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SimCardioTest - Simulation of Cardiac Devices & Drugs for in-silico Testing and Certification

SIM CARDIO TEST

Technical Report

D 8.6 - Final Advisory Board recommendations & Stakeholders Group requests

Work Package 8 (WP 8)

Project Coordination & Management

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Table of Contents

EXECUTIVE SUMMARY

SimCardioTest has implemented an Advisory Board (AB) with representatives from non-partners who can guide SimCardioTest with reference to the needs and viewpoints of key stakeholders. Among the stakeholder's groups, SimCardioTest is targeting the medical community. This is why, beside the feedback received by the various stakeholders represented in the Advisory Board, clinicians and patient organisations were also consulted through an online survey and through a focus group workshop.

This deliverable reports on the stakeholder's request, feedback or questions to increase quality, appeal, and ultimately to ensure that the needs of key stakeholders are met.

1- INTRODUCTION

One of the strategies of SimCardioTest is to establish a continuous assessment of the project's impact by independent scientific experts through an Advisory Board and stakeholder groups through two-way dialogue in order to help keep pace with the latest developments and to define new strategies to maximise the project's ultimate societal impact.

1.1. The Advisory Board

The Advisory Board consists of representatives from non-partners who can guide the partnership SimCardioTest with reference to the needs and viewpoints of key stakeholders. It is intended to be representative of various stakeholder communities interested in model simulation and in-silico trials.

Advisory Board composition:

Name	Position	Role	Organisation
Flora Musuamba-Tshinanu	Vice chair	EMA Modelling and Simulation	EMA
Richard Gray	Senior Scientist	Center for Devices and Radiological Health, Cardiac Modelling Research Program	FDA
Duchateau Nicolas	Associate Professor	CREATIS lab	Lyon University 1
Levine Steven	Executive Director	Living Heart Project	Dassault Systèmes
Wang Ken	Principal Scientist	Translational modelling & simulation group	CH Roche
Virag Nathalie	Senior Principal Scientist	Modelling and devices	Medtronic
Peter Hunter	Director	Model standardisation	Auckland Bioengineering Institute

SimCardioTest Advisory Board members are already very active on the topic of in silico trials, including CM&S for medical device regulation since 2018 with its Office of Science and Engineering Laboratories, as well as for drug cardiotoxicity assessment (CiPA initiative). These initiatives set the stage for the current project, which will take a step forward by incorporating in-silico tools in the regulation routine for cardiac devices and drugs of European companies.

EMA and FDA involvement in the advisory board ensured that efforts are in line with current regulatory and clinical standards.
The Auckland Bioengineering Institute has been pioneering this standardisation work, and whose seminal work inspired such activity within the Virtual Physiological Human (VPH) program.

In addition, uncertainty quantification and parameterisation of such models is currently a subject of major interest and has also been studied by members of the consortium. A commercial product exists for cardiac electromechanical simulations (the Living Heart Project from Dassault Systèmes), however it does not enable personalisation of parameters, therefore comparison with validation data is not yet feasible.

Interactions with Policy-makers involved in healthcare, industry and innovation policy, are assured through the participation of Flora Musuamba-Tshinanu (EMA) and with American regulators thanks to interactions with the FDA assured through direct participation of Richard Gray (FDA) to the Advisory Board.

1.2. Stakeholder group consultation

The purpose of the Stakeholder Group was to raise awareness towards the end-users of the medical devices being developed with the in-silico technology proposed by SimCardioTest, and allow key players to connect and co-design the approaches and priorities of the transition towards digitalized in-silico trials initiatives. The work on establishing the SG has begun at the proposal phase from interactions with partners and the VPHI. The deliverable D8.5 Intermediate Advisory Board recommendations and stakeholder group request, provides extensive details on this task. Stakeholders have been informed of project progress and have been invited to participate to targeted project workshops and meetings. The results of the clinical survey and their analysis has been published in a scientific report to inform the in-silico scientific community and a general communication brochure with accessible info-graphics was also produced to reach out and inform non-in silico experts' stakeholders (clinicians but also regulators, policy makers and so on).

2- Main results presented during the final conference.

For the SimCardioTest final event organized at UPF, Barcelona on 16-17 June, SimCardioTest's partners decided to present the main outcomes of the work done and to open the discussion with the EU funded sister projects (SIMCor, SimInSitu, In Silico World and EDITH) and to the Advisory Board members (Agenda available in Annex 1).

The advisory board members were invited to attend online and participated to the discussion. As not all members could attend, a summary (below) as well as the slides (Annex 2) have been sent to them for their feedback, and are included in the report.

