factors should be taken into consideration in the virtual cohort generation. An example is age, which could be estimated via vessel stiffness. The relevant risk factors will be taken from the literature and communicated to the virtual cohort generator. Guidelines from Scientific Societies, risk scores and other studies will be taken into consideration. Examples are the 2021 ESC/EACTS guidelines for the management of valvular heart disease and the PARTNER and FRANCE-2 TAVI risk score models[61].

The specification and analysis of in-silico trials will be performed within a statistical environment. In SIMCor it was decided to use free and open-source software for statistical planning and analysis, such as R and RStudio. The R-statistical environment provided for the SIMCor project should cover the following functionalities:

- **Specification of trial design**
  Different trial designs will be applied for the in-silico trials. The options should cover the parameters listed above.

- **Specification of trial data structure**
  Trial data will come from the virtual cohort generator according to the specifications provided by the analysis group (e.g., specification of outcome criterion, sample size, duration).

- **Importing virtual cohort data to the R-environment**
  The individual virtual cohort datasets generated by the virtual cohort generator have to be imported into the R-statistical environment.

- **Analysis of in-silico trial**
  The individual data will be analysed according to the trial specification. Adequate tables and figures, summarising the results will be prepared (e.g., ROC-curves).

- **Assessment of results**
  The results of the analysis will be assessed and prepared for transferral to the partner dealing with evaluation of the socio-economic impact.

- **Export of results to computing environment**
  The scripts for trial specification, the analysis scripts and the results of the analysis will be transferred to the VRE for archiving. Together with the individual virtual cohort data, all components necessary for transparency of the process and repeatability will be kept on the VRE.

- **Systematic variation of in-silico trials**
  The analysis environment should provide possibilities for systematic variation of trial designs as well as replication of a specific design with different virtual cohorts to estimate variation of results.

A workshop with participants from WP3, WP7 and WP10 and external statistical experts was performed to discuss the conception and implementation of the R-statistical environment as a

[61] Vahanian et al., ESC/EACTS Guidelines for the management of valvular heart disease: Developed by the Task Force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS), European Heart Journal*, 2021;* ehab395.

component of Task 10.2. The virtual workshop entitled "Statistical environment for in-silico trials" was organised by SIMCor and took place on 6 December 2021 with around 50 participants, including representatives from the other in-silico projects (In-silico World, SimInSitu, SimCardioTest).

Management of real clinical trial data

It is foreseen to validate the results of in-silico trials against additional real clinical trial data, if available. For that reason, a search has been performed, identifying randomised TAVI trials with the intention to share data for secondary research. This search, which is continuously updated, has identified 5 trials, where data sharing may be possible. The trials are summarised in the table.

Trial Name and Initial Date	Trial Registry Number	IPD Availability per Manuscript*	Data Sharing Statement per MDR	Consent Form Available per MDR	IPD Sharing Statement per CT.gov
REPRISE3 2014	NCT02202434	Yes	None	No	No
SCOPE1 2017	NCT03011346	Yes	None	No	No
ACURATEIDE 2018	NCT03735667	Unknown	Yes	No	Un-decided
TEAmBR 2019	NCT04067089	Unknown	None	No	Yes
PROTECTED 2019	NCT04149535	Unknown	None	No	Un-decided

*Table 2: TAVI RCTs with intention to share trial data. *Individual Participant Data (IPD) availability as stated in any published manuscript.*

It remains to be decided where the management of anonymised/pseudonymised data from real TAVI-/PAPS trials for validation of in-silico trial results is performed. This is dependent on the data transfer and data use agreements concluded by the data generators/sponsors. It may be that data transfer to a secure analysis environment is possible, but this is not guaranteed. Whether this can be performed in the VRE has to be sorted out.

Data management for the VRE is described in *Deliverable 1.9 - Ethical and legal compliance final assessment (LYN, M9)*. Pseudonymised data will be processed and stored in the temporary cloud repository (or VRE Drive) as well as in the VRE, to allow the sharing of data between data providers and modelling partners (BIO, IIB, PHI, TUE, TUG), as well as the execution of some modelling activities and virtual cohort generation activities, even though most of them will be carried out in the local environments of the relevant partners. This will also cover the management of individual participant data from TAVI- and PAPS clinical trials if available, accessible and transferable. Moreover, encryption measures will be applied and different access rules and conditions will be deployed through an *identity and access management* (IAM), to guarantee effective segregation of duties and the enforcement of strict authorization-based rules within the systems, also thanks to a tool for recording accesses to resources and various parts of the system at a reasonable and suitable granularity level. The VRE Drive is a cloud storage server based on Nextcloud, deployed at the top of UTBV private cloud infrastructure and intended to be the data archive for SIMCor. To fulfil the project's needs, data stored in SIMCor VRE Drive can have the following privacy levels: private access (only the owner can see the data), internal access (the owner can share data with consortium members) and public access (anyone with the link can access the data). In addition, a plug in for visualising .stl 3d models is also configured in the environment. Therefore, not only confidentiality is granted, but also integrity of data, both at rest and in transit, by allowing only duly authorised entities (e.g., users, software components etc.) to make changes and only in accordance with permitted procedures. For ensuring data protection and appropriate levels of security in-transit, the SIMCor VRE will use end-to-end SSL/TLS encrypted

connections. In addition, it will store data on encrypted volumes to ensure data protection also at rest. Finally, the SIMCor VRE will provide data safety by using a RAID system for data storage.

If the VRE is able to manage and store (pseudonymised) individual participant data from TAVI- and PAPS trials compliant to GDPR and other rules and regulations, it needs to be sorted out how the validation of in-silico trials could be performed on the VRE. To enable this, specific analysis procedures should be available and applicable to the involved data sets (in-silico trial data, real clinical trial data).

Further steps

Based on the conceptual framework, the clinical impact of in-silico trials will be assessed, and benefits allowed by in-silico device testing technologies along several outcome dimensions will be estimated. This includes, as examples, reduction in the duration and sample size of clinical human trials and preclinical animal studies and increased clinical efficacy and patient safety, through the reduction in adverse events thanks to predictions on failure patterns and by improving clinical indications, implantation strategies and device designs, based on clinical endpoints specified in the project. The results achieved by the in-silico trials will be injected into the quantitative assessment of socioeconomic effects performed by IHS.