EU Horizon 2020 Research & Innovation Program
Digital transformation in Health and Care
SC1-DTH-06-2020
Grant Agreement No. 101016496

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

Technical Report: D6.3

Interactions with regulatory bodies on in-silico trials

Work Package 6 (WP 6) – VERIFICATION, VALIDATION, UNCERTAINTY QUANTIFICATION & CERTIFICATION

Task Lead: MPC, France

WP Lead: MPC, France

PUBLIC

DELIVERABLE INFORMATION

Deliverable number	6.3
Deliverable title	Interactions with regulatory bodies on in-silico trials
Description	Meeting with regulatory bodies to discuss results (M40, WP6, minutes of the meeting)
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Due date	April 2024
Submission date	1 June 2024
Comments	NA

Document history			
Date	**Version**	**Author(s)**	**Comments**
11-04-2024	1	Valerie Centis	NA
29-04-2024	1	Arten Platnov	Quality check, comments
13-05-2024	1	Valerie Centis	Revised version
13-05-2024	FINAL	Governing Board members	Validation

Table of Contents

EXECUTIVE SUMMARY

The report and its attachments comprise Deliverable D6.3 of the SimCardioTest (SCT) project's Work Package 6, scheduled for completion by April 2024. It describes the interactive activities undertaken with a chosen Notified Body (NB), commencing from M33 (September 2023). The aim of this deliverable was to obtain feedback on SCT's in-silico trials submission strategy and the overall handling of in-silico trials for device submissions to health authorities, with the ultimate goal of securing potential approval. Interacting with NBs in Europe poses challenges due to the Commission's strict guidelines on permissible exchanges. Therefore, the aim was to share insights into their current perspectives on utilizing in silico data and to grasp their expectations for future submissions supporting medical device approvals using such data.

Several attachments included into the deliverable contain materials from the scheduled meeting with NB as well as minutes from this event.

This deliverable is closely linked to the WP7 activities and its results will significantly inform the subsequent steps needed for dissemination activities.

1- INTRODUCTION and OBJECTIVES

Normally, European NBs do not provide "consultation services" to their clients due to potential conflicts of interest. Consequently, the European Commission and various trade associations typically advocate for structured dialogue between manufacturers, their Certifying Body, and Competent Authority. There are no clear guidelines on how to conduct such interactions, and most NBs directly refuse any type of conversations with Manufacturers and rather expect this dialogue to be engaged once a submission is fully completed and submitted via the usual administrative channels. This leaves little room to comply with any recommendations which could otherwise become very beneficial for the project if given prior or during the lengthy submission process.

2- METHODOLOGIES

Given the challenges associated with fostering productive discussions, the SCT team successfully commenced an initial informal dialogue with a reputable and recognized Notified Body (TÜV SÜD, Munich, Germany) by the end of 2023. This engagement aimed to gauge their interest in participating in a structured conversation regarding the utilization of in-silico data. The general idea was to try putting together a team of experts and reviewers involved in medical device approval process for exchanging their current understanding of in-silico data applications as well as their expectations concerning submission process of materials for a medical device approval.

In order to maximize the information we could obtain, while at the same time taking into account all the limitations, a short side desk containing direct questions (refer to Appendix 1) was put in place. The invited NB's representatives were familiarized with this side deck a few days before the meeting to avoid the element of surprise about the feedback expected from them.

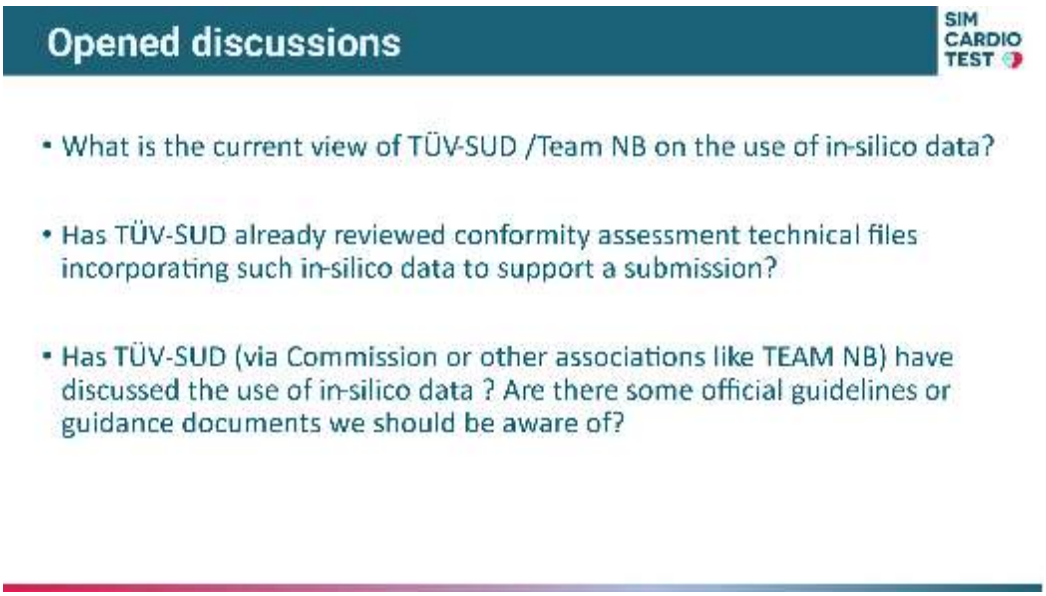


Figure 1. Excerpt from shared slide deck on Questions shared with NB.