The main results of SimCardioTest were presented and summarized below:

2.1. Project Background and Objectives

- Full pipeline from academic research to industrial application, targeting healthcare innovation through computer modelling and simulation.
- Objectives: demonstrate feasibility of in silico trials, establish communication tools among patients, industry, regulatory bodies, and researchers, and reduce time and costs in medical device and drug development.
- The project aimed to complement traditional in vitro, preclinical, and clinical trials by validating computational models on a cloud-based platform.

2.2. Use Case 1: Pacing Leads and Catheters

- Collaboration among University of Bordeaux, INRIA, and Microport focused on catheter navigation, mechanical interaction with tissue, and electrophysiological pacing efficacy.
- Key tasks:
  - Construct anatomical models from clinical CT images and experimental images to recreate vascular anatomies and cardiac geometries for simulation and experimental validation.
  - Develop simulation models using the SOFA platform to study device navigation with bench-derived mechanical properties.
  - Dual-level analysis of lead-tissue interaction:
    - Identify deformation regions via simulation.
    - Create detailed localized models
      - use a beating heart phantom “Apollo” to record force sensors and validate tissue interaction.
  - Develop a comprehensive electrophysiology model based on bi-domain equations with bench and ex vivo validations, sensitivity analyses, and meta-modelling approaches.
- Final results: Verified open-source software modules (SOFA module and CEPS code) capable of running in silico capture tests and statistical studies to predict outcomes in the presence of fibrosis and other variability factors.

2.3. Use Case 2: Left Atrial Appendage Occluders

- Addressed interventional procedures in atrial fibrillation patients, especially those contraindicated for anticoagulants.
- Key objectives:
  - Develop a computational pipeline for patient-specific fluid dynamic simulations.
  - Run a large number of automated, patient-specific simulations to assess device performance.
  - Perform sensitivity analyses on boundary conditions (e.g., time-step convergence, number of cardiac cycles) to validate and optimize simulation practices.
  - Establish VV-UQ guidelines and integrate experimental in vitro and MRI data to compare and build model credibility.
  - Evaluate alternative interventions (e.g., surgical excision of the left atrial appendage) through comparative simulations.
- Outcome: Enhanced simulation credibility led to wider clinical acceptance, presentations at clinical conferences, and spin-offs (e.g., VirTest).

2.4. Use Case 3: Drug Efficacy and Cardiotoxicity

- Designed an in-silico trial pipeline for assessing pharmacokinetics (PK) and pharmacodynamics (PD) of cardiac drugs, including safety and efficacy endpoints such as action potential duration and mechanical performance.
- Stages:
  - Use compartmental PK models to predict plasma drug concentrations.
  - Integrate these concentrations in detailed cellular and 3D cardiac electrophysiological models.
  - Generate populations of models for healthy, heart failure, and ischemic conditions—including gender-specific populations.
  - Build whole heart models (atrial and ventricular) using patient-specific imaging data with fibre orientation and conduction system details.
  - Evaluate drug safety by comparing model predictions (e.g., QT prolongation, arrhythmia risk) against experimental/clinical data.
  - Optimize dynamic drug-ion channel interaction models (including a patented pipeline) to analyse dose effects under variable conditions.
  - Applications demonstrated differences in drug responses between male and female populations and assessed multi-dimensional endpoints such as ejection fraction, contraction, and re-entrant arrhythmia inducibility.

2.5. Verification, Validation, and Uncertainty Quantification (V&V/UQ)

- Standardized process using VV40 (and modified procedures) across domains from device mechanics to drug effects.
- Focus:
  - Establish well-defined “questions of interest” to limit scope and set comparators.
  - Rigorous verification of simulation code (often automated) and detailed validation against experimental and clinical data.
  - Employ uncertainty quantification methods (UQ analyses with sensitivity studies) to benchmark model credibility.
- Lessons learned:
  - Continuous model evolution required repetitive V&V efforts.
  - Challenges in selecting comparators and separating training from validation datasets remain areas for improvement.

2.6. Cloud-Based Platform Integration

- Developed an easy-to-use, safe and scalable cloud-based platform to make in silico trial pipelines accessible.
- Key features:
  - User-friendly web interface for end-users, with no simulation expertise or computational resources requirements (clinicians, device manufacturers, pharma companies).

- Ability to set up simulations for different use cases (pacing devices, occluders, drug trials) with graphical interfaces for patient-specific data, device parameters, or drug dosages.
- Automated simulation set-up and running and advanced result visualization (e.g., graphical plots, velocity fields, ECG outputs), encapsulating complex computational processes into a simple workflow.
- Integrated workspaces for team collaboration with configurable access rights.

