SIMCor

In-Silico testing and validation of Cardiovascular IMplantable devices

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

Topic: SC1-DTH-06-2020 (*Accelerating the uptake of computer simulations for testing medicines and medical devices*)

Grant agreement No: 101017578

Deliverable 1.2

Kick-off meeting report

Due date of delivery: 28 February 2021

Actual submission date: 24 February 2021

Start of the project: 1 January 2021
End date: 31 December 2023

This project has received funding from the European Union's Horizon 2020 research and innovation programmeunder grant agreement N° 101017578

Reference

Name	SIMCor_D1.2_Kick-off meeting report_LYN_24-02-2021
Lead beneficiary	Lynkeus (LYN)
Author(s)	Mirko De Maldè (LYN)
Dissemination level	Confidential
Type	Report
Official delivery date	28 February 2021
Date of validation by the WP Leader	24/02/2021
Date of validation by the Coordinator	**24/02/2021**
Signature of the Coordinator	Titus Kuehne Digital unterschrieben von Titus Kuehne Datum: 2021.02.24 12:14:10 +01'00'

Version log

Issue date	Version	Involved	Comments
09/02/2021	v1.0	Mirko De Maldè (LYN)	First draft
10/02/2021	v2.0	Anna Rizzo (LYN)	First internal revision
11/02/2021	V3.0	Mirko De Maldè, Anna Rizzo (LYN)	Second draft
15/02/2021	V4.0	Davide Zaccagnini, Edwin Morley-Fletcher (LYN)	Second internal revision
19/02/2021	V5.0	Titus Kuhne, Jan Bruning, Anja Hennemuth (CHA), Ludovica Durst, Anna Rizzo (LYN), Andreas Ardnt (BIO), Maria Panagiotopoulou (ECRIN), Thomas Czypionka (IHS), Michael Stiehm (IIB), Valentina Lavezzo (PHI), Wouter Huberts (TUE), Malte Rolf-Pissarczyk (TUG), Lucian Itu (UTBV), Claudio Capelli (UCL), Liesbet Geris (VPH)	Review by kick-off meeting speakers from all consortium partners
22/02/2021	V6.0	Anna Rizzo (LYN)	Final review and formal checking by PM
24/02/2021	Final	Jan Bruning, Grischa Gabel (CHA)	Final submitted version

Executive summary

The kick-off meeting report is a document aimed at summarising the kick-off meeting, including the general overview of the project, the work package presentations, and the discussions amongst the partners of the SIMCor Consortium. Beside presenting the project and its main activities, the kick-off meeting was also meant to facilitate alignment amongst partners both regarding their respective activities and towards the achievement of the overarching goals of the project. This document constitutes the basis of the common understanding and alignment achieved during the kick-off meeting and will be used as reference for guiding the project execution and dissipating doubts on the future implementation of the project.

Table of contents

Acronyms

Acronym	Full name
AB	Advisory board
AVD	Aortic valve disease
CHA	Charité – Universitätsmedizin Berlin
CT	Computed tomography
BIO	Biotronik SE & Co. KG
DMP	Data management plan
ECG	Electrocardiogram
ECRIN-ERIC	European Clinical Research Infrastructure Network
ELSI	Ethical, legal and social implications
EOSC	European Open Science Cloud
ESR	Ethics Summary Report
EU	European Union
GA	Grant Agreement
GOSH	Great Ormond Street Hospital
GPU	Graphics processing unit
HF	Heart failure
ICT	Information and communication technologies
IHS	Institut für Höhere Studien – Institute for Advanced Studies
IIB	Institut für ImplantatTechnologie und Biomaterialien e.V.
LYN	Lynkeus
M	Month
MRI	Magnetic resonance imaging
PAPS	Pulmonary artery pressure sensors
PC	Project Coordinator
PHI	Philips Electronics Netherlands B.V.
R&D	Research and development
SME	Small and medium-sized enterprise
SOP	Standard operating procedure
TAVI	Transcatheter aortic valve implantation
TUE	Eindhoven University of Technology
TUG	Graz University of Technology
UCL	University College of London
UTBV	Universitatea Transilvania Din Brașov
V&V	Verification and validation
VPH/VPHi	Virtual Physiological Human Institute for Integrative Biomedical Research VZW
VRE	Virtual research environment
Y	Year
WP	Work package

Meeting agenda

Rationale of the agenda

The kick-off meeting agenda was conceived to allow: 1) overall presentation of the project and its main objectives; 2) alignment amongst partners and activities towards the SIMCor overarching aim; 3) description of the activities in each WP; 4) discussion in regard to activities particularly urgent and/or with a specific need of cross-WPs collaboration (e.g., system requirements, data management procedures, virtual cohorts generation); 4) planning of the first year of the project and agreement on the immediate next steps of the project; 5) presentation of the tools and modalities for the collaboration among partners. The detailed agenda, including GoToMeeting connection details, participants, titles, contents and speakers for each session, as circulated within the consortium, is reported below.

Agenda

Kick-off e-meeting

Thursday, Friday 14-15 January 2021

Connection details

SIMCor kick-off e-meeting - Day 1 Thu, Jan 14, 2021 11:30 - 18:15 PM (CET)	SIMCor kick-off e-meeting - Day 2 Fri, Jan 15, 2021 14:00 PM - 17:15 (CET)
Join meeting from computer, tablet or smartphone https://global.gotomeeting.com/join/537734981 **Dial in using your phone** Germany: +49 891 2140 2090 Austria: +43 7 2081 5427 Belgium: +32 27 00 6378 France: +33 170 950 594 Italy: +39 0 230 57 81 42 Netherlands: +31 207 941 377 Romania: +40 31 780 1158 United Kingdom: +44 330 221 0088 United States: +1 (646) 749-3129 **Access Code:** 537-734-981 New to GoToMeeting? Get the app now and be ready when your first meeting starts: https://global.gotomeeting.com/install/537734981	**Join meeting from computer, tablet or smartphone** https://global.gotomeeting.com/join/164739845 **Dial in using your phone** Germany: +49 721 6059 6510 Austria: +43 7 2081 5337 Belgium: +32 28 93 7002 France: +33 170 950 590 Italy: +39 0 230 57 81 80 Netherlands: +31 207 941 375 Romania: +40 31 780 1159 United Kingdom: +44 20 3713 5011 United States: +1 (571) 317-3116 **Access Code:** 164-739-845 New to GoToMeeting? Get the app now and be ready when your first meeting starts: https://global.gotomeeting.com/install/164739845

Participants

Partner	Members
European Commission (EC)	Christos Maramis (PO)
Charité - Universitätsmedizin Berlin (CHA)	Titus Kühne (PC, PI, WPL/6), Jan Brüning, Leonid Goubergrits, Anja Hennemuth, Friederike Fenske, Grischa Gabel
Lynkeus (LYN)	Mirko De Maldè (PM, WPL/1), Anna Rizzo (WPL/2), Davide Zaccagnini (IPRM), Edwin Morley-Fletcher, Ludovica Durst, Antonella Trezzani, Beatrice Bressan
Biotronik (BIO)	Andreas Arndt (PI, WPL/9), Torsten Luther
European Clinical Research Infrastructure Network (ECRIN)	Jacques Demotes (PI), Christian Ohmann

Institut für Höhere Studien – Institute for Advanced Studies (IHS)	Thomas Czypionka (PI, WPL/10), Markus Kraus, Miriam Reiss
Institut für ImplantatTechnologie und Biomaterialien e.V. (IIB)	Michael Stiehm (PI), Klaus Peter Schmitz
Philips Electronics Netherlands B.V. (PHI)	Valentina Lavezzo (PI, WPL/8), Olaf van der Sluis
Technische Universität Eindhoven (TUE)	Wouter Huberts (PI, WPL/7), Clemens Verhoosel
Technical University Graz (TUG)	Gerhard A. Holzapfel (PI), Malte Rolf-Pissarczyk
Universitatea Transilvania Din Brașov (UTBV)	Lucian Itu (PI, WPL/3), Constantin Suciu
University College of London (UCL)	Silvia Schievano (PI, WPL/5), Claudio Capelli (EM)
Virtual Physiological Human Institute for Integrative Biomedical Research VZW (VPH)	Liesbet Geris (PI, WPL/4), Martina Contin
Roles: *Project Coordinator (PC), Project Manager (PM), Institution Principal Investigator (PI), Work Package Leader (WPL), Ethical Manager (EM), Exploitation & IPR Manager (IPRM), Project Officer (PO)*	

Agenda

Day 1 – Thursday, 14 January 2021 (11:30 – 13:00, 14:30 - 18:15 CET) Project overview and work package (WP) presentation		
Time	**Details**	**Lead**
11:30 – 12:00	**Greetings and introduction** Introduction, presentation of the agenda, partners and role in the project	**Titus Kühne (CHA)** Mirko De Maldè (LYN)
12:00 – 12:10	**Few words from the PO**	**Christos Maramis (EC)**
12:10 - 13:00	**Project overview and discussion** ▪ Overview of project rationale, mission, objectives, major challenges, workplan, expected results and impacts ▪ Workplan for Y1: action plan for M1-M6/M7-M12, key issues and proposed working groups, governance structure, advisory boards and ELSI working group	**Titus Kühne (CHA)** Jan Brüning (CHA) Anna Rizzo (LYN)
13:00 – 14:30	*Break*	
14:30 – 14:45	**Implementation of the virtual research environment (WP3)** WP overview, objectives and tasks, dependencies, action items for M1-M6/M7-M12, immediate next steps	**Lucian Itu (UTBV)**
14:45 – 15:00	**Preclinical and clinical data acquisition (WP5)** WP overview, objectives and tasks, dependencies, action items for M1-M6/M7-M12, immediate next steps	**Claudio Capelli (UCL)**
15:00 – 15:15	**Data processing for anatomy and function (WP6)** WP overview, objectives and tasks, dependencies, action items for M1-M6/M7-M12, immediate next steps	**Anja Hennemuth (CHA)**
15:15 – 15:35	**Joint discussion session (WP3, WP5, WP6)**	
15:35 – 15:45	*Break*	
15:45 – 16:00	**Virtual cohort generation and validation (WP7)** WP overview, objectives and tasks, dependencies, action items for M1-M6/M7-M12, immediate next steps	**Wouter Huberts (TUE)**
16:00 – 16:15	**Virtual device implantation (WP8)** ▪ WP overview, objectives and tasks, dependencies ▪ *Device model design* ▪ *Vessel model design and validation* ▪ *Device deployment modelling and simulation* ▪ *Device vessel interaction modelling* ▪ Action items for M1-M6/M7-M12, immediate next steps	**Valentina Lavezzo (PHI)** Gerhard A. Holzapfel (TUG) Leo Goubergrits (CHA)
16:15 – 16:30	**Device effect simulation (WP9)**	**Andreas Arndt (BIO)**

	WP overview, objectives and tasks, dependencies action items for M1-M6/M7-M12, immediate next steps	
16:30 – 16:50	**Joint discussion session (WP7, WP8, WP9)**	
16:50 – 17:00	*Break*	
17:00 – 17:15	**Definition of standard operating procedures (SOPs) (WP4)** ▪ WP overview, objectives and tasks, dependencies ▪ *Data collection and processing SOPs* ▪ *Virtual cohort generation and validation SOPs* ▪ *In-silico model development, V&V[1], documentation and approval* ▪ Action items for M1-M6/M7-M12, immediate next steps	**Liesbet Geris (VPH)** Michael Stiehm (IIB) Andreas Arndt (BIO)
17:15 – 17:30	**Quantification of healthcare, industry and socioeconomic effects (WP10)** ▪ WP overview, objectives and tasks, dependencies ▪ *In-silico trial impact assessment framework development and application* ▪ *Medical device industry and market impact assessment* ▪ *Socio-economic impact assessment* ▪ Action items for M1-M6/M7-M12, immediate next steps	**Thomas Czypionka (IHS)** Jacques Demotes (ECRIN)
17:30 – 17:45	**Engagement, communication, dissemination and exploitation (WP2)** WP overview, objectives and tasks, dependencies, logo presentation and live survey, CDE[2] strategy plan, first press release, action items for M1-M6/M7-M12, immediate next steps	**Anna Rizzo (LYN)**
17:45 – 18:05	**Joint discussion session (WP4, WP10, WP2)**	
18:05 – 18:15	**Final wrap up**	**Titus Kühne (CHA)** Anna Rizzo (LYN)

Day 2 – Friday, 15 January 2021 (14:00 – 17:15 CET) Collective sessions on key topics and project management		
Time	**Details**	**Lead**
14:00 – 14:15	**Summary of Day 1 and introduction**	**Titus Kühne (CHA)** Anna Rizzo (LYN)
14:15 – 14:45	**Data collection, processing and management and relevant ethical and regulatory issues collective session (Data management & ethics WG)**	**Ludovica Durst (LYN)** Titus Kühne (CHA) Claudio Capelli (UCL) Mirko De Maldè (LYN)
14:45 – 15:15	**System requirement elicitation collective session (WP3)**	**Lucian Itu (UTBV)** Titus Kühne (CHA)
15:15-15:45	**Virtual cohort generation collective session (WP7)**	**Wouter Huberts (TUE)** Titus Kühne (CHA)
15:45 – 16:00	*Break*	
16:00 – 16:45	**Project management (WP1)**	**Mirko De Maldè (LYN)**

[1] Verification and validation

[2] Communication, dissemination and exploitation

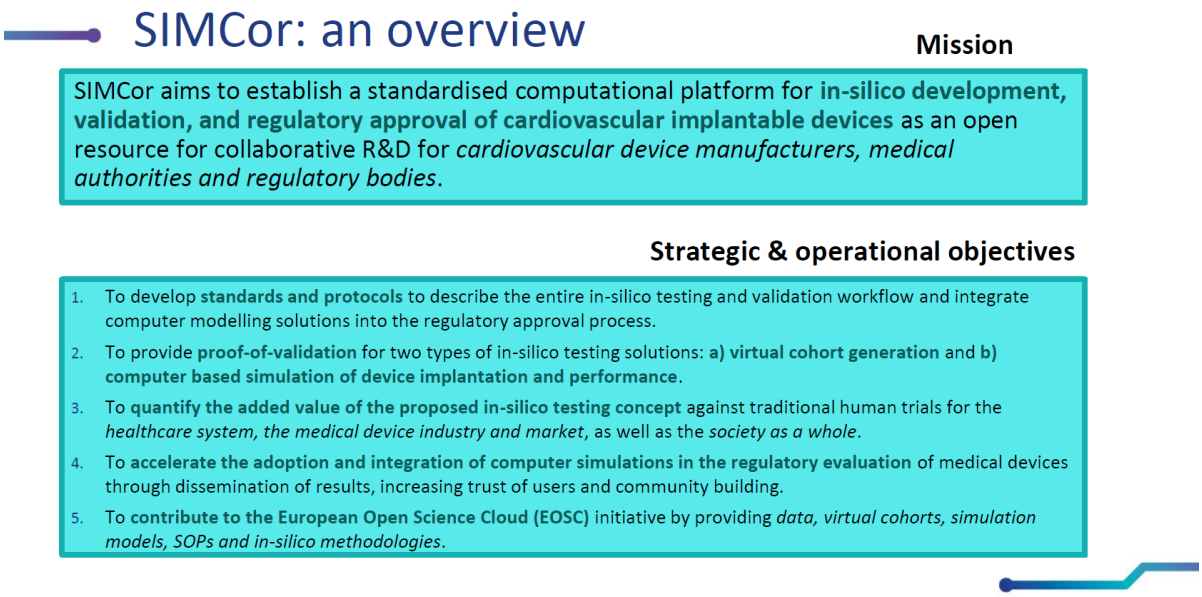
	Governance structure, management procedures and tools, mailing lists, meeting and TC calendar, payment schedule, deliverable and reports preparation	
16:45 – 17:05	**Action items M1-6 and immediate next steps**	**Anna Rizzo (LYN)**
17:05 – 17:15	**Final wrap up**	**Titus Kühne (CHA)**

Inaugural session

The inaugural session included partners' presentations, a project overview offered by the Project Coordinator, Prof. Titus Khune, and by the Scientific Project Manager, Anna Rizzo. The overall exploitation strategy was also presented by Davide Zaccagnini (LYN), SIMCor's IPR and Exploitation Manager. The inaugural session also saw the participation of the EC Project Officer (PO) Christos Maramis, who offered an overview of the vision underlying the project call and key priorities from the EC perspective as useful guidance for the project implementation, as further specified in the dedicated section below.

Introduction by the Coordinator

Titus Kühne (CHA)

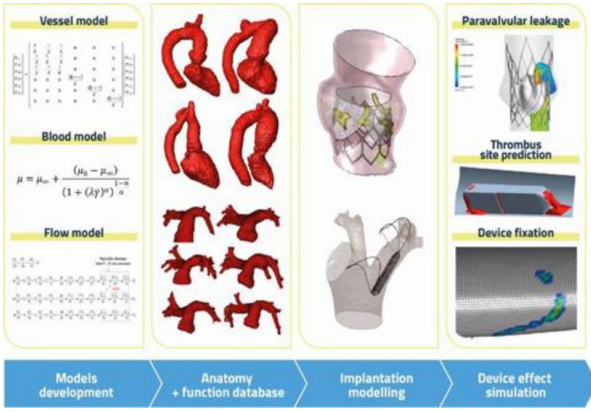


Key messages

- Scope of the presentation is to provide a broad, high-level, overview of the project scope.
- The project focuses on two cardiovascular devices (likely to be more frequently used in the future): the *transcatheter aortic valve implantation* (TAVI) devices and the *pulmonary artery pressure sensors* (PAPS).
- The global idea is to:
  - perform in-silico trials for these devices in particular, and for cardiovascular devices in general;
  - implement new tools that allow companies and researchers to evaluate different features of the devices under development in a more time-efficient and cost-efficient way, towards the development of better devices with higher levels of sensitivity in the future.
- the essence of what we want to do in the next 3 years:
  - implement a device tech simulation for end points that are very important for the evaluation process;
  - we cannot do everything which is on the pipeline for developing and getting a new device in the regulatory process;

- we are focusing on things where we believe that in-silico tools are particularly strong; these endpoints might be not so clinically important, but they are important for the evaluation process in terms of the regulatory pipeline.