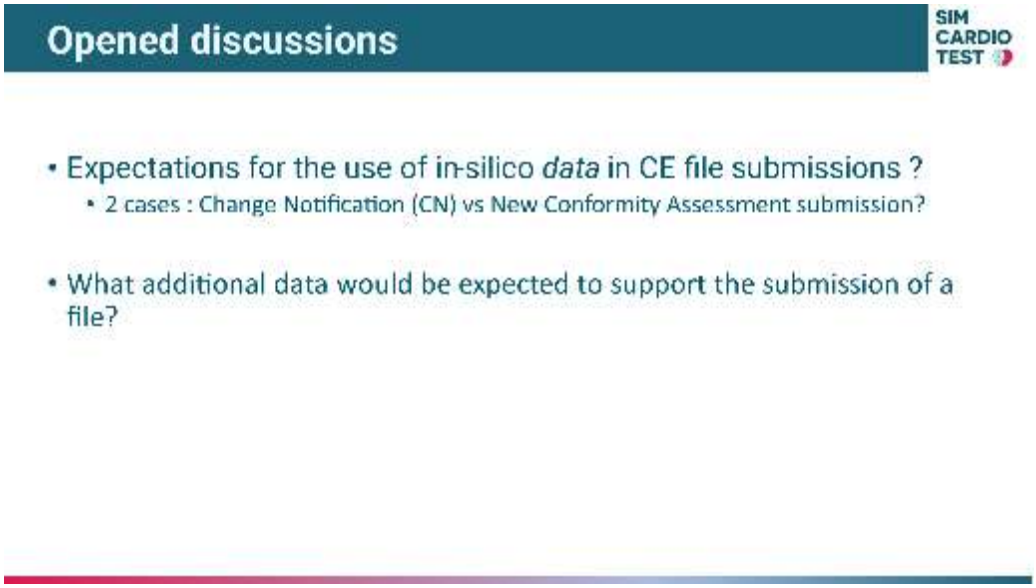


Figure 1. Excerpt from shared slide deck on Questions shared with NB.

In order to make the situation more realistic and provide a better insight into how in-silico data can potentially be applied, a real-life example was used for the call. One of the most advanced Used-Cases (UC), UC2 was presented after the general overview of the SCT main goals and objectives.

The following up discussion was based both on the previously shared side deck and the board's comments, questions and remarks. The short demonstration of the platform by SCT was done at the end of the meeting. The discussion resulted into minutes file (Appendix 2) documenting interactions and highlighting main takeaways.

3- RESULTS and CONCLUSION

Despite the difficulties in organizing such meetings, described above, it evoked a lot of interest from the NBs. More specifically, the two leading clinical experts, the innovation experts and the technical file subject matter expert attended the meeting. The experts demonstrated a high level of curiosity and interest in in-silico trials and data combined with a shortage on knowledge about in-silico methods. This suggests the need for formal training of NBs contrary to the current situation where experts have to teach themselves about in-silico methods.

Such training can be conducted both on an individual basis and within entire organizations to raise awareness and disseminate educational materials. One avenue to pursue this is by engaging with relevant trade associations such as TEAM NB. Efforts could involve promoting key concepts and principles of in-silico medicine. As an initial step, a series of educational videos aimed at the general public has been developed (available at https://www.vph-institute.org/videos.html). Additionally, supplementing this training with guidance similar to that provided by MDCG could enhance understanding of how to utilize in-silico data effectively.

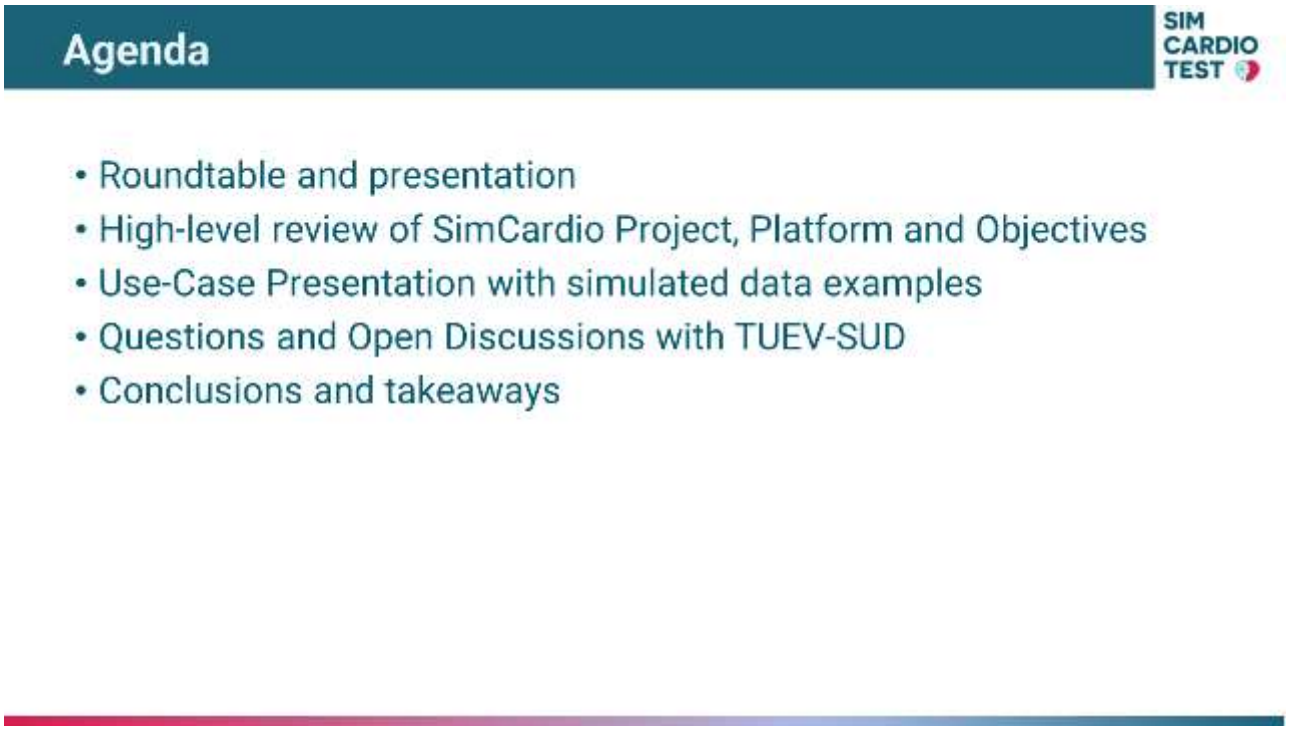
However, it was noted that practical examples are deemed more beneficial than theoretical discussions.

