EDITH-CSA: Building an Ecosystem for Digital Twins in Healthcare

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EGI-GÉANT joint workshop on eHealth and Digital Health Data

9/6/2023

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EDITH project has received funding from the EU H2020 Research and Innovation Programme, under Grant Agreement n. 101083771

Background

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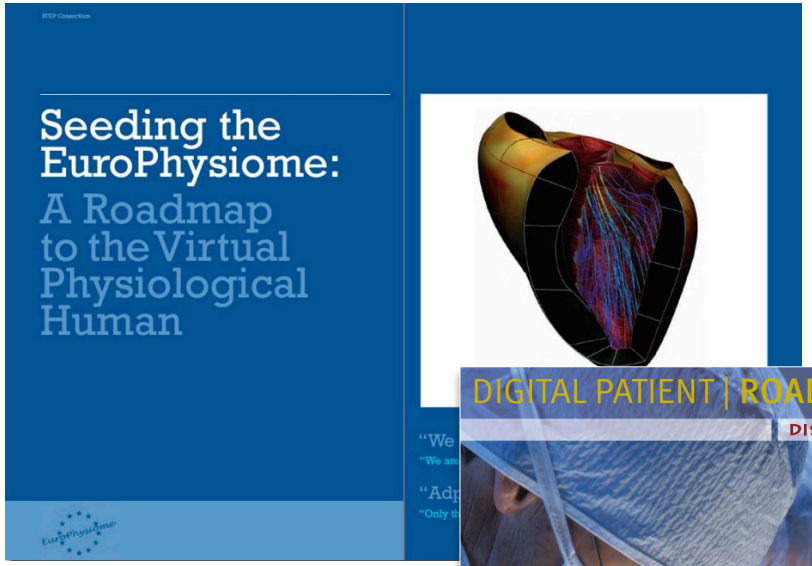
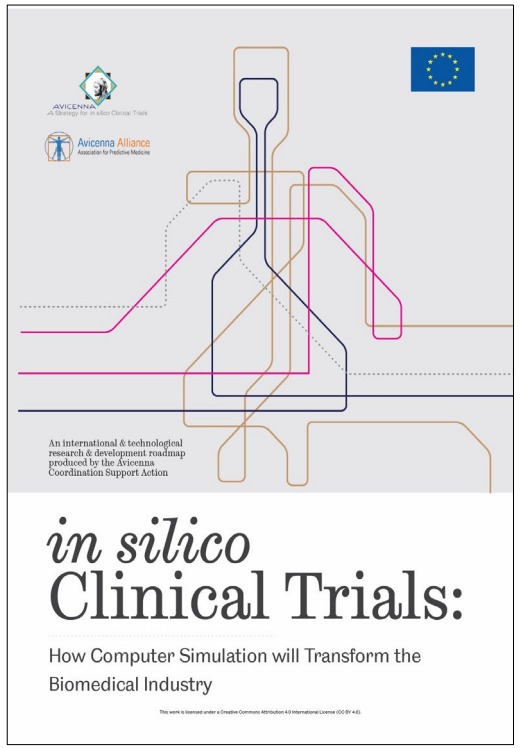
Background: EU investments





Health EU

Per Med CoE

CompBioMed

Background: EU industrial activity

EDITH Introduction

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EDITH objectives

Ecosytem

Roadmap

Repository

Simulation Platform

EDITH consortium

The Vision for the Virtual Human Twin

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Vision for the Virtual Human Twin