SIMCor technical objectives

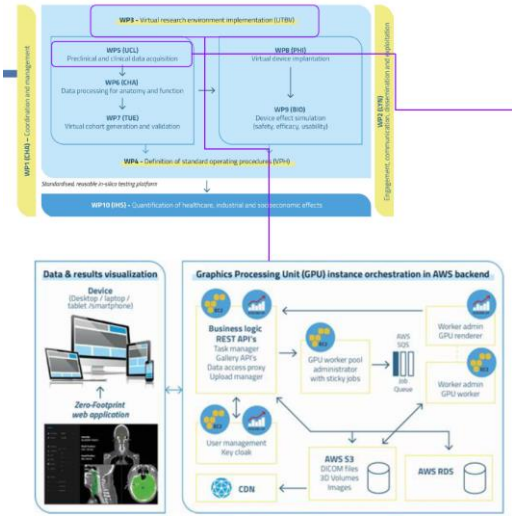


- **Paravalvular leakage** (endpoints: leakage after implantat)
- **Durability** (endpoint: structural and fatigue simulations; fractures)
- **Thrombosis** (endpoints: shear rates distribution, platelet activation, washout behavior

- **Migration** (endpoint: axial retention force)
- **Perforation** (endpoint: contact length and forces)
- **Thrombosis** (endpoint: regions of high and low wall shear stress and oscillatory shear index)

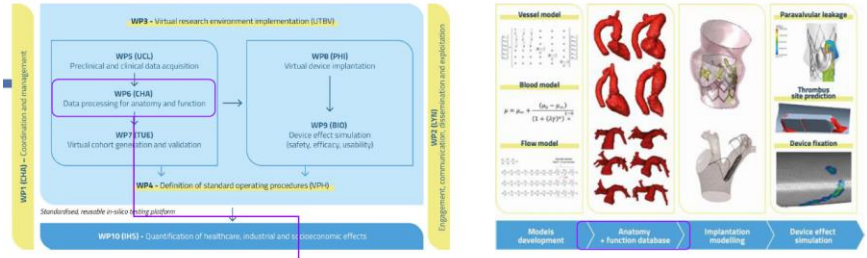
Scientific WPs: objectives and interactions

- WP3: Virtual research environment; all the infrastructure we need for sharing the data, sharing the models, and as a knowledge management tool.
- WP3 is strongly connected with WP5: the data that the project will use for building the virtual cohorts for the validation of the simulation results. UCL will lead this WP and CHA will be deeply involved.
  - We selected the data that should be used (at least as starting point):
    - clinical data, coming from hospitals;
    - retrospective data, clinical data from previous studies (including previous EU funded projects);
    - publicly available data from clinical trial data sources;
    - for the PAPS device: prospective animal data and preclinical data;
  - We are not acquiring prospective data.



Source	Type	Size	Focus	Usage
Dataset / project name (clinical trial number)	**Cath** cardiac catheter suite laboratory, **CT** computed tomography, **ECG** electrocardiogram, **Echo** echocardiogram, **MR** magnetic resonance, **VRD** valve related dysfunction			
G1. CLINICAL DATA from hospital repositories (CHA, UCL)				
Group R1: AVD, undergoing TAVI (2014–2020)	Retrospective data collected before TAVI (Cath, CT, Echo, ECG) and 1-year follow up (Echo, ECG) and 10% controls. Any event related to TAVI is recorded	250	AVD	TAVI: VC-generation', VC-validation'
Group R2: HF, requiring PAPS (2014–2020)	Retrospective data with heart failure and a subgroup before PAPS (CT, Cath, ECG, Echo, MR) and 1-year follow up (Echo, ECG). Any event related to PAPS is recorded	250	HF	PAPS: VC-generation', VC-validation'
G2. CLINICAL TRIAL DATA from CHA and UCL research (M2020, 7FP, BAMP)				
SMART (NCT01172334)	Retrospective data (Cath, CT, ECG, Echo, MR)	40	HF	PAPS VD
EurValve (NCT04068740)	Retrospective data before and after aortic valve replacement (Cath, CT, ECG, Echo, MR)	120	AVD	TAVI VD
Cardioproof (NCT02591940)	Retrospective data before and after aortic valve replacement (CT, Cath, ECG, Echo, MR)	120	AVD	TAVI VD
ArtiCardio	Synthetic datasets of aortic stenosis (CT, Cath, ECG, Echo)	1,200	AVD	TAVI VD
G3. TAVI clinical trial data from BIO research				
BIOVALVE (NCT02249000)	Retrospective data (CO, CT, Echo, 30-day efficacy)	86	AVD	TAVI VD
G4. PAPS clinical trial Open Data				
CHAMPION (NCT00531661)	Retrospective data (CO, freedom of device failure, hospitalization rate, freedom from device-related complications)	550	HF	PAPS VD
G5. PRECLINICAL DATA from prospective study (CHA) and previous research (BIO, TUE)				
Prospective acute pig study - PAPS	Invasive tests on implantation procedure (e.g., pull tests), Cath, CT, MRT, Echo, ECG	10	Con	PAPS: VC-validation
Prospective chronic pig study - PAPS	Visit 1: at baseline (pre-intervention) Visit 2: at 6 months follow-up For both: Cath, CT, Echo, ECG	10	Con	PAPS: VC-generation', VC-validation'
Retrospective acute and chronic animal studies of TAVI project	Visit 1: at baseline (pre-intervention) and peri-implant Visit 2: at explant 1 to 12 months follow-up For both: Cath, CT, Echo, ECG, VRD	10	Con	TAVI: VC-generation', VC-validation'
Preclinical study from SCATh	Uniaxial extension, biaxial extension and simple shear tests with animal and human tissue	30	AVD, Con	TAVI VD

- WP6: data processing for anatomy and functions; processing pipelines in setting the boundary conditions and a library for building models in terms of anatomical information;
- this data will be then used (together with the data collected in WP5) in WP7, which is the generation of virtual cohorts, for the device implantation and device effects simulation WPs.



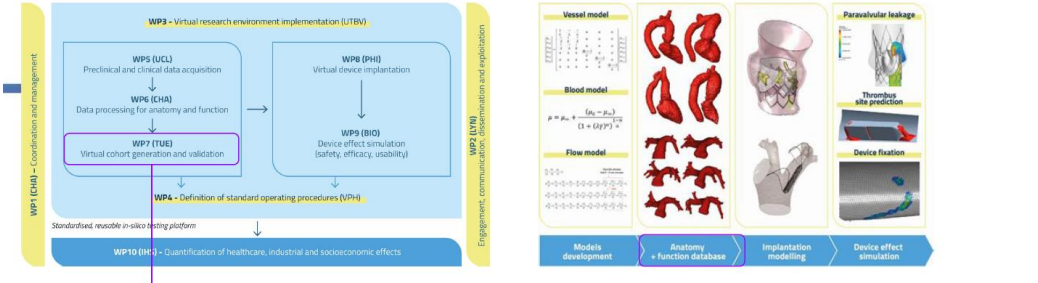
Data preprocessing and boundary conditions (Library for models)

- *anatomical information* (i.e., geometric representations of heart chambers, heart valves, large vessels),
- *functional information* (i.e., parametric representation of hemodynamics and ventricular function) and
- *material properties* (i.e., distribution of strains, compliance/distensibility with regard to the anatomy).

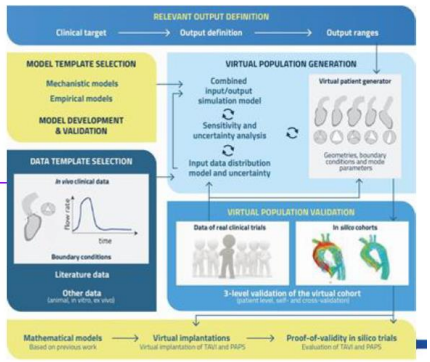
Used for virtual

- virtual cohort generation (WP7),
- subject-specific and cohort-based simulation and modelling (WP8, WP9)

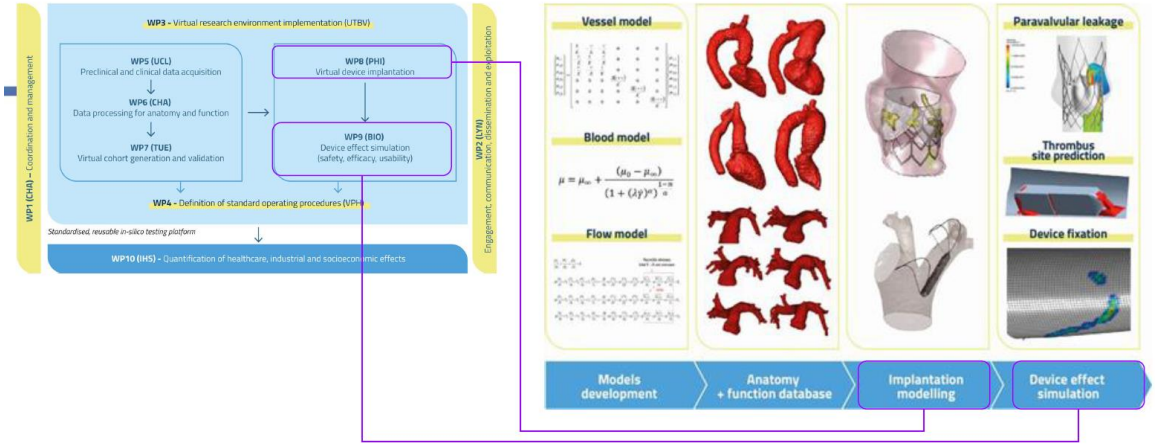
- WP7: build from the data virtual cohorts and validate them;
- it is important to discuss and decide:
  - how to validate our studies in a meaningful way that can also be accepted by the regulatory bodies;
  - how can we define standard operating procedures for building products;
  - how can we define standard operating procedures for validation;
- the validation scheme, that is tackling a couple of things like low-fidelity validation of the modelling tools, but also high-fidelity validation of device simulations by virtual cohorts.



1. **Low-fidelity validation of modelling tools (bench and acute animal tests)**
2. **High fidelity validation of device simulations by virtual cohorts**
   a) Patient-specific validation
   b) Self validation
   c) Cross validation

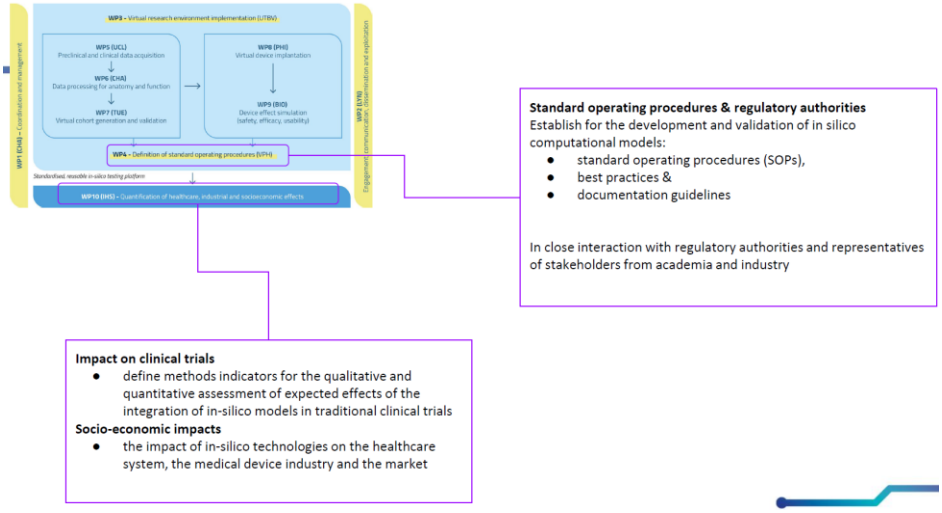


- WP8-WP9: once virtual cohorts are defined, comprising information about anatomy and function, then the next step is to deploy virtually the different devices. It will be interesting to assess how much details we are going to need to deploy the devices because we can run into very detailed modelling approaches (using a lot of resources) or maybe simple model approaches which are good enough for implementing devices for making functional assessment.



- WP4: once all this scientific part is completed, then the project will translate all things learned in the process into the regulatory framework, reusing tools and data for building new devices, defining best practices and guidelines;
  - the VPH Institute is leading this work package, which is extremely important also to have a close liaison with relevant regulatory bodies;
  - WP4 will also disseminate our lessons learned to these institutions.

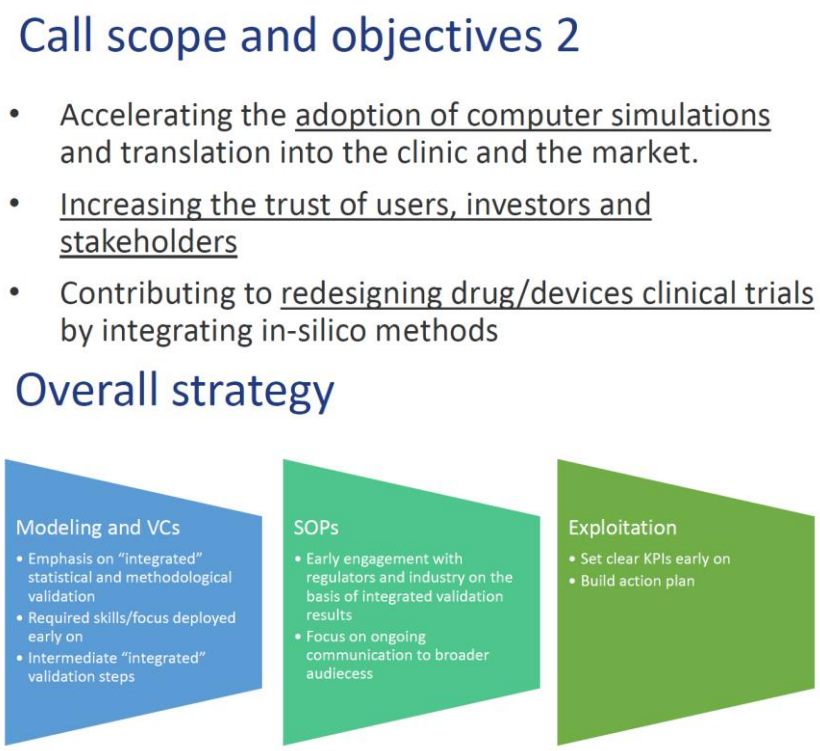
- WP10 will explore what is the impact on clinical trials and healthcare at large, and in turn on the medical industry, market and society:
  - IHS will be leading this WP;
  - the WP will assess how these virtual components will in the future impact the definition of clinical trials, how much can we reduce the number of subjects included in such trials, or trial duration, also assessing social economic impact, implications on safety and so on.



Goals of the project and perspective on the exploitation of results

Davide Zaccagnini (LYN) – SIMCor's IPR and Exploitation Manager

- It is important to start focusing early on exploitation.
- The Call itself focuses on the acceleration of the uptake of computer simulations for medicine and medical devices.
- General strategy: the exploitation focus is inserted very early on in the overall flow of our activity: start thinking in terms of integrated validation (i.e., validation not strictly bound to the statistical criteria of a given technology or prediction but also able to include important pointers to the general framework in which we are operating).

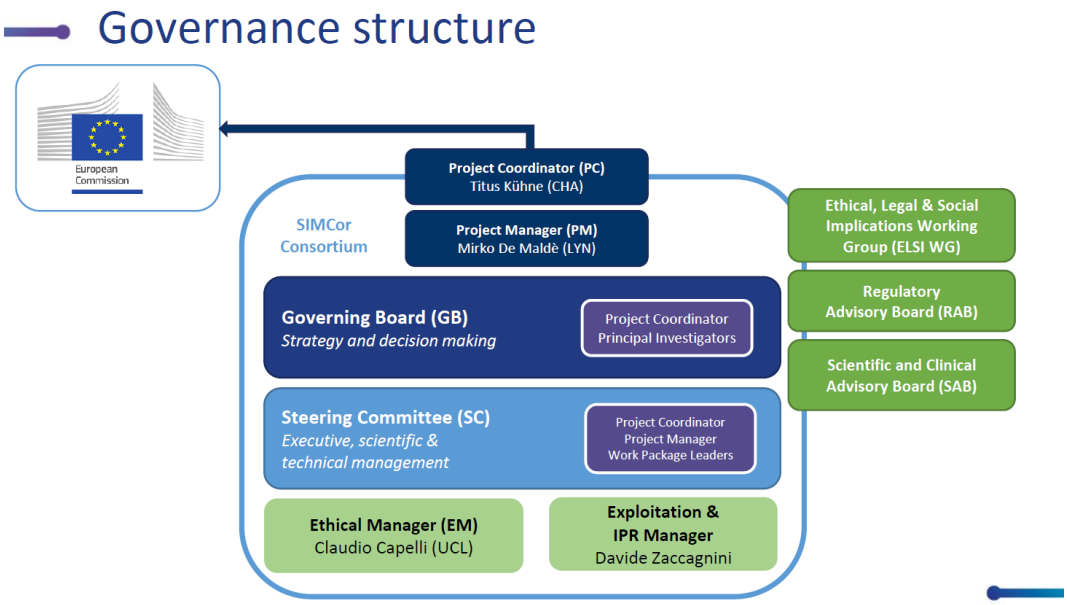


- We will look for resources that can be dedicated to this type of activity and support them in profiling the right type of people to interact with.
- It will be important to create multidisciplinary task forces or working groups to take into account these implementation aspects.
- We also want to sort of break down the process of developing and testing the technologies in as many as possible validation steps with this concept of integrated extended validations.
- With this type of multidisciplinary type of work we should be able to get to the definition of standard operating procedures and allow early engagement of regulators and industry stakeholders in this process.
- SOP will not be a top-down recommendation from a project to the rest of the world, but they are rather the fruit of collaborative work with both regulators and industry stakeholders.
- The exploitation plan will emerge from this activity.
- We will create KPIs in terms of what we really want to achieve with the exploitation. We will then monitor these KPIs in terms of intermediate achievements, developing a multi-stage action plan, the fruit of which will be the final exploitation strategy. LYN will interact soon with partners to establish this process. All teams will be asked to contribute.