The overall opinion was that the involvement of NBs is essential for integrating the modeling community into in-silico trial practices, including both clinical and preclinical trials. There is a consensus that the European Commission (EC) should prioritize the use of in-silico data over clinical data, aiming to make them more prevalent, especially in scenarios where short-term objectives (i.e., within 12 months) currently preclude the application of in-silico data.

4- BIBLIOGRAPHY

- Good simulation practice (ebook should come out soon!): https://link.springer.com/book/9783031482830
- White papers with EMA: https://pubmed.ncbi.nlm.nih.gov/34102034/
- White paper on medical device & modeling: https://pubmed.ncbi.nlm.nih.gov/35951559/
- First draft of the roadmap towards Virtual Human Twin & public infrastructure (EDITH project): https://zenodo.org/records/8200955
- FAIRsharing collection on standards & guidelines for Virtual Human Twin (EDITH project): https://fairsharing.org/4787

Appendix 1 – Slide deck support of Notified Body discussion



Call Attendees

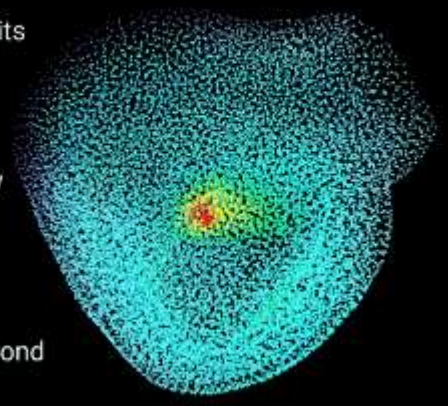
SIM CARDIO TEST

- *Confidential*

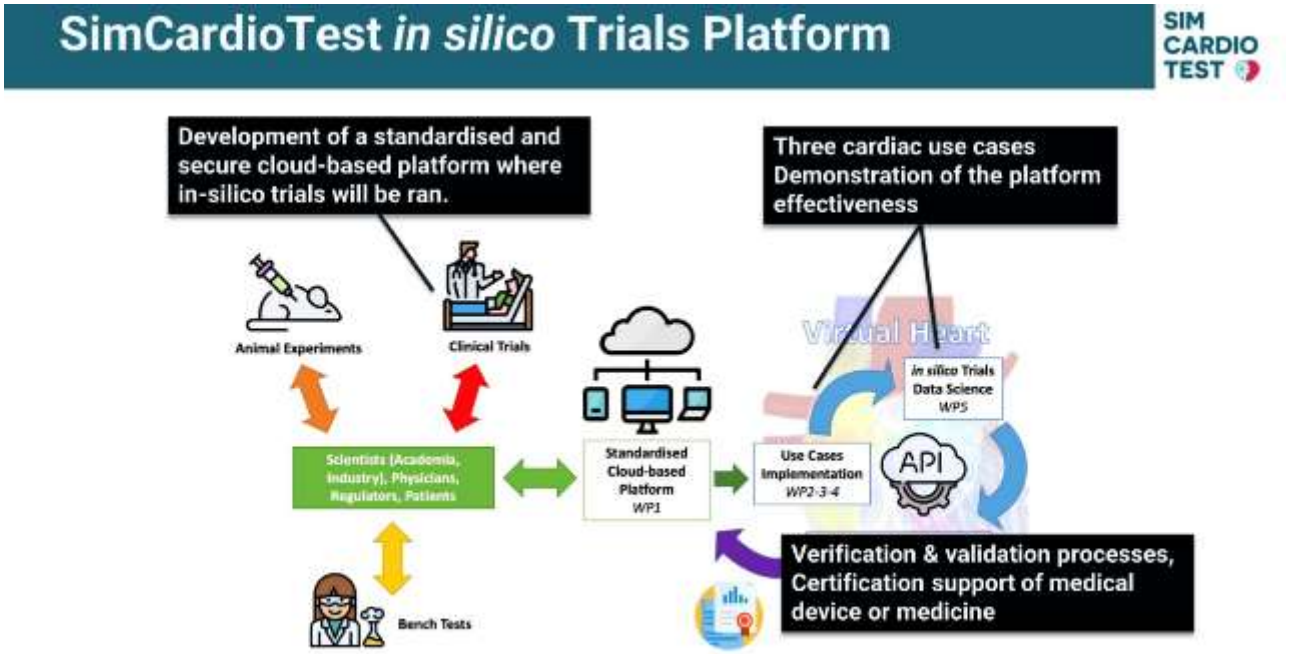
Objectives of SimCardioTest

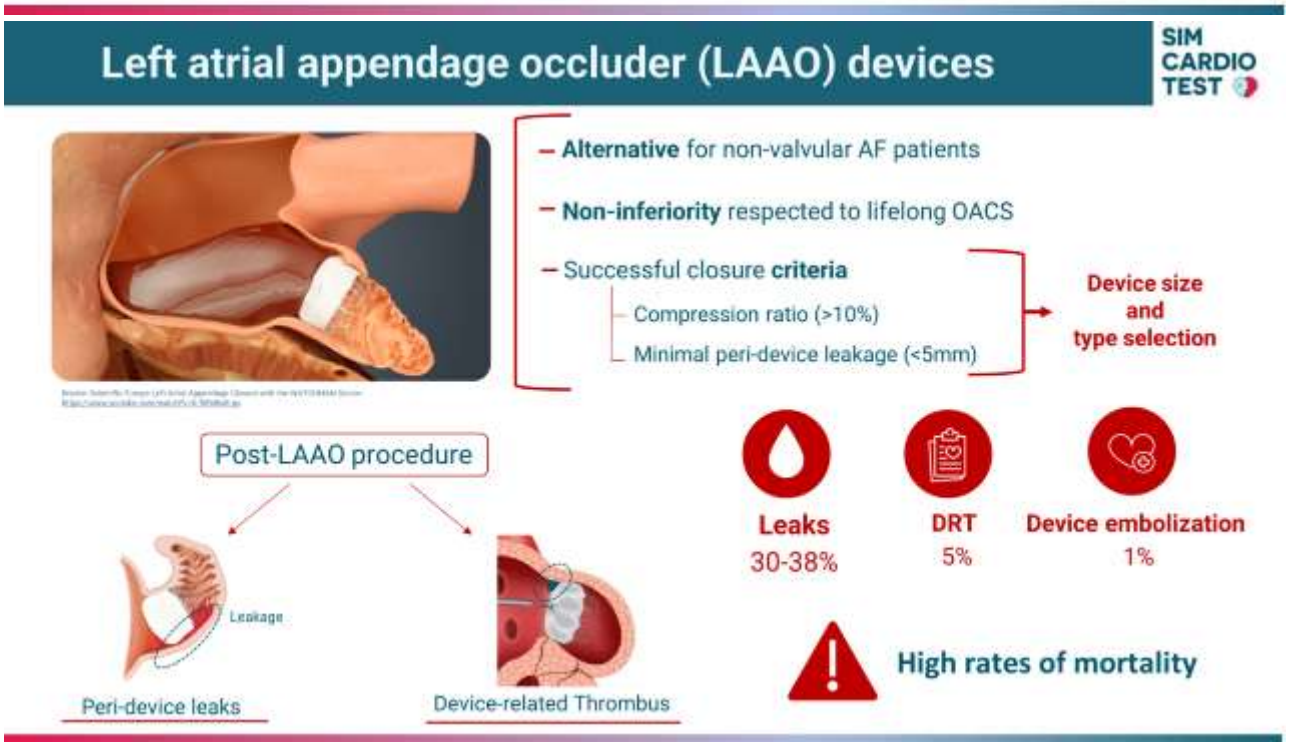
SIM CARDIO TEST

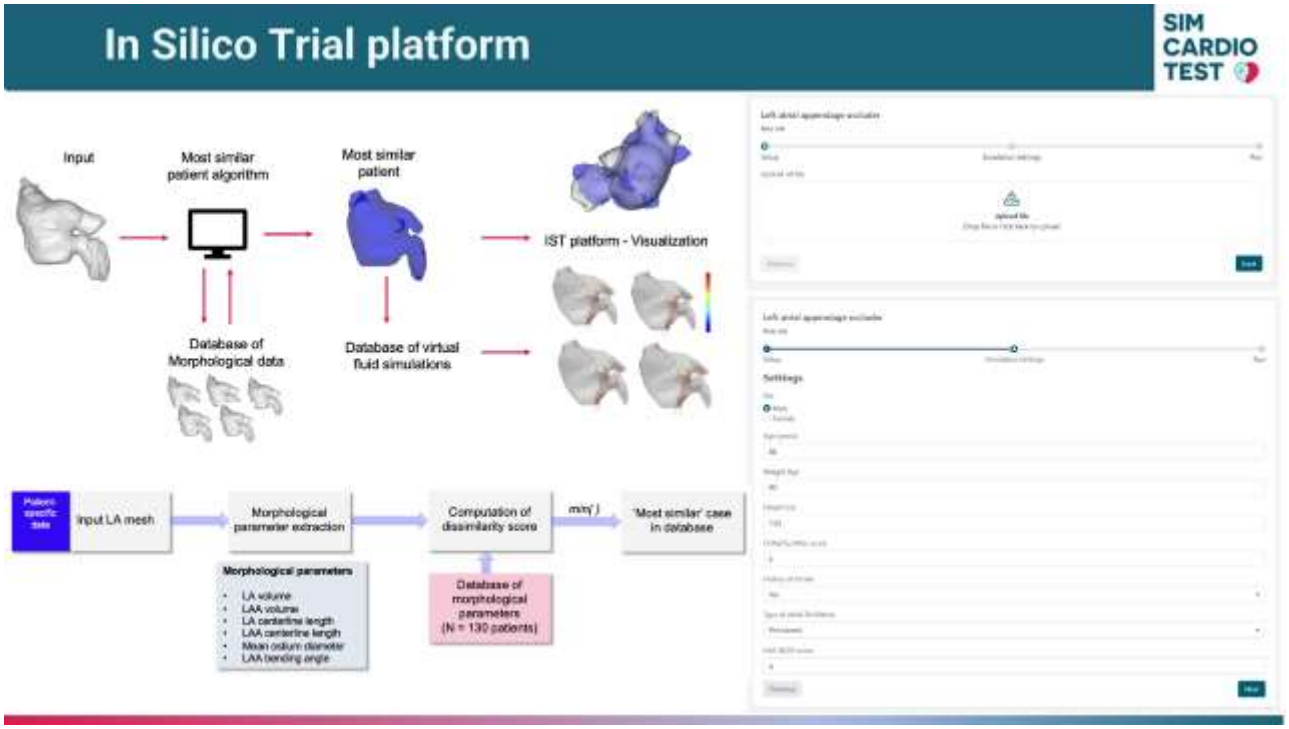
- To demonstrate feasability, effectiveness and benefits of in-silico trials for cardiac devices & drugs
- To gain the trust of scientists, companies, regulatory bodies, physicians, patients
- To promote healthcare innovation in Europe and beyond