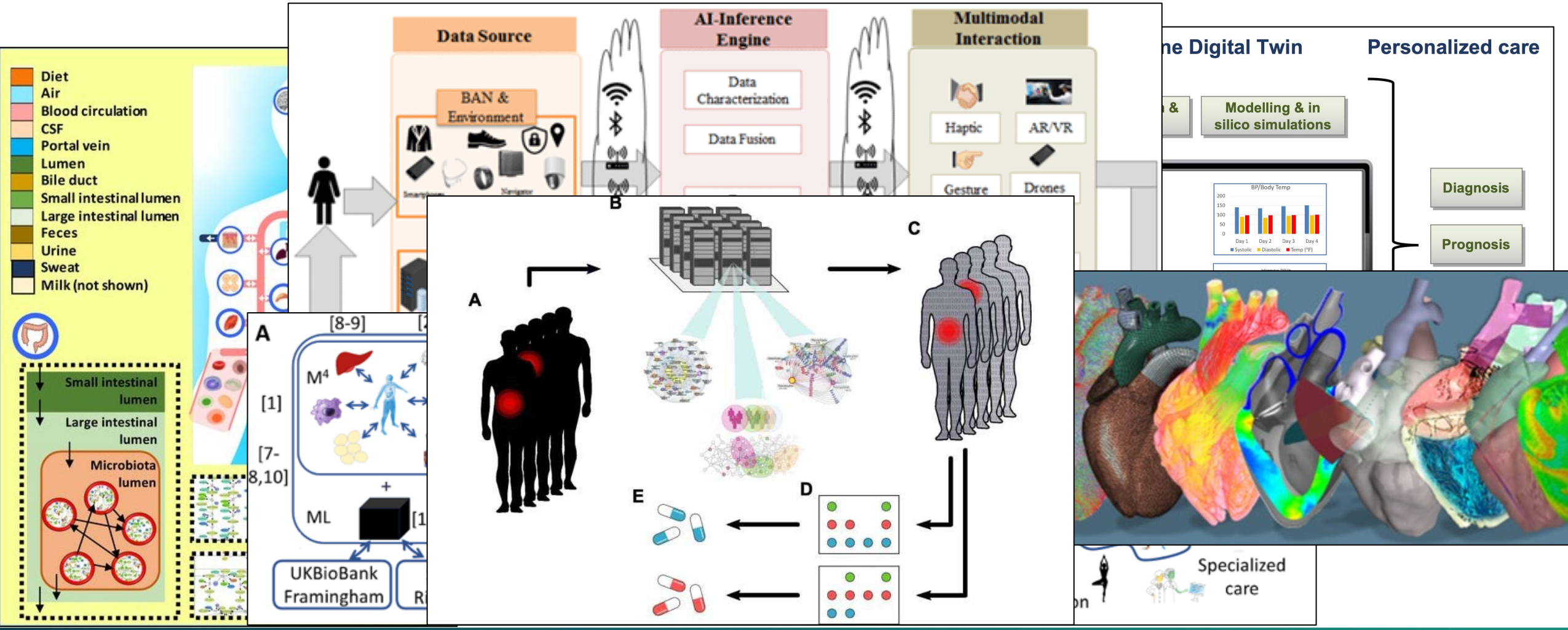
The Virtual human twin (VHT) is

an **integrated multi-scale, -time and -discipline digital representation of the whole body**

enabling the comprehensive characterization of the physiological and the pathological state in its heterogeneity and

allowing **patient-specific predictions** for the prevention, prediction, screening, diagnosis and treatment of a disease, as well as the evaluation, optimization, selection, personalization and de-risking of intervention options.

Vision for the Virtual Human Twin



A more practical definition

The Virtual Human Twin (VHT) is

a systematic, ever-growing **digital and quantitative representation** of the actionable knowledge available on human pathophysiology.

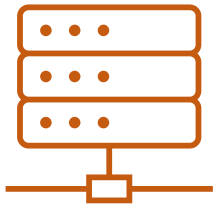
The European VHT platform will enable the **pooling of resources and assets** to develop digital twins in healthcare and assess their credibility.

It entails the development of a **federated public infrastructure and the collection of appropriate resources** (data, models, algorithms, computing power, storage etc.), driven by the engagement of a collaborative ecosystem.

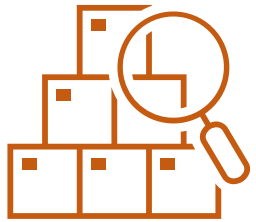
So what can the VHT look like?

$$I(x,t) = \int_0^1 xy^{\ln(t)}\,dx$$

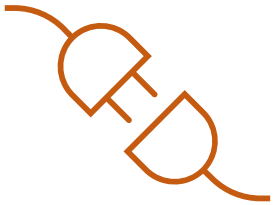
you can access every digital twin developed so far by anyone in Europe, including your own



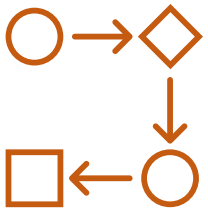
you can run all those models on every digital dataset available in Europe on human health



you can search data by data type, anatomical location, age of the patient, and many other attributes



you can execute any digital twin on any available dataset that is a valid input for that model



you can orchestrate multiple digital twins to build multiscale or multisystem models

```
# Program adds two numbers
num1 = 1.5; num2 = 6.3
sum = num1 + num2
```

You can script the whole VHT, and save your scripts for automation or reuse by you or others

To realise the VHT, work is required on:

- **Technology**
  - Individual resources: data, models, algorithms
  - Integration of resources
  - APIs
  - Infrastructure, networks
  - Connection EHDS, SIMPL
- **ELSI**
  - Access, privacy
  - Ethics, code of conduct
  - Legal & policy aspects
  - Regulatory considerations
- **Users**
  - Different profiles
  - Access & workflows
  - Interaction with other platforms & repositories
- **Sustainability**
  - Clinical uptake
  - Large companies
  - Start-ups
  - Marketplace
  - business modelling
  - ERIC, EDIH

Integration

- Model – data (same organ, same level)
- Different levels (tissue & intracellular)
- Different organ systems (e.g. heart & lung)
- Different types of data (e.g. images & wearables, omics & wearables)

- Orchestration
  - Remote execution: data and models are not co-located
    - Data replication services & model containerization
    - Case-by-case decision to move data/models
  - Orchestration
    - Strongly coupled vs loosely coupled models