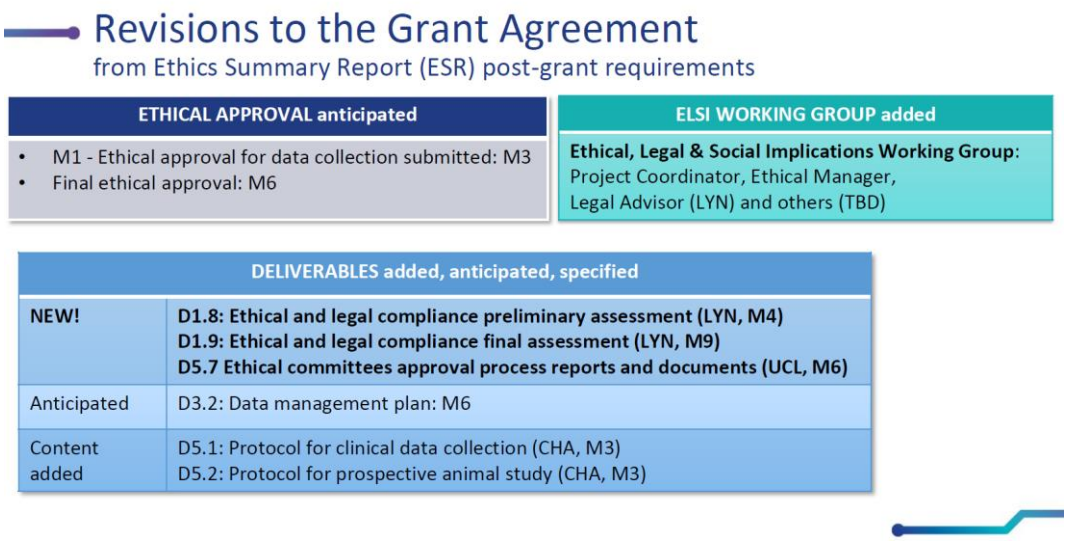
Overview on the project plan, structure and implementation

Anna Rizzo (LYN) – SIMCor's Scientific Project Manager

- Governance structure: there have been changes with respect to the proposal. The new structure is presented. Advisory Boards will support the definition of SOPs, the formulation of the roadmap for integration, and support ethical and regulatory compliance analysis. The composition has been slightly changed.

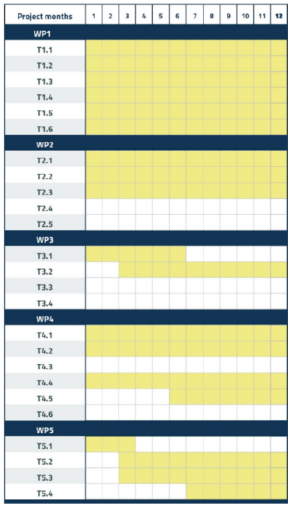


- Revision of the *Grant Agreement* (GA): news in terms of ethical requirements and relevant activities, made to address the EC's requests included in the *Ethics Summary Report* (ESR):
  - the ethical approval has been anticipated from M9 to M6;
  - we have introduced a *Ethical, legal and social implications* (ELSI) working group;
  - 3 deliverables have been added.



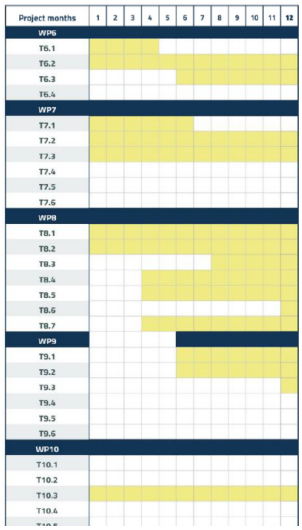
- Y1 activities are presented via Gantt chart.

Gantt chart (M1 – M12): WP1-5



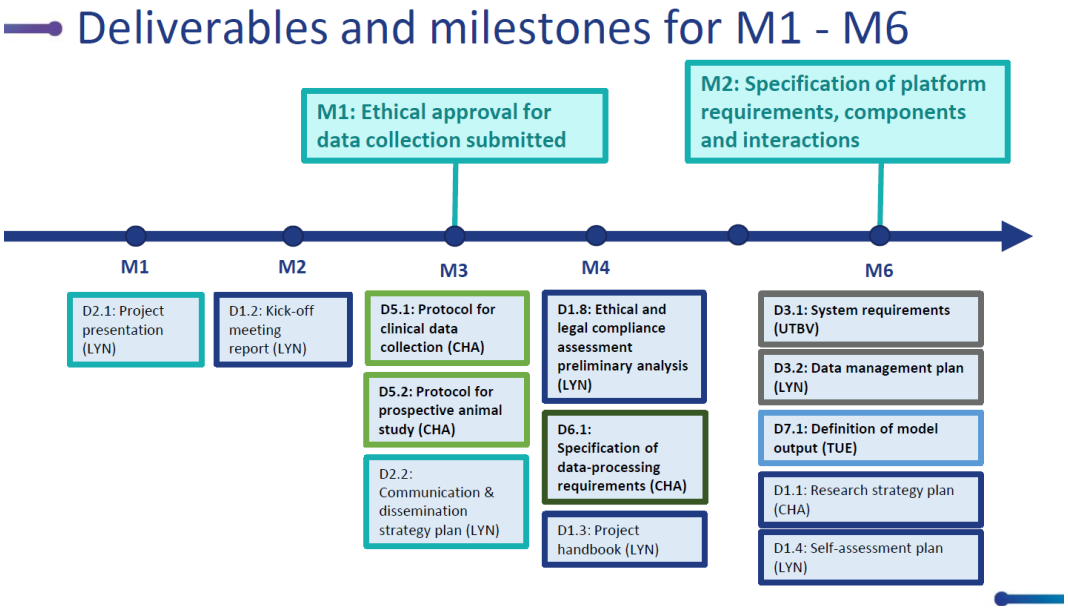
WP	Tasks
WP1 – Coordination & management	• T1.1: Research strategy and project steering (CHA) • T1.2: Operational management (LYN) • T1.3: Project reporting (LYN) • T1.4: Risk management and mitigation (LYN) • T1.5: Financial, administrative and contractual coordination (CHA) • T1.6: Ethical and legal clearance and monitoring (LYN)
WP2 – Engagement, communication, dissemination &exploitation	• T2.1: Communication and dissemination strategy, branding and tools (LYN) • T2.2: Dissemination events (LYN) • T2.3: Liaison with regulatory authorities (VPH)
WP3 - Virtual device environment implementation	• T3.1: **Computational platform requirements** for infrastructure adaptation and extension (UTBV) • T3.2: **Implementation of extensions** to data repository (UTBV)
WP4 - Definition of standard operating procedures	• T4.1: Elaboration of the SOPs for the **preclinical and clinical data acquisition** for in-silico models (VPH) • T4.2: Elaboration of SOPs for the **processing of preclinical and clinical data** (VPH) • T4.4: Elaboration of guidelines for **documentation of in-silico models and simulation results** for approval process (IIB) • T4.5: Elaboration of SOPs for the **in-silico model development, verification and validation** (IIB)
WP5 - Preclinical and clinical data acquisition	• T5.1: Protocol definition for data collection tasks (UCL) • T5.2: Collection of retrospective and acquisition of prospective preclinical data from pig study (CHA) • T5.3: Collection and organization of retrospective clinical data (UCL) • T5.4: Creation of synthetic data (UCL)

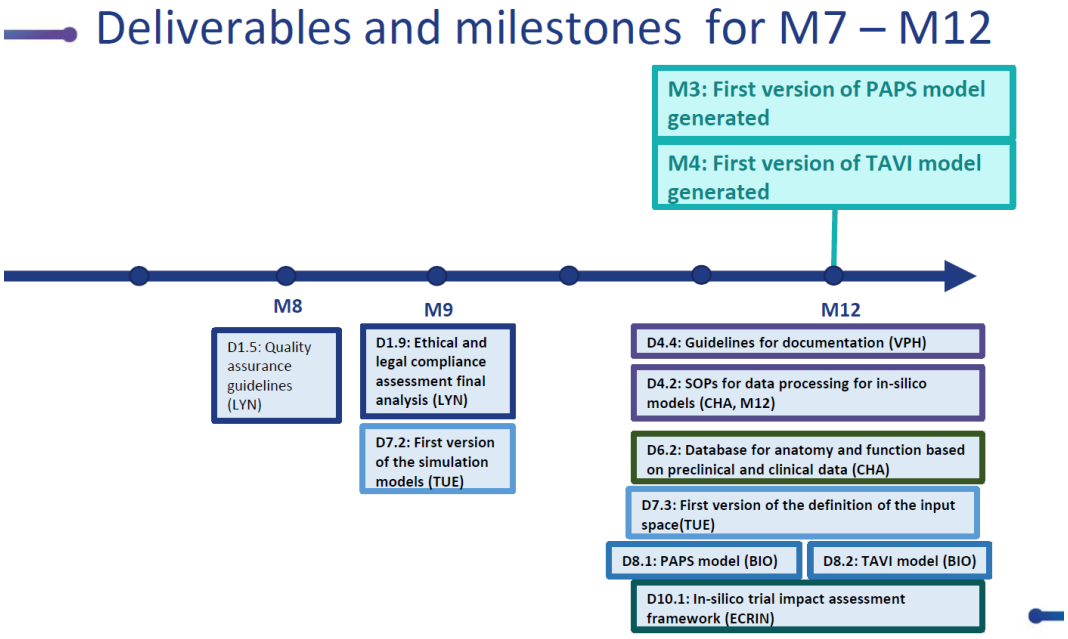
Gantt chart (M1 – M12): WP6-10



WP	Tasks
WP6 - Data processing for anatomy and function	• T6.1: **Processing pipeline and database concept** for TAVI and PAPS (CHA) • T6.2: **Anatomical and functional information from image data** (heart, heart valves, large vessels) (CHA) • T6.3: **Boundary conditions** for subject-specific simulations (4D and local properties) (CHA)
WP7 - Virtual cohort generation and validation	• T7.1: Definition of **model output** (TUE) • T7.2: Selection of **model templates** (TUE) • T7.3 Selection of **data templates** (TUE)
WP8 - Virtual device implantation	• T8.1: Device model enhancement (BIO) • T8.2: Simplified vessel model design (TUG) • T8.3: Validation of simplified vessel models (TUG) • T8.4: Fast device deployment modelling (CHA) • T8.5: 3D finite element implant simulation (PHI) • T8.6: Model order reduction (PHI) • T8.7: Isogeometric analysis (TUE)
WP9 - Device effect simulation	• T9.1: **Enhanced constitutive vessel model** (TUG) • T9.2: **Device-specific effect models** (IIB) • T9.3: **Low-fidelity validation of modelling tools** (bench and acute animal test) (BIO)
WP10 - Quantification of healthcare, industry and socioeconomic effects	• T10.3: Development of **a conceptual framework** for the analysis of socio-economic effects (IHS)

- Milestones and deliverables for Y1 are reported in the timelines illustrated below.





- Priorities for M1-6:
  - obtaining ethical clearance;
  - defining the data collection processing and privacy and security management specifications;
  - system requirements elicitation.
- Priorities for M7-12:
  - virtual cohort model definition: simulation model outputs and templates, data templates;
  - device and vessel model definition: refinement of existing device models, definition of simplified vessel models;
  - SOPs definition: SOPs for documentation and data processing;
  - theoretical frameworks for impact assessment.

Project Officer intervention

- The title of the Call topic was *"Accelerating the uptake of computer simulations for testing medicines and medical devices, and bringing them closer to the market"*.
- The real problem starts with the high costs for developing medical devices and pharmaceutical products, with most of these resources absorbed by clinical trials.
- The EC has acknowledged the predictive power of individualised computer simulations, and also the fact that for these simulations and in-silico models to be adopted, the trust of the users involved needs to be insured.
- Achieving this goal requires:
    - multidisciplinary efforts and of course, appropriate validation measures like human trials, animal studies;
    - other measures need to be applied in real clinical settings;
    - the proof of validation needs to be delivered as part of the product;
    - engagement with regulators and considerations from the regulatory framework were encouraged by the call.
- Several points of expected impact have been identified by the Call and many were addressed by SIMCor, thus the high evaluation.

- Under this topic, the following 4 projects were funded. Interactions among these projects will be encouraged by the EC.

- The timeline for the GA signature was very tight due to budgetary reasons.

Grant Agreement Timeline

- 16 new ethical requirements were introduced via the post-grant ESR:
  - The consortium should pay extra-attention to meet the deadlines for these requirements;

Ethics requirements & deliverables (I)

			Ethics requirements	Due Month	Addressed in
H	1	2.1	The procedures and criteria that will be used to identify/recruit research participants must be submitted as a deliverable.	3	**D5.1 (M3)**
		2.2	The informed consent procedures that will be implemented for the participation of humans must be submitted as a deliverable.	3	**D5.1 (M3)**
		2.3	Templates of the informed consent/assent forms and information sheets (in language and terms intelligible to the participants) must be kept on file.	3	**D5.1 (M3)**
		2.5	In case children and/or adults unable to give informed consent are involved, details on how the consent of the legal representatives (and assent, when applicable) will be acquired must be submitted as a deliverable.	3	**D5.1 (M3)**
		2.9	Copies of opinions/approvals by ethics committees and/or competent authorities for the research with humans must be submitted as a deliverable.	3	**D5.1 (M3); D5.7 (M6)**
		2.10	For each clinical study, the following documents/information must be submitted as a deliverable (in one package) prior to enrolment of first study subject: (i) Final version of study protocol as submitted to regulators/ethics committee(s), (ii) Registration number of clinical study in a WHO-or ICMJE- approved registry (with the possibility to post results), (iii) Approvals (ethics committees and national competent authority if applicable) required for invitation/enrolment of first subject in at least one clinical centre.	3	**D5.1 (M3); D5.7 (M6)**
H	2	2.10	For each clinical study, the following documents/information must be submitted as a deliverable (in one package) prior to enrolment of first study subject: (i) Final version of study protocol as submitted to regulators/ethics committee(s), (ii) Registration number of clinical study in a WHO-or ICMJE- approved registry (with the possibility to post results), (iii) Approvals (ethics committees and national competent authority if applicable) required for invitation/enrolment of first subject in at least one clinical centre.	12	*Covered above*

Ethics requirements & deliverables (II)