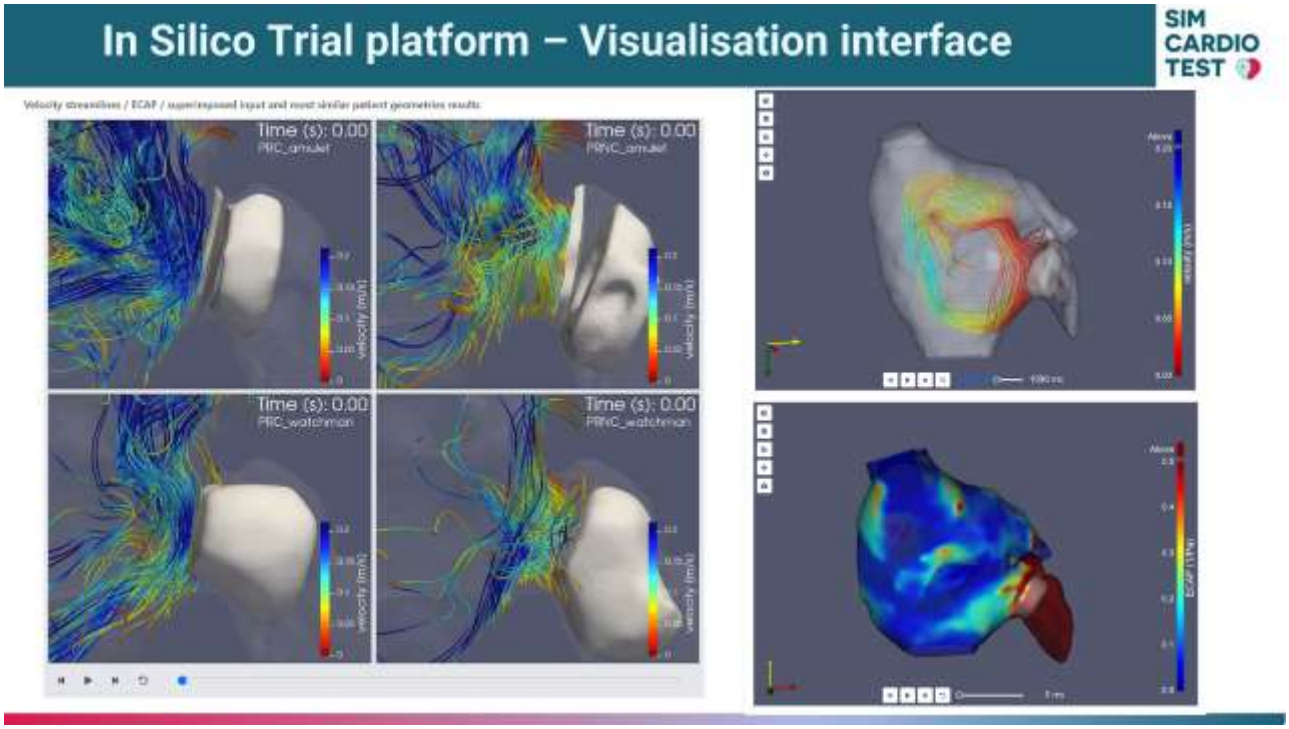


©Alexandre Dizeux


SimCardioTest *in silico* Trials Platform
SIM CARDIO TEST
Development of a standardised and secure cloud-based platform where in-silico trials will be ran.
Three cardiac use cases Demonstration of the platform effectiveness
Animal Experiments
Clinical Trials
Virtual Heart
in silico Trials Data Science WP5
Scientists (Academia, Industry), Physicians, Regulators, Patients
Standardised Cloud-based Platform WP1
Use Cases Implementation WP2-3-4
API
Bench Tests
Verification & validation processes, Certification support of medical device or medicine


Left atrial appendage occluder (LAAO) devices
SIM CARDIO TEST
– Alternative for non-valvular AF patients
– Non-inferiority respected to lifelong OACS
– Successful closure criteria
Compression ratio (>10%)
Minimal peri-device leakage (<5mm)
Device size and type selection
Post-LAAO procedure
Leakage
Peri-device leaks
Device-related Thrombus
Leaks 30-38%
DRT 5%
Device embolization 1%
High rates of mortality

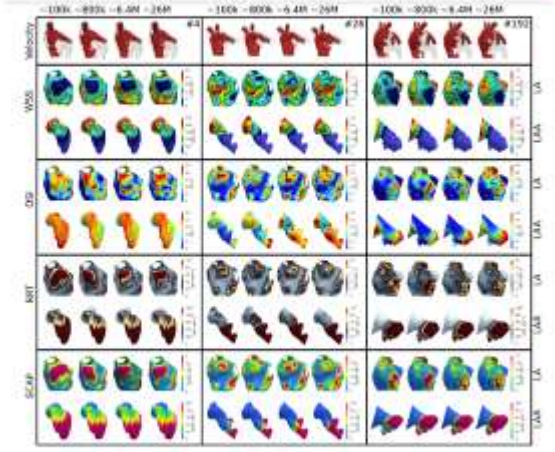

In Silico Trial platform
SIM CARDIO TEST
Input
Most similar patient algorithm
Most similar patient
IST platform - Visualization
Database of Morphological data
Database of virtual fluid simulations
Input LA mesh
Morphological parameter extraction
Computation of dissimilarity score
'Most similar' case in database
Morphological parameters
LA volume
LAA volume
LA centerline length
LAA centerline length
Mean ostium diameter
LAA bending angle
Database of morphological parameters (N = 130 patients)

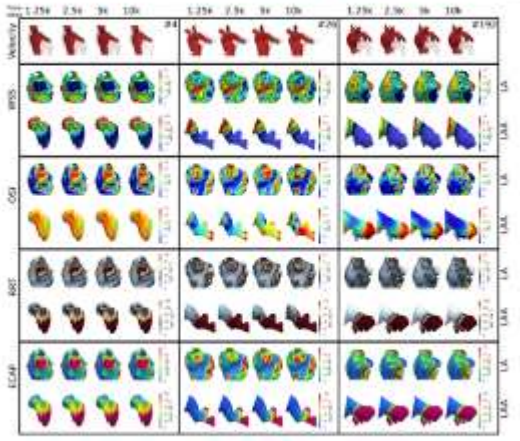

In Silico Trial platform – Visualisation interface
SIM CARDIO TEST
Time (s): 0.00
Time (s): 0.00
Time (s): 0.00
Time (s): 0.00

Sensitivity analysis

SIM CARDIO TEST

V&V 40 guidelines *Khalili et al., International Journal for Numerical Methods in Biomedi Engineering, 2024*





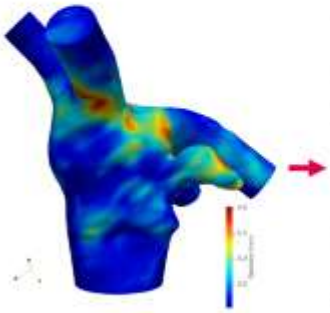
QoI: Can we measure low velocities close to the device?