2.7. Stakeholder Engagement, Dissemination, and Communication

- Iterative, multi-stakeholder engagement strategy:
  - Desk reviews mapping stakeholder networks and literature on in silico medicine.
  - Delphi and clinical surveys gathering opinions on barriers, trust, and integration of these tools in clinical practice.
  - Focus groups and scenario-based workshops discussing ethical, legal, and social implications (ELSI), including trust, transparency, and patient agency.
  - Engagement with regulatory and notified bodies to discuss the future role of in silico data in certification and submissions.
  - Dissemination activities: video series (Code & Cure), podcasts, and open-access resource (InfoKit) to share best practices and learnings with the broader community.

2.8. Q&A and Discussion Highlights

There was extensive discussion on these topics

- **Summary**

A key question has been answered: are the proposed in-silico trials tools reliable enough for transfer? The three use-cases demonstrated strong advances in preparing this question, with outputs beyond expectations in some cases.

The project delivered many scientific and experimental outputs, with a very dynamic environment, allowing to demonstrate the feasibility of these concepts three complementary concrete use cases, each delivering honest conclusions on the three main objectives (verification / validation / applicability).

- **General questions:**

How much have you advanced in approaching people potentially targeting clinical trials?

On May 30th and 31st 2024, the SimCardioTest consortium organized the “Exploitation & standardisation workshop” with the objective to disseminate the project outcomes and collect feedback from stakeholders. The event, called “Next-Generation Cardiac Care: discover SimCardioTest in silico trials platform”, was an interactive initiative on cardiac medical devices for atrial fibrillation and bradycardia, as well as on drugs and cardiotoxicity. The interactive sessions aimed to foster a deeper understanding of the three new products integrated into the platform, allowing us to refine and optimize their functionalities based on the real-world perspectives of

industry experts. Invitees were researchers, clinicians, and industry stakeholders, and we were able to collect valuable feedback and crucial insights.

From this workshop, we learned that in silico tools are increasingly well-known and accepted; however, significant challenges remain, including the following: acceptance by regulatory bodies, unclear guidelines and steps to follow, the need for regulatory standardization, computational costs, data privacy concerns, limited historical evidence, clinical adoption hindered by resistance, and difficulties related to verification and validation (V&V) processes.

It is worth to note that partners VPHI and IST have brought SimCardioTest experience into the preparation of an updated SWOT Analysis published by the sister project In Silico World (https://zenodo.org/records/14221258). The targets of this document are the executives of biomedical companies, large and small, who must decide if, when, and how much to invest in In Silico Trials. The aim of this well-documented SWOT analysis is to facilitate this task and favour more extensive investments toward their adoption.

How are you / will you approach larger communities working on comparable topics?

Several actions are already on-going through new collaborative projects and communication events. But the scale up of this approach is a community-led effort, therefore, VPHI will be instrumental in achieving this. There are important discussions with regulatory bodies that can unlock the dissemination of in silico trials.

Which project type will you continue after SimCardioTest has finished? (complementary European projects, demonstration on more use cases, commercialization, etc.)

There will be several following project types. Some EU projects already started (GEMINI), research contracts with companies are also being signed, and the IST platform is also developed. The first level of evidence for this last point is the list of European research projects in which the results of the cloud-based platform developed within the SimCardioTest project are being exploited or further advanced:

- METASTRA – Computer-Aided Effective Fracture Risk Stratification of Patients with Vertebral Metastases for Personalised Treatment Through Robust Computational Models Validated in Clinical Settings [https://www.metastraproject.eu/]
- SMASH-HCM - Stratification, Management, and Guidance of Hypertrophic Cardiomyopathy Patients using Hybrid Digital Twin Solutions [https://smash-hcm.eu/]
- Platform for Advanced Virtual Human Twin (VHT) Models [https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/tender-details/16cc3c6a-844a-42d4-9746-dcc7444b8001-CN]

How would you guarantee the maintenance and potential evolution of the developed tools once this project is finished?

In order to provide a comprehensive and feasible exploitation plan, the SimCardioTest consortium, led by IST, worked together in a cocreation process to carry out an in-depth analysis comprising the following elements:

- exploitation vision including the outputs description for each of the three use cases identified at the beginning of the project
- a thorough market analysis including industry overview, market size, stakeholders, competition and competitive advantage of the cloud-based platform, the app and e-health solutions
- a detailed exploitation strategy including a business model canvas, sustainability plans, future roadmap and IPR protection.

The exploitation strategy has been regularly updated during the project's lifecycle, to reflect the evolution and the developments in the project outcomes, and taking into account the valuable comments and response collected from relevant industrial, research and clinical market players, especially during the SIMCARDIOTEST Exploitation Workshop held at M42.