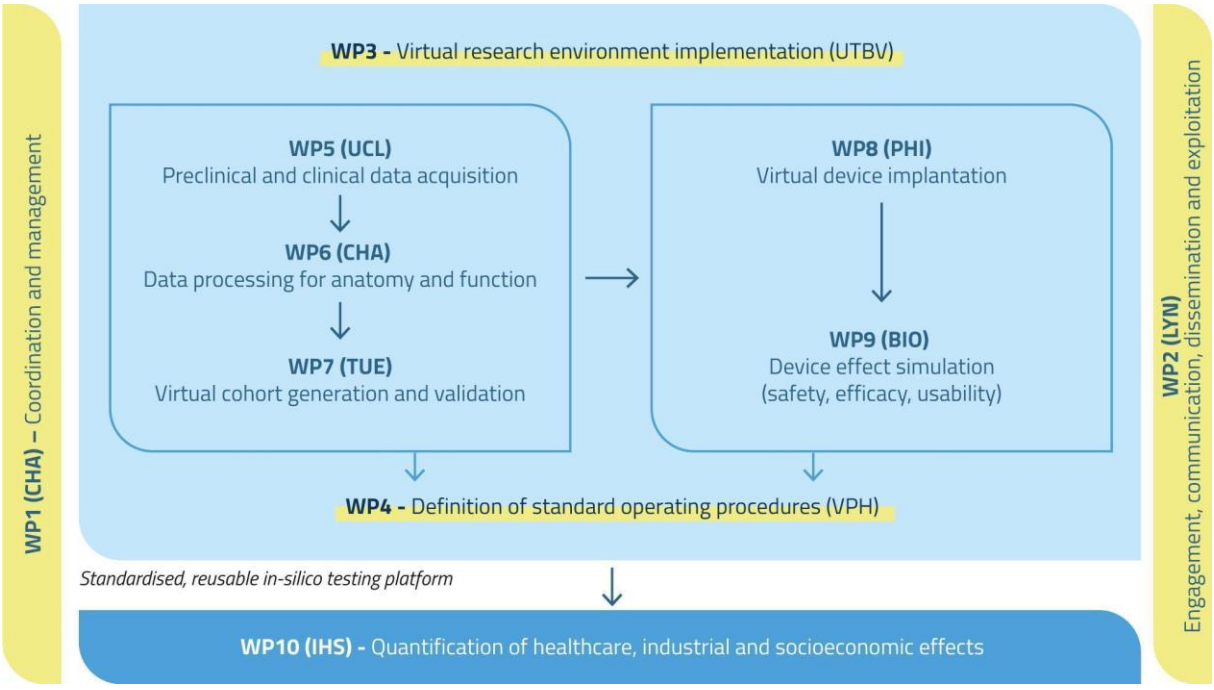
			Ethics requirements	Due Month	Addressed in
A	3	5.1.	Copies of relevant authorisations for animal experiments (covering also the work with genetically modified animals, if applicable) must be kept on file.	4	**D5.2 (M3); D5.7 (M6)**
		5.2.	General information on the nature of the experiments, and the procedures to ensure animal welfare and adherence to the Three Rs principle must be kept on file.	4	**D5.2 (M3)**
		5.3.	If applicable, copies of training certificates/personal licenses of the staff involved in animal experiments must be kept on file.	4	**D5.2 (M3)**
POPD	4	4.6	A description of the technical and organisational measures that will be implemented to safeguard the rights and freedoms of the data subjects/research participants must be submitted as a deliverable.	9	**D1.8 (M4) & D1.9 (M9)**
		4.10	In case personal data are transferred from a non-EU country to the EU (or another third state), confirmation that such transfers comply with the laws of the country in which the data was collected must be submitted as a deliverable.	9	**D1.8 (M4) & D1.9 (M9)**
		4.11	Detailed information on the informed consent procedures in regard to data processing must be kept on file.	9	**D1.8 (M4) & D1.9 (M9)**
		4.12	Templates of the informed consent forms and information sheets (in language and terms intelligible to the participants) must be kept on file.	9	**D1.8 (M4) & D1.9 (M9)**
		4.16	The beneficiary must evaluate the ethics risks related to the data processing activities of the project. This includes also an opinion if data protection impact assessment should be conducted under art.35 General Data Protection Regulation 2016/679. The risk evaluation and the opinion must be submitted as a deliverable.	9	**D1.8 (M4); D1.9 (M9)**
POPD	5	4.1	The beneficiary must check if special derogations pertaining to the rights of data subjects or the processing of genetic, biometric and/or health data have been established under the national legislation of the country where the research takes place and submit a declaration of compliance with respective national legal framework(s).	4	**D1.8 (M4)**

Work package overview presentations: key items and priorities

Workplan and work packages

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

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



WP1 – Coordination and project management (CHA)

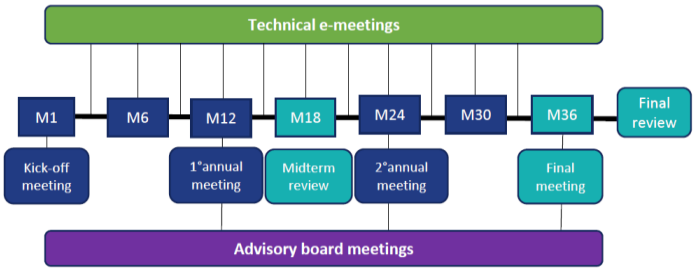
Mirko De Maldè (LYN)

- WP objectives
- Management procedures
- Working groups
- Management and collaboration tools
- Procedures for deliverable presentation
- Financial provisions and pre-financing distribution

Objectives

1. scientific planning and coordination
2. monitoring, reporting and quality control
3. risk management and mitigation
4. administrative and financial management
5. internal communication
6. interface with the European Commission

Management procedures and tools

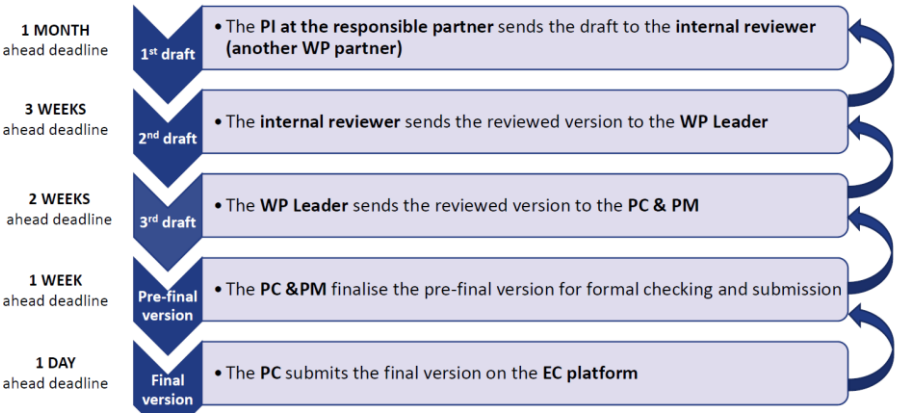


- **Project general meetings**: every 6 months (M6, M12, M18, M24, M30, M36)
  - Doodles for M6 and M12 will be sent shortly
- **Advisory board meetings**: M12, M24, M36
- **Review with EC**: M20 (Midterm review), M38 (Final review)

Working groups

Working group	Members	Meetings schedule	Next meeting
Data management & ethics	**LYN (Lead)**, CHA, UCL (BIO, IIB, TUE, UTBV)	Monthly	W1 of February
Virtual cohorts	**TUE (Lead)**, CHA, BIO, IIB, PHI, TUG	Biweekly	W3 and W4 Jan - 1st TC: Data flow and formats (W1, TUE CHA BIO TUG UCL) - 2nd TC: Data template, models (W2, TUE PHI BIO IIB TUG)
Regulatory issues and SOPs	**VPH (Lead)**, LYN, …	TBD	W3/4 of January
System requirements	**UTBV (Lead)**, CHA, IIB, TUE, UCL	TBD	W3/4 of January

Deliverable preparation and review process



WP2 – Engagement, communication, dissemination and exploitation (LYN)

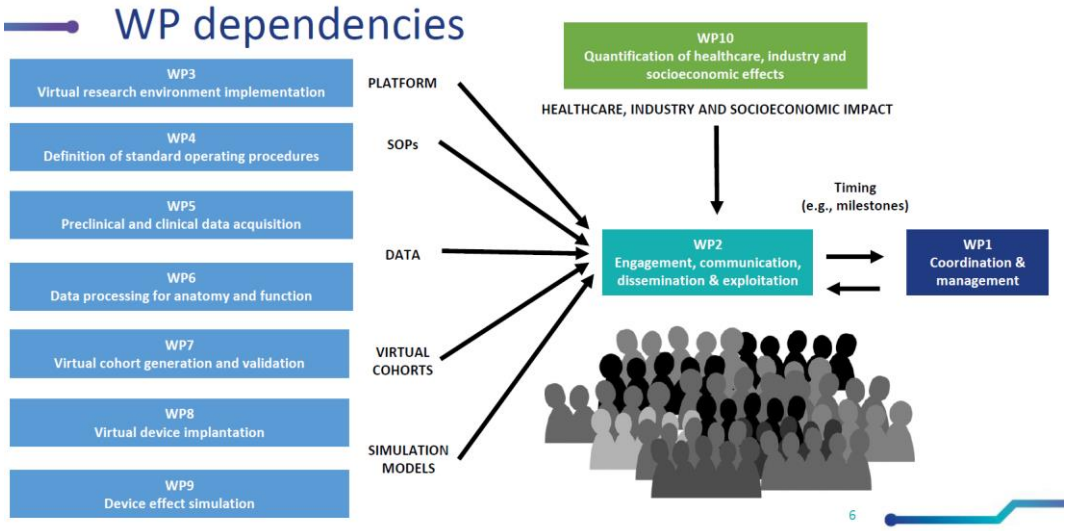
Anna Rizzo (LYN)

- The objectives of WP2 can be summarised as follows:
    1. engage with project-relevant stakeholders, including primary audiences (clinicians, researchers, medical device manufacturers, regulatory authorities) for dissemination and exploitation of results, and secondary audiences (patients, mass media, policy makers and society at large) for broader communication;
    2. disseminate research results to relevant audiences;
    3. communicate to society, enhancing the impact of project results on EU citizens' life;
    4. take the best out of project results with appropriate exploitation and IPR management strategies, for commercial, open science and policy making purposes.
- All these will in turn contribute to our overarching aim of sustaining the integration of in-silico testing solutions in the medical device development, validation and regulatory approval process.

- To fulfil these objectives at best, we expect a close interaction with the other WPs:
    - WP3-8 will contribute by providing project results to be communicated/disseminated/exploited, including the platform itself, data, SOPs, virtual cohorts and simulation models;
    - WP10 will give a fundamental contribution by assessing potential impacts of project outcomes on healthcare, medical device industry/market and society, to be leveraged for dissemination and communication;
    - close coordination with WP1 will be sought for planning of communication, dissemination and exploitation (CDE) activities in alignment with project milestones, phases of implementation and achievements.

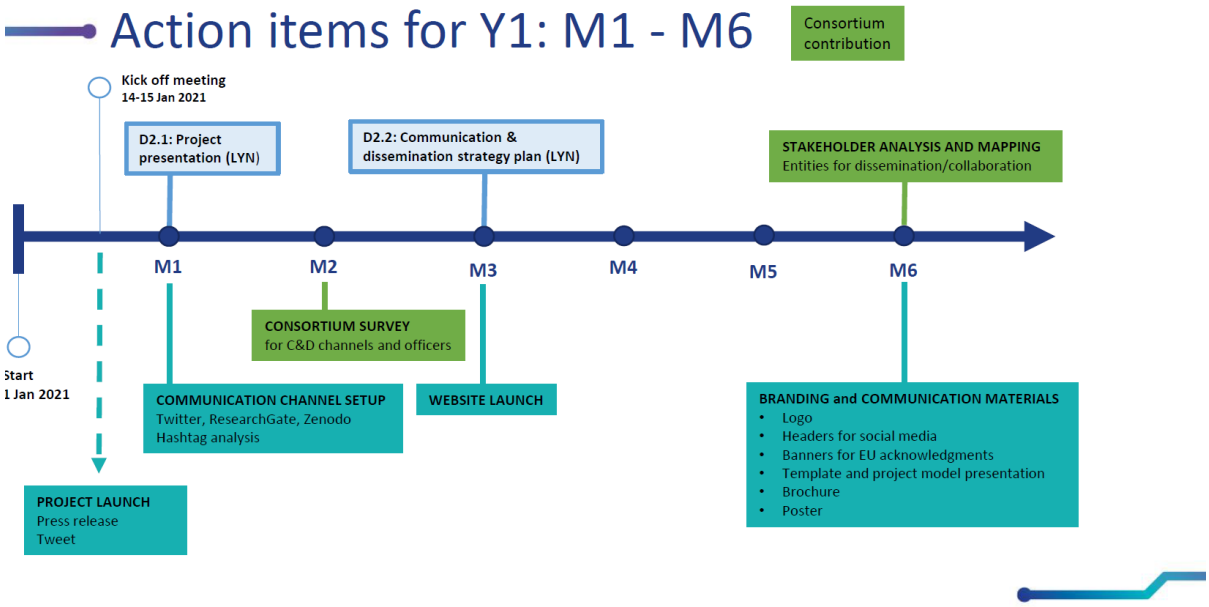
- Partners contribution to the dissemination effort, beside specific tasks (e.g., engagement with regulatory authorities by VPH), shall consist of:
    - Speak about the project with people in your network, and engage with potential contributors for feedback and collaboration;
    - Disseminate results through peer-reviewed or specialised publications, and with public presentations at research and business conferences (please inform the WP2 Leader in advance in order to allow us to properly showcase your publication or public presentation on the project channels);

- Amplify messages: by leveraging the «network effect», support project C&D through your institution or individual channels by:
  - Following project channels (Twitter)
  - Like and re-share updates
  - Post about the project



- Our CDE strategy will be articulated into three phases:
  - Phase I (M1-M12): here we will elaborate the strategy, set up communication channels and prepare materials for communication and dissemination (C&D) throughout the project, start to engage and consolidate our audiences and make a general promotion of project mission, content and objectives.
  - Phase II (M13-M30): during this long phase, we will enlarge and consolidate our audiences, dissemination results through publications and events, and start planning the exploitation and IPR management strategies;
  - Phase III (M31-M36): in the last six months of the project, we will capitalise our efforts to maximise C&D, gather strategic feedback from stakeholders on our technologies and put in place exploitation strategies.

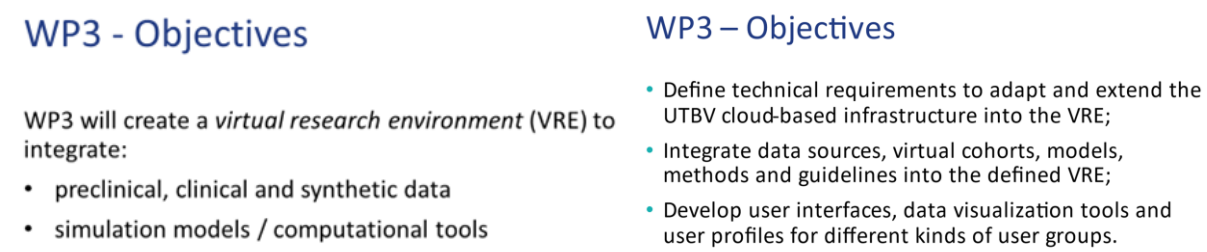
- For the next six months, we envisage the following steps:
  - announce project inception on Twitter and through a press release, to be circulated right after the end of our meeting;
  - by M1, we will setup the project communication channels, including Twitter, ResearchGate and Zenodo and submit D2.1 - Project presentation, a deliverable where we will provide a high-level presentation of the project in its main aspects (rationale, mission, strategic objectives, consortium, implementation phases and envisaged impacts) to serve as base for C&D materials (website, brochures, posters, presentations, etc.);
  - by M2, we will send out a survey to the consortium where we will ask you to indicate your institutional communication channels and press/communication officers, if any, to foster mutual collaboration;
  - by M3, we will submit D2.2 - Communication and dissemination strategy plan and launch our website;
  - by M6, we will complete the analysis of project stakeholders (where we will ask you to contribute with people and institutions in your network) and complete our branding and communication materials, including the logo, headers for social media, banners for acknowledgment of EU funding, presentation template and model presentation, project brochure and general poster.



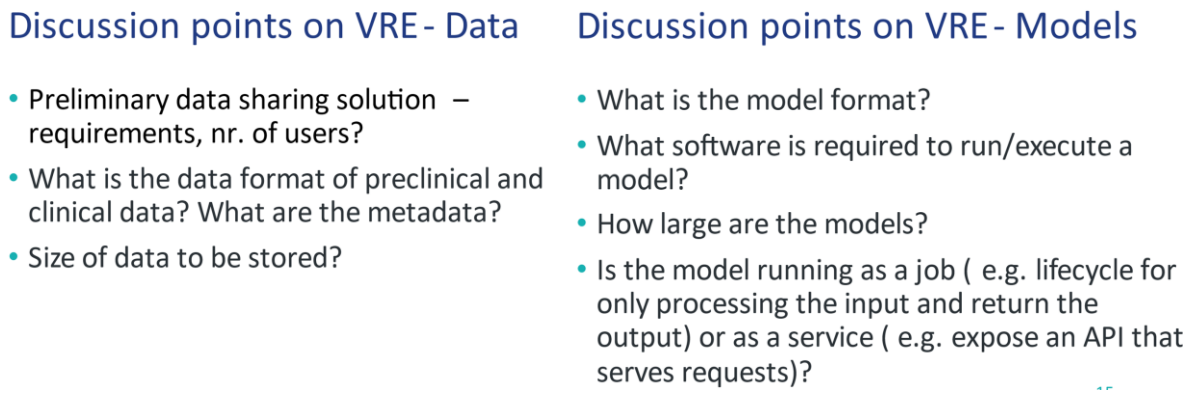
WP3 - Virtual research environment implementation (UTBV)

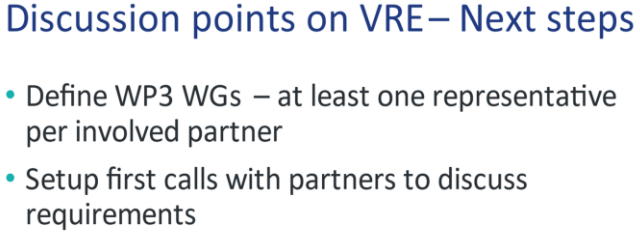
Lucian Itu, Alex Cracanel (UTBV)

- WP activities and objectives are mainly sequential.
- Within the first 6 months the requirements will be defined, so to adapt and extend existing infrastructures.
- The project IT infrastructure is not going to be a public cloud, but it is going to be a cluster where the cloud-based infrastructure will be hosted and where the environment will be virtually deployed.
- After requirements, the focus will be on data, to allow the integration of different types of data and virtual cohorts, and then run models and algorithms and data pre- and post-processing activities.
- The VRE will also have a user interface so that it can be accessed, and there will be different user profiles, with different authorizations; some material will be available based on registration and some material will be available to the open public (to be defined in agreement with the concerned partners).
- Data management plan: this deliverable will be the responsibility of Lynkeus. Close collaboration between UTBV and LYN is expected in this area.