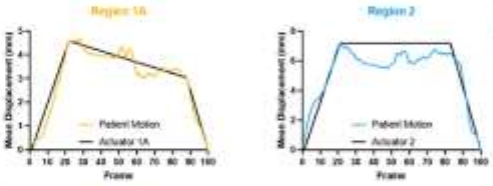
In-vitro validation

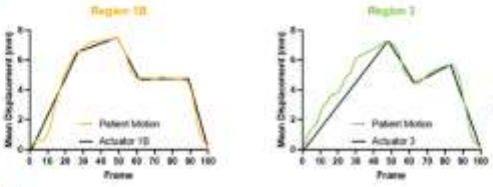
SIM CARDIO TEST

LA wall motion from dynamic CTs

LA wall motion simplification







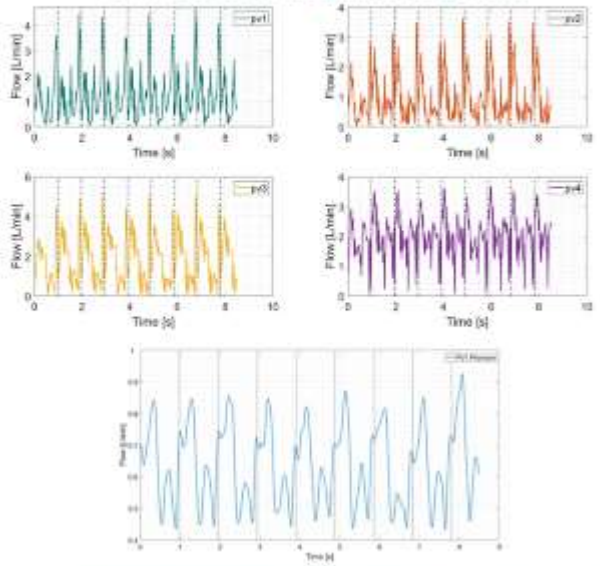
Anterior Actuator

Mitral Actuator

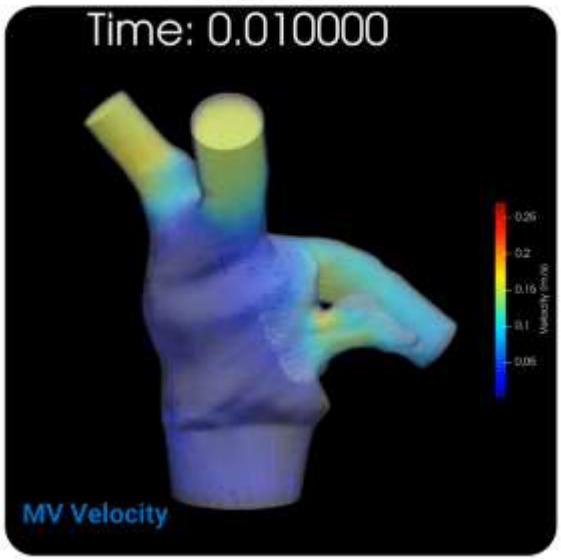
Validation with in-vitro experiments. Configuration 1

SIM CARDIO TEST

Flow results on the pulmonary veins



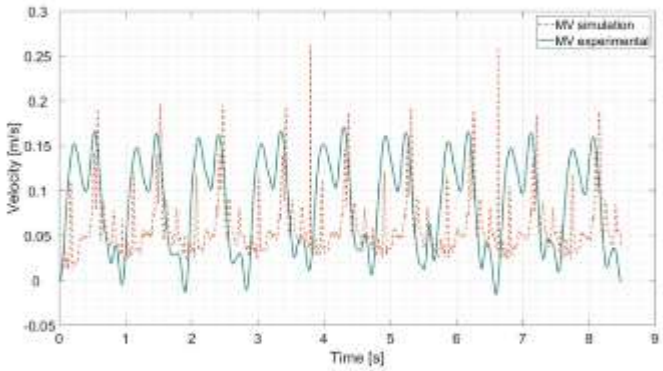
Control case



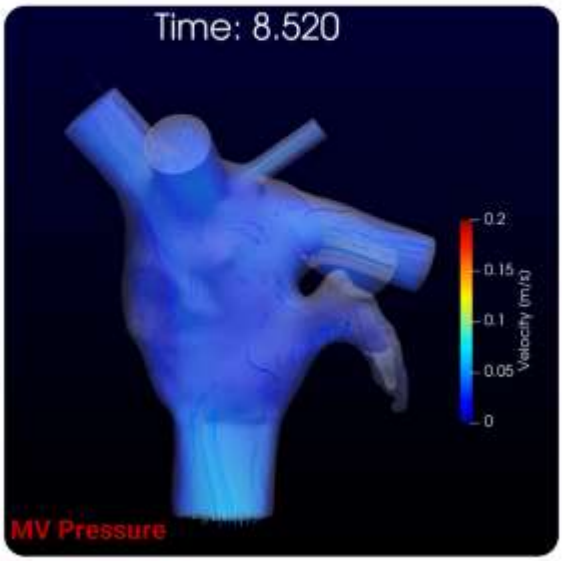
Validation with in-vitro experiments. Configuration 2