The deliverable D7.5 "Final exploitation and market uptake strategy" represents the final version of the SimCardioTest Exploitation strategy, with updated considerations related to feasible business pathway, and Intellectual Property Rights protection and is summarised below:

SimCardioTest consortium has developed a streamlined and secure cloud-based platform (developed by partner InSilicoTrials Technologies - IST) where in-silico trials run seamlessly. Three cardiac use cases have been used to demonstrate the platform effectiveness, along with the required verification & validation processes and certification support of the medical device or medicine.

Therefore, the maintenance and potential evolution of the cloud-based platform will be performed by InSilicoTrials, and for the models, it will be done by the academic partners through new projects.

- **Use-case 2:**

How did you reduce the computational times in Use Case 2?

The reduction of the computational times during the project was mainly due to the optimisation of the whole modelling pipeline, automatizing the mesh preparation prior to the solving, making use of parallel versions of the solvers in Ansys, and having access to more HPC resources.

Some analysis methods may be a bit old given the advent of transformers / cross-attention mechanisms for information fusion. How much would this affect your conclusions?

We agree with the advisory board member that new methodologies for exploring the data should be investigated, to identify if they come with different conclusions from classical unsupervised machine learning techniques like the employed MKL. However, we also need to check if the available data is enough to satisfy the requirements of recent data-hungry techniques.

SimCardioTest has helped to improve and validate flow simulations in the LAA, leading to the development of a web platform that simulates the behaviour of LAAO devices within each patient left atrial appendage. This personalized simulation platform serves as the foundation for a new spin-off emerging from Universitat Pompeu Fabra (UPF), called VirTest Technologies. The startup aims to address issues such as: leaks, device-related thrombus and device embolization, while significantly reducing intervention time and minimizing patient radiation exposure.

- **Use Case 3**

Could more variety be reached by using statistical models developed at some partner institutions? (ex: statistical shape modelling with confounding factors that could be age / see Bernardino et al. @UPF)

In a first stage, personalised anatomical models were built based on real patients imaging data. Our clinician partners provided data corresponding to different ages and sex. We plan to maintain the collaboration with the clinical team to extent the available database. However, in parallel the population of models can be further extended using indeed statistical methods to perform variations in the anatomical features, but also introducing changes in the electrophysiological features can give rise to an extended combination of models which would increase the virtual population.

- **Validation strategies and future strategies:**

Questions on separating training and validation datasets and selecting comparators for multiple endpoints (e.g., contraction vs. QT prolongation).

SimCardioTest partners emphasised the need for further collaboration with pharma companies to obtain robust datasets and enhance credibility for regulatory decision-making.

- **Future integration with complementary projects (e.g., Gemini, Vital) proposed to build a unified digital twin ecosystem.**

SimCardioTest acknowledged ongoing work in standardising V&V processes and expressed optimism for expanding these methodologies in upcoming European calls, including projects on cardiovascular digital twins and broader human digital representations.

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ANNEX 1 – AGENDA

FINAL GENERAL ASSEMBLY

SIMCARDIOTEST

16 & 17 June 2025

Agenda

17th June: Online open meeting (visio)
https://upf-edu.zoom.us/j/2297865582?pwd=RjNJMVNvNzJoTFZJTm8wQTRkalgwQT09

9h00-9h10: Welcome note, Maxime Sermesant, Inria

9h10- 9h20: LAAO, Oscar Camara, UPF
9h20-9h30: Pacing leads and catheter, Yves Coudière, UBordeaux

9h30-9h40: Drug safety and security, Beatriz Trenor, UPV

9h40-10h00 Q&A

10h-10h10: Verification, Validation, Uncertainty Quantification & Certification, Romano Setzu, Microport

10h10-10h20: in-silico trial platform demo, Vincenzo Carbone, IST
10h20-10h30: Info Kit, VPHi

10h30-10h50: Q&A

10h50-11h10: Coffee break

11h10-12h10: Round table with sister European projects: feedback, gained experience, new technology?

invited speakers (on line): 10 min. each

11h10-11h20: Jan Brüning, Charité (SIMCor) In Silico testing and validation of Cardiovascular Implantable devices,

11h20-11h30: Nils Götzen (SimInSitu): "Model Credibility Assessments – Do We Have More Confidence Now?"

11h30-11h40: Marco Viceconti, University of Bologna "IN SILICO WORLD: lowering the barriers to the adoption of In Silico Trials"

11h40 - 11h50: Liesbet Geris, VPHi (EDITH) The Future of European Virtual Human Twin

11h50- 12h00/ Q&A

12h00-12h30: Discussion

End of the meeting: 12h30/13h00

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