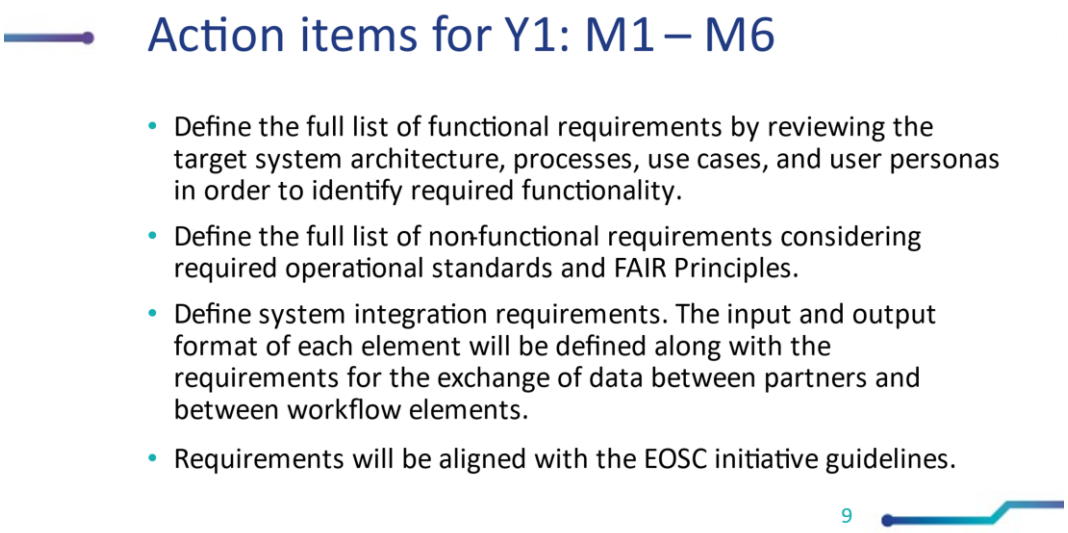


- For deploying this WP, a very close collaboration between partners will be needed (in particular with those responsible for the data, virtual cohorts data and modelling).
- Within the WP, two working groups will be created: one on data and one on simulation and modelling, to properly define requirements and features of the IT system.
- System requirements: defined in nuclear categories, functional and non-functional requirements.





- We have defined the following action items for the months 1 to 6:
    - first step: defining the full list of functional requirements by reviewing the target system architecture processes, use cases in order to identify required functionality.
    - second step: defining the full list of non-functional requirements, considering the required operational standards and FAIR principles.
- The next action item is to start defining the system integration:
    - Define of input and output format of each element;
    - requirements for the exchange of data between partners and between workflow elements;
    - alignment with the European Open Science Cloud (EOSC) initiative guidelines.
- Data repository:
    - implementation of extensions to data repository based on platform requirements defined in deliverable 3.1;
    - ensure that SIMCor data will be made available following FAIR principles and the EOSC initiative guidelines; the future research environment infrastructure will fully support the contribution to the EOSC with reusable data tools, methods, guidelines, and standard operating procedures developed.
    - The WP goal is to build a local cloud-based solution where the VRE will be deployed and will operate and fulfil our non-functional requirements like performance, availability, security.



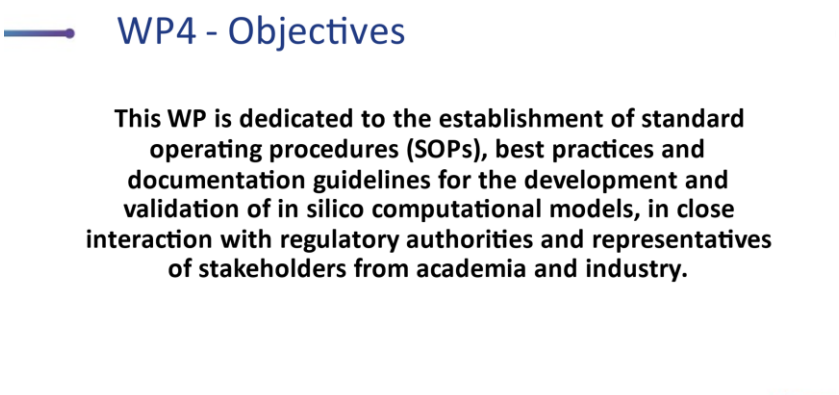
QUESTIONS on WP3

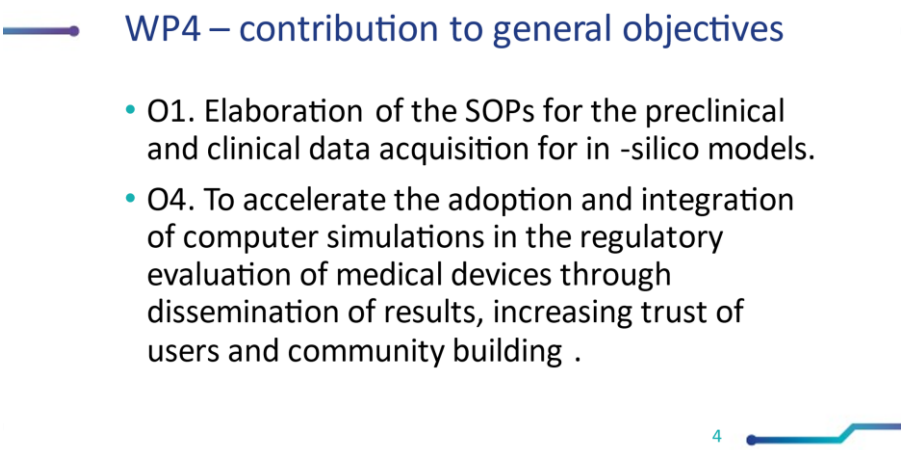
- Q: *we will need to define preliminarily, in the design of this platform, the type of access that the members in the consortium will have, but also any idea regarding potentially opening the platform to outside users?*
  A: there should be three different access types for the users and then for external users, but only based on registration and then completely open to the external user without registration. This will be aligned with the underlying repositories for data and potentially technologies that we want to make public versus restricted versus entirely private.
- Q: *we want to indeed implement FAIR principles in this platform or we may consider to integrate or just reference/loosely connect this platform with other European repositories of the same type.*
  A: this needs to be discussed later on.
- Q: *what is the process or what is the idea for handling metadata (this also opens up a discussion in regard to searchability of both data and technologies inside the platform and how much we want to make the contents accessible).*
  A: there is not a detailed plan on this but this will be discussed as part of the definition of requirements.

WP4 - Definition of standard operating procedures (VPH)

Liesbet Geris (VPH)

- WP4 objective is to:
  - establish the SOPs, best practices and the guidelines, all of the development of validation of these models;
  - interact with regulatory authorities, but also representatives of our stakeholders or fellow academics and industry members;
  - accelerate adoption and integration of computer modeling and simulation for other people by showing how it is supposed to be done.
- VPH is leading the WP but the SOPs related deliverables are assigned to partners that have already developed the work in their respective WPs.

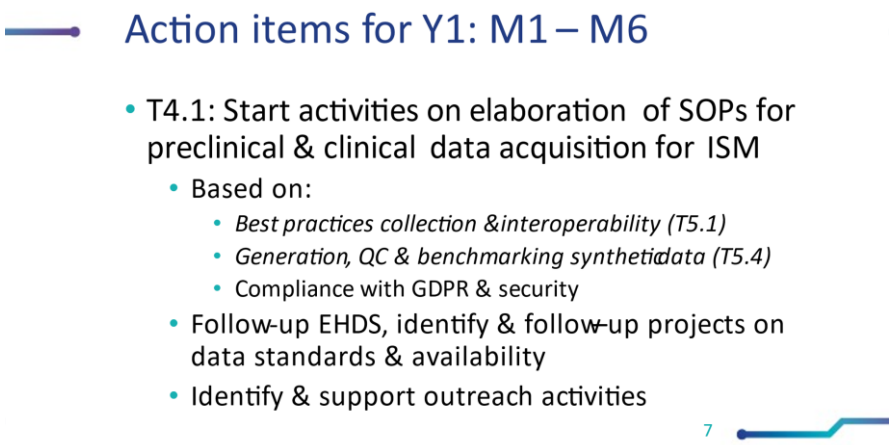


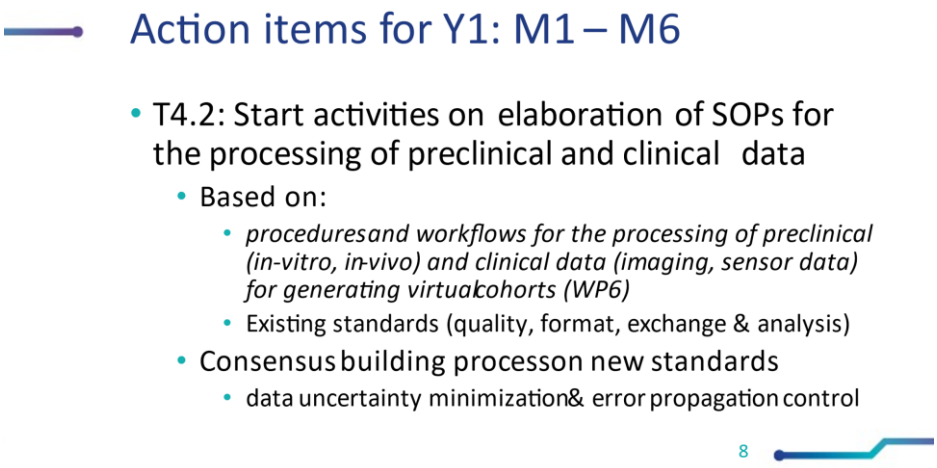


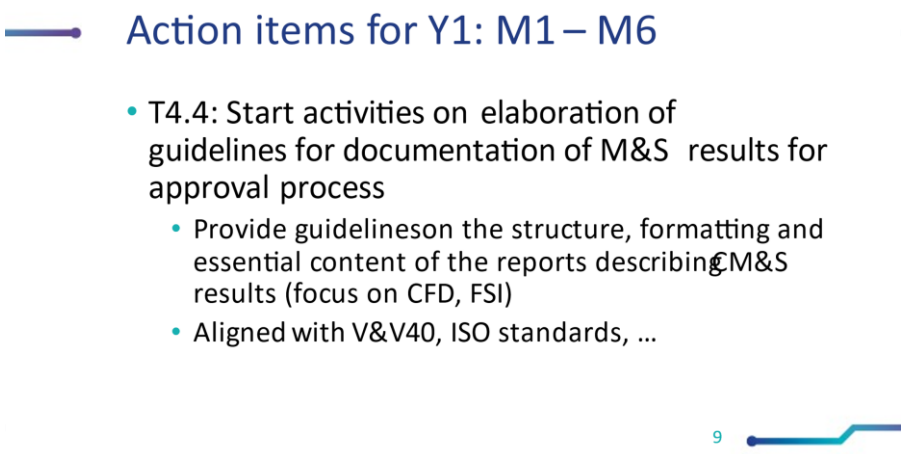
Three action items in the first year:

- the first SOP: preclinical and clinical data acquisition for in silico modelling.
  - This will happen in close cooperation with WP5. GDPR compliance and data security also need to be taken into account.
  - Additionally, in order to build this SOP, we need to:
    - follow up on the European Health Data Space;
    - identify and follow up other projects that have to do with data standards and availability;
    - identify and support specific outreach activities to which we could participate.
- The second task in the WP, also starting in M1, is the elaboration of SOPs for the processing of clinical and preclinical and clinical data, which is completely based on WP6.

    - There are a lot of existing standards on the quality of format exchange and analysis that exists that should be taken into account when writing this SOP.
    - Also in this task: consensus building process on new standards, on data, on certainty minimisation, and error propagation control.
- The third tasks that is starting in M1 is task 4.4., the elaboration of guidelines for documentation of modelling and simulation results from the approval process:
    - we provide guidelines on the SOP on structure formatting and the content of the reports that describe modelling and simulation, when you want to include it, in a regulatory submission;
    - the focus will be mostly on safety and fluid-structure interaction, and of course, these all need to be aligned with existing standards, like the and whatever there is available in terms of ISO standards.
- Additionally, in Y1 also the task on the elaboration of the SOP is for in-silico modeling development, verification and validation will start, using input from WPs 7, 8, and 9.







- We will participate in the data collection and processing WG and in the virtual cohort WG.

- Immediate next steps:
  - define the infrastructure to collect and share documents and data (UTBV);
  - set a meeting for WP for defining a template for the SOPs in general, in cooperation with all partners responsible for each SOPs development;
  - meeting or interacting with regulatory organizations: bringing together all partners that have interactions with regulatory agencies and standards bodies, to just keep each other informed that we are not asking the same questions to the same organizations.

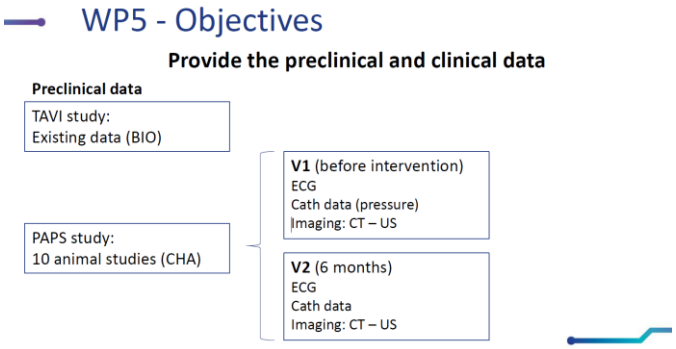
Question on WP4

- Q: *how do we interact with the relevant regulatory bodies? What is the process?*
- A: there is no way to have these institutions to endorse our SOPs. SOPs can be discussed with regulators and could become guidelines for academia and industry. SOPs are not standard by themselves. If you want them to be recognised as standards (e.g., ISO) we would need to follow the relevant procedures.
  - A possibility is to draft a white paper and involve regulatory bodies in the discussion.
  - Such a white paper could become a KPI for exploitation.
  - We could also start exploring and interacting with relevant bodies through the Avicenna Alliance.
  - Action items – for the interaction with the project AB members:
    - Liesbet to interact with Tina to check her availability;
    - other people might be involved in the board using contacts from other partners interacting with other regulatory bodies.

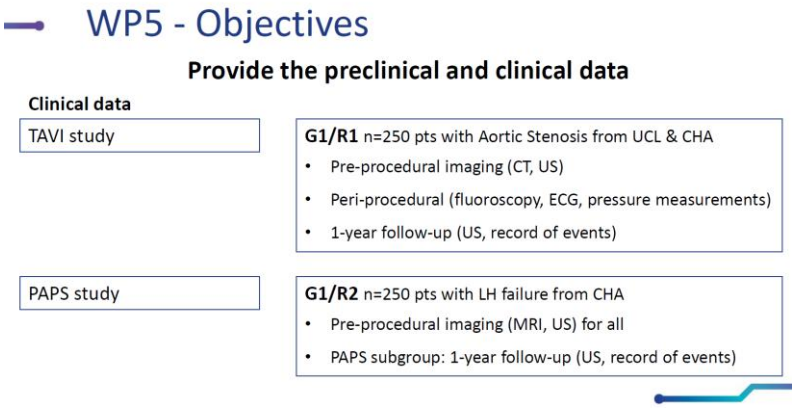
WP5 - Preclinical and clinical data acquisition (UCL)

Claudio Capelli (UCL)

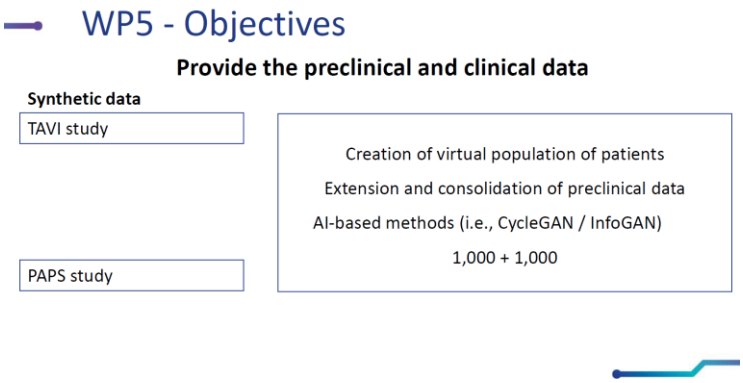
- The main objective of WP5 is to provide the preclinical and clinical data.
- Data collected here will be used by several other WPs.
- The WP will deal with two-three kinds of data.
- Preclinical data for the TAVI study:
    - we are going to engage with Biotronik (BIO) to acquire the existing preclinical data on TAVI and PAPS;
    - preclinical data will be collected through animal studies;
    - data will be acquired at two timepoints: one before the intervention, with the acquisition of ECG Cath data and imaging, CT and ultrasound; and time two, 6 months after the intervention with ECG and imaging data.



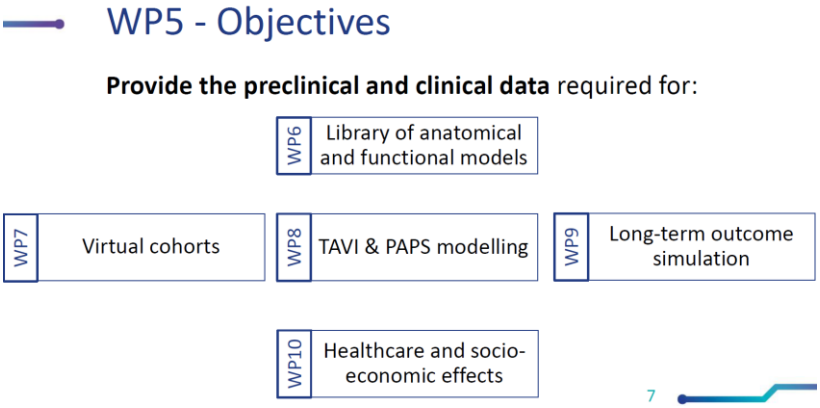
- In terms of clinical data, the plan is to acquire 250 data sets of patients referred with aortic stenosis who underwent the implantation of a device.
    - These are all retrospective data or which patients provided consent for using their data for research.
    - We do not need to recruit new patients for these parts of the study, and we will acquire data from a retrospective database including the pre-procedure with imaging, data, ultrasound and computer tomography.
    - We will have information about the procedure itself, including image data from the cath lab, ECG and pressure measurements, and obviously the device used. In addition to that, we also have a one year follow-up data, controls with sound and record of events. Once more, these are all data which are routinely acquired.
    - For the PAPs study, the plan is to acquire a dataset from 250 patients referred with left *heart failure* (HF) and the indication for the PAPS implantation. This kind of data will mainly come from CHA, as the Great Ormond Street Hospital (GOSH) does not perform this procedure.
    - GOSH can contribute with *magnetic resonance imaging* (MRI) and ultrasound data.
    - For patients who underwent a biopsy, there will be a subgroup with a one-year follow-up data.