Pre-selected use cases

Partner	Topic	Model	Data	Computation	Integration	Use case(s)
BSC	Cancer (*PerMed Coe)*	Multiscale, agent-based	Single cell sequencing, images	HPC	Workflow in development	Personalised health forecast
U.Liège & UKA	Intensive Care *(MII, STAR)*	Pharmaco- dynamics	Nutrition intake, glucose measurements, mechanical ventilation	Bedside, realtime	Parameter sensitivity	In silico clinical trials, Personalised treatment
QMUL & EPFL	Cardio-vascular *(CVDHub)*	mechanistic electromechanical model + with ML algorithm	Medical images (CT, MRI), electroanatomic mapping	HPC, GPU	Single-organ workflow established; integration with cancer use case	In silico clinical trials, Personalised treatment planning
UNIBO	Osteo-porosis *(BBCT)*	Mechanical model	Medical images	HPC	Single-organ workflow established	Personalised health forecast
JFZ + QMUL	Brain (*BigBrain*)	Data-driven model	Very large data-sets (1TB)	Distributed	Single-organ workflow established, integration with CV use case	Personalised treatment planning
HITS	Platform *(SEEK)*	Repository	Repository	Cloud	Development of API to link to EDITH repository	Linking EDITH to existing repositories

Implementing the Vision for the Virtual HumanTwin

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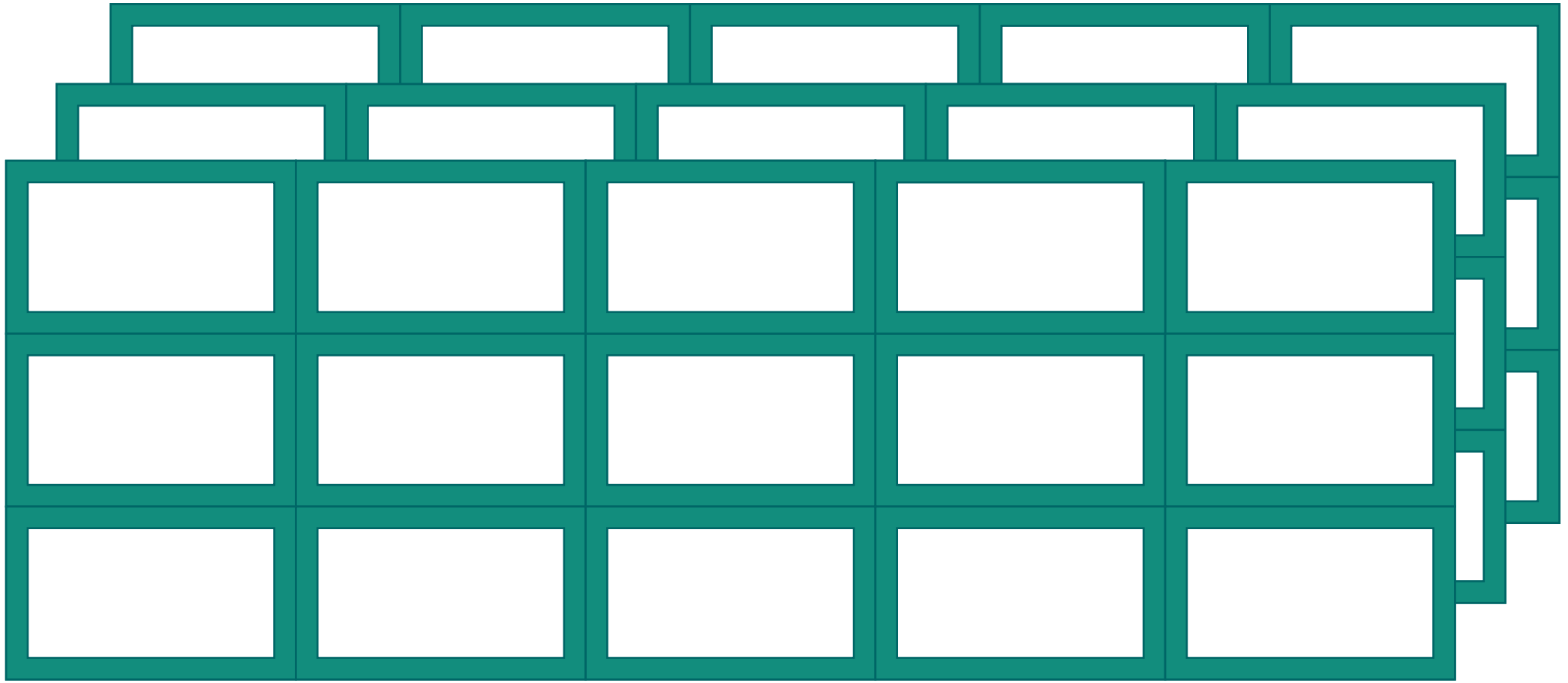
Vision for the VHT: a 6D scaffold