SIM CARDIO TEST

Flow results on the pulmonary veins



AF case

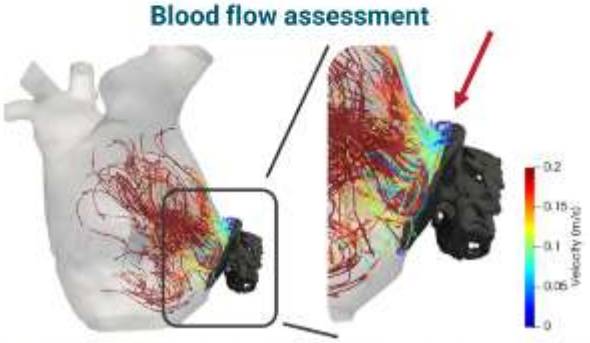


Multi-centric retrospective study - IDEAL study

SIM CARDIO TEST

Particles deposition

Blood flow assessment



CHU de Québec Université Laval
CLÍNIC BARCELONA Hospital Universitari
COMPLEJO ASISTENCIAL UNIVERSITARIO DE SALAMANCA
CHU BDX
HOSPITAL DE LA SANTA CREU I SANT PAU
Aarhus University Hospital
Rigshospitalet
ICP
C.H.U. de Charleroi

>200 cases

Opened discussions

SIM CARDIO TEST

- What is the current view of TÜV-SUD /Team NB on the use of in-silico data?
- Has TÜV-SUD already reviewed conformity assessment technical files incorporating such in-silico data to support a submission?
- Has TÜV-SUD (via Commission or other associations like TEAM NB) have discussed the use of in-silico data ? Are there some official guidelines or guidance documents we should be aware of?

Opened discussions

SIM CARDIO TEST

- Expectations for the use of in-silico *data* in CE file submissions ?
  - 2 cases : Change Notification (CN) vs New Conformity Assessment submission?
- What additional data would be expected to support the submission of a file?

Thank you

SIM CARDIO TEST

@simcardiotest

Simcardiotest EU project

Inria

European Commission

Appendix 2 – Minutes from Notified Body meeting that occurred on February 22nd, 2024

Minutes from meeting that occurred on Thursday February 22nd, 2024 from 2PM to 3 :30PM CET.

The names of the attendee list on both sides are kept confidential. All interactions by the different members are classified either as NB (for Notified Body) and SCT (for SimCardio Test consortium members).

High-Level Overview of the meeting

- Slides of the presentation were sent in advance to the NB team and they confirmed that they took the time to review them prior to the call.
- A short roundtable with presentations were made of both SCT and NB team.
- SCT confirmed that the objective of the call with NB was not to submit a Technical File for review and approval using In Silico data in the very short future but to get some feedback about their current view of the use of such data. Indeed, as very few official guidance exists at present for medical devices in Europe, the idea is to take the current *temperature* of the current thinking of the NB.
- SCT quickly went on with a presentation of the SimCardioTest (SCT) Consortium (Companies, Research Organizations, Academics, Non-Profit, etc.), the outreach of the project and the advisory board composed, in part, by FDA, companies, etc.
- SCT explained that 3 use-cases were studied within the SCT consortium and that we would be presenting the one which is the most advanced to have a true example of the data and the use we would be wanting to use and push forward.
- SCT started his presentation (cf slides -Appendix 1) explaining the global case study of the Left Atrial Appendage Occluder (LAAO) devices. See dedicated slides for details.
- Few questions were asked during SCT's presentation and we then moved forward to the "Questions" slides which had been previously shared with the NB team.
- At the end of the discussion, SCT was able to perform a "live" demonstration of the platform to the participants which also generated some comments and questions.

Questions from the slides provided:

1. ***What is the current view of TÜV-SUD /Team NB on the use of in-silico data?***
2. ***Has TÜV-SUD already reviewed conformity assessment technical files incorporating such in-silico data to support a submission?***
3. ***Has TÜV-SUD (via Commission or other associations like TEAM NB) have discussed the use of in-silico data ? Are there some official guidelines or guidance documents we should be aware of?***
4. ***Expectations for the use of in-silico data in CE file submissions?***

5. ***2 cases : Change Notification (CN) vs New Conformity Assessment submission?***
6. ***What additional data would be expected to support the submission of a file?***

- NB commented that "We need to be ready for these kinds of data. FDA is setting the rules and is not in the same position as NB. However, MDR is encouraging the use of computer models so SCT is really in good". Very good point that we need to be ready to this kind of data, to make them suitable acceptable of regulators. FDA has the advantage of being the regulator and the one approving.

  Indeed, FDA is the Regulator and the health authority which is not the case for Notified Bodies who do not "make the law" but apply it from the CE which leaves little room for interpretation and adaptation.

- NB: in the past, there is a lot of modeling, cf. MRI, thrombus and flow dynamics for modeling the blood flow. So how different is this to "standard" modeling? There is currently no ISO standards and EU regulations, especially in clinical cases. All the "standard" modeling is for preclinical and not for clinical. The MRI modeling came before the standards and this is all for pre-clinical. Would it be ok for physicians? Where is the physician in the modeling? The exact positioning, procedure.

  NB: questions of the slide 14: never had a case of in-silico yet. But clearly open for it. Not a hot topic at TEAM NB, clearly not in the top list. Use the data to complement but not exclusive. Use a submission to get a case of what is coming. If there is a standard, it is always good to use it (or have a good argument for not using it).

LAAO specific questions

- NB: How is the population distribution to find the closest patient? Is the population good enough to predict on a new patient?
- SCT: Since it is a deterministic model, it can easily adapt to a new case.
- NB: Would the population include new patients? = Yes
- NB: Is there any measure of uncertainty / differences / risks because the simulation is not done on exactly the same patient? (Did not really answer the question)

Knowledge and skills transmission/education

- NB: What are the key knowledge/skills needed to for regulatory bodies and RA within companies to speak the in silico language?
- SCT: There is a plan for wide training in the coming years.
- SCT: How is the training done/performed in regulatory bodies?
- NB : For the moment, from people joining in with their expertise. NB can also ask some academics to introduce new topics/technologies to NB.
- NB: The state of the art of clinical evaluation report helps us understand

- NB: In-house clinicians get to go to conferences and other meetings in order to learn about new technologies and ways. MDR encourages the use of in silico data. It's up to us to make them acceptable.
- NB: Agree. We are expanding our knowledge. It's actually real!