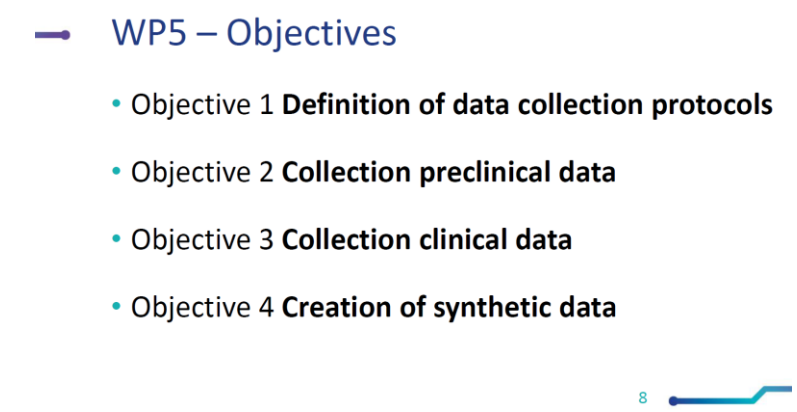
- The third category will be the synthetic data (i.e., the creation of a population of patients, with the aim of extending the clinical data available). The target is creating a dataset of 2000 synthetic patients.



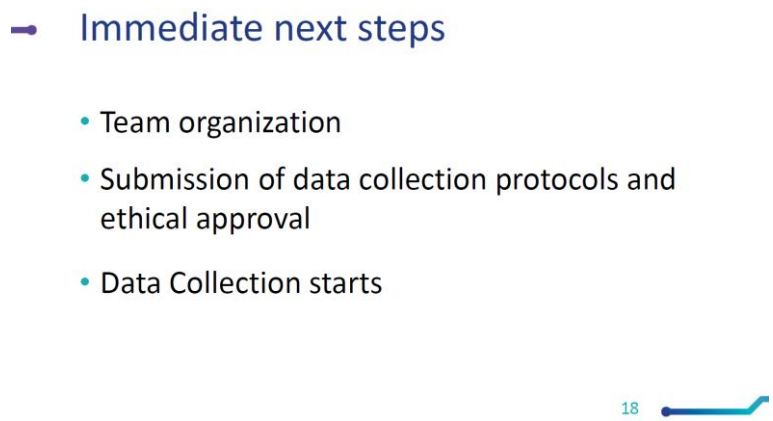
- Cooperation with other WPs: this WP will strongly cooperate with WP6 for the creation of library and anatomic and functional models, and then with WP7, 8 and 9 for creation and validation of useful cohorts and modelling.



- Objectives and activities:
  - we need to define the data collection protocols; this has been anticipated to M3 and is the first milestone for the project;
  - task 5.2 is collection of retrospective and acquisition of prospective preclinical data for many more studies; these cases will be deleted, and these will be completed by M18 with the completion of the animal study report;
  - task 5.3 is related to the collection and organisation or retrospective clinical data; two deliverables are related to this task, the TAVI one will be completed by M16.
- We aim to complete our activities by M18. For this reason, we have quite a busy start, the first 6 months in particular, the priority will be related to defining the protocol for data collection processing and management specifications and getting ethical clearance for starting the collection.
- In the second half of the year, we will focus on the definition of virtual cohorts, in cooperation with TUE. We aim to reach 60% of the data collection completed by Y1.



- Immediate next steps: organize the work to submit data collection protocol and obtain ethical approval.



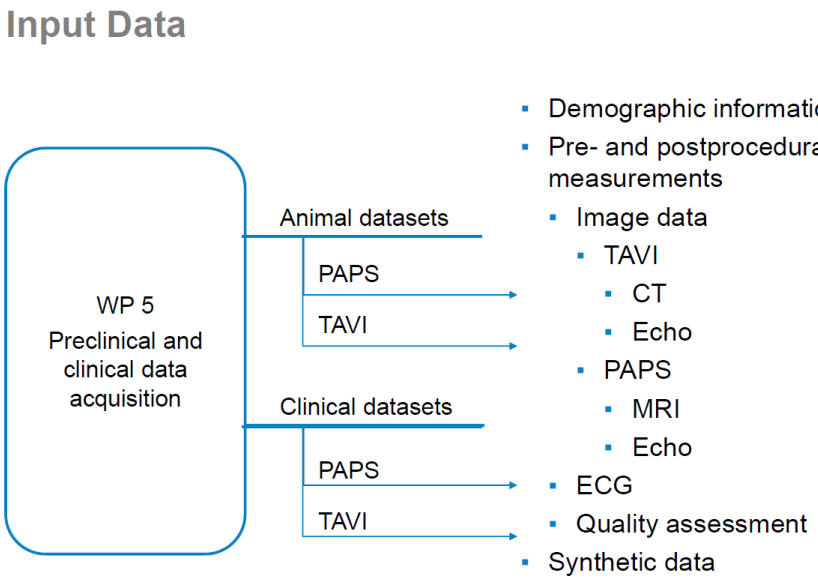
QUESTIONS on WP5

- Q: *do SOPs exist already for secondary use of routine clinical data in clinical trials? And for generating virtual cohorts?*
- A: secondary use for clinical trials, standard procedure is checking with the local/national committee responsible for regulating this scenario (differences among UK and Germany can be encountered). As far as virtual cohorts are concerned, there is no SOP available, also because there is not complete consensus over what a virtual cohort is.
- Comment: we should in any case define a protocol for both scenarios, allow a comparison with standard processes to collect data and clinical trials, allowing a comparison in terms of cost benefit analysis. Also, it would be important to assess early in the process which kind of data are really needed for the models, so to avoid collecting unnecessary datasets.

WP6 - Data processing for anatomy and function (CHA

Anja Hennemuth (CHA)

- WP6 is about data processing for the anatomical and functional model.
- The WP depends on the input of WP5 and generally output towards the virtual cohorts generation (WP7), as well as to the direct testing of the device implantation (WP8-WP9).
- Several types of data will feed this WP5, as illustrated below.



- Possible issues with the re-use of available data sets from previous projects: depending on the context in which data has been acquired, we have different labels and formats and in the coverage.
- major tasks: to define how to deal with the different types of inputs and how to characterize the data to not transfer input uncertainty also in the models.

Source Dataset/ project name (clinical trial number)	Type Cath: cardiac catheterization laboratory, CO: clinical outcomes, CT: computed tomography, ECG: electrocardiogram, Echo: echocardiogram, MR: magnetic resonance, VRD: valve related dysfunction	Size	Focus	Usage
G1. CLINICAL DATA from hospital repositories (CHA, UCL)				
Group R1: AVD, undergoing TAVI (2014–2020)	Retrospective data collected before TAVI (Cath, CT, Echo, ECG)1 and 1-year follow up (Echo, ECG) and 10% controls. Any event related to TAVI is recorded2	250	AVD	TAVI: VC-generation1, VC-validation2
Group R2: HF, requiring PAPS (2014–2020)	Retrospective data with heart failure and a subgroup before PAPS (CT, Cath, ECG, Echo, MRI)1 and 1- year follow up (Echo, ECG). Any event related to PAPS is recorded2	250	HF	PAPS: VC-generation1, VC-validation2
G2. CLINICAL TRIAL DATA from CHA and UCL research (H2020, 7FP, BMBF)				
SMART (NCT03172338)	Retrospective data (Cath, CT, ECG, Echo, MRI)	60	HF	PAPS VD
EurValve (NCT04068740)	Retrospective data before and after aortic valve replacement (Cath, CT, ECG, Echo, MRI)	120	AVD	TAVI VD
Cardioproof (NCT02591940)	Retrospective data before and after aortic valve replacement (CT, Cath, ECG, Echo, MRI)	120	AVD	TAVI VD
ArtiCardio	Synthetic datasets of aortic stenosis (CT, Cath, ECG, Echo)	1,200	AVD	TAVI VD
G3. TAVI clinical trial data from BIO research				
BIOVALVE (NCT02249000)	Retrospective data (CO, CT, Echo, 30-day efficacy)	86	AVD	TAVI VD
G4. PAPS clinical trial Open Data				
CHAMPION (NCT00531661)	Retrospective data (CO, freedom of device failure, hospitalization rate, freedom from device-related complications)	550	HF	PAPS VD
G5. PRECLINICAL DATA from prospective study (CHA) and previous research (BIO, TUG)				
Prospective acute pig study - PAPS	Invasive tests on implantation procedure (e.g., pull tests), Cath, CT, MRT, Echo, ECG	10	Con	PAPS: VC-validation
Prospective chronic pig study - PAPS	Visit 1: at baseline (pre-intervention) Visit 2: at 6 months follow-up For both: Cath, CT, Echo, ECG	10	Con	PAPS: VC-generation1, VC-validation2
Retrospective acute and chronic animal studies of TAVI project	Visit 1: at baseline (pre-intervention) and peri- implant Visit 2: at explant 1 to 12 months follow-up For both: Cath, CT, Echo, ECG, VRD	10	Con	TAVI: VC-generation1, VC-validation2
Preclinical study from SCATh	Uniaxial extension, biaxial extension and simple shear tests with animal and human tissue	30	AVD, Con	TAVI VD

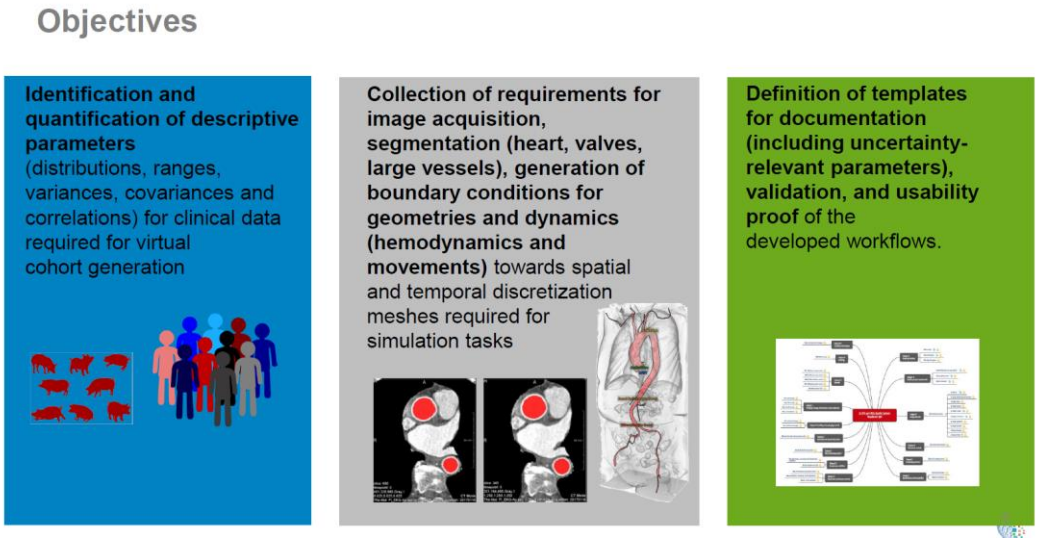
Datasets

Available datasets are processed, but

- Label formats differ
- Coverage of anatomical structures differs
- For some datasets only derived parameters available
- Measurement concepts are different
- Assessment of image properties and resulting parameter uncertainty is missing

WP6 objectives

- Identify and quantitatively describe the parameters of different types of cohorts.
- Collect the requirements for the image acquisition for processing. It is important to carefully assess differences in sampling as this could affect the accuracy of the derived method.
- Definition of templates for documentation (very important, especially for the regulatory aspects), validation and usability proof of the developed workflows.

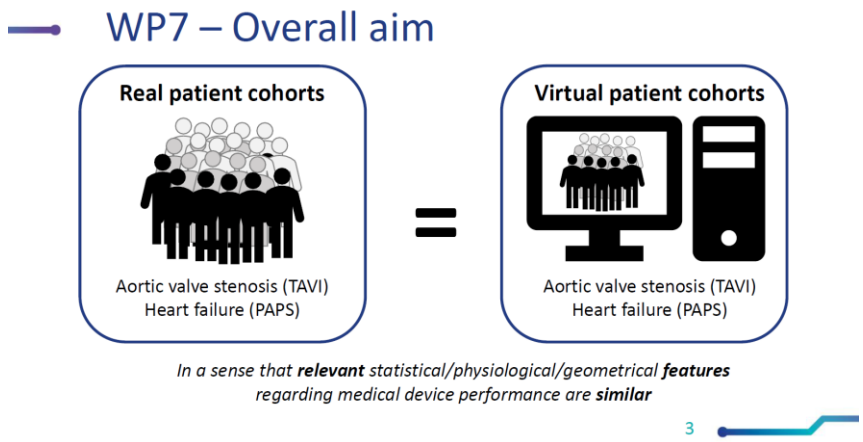


- Important next steps: T6.1 - Processing pipeline and database concept for TAVI and PAPS : meetings need to be organised for defining these aspects properly (file formats, data structure and type, image appropriateness, resolution, artifacts, sampling) image data processing steps to enable an exchange and seamless integration of software modules under development for the virtual cohorts generation.

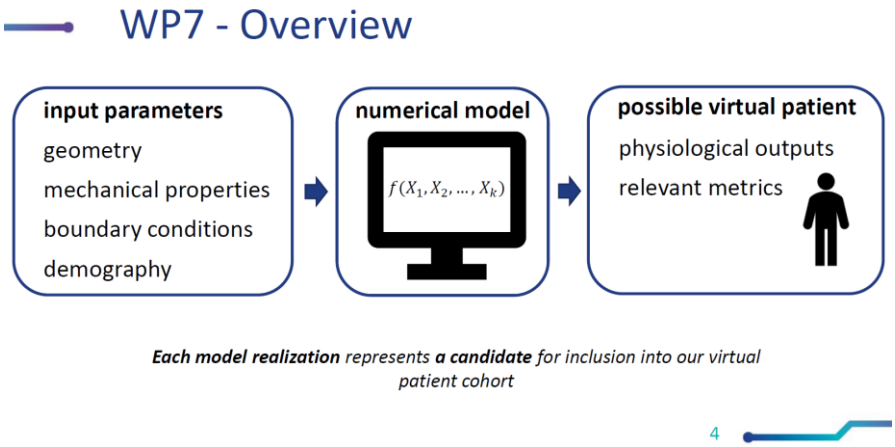
WP7 - Virtual cohort generation and validation (TUE)

Wouter Huberts (TUE)

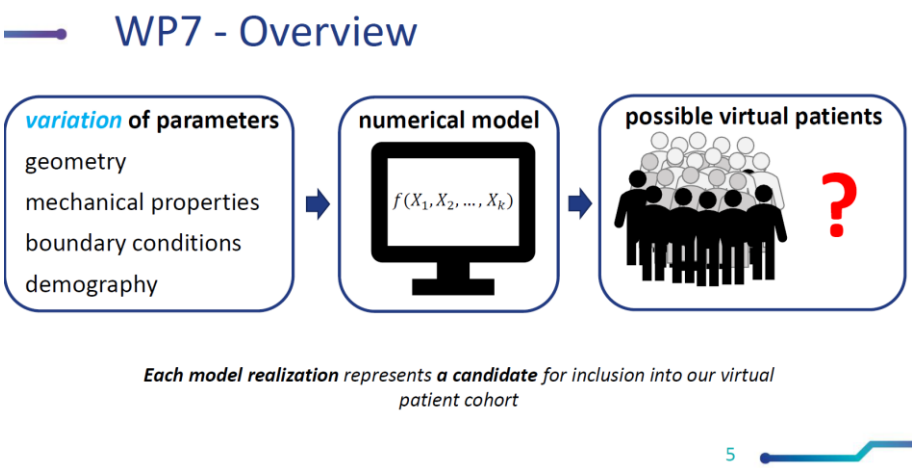
- Objective: find a numerical model, able to simulate a procedure (e.g., TAVI or PAPS) on the basis of geometrical data and mechanical properties, boundary conditions, demographic data, and that is able to simulate a patient, and to represent the physiological output or relevant metrics that we define.



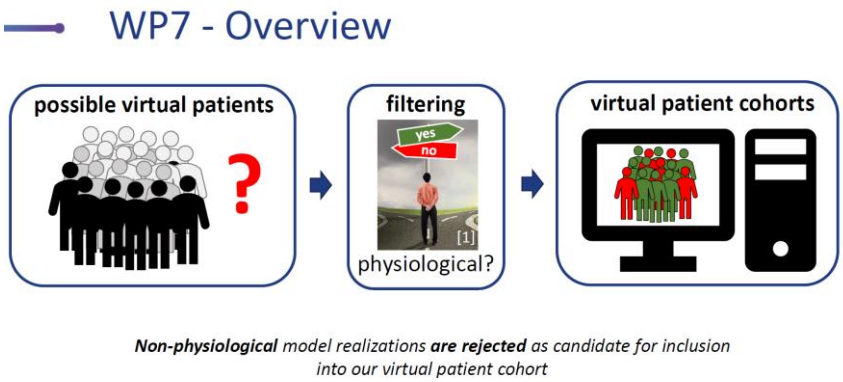
- First, we validate on a patient level, then vary input parameters and be able to generate all kinds of possible virtual patients.



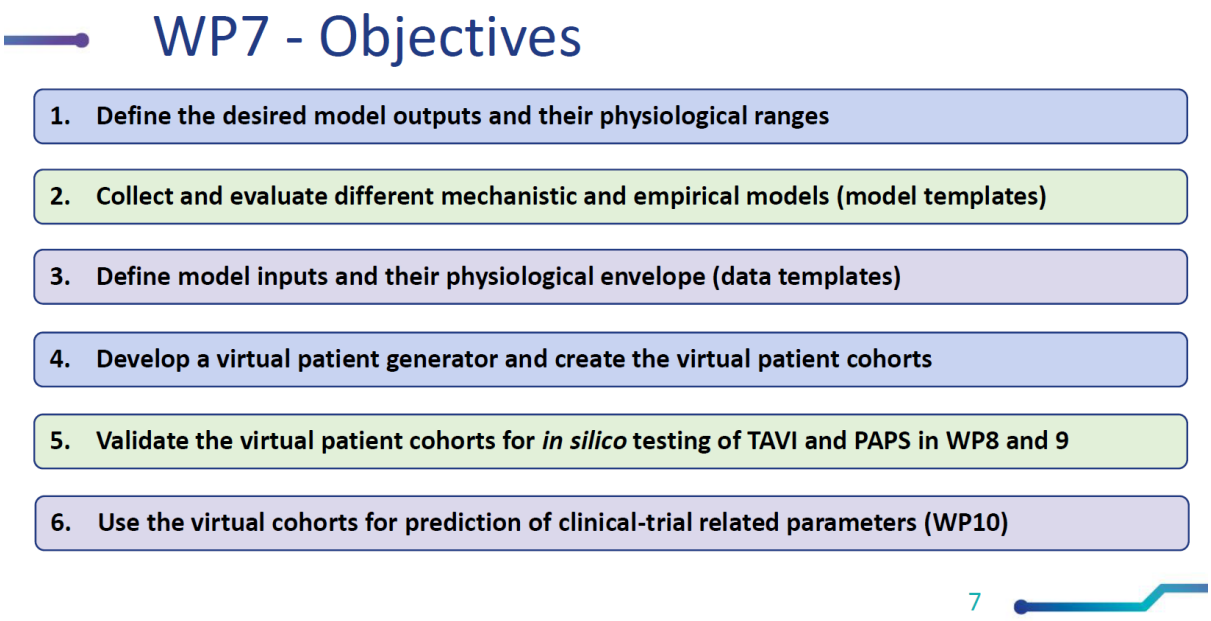
- We sample the input space: all kinds of geometries, mechanical properties, etc., we put it into a model and we get virtual patients.



- Because it is hardly impossible to define all statistical dependencies between model inputs based on the available data, we explore an input space, defined on (marginal) distributions of available data, by sampling randomly and subsequently apply a filtering approach to decide whether the virtual patients are realistic or not. And for doing so, it is important to define realistic output ranges and output criteria. Non-realistic realizations will be then excluded.



- Objectives of the WP

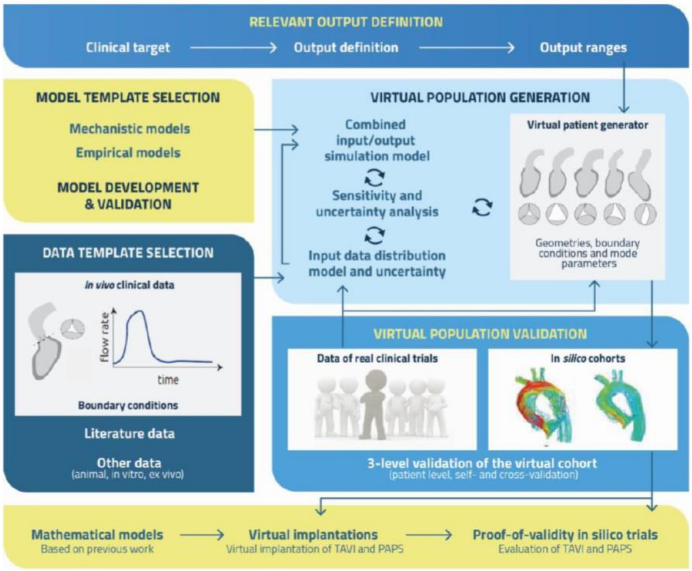


- Interaction with WP5 is very important.
- Interaction with WP3, for making sure to have appropriate resources to run the simulation, as virtual cohorts are not limited to patients but could also be simulations that take time to be executed, thus is important to make sure we have computational resources for running different scenarios.
- The WP will closely cooperate with WP8 and WP9.
- Immediate next step is to launch the virtual cohort working group and start discussing data models, simulation, models available, etc.
    - For defining model outputs, we will use clinical data to define physiological envelopes on the basis of which we will try and derive distributions. This will be done in close cooperation with WP5 and WP6.
    - We also need to find a proper balance between model complexity and the number of inputs, also considering computational constraints and the need of generating several patients (possibly using emulators).

- we need to understand which models are available, through interaction with WP8, and then select the model templates and data templates.
- For data templates, we need to find the physiological envelope of inputs, parameters and boundary conditions for our model. We can also perform a sensitivity analysis, for determining which input factors, assumptions, boundary conditions, measurements, are most relevant for our output of interest. This will help define which kind of data we will need. Here, the cooperation with WP5 and WP6 is crucial.
- Important to interact early with WP3 for benchmarking: virtual cohorts also means in-silico simulation of in vitro tests.
- We also need to define which kind of data we need for the model.

- Finally, the WP will perform validation. Different levels of validation will be considered.
- The whole WP outcome will feed WP9 and WP10.

Wrapping Up



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WP8 - Virtual device implantation (PHI)

Valentina Lavezzo (PHI)

- WP8 focuses on virtual device implantation, and its overall objective is to define a standardised framework for the virtual device implantation of both PAPS and TAVI devices.

WP8 – Overall objective

*This WP is responsible for the elaboration of a **standardized framework** for the **virtual implantation of PAPS and TAVI** on bench test environments, animal and patient cohorts developed in WP7, elaborating a **methodological approach** that will be applicable to other cardiovascular devices and clinical use cases. The results of these approaches will be analysed and compared to provide best practices as input to the SOPs definition of WP4.*

3

WP8 – Objectives

- **Improve and validate robust constitutive models of virtual devices and vessel walls** predicting their deformation during device deployment, as well as the geometrical fit of virtual devices to generic and subject-specific vessel geometries;
- **Implement and verify the constitutive models into a finite element environment** to perform virtual device implantation;
- **Formulate model reduction strategies to improve computational performance whilst maintaining the predictive power of the modelling approach**: in particular, we will develop and validate a separate physically-based approach for modelling vessel deformation at virtual device deployment, less computationally demanding and simpler to parameterize, enabling to process entire virtual cohorts in a highly automated fashion;
- **Perform *iso geometrical* and *immerso-geometric analysis* (IGA) based methods for advanced discretization and accurate description of devices, vessels and device-vessel interaction during deployment**: in particular, these discretization techniques will improve the geometric versatility of patient-specific models and ensure high-fidelity simulations, required to accurately calculate vessel critical strain values of device deployment in large-scale clinical applications

4

Action items for Y1: M1 – M6

- Review, update and refine CAD and FE models for PAPS and TAVI
- Review existing CAD models and FE models for PAPS
- Model sensor housing and tissuediaphragm interaction for PAPS
- Refine models for fixation for PAPS
- Develop CAD models and FE models for TAVI
- Set up experiments to be used as input for simplified vessel geometry
- Initiate ethical and privacy assessments for geometry and patient data exchanges

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- Dependencies: WP7 is important for providing the input for the models.
- The immediate next step is to organise a WP meeting to define how to proceed.

Immediate next steps

- Organize WP8 meeting to define:
  - Way of working
  - Common tools (if possible)
  - Data sharing
  - Etc.
- Initiate work according to action items

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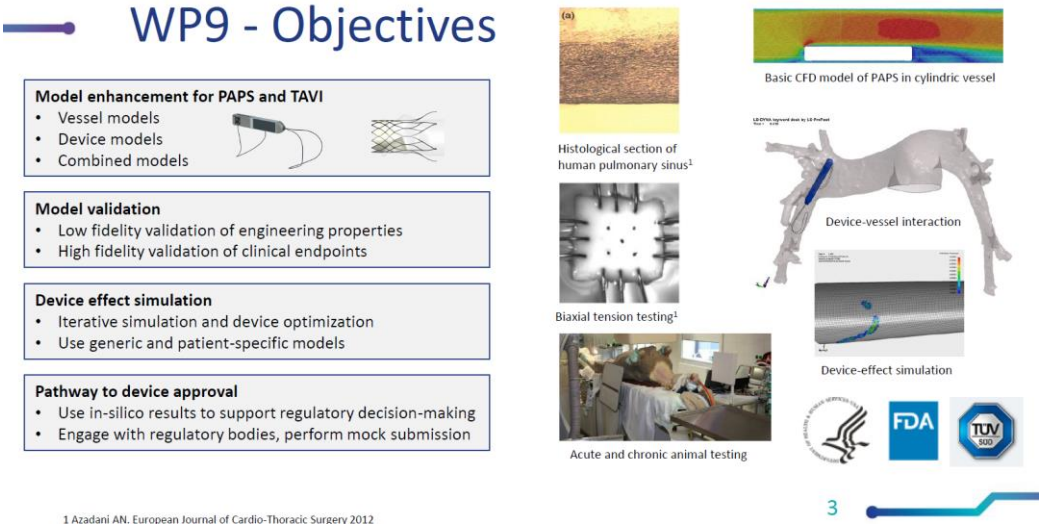
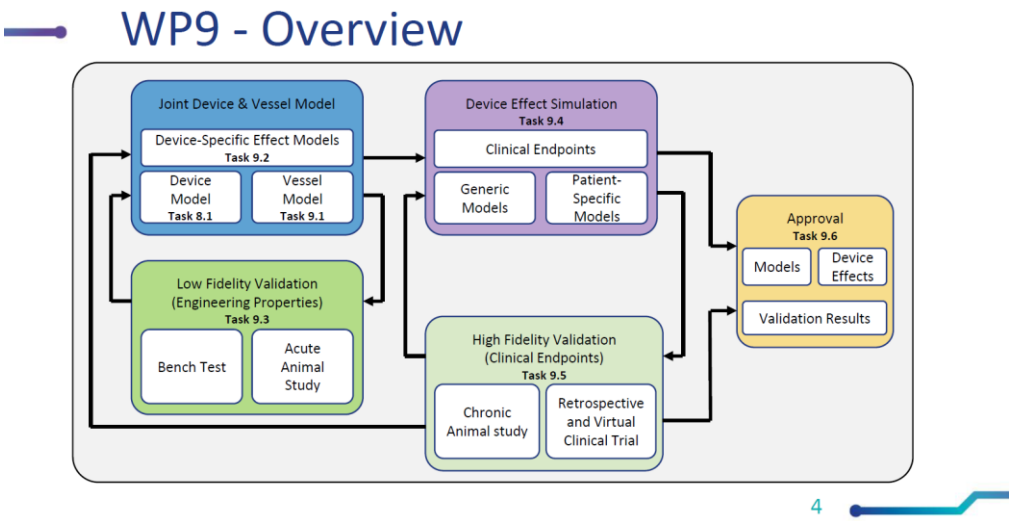
WP9 - Device effect simulation (BIO)

Andreas Arndt (BIO)

- WP9 focuses on device effect simulations for both PAPS and TAVI devices.
- WP9 comprises tasks of model enhancement. These include vessel models and device models, and we will combine these models.
- WP8 will feed WP9 with models and we will also use pre-existing models.
- WP9 will also perform validation, including low-fidelity validation of engineering properties and high-fidelity validation of clinical end points.
- Once the models are developed and validated, we can use the models to perform device effect simulations.
- This is being done iteratively to optimise the device design, and for that, we use generic as well as patient specific models we receive from WPs 5, 6, and 7.
- Finally, we will develop a framework for device approval using the in silico results, to support clinical decision making.

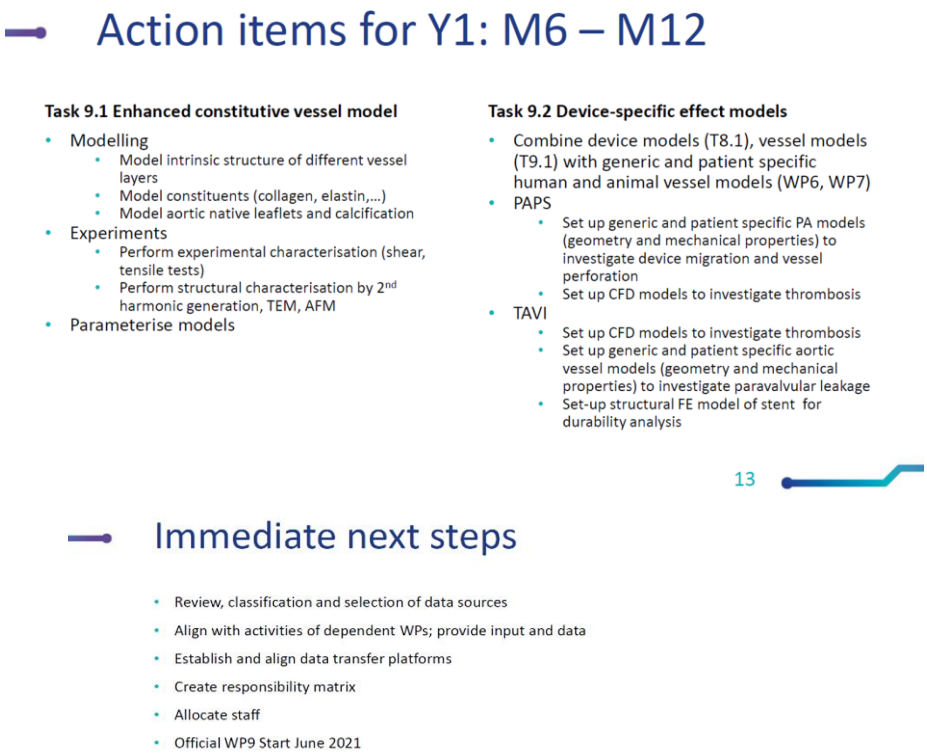


- We will engage with regulators and we will use the vehicle of a mock submission. The structure of the WP is shown below.



- In the blue box, we have a couple of modelling tasks. WP9 will leverage a device model developed in WP8 and combine it with an enhanced vessel model developed in T9.1, based on results from WP8. The combined model will be further developed in T9.2 to include device specific effect models.
- Once we have these models, we can subject them to a low fidelity validation step in Task 9.3.

- Once these models are developed and validated, we can use them to perform the device effects simulation in Task 9.4. Here, we address the clinical endpoints with generic models and patient-specific models.
- The outputs of these model simulations will be subjected to a high fidelity validation step where we address the clinical endpoints.



- Responsibilities:
  - Biotronik is leading the WP and will closely collaborate with IIB.
  - Both will develop implant models for device effect simulations, and perform validation steps.
  - TUG will provide the vessel models.
  - CHA will provide subject-specific human and animal data sets. CHA will perform hemodynamic model validation and conduct preclinical studies.
  - UTBV will provide a cloud-based data infrastructure.
  - PHI will provide us with reduced order models.

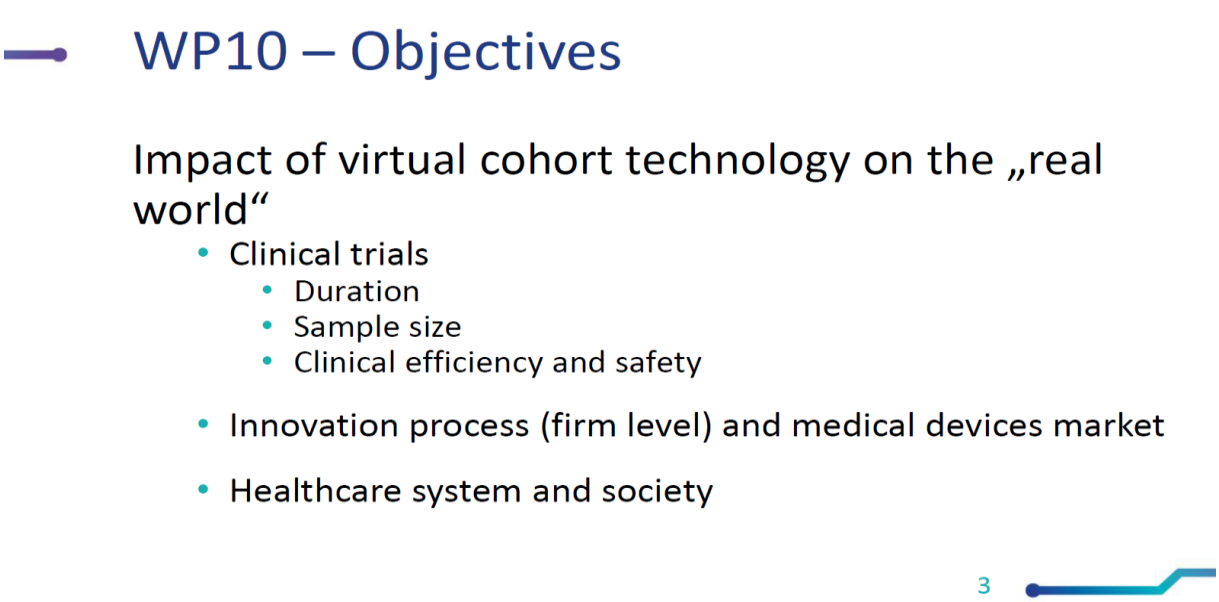
- Dependencies between the different WPs:
  - WP5, 6, 7, and 8 as input to WP9.
  - From WP5-WP7 we will receive clinical and preclinical data, both prospective and retrospective data, in different stages of processing.
  - WP8 will develop device and vessels models, which will then be further developed in WP9.
  - WP9 will deliver input to WP4, which is the definition of SOPs, and to WP10, to assess the impact on the device industry and the market.

- Issues to be addressed:
  - Some of the domains addressed by the model implementation are well understood (e.g., computational fluid dynamics) but there are other properties which are quite more difficult to validate with bench tests, for example the vessel perforation (for which no good models are available).
  - We need to develop very good models and then transfer them in a proper bench test.
  - We need to understand how far we can validate our models.
  - Perforation could be interesting to investigate also in terms of device safety – for patient safety and regulatory adaptation.

WP10 - Quantification of healthcare, industry and socioeconomic effects (IHS)

Thomas Czypionka (IHS), Christian Ohmann (ECRIN)

- **Objectives**



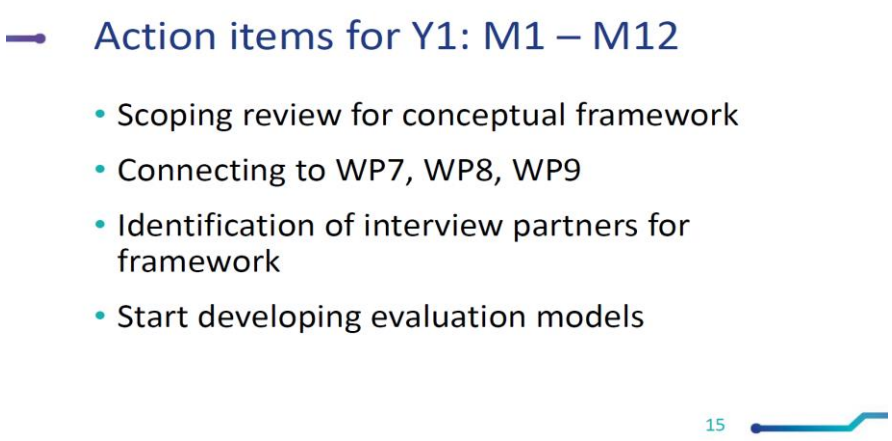
1) develop a conceptual framework to model effects of computer simulation for medical device testing on clinical trial planning;

2) based on that framework, assess the clinical impact of in-silico trials and estimate benefit allowed by in-silico device trials technologies in several outcome dimensions (e.g., quantify the reduction in the duration and sample size of clinical human trials but also the impact on animal studies, increased clinical efficacy and safety for patients via reduction of adverse events);

3) develop a conceptual framework of how the technology of virtual cohorts can influence healthcare and medical devices market – what does it mean for the firm level, the market level as well as the healthcare system and wider society;

4) Impact assessment based on the conceptual framework (enriching the framework with empirical data, describe and quantify impacts for the stakeholders) in order to perform an overall health policy assessment, upon which to develop recommendations for regulators and policy makers.

- **Action items for Y1**



Partners contribution and dependencies:

- Provide real-world data;
- Feedback on the models and the assessments;
- WP7-WP8 and WP9 will provide input for this WP;
- **Issue:** according to the Grant Agreement, D10.1 - In-silico trial impact assessment framework, is due at M12; however, the relevant task (T10.1) is starting at M13 (timeframe M13-M24); to realign the two, ECRIN will start the task at M1 and conclude it at M12, together with D10.1 submission.
- **Immediate ACTION item:** it is important that once all parameters to be inputted in the models are defined, concerned partners make the effort to provide at least rough estimation of the relevant data for assessing relevant economic weight and subsequently the impact of the project innovations. We need to discuss as soon as possible the parameters and whether we might end up getting no data at all on any of those.

Discussion sessions – DAY 2

Data management and ethics WG

Lead: Ludovica Durst (LYN)

- **Objectives:**
  - to define data collection, processing and management protocols and relevant regulatory issues;
  - prepare and submit documentation for ethical approval by ethical committees by M6.

- SIMCor utilises mainly two kinds of data sources, human retrospective data, both existing and new clinical records, as well as animal prospective and retrospective data sources.

- **Ethical clearance and consent:**
  - for existing data, we already obtained consent and ethical clearance, and only secondary analysis will be performed. So not specific ethical clearance is required. However, we need to have it certified by relevant committees to the European Commission;
  - for new data:
    - preclinical studies: ethical clearance is needed;
    - clinical routine data: no ethical clearance needed for the project-specific research usage purposes.

- **Relevant deliverables**
  - M3, two deliverables
    - D5.1 - Clinical data collection protocol (CHA), which is needed to describe methodology criteria, procedures, and documents for human data collection. It will include all the procedures and documents, informed consent and copies of a documentation obtained from ethical committees for ethical clearance;
    - D5.2 - Animal study protocol, regarding description of the methodology and procedures related to animal studies; it will include all information related to animal studies, such as justification of animal use, details of experimental design methodology, measures for animal welfare and copies of certificates of licenses of operators, a well as authorisation from ethical committees.
  - M4
    - D6.1 - Specification of data processing requirements, a protocol specifying the imaging modality settings for TAVI and PAPS;
    - D1.8/1.9 (M4-M9) ethical and legal compliance assessment, which means to analyse all ethical and legal issues relevant to the collection and processing of personal data.

- **Current status:**
  - CHA and UCL already contacted and activated their ethics committees, which confirmed that no approval is needed for reuse of existing data. These committees will provide a waiver of approval, although we still need to identify who will provide such a document.
  - For animal studies we are waiting for CHA to get the approval, with the support of Biotronik. An updated protocol on the basis of the one available at BIO should be submitted soon.

- **Data processing:**
  - processing is referred to personal data sets which are available for secondary usage, and that will be de identified at the source (i.e., in the clinical centers by local data controllers prior to sharing), external parties will be able to locally process the private data through anonymisation, perturbation or other measures, and send the transform data to the cloud, as input for the algorithms;
  - we are expected to contribute to the EOSC;
  - hopefully we will allow users a quite wide open access, which means public available with no registration needed;
  - we'll also use more controlled forms of access (upon registration or for authorized users).

- ***Data management plan*** **(DMP):**
  - It will describe how data will be acquired, processed and stored, in compliance with both privacy and security obligations, along with technical and organizational measures, that will be implemented to safeguard the rights and the freedoms of data subjects and research participants;
  - this will be carried on in a tight connection with the ethical and legal compliance assessment, but focusing mainly on data protection policy, which means also on security measures to prevent unauthorised access on purpose limitation, according to the minimisation principles and other relevant principles set forth in the GDPR with the identification techniques and data transfers procedures, as well as on synthetic data generation processes and measures adopted to prevent the identification attribute disclosure;
  - the DMP will be a living document, which will evolve and be updated over the course of the project.

- **Questions**
  - *Do we need to put in place data transfer agreements / data usage agreements?*
  - A: it should be discussed.
    - the consortium as a whole should not find itself liable for inappropriate data sharing processes;
    - For what concerns project partners, as data controllers they already have all procedures in place for data pre-processing and sharing (with data already de-identified, although it might be useful to discuss the de-identification procedures in place). In a way, the consortium relies on the fact that the procedures at these clinical centres are robust and reliable.
    - For what concerns future contribution of data by new partners (joining the platform at a later stage), some sort of data sharing agreement should be put in place, in particular to certify that appropriate de-identification procedures have been put in place. This should be discussed in the WG.

System requirements WG

Lead: Lucian Itu (UTBV)

- A preliminary data sharing solution will be available before the release of the VRE.

- Two main functionalities:
  - Sharing of data (pre-clinical or synthetic) and data for SOPs;
  - Support in running the simulation models / computational models;
  - Additionally, data repository and collaboration features will be offered.

- Complex models will be run locally in the different responsible partners internal environments. Reduced-order models will be run on the VRE environments, where models will be also shared among partners and saving them. On the platform, it will also be possible to run small simulations.
- The VRE is not including high performance computing clusters on the VRE. Graphics processing units (GPUs) will be available but that might not be sufficient for running particularly complex models.

- **Action items:**
  - We need to identify requirements for different use cases (e.g., data, virtual cohorts, models);
  - Provide a data sharing solution;
  - Understand potential data sharing issues in terms of GDPR compliance;
  - Define accesses and users per partners to the VRE.

Virtual Cohorts WG

Lead: Wouter Huberts (TUE)

- As the first step, we need to discuss input data to quantify differences between real and synthetic data:
  - We are going to evaluate some kind of numerical model multiple times;
  - We are going to vary the input parameters;
  - We can start with dummy models, but then we need to put in numbers relevant to models that are simulating TAVI procedures or PAPS, and also at some point we need to put in the data that clinical and representative for the virtual cohorts;
  - for those reasons, we need to have discussions with modelling partners to get insights in regard to the models that we are planning to use.

- Then we need to clarify the model we will use, and then define input parameters for each model, with steps below:
  - Define patient-specific parameters and parameters based on literature and statistics;
  - Understanding the needed data;
  - take into account which of the parameters or assumptions are most important to get some specific realization of the model that we want, as well as some outputs of interest.

- **Action item:** establish a WG with modellers and people dealing with data (from clinical perspectives):
  - Considering that modelling will be initially run in local environments, it makes sense to share the variations of parameters and then perform the simulation on each partner's side.
  - We need to discuss how many simulations are necessary (in the case of lumped elements models, for instance, we can run thousands of simulations easily while in other cases simulation can take days or weeks). Thus we need to discuss a good way to reduce the required number of simulations.
  - The number of simulations that you need to do is related to the number of parameters that we have in the model.
  - where I am aiming to develop an emulator, and so we need only the simulation to train that emulator, and then we can create virtual cohorts and we have input variations.

- **Action item:** share some documentation on the governing equations that are solved by the modelers, and what are the parameters that are in there (a paper can be sufficient), needed for sensitivity analysis and uncertainty quantification.

- Note: it's not necessary to discuss this for all models which will be used in our project. We have two devices and we have for each device, at least, high-fidelity and low-fidelity models, and we can obtain 4 different endpoints. This would allow us to make a selection toward a proof of principle.

- **Action item:** to demonstrate that synthetic data are similar to the real data, what measures are we going to use to quantify the difference between real and synthetic data?
  - Differences in distributions is a way. We will also generate synthetic data in the sense of synthetic geometries, synthetic flow rates, etc., and our experience is that this data is much smoother compared to real data.
  - For distributions, it is much easier: it can be analysis of histograms, cross correlations, correlations between synthetic and real parameters.

    - We need to discuss this in a dedicated meeting.

- **Extra validation step:** in addition to the, let's say 3 step validation already foreseen in WP7, to find an independent set of trial data from TAVI patients for an additional validation.
    - If we split a cohort in a cross-validation process, we keep having data from one environment (e.g., one data set divided in the 3 sets, and then do some kind of cross validation).
    - But if we have a completely independent set for validation, that will make the validation even stronger.

- **Open issue:** what is our ability to extract the needed parameters from the data sources (e.g., geometry data can be extracted, but mechanical properties, not so well). We need to define a process for selecting the parameters. This can be addressed via different approaches but first data and model templates need to be provided.

- **Action items for data templates and model templates:**
    - involve partners responsible for data collection and processing to define various parameters (e.g., data format, type of models, input parameters, and relevant properties) and partners responsible for modelling;
    - organise mailing list and TC;
    - define what kind of models will be used: partners to prepare slides to initially define what kind of model they use and what kind of input and output data they generate;
    - define a template that everyone fills out for models, with an example of the model and inputs and outputs and equations.

Press release

PRESS RELEASE n.1/2021
15/01/2021 (for immediate release)

Horizon 2020 Research and Innovation Action kick-off:
SIMCor (*In-Silico testing and validation of Cardiovascular IMplantable devices*)

Berlin, 15 January 2021

Today, 15 January 2021, the Charité – Universitätsmedizin Berlin has concluded the kick-off e-meeting of the new EU-funded research project SIMCor (*In-Silico testing and validation of Cardiovascular IMplantable devices*). The project will create an in-silico platform and simulation tools for the development, validation and regulatory approval of cardiovascular devices, providing tangible value to patients and clinicians, device manufacturers, clinical researchers, medical authorities and regulatory bodies.

Cardiovascular implantable medical devices are among the most life-sustaining treatments in cardiology. According to the Regulatory Affairs Professionals Society, verification and validation are amongst the most critical activities in the medical development lifecycle. Inadequate validation is one of the most common issues leading to clinical complications, warnings from the US Food and Drug Administration and subsequent device recalls which cost companies tens of millions of dollars. In-silico methodologies for medical device testing and validation and the use of virtual cohorts of animal and human patients represent a clear opportunity for enhancing the quality of medical devices released into the market, increasing their efficacy and safety, meanwhile reducing costs and time-to-market, minimising the need for live testing on animal and human subjects.
However, the complexity and speed of technological innovation strongly demands the establishment of agreed protocols, standards and shared resources between device manufacturers, authorities and regulatory bodies, allowing for a standardised, reliable and integrated use of in-silico methodologies into the entire product cycle of medical device development, validation and regulatory approval.

To address this challenge, SIMCor aims to establish a computational platform for in-silico models development and validation as an open resource for collaborative R&D among cardiovascular device manufacturers, researchers and medical authorities.
SIMCor will specifically focus on two clinically and economically relevant cardiovascular procedures and devices: *transcatheter aortic valve implantation* (TAVI) and *pulmonary artery pressure sensors* (PAPS), having taken into account their large socio-economic impact, the wide range of pathophysiologic conditions and biomechanical parameters involved. SIMCor will also extrapolate best practices for in-silico trials that, through a strict collaboration with regulatory authorities, clinicians and the industry will be translated into *standard operating procedures* (SOPs) for the entire cardiovascular device manufacturing and clinical communities.

SIMCor will define a methodology for the generation of *virtual cohorts* for in-silico tests to lower the burden of preclinical tests in animals, as well as of clinical I-III stage human trials. The virtual

cohort technology will allow exposing new devices to a variety of geometries, pathophysiologic conditions and clinical parameters relevant to both adults and children, to meet the critical need of making new devices usable in young patients.

SIMCor will also elaborate a standardized framework for the virtual implantation of TAVI- and PAPS-devices on bench test environments, animal and patient cohorts, and then generalise the approach for other cardiovascular devices and clinical use cases.
The consortium will also develop device-specific models to predict device performance in terms of safety, efficacy and usability endpoints, utilising simulations of generic and individualised geometries assessing variability, uncertainty and sensitivity against anatomical and pathologic variations beyond current ISO norms.

SIMCor will assess and quantify the impact of virtual cohorts and computer simulations in "real world". SIMCor will evaluate benefits on clinical research workflows, industrial development and business dimensions at large, as well as on societal benefits. Expected value include increased treatment efficacy and patient safety through reduction of device failures and adverse events; more personalized clinical indications and implant strategies; reduced use of animal and human subjects; lower costs and time-to-market for medical device validation and regulatory approval; reduced costs and wider accessibility of device-based treatments; boosting innovation and creation of economic added value.

SIMCor will actively disseminate its results to the medical device industry, researchers, investors, authorities and regulatory bodies, healthcare professionals and patients. The Project Coordinator, Titus Kühne, commented *"We firmly believe that SIMCor will accelerate the adoption of in-silico technologies in the development, validation and approval of new and better cardiovascular devices through the use of computer simulations and virtual trials methodologies."*

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

Consortium structure and participants
The Consortium consists of 12 partners from 8 countries, including clinical centres, academia, industry and small and medium-sized enterprises (SMEs):
Charité – Universitätsmedizin Berlin, Germany
(*Coordinator*) Lynkeus (LYN), Italy
Biotronik (BIO), Germany
European Clinical Research Infrastructure Network (ECRIN), France Institut für Höhere Studien – Institute for Advanced Studies (IHS), Austria Institut für ImplantatTechnologie und Biomaterialien e.V. (IIB), Germany Philips Electronics Netherlands B.V. (PHI), Netherlands
Eindhoven University of Technology (TUE), Netherlands Technical University Graz (TUG), Austria
Universitatea Transilvania Din Braşov (UTBV), Romania University College of London (UCL), United Kingdom

Virtual Physiological Human Institute for Integrative Biomedical Research VZW (VPH), Belgium

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About the coordinating institution: Charité – Universitätsmedizin Berlin

Charité – Universitätsmedizin Berlin is one of the largest university hospitals in Europe. All its clinical care, research and teaching is delivered by physicians and researchers of the highest standards, and it is internationally renowned for its excellence in teaching and training. Charité extends over four campuses, and has close to 100 different Departments and Institutes, which make up a total of 17 different centres. Innovative capacity and responsible governance, for the benefit of patients and society, are the central tenets behind all of Charité research endeavours. At Charité, approximately 3,700 researchers are actively engaged in the development of pioneering innovations in the field of medicine. Committed to the highest standards of quality and sustainability, they work across 1,000 projects, working groups and collaborative projects.

The responsible Institute for Imaging Science and Computational Modelling in Cardiovascular Medicine (ICM) is the innovation driver in the field of digital transformation in cardiac medicine in Berlin. The institute combines modern imaging methods with data science methods (e.g., AI, visual analysis) and biophysical modelling (e.g., haemodynamics, metabolism) to develop methods for diagnostics, therapy planning and decision support systems. The work is therefore always in a direct clinical context (bench-to-bedside) and unites interdisciplinary teams of physicians, mathematicians, computer scientists, physicists and engineers.