It seems that there are no formal training programs within Notified Bodies and that they mostly benefit from knowledge their employees are bringing in from the "outside" world. ***This is definitely a point that can be improved.*** *They seem to be extremely opened to getting access to the latest information about new technologies and applications.*

SCT shared the following links for NB use:

- Good simulation practice (ebook should come out soon!): https://link.springer.com/book/9783031482830
- White papers with EMA: https://pubmed.ncbi.nlm.nih.gov/34102034/
- White paper on medical device & modeling: https://pubmed.ncbi.nlm.nih.gov/35951559/
- First draft of the roadmap towards Virtual Human Twin & public infrastructure (EDITH project): https://zenodo.org/records/8200955
- FAIRsharing collection on standards & guidelines for Virtual Human Twin (EDITH project): https://fairsharing.org/4787

Past and present use of modeling data – V&V

- NB: In the past from a technical perspective, we already used a lot of modeling (MR pacemakers, left ventricular assisting device, thrombus formation). It is really new? Except to transfer it to clinical trial?
- SCT: For MRI there are specific standards. In this specific case the standard does not exist.
- SCT: There is not EU or national standard for modeling these types of devices. There was a meeting to harmonize V&V40 into an ISO standard. The biggest issue is MDR which allows M&S in preclinical and not in clinical.

- NB: Models come before the standard. All this modeling is preclinical. I am looking to my clinical colleagues now. It's nice to have these models, but how does it account the physician, who is not there? Where is that part in the modeling?
- NB: There are multiple phases in the use of a device. M&S is not replacing a procedure to place the device, but maybe in the future. I agree that the model comes before the standard.

- NB: V&V40 does not explicit the risks
- SCT: V&V is not used itself as a way to determine the risk
- NB: Difficult to do risk/benefit analysis and understanding of the risks.
- SCT: Medtronic used only in silico data for its pacemaker change approval in 2018. The change was about the adaptation of lead wire, they took the in silico trial and were allowed to go to market.

- SCT: Would you consider M&S alone?
- NB: We should use that framework with freedom. There is going to be submissions with data that complement preclinical data.
- SCT: Would you hold manufacturer to follow V&V40 for example?
- NB: If there is a standard, it's always beneficial to use it (or have an argument why not to consider it)
- NB: Model credibility. If guidelines go towards model credibility, I would definitely go for it
- SCT: Would in silico data be treated differently? Would you see use of in silico data being strong enough for a change vs. new device?
- NB: Difficult to answer. Depends on how big of a change. I would not differentiate at this time. In our approach in leveraging in silico data. In silico would need to be together with in vivo data.
- NB: I assume it's always in silico CLINICAL data.
- SCT: Preclinical in silico data is more easily/widely accepted, whereas in silico CLINICAL data could be the point to investigate what is the scope within MDR.
- NB: Preclinical data: it has been used before, of course you need validation of the model and it's usually something to complement the bench testing. Never seen a submission with only in silico data in the past 10 years.

- SCT: Question 5
- NB: You need to rationalize why, for example, V&V40 is appropriate. Or any kind of modeling choice.
- NB: Depending on the model that's used there need to know how it will affect the safety of the device. Supportive Data to understand what we are talking about. If you don't understand it, you can't understand its effects.
- SCT: mechanistic models are deterministic; AI models are not covered by V&V40 and FDA is discussing how to manage it. We are not talking about these kinds of models.

High level expectations for submissions

- NB: We should be able to have enough info to provide the basics in reg submissions. When going to EMA there's a lot of language barrier.
- SCT: what type of explanation would you expect to make sure there is an understanding of what we are actually talking? Part of the submission?
- NB: for MDR. I would expect the same things applicable to a submission as a real clinical trial. Try to follow MDR and CER guidelines.
- SCT: Clinical confirmation with data that already exist vs. full review of a clinical module, would In silico clinical data be used for clinical confirmation?
- NB: The very first time using in silico I would make it complementary; I would not try to lower the bar. We all need to familiarize ourselves with the value of the data.

Current use of In Silico data/Simulations

- NB: How many companies are doing these kinds of simulations?
- SCT: IST is planning to certify its products as there are very few companies like IST. However, big companies have large simulation departments, but this is usually used very upstream of the product or very late and usually not much used for supporting product submission files. It seems that EMA (at least), although they receive some files with CS, they do not have time/expertise/training to analyze them properly and there is a lot of pushbacks. Avicenna alliance has a branch for the regulatory bodies.

General conclusion

From this meeting it is evident that there is a huge opportunity to train the Notified Bodies on the use of in silico data. One of the questions that remains is « should the training be *individual* or as an *whole organization*? ». It might be a good idea to reach out to Notified Bodies trade associations globally (ex. TEAM NB) in order to streamline the trainings or at least awareness on the subject. In addition, and for a first start, a series of videos have been prepared and are shared (see below for direct links).

https://www.vph-institute.org/videos.html

https://www.vph-institute.org/video/code-cure-episode-1-understanding-in-silico-medicine.html

https://www.simcardiotest.eu/wordpress/next-generation-cardiac-care-discover-simcardiotest-in-silico-trials-platform/

https://insilico.world/category/press-release/

We also all acknowledge that there is a gap in the understanding between modeling and in silico trial, especially with its use: clinical vs preclinical/bench data. Notified Bodies have shared those practical cases would make more sense than theoretical.

In addition to training *per* se, there is also probably the need for the constitution of MDCG-type guidance so that all can be aligned on the expectations, but most importantly the understanding of the use of such data. The use of in silico data should also be prioritized at EU level in order to have this subject at the top of the list. Currently, short term priorities (i.e. 12 month) absolutely do not include in silico subjects.

The meeting highlighted the enthusiasm of NBs for in-silico methods, alongside a general deficiency in systematic knowledge within the field. It was suggested that strengthening connections between NBs and the modeling community, along with implementing various legal measures, could potentially improve this situation and encourage the adoption of in-silico methods in clinical practice.

This project SimCardioTest received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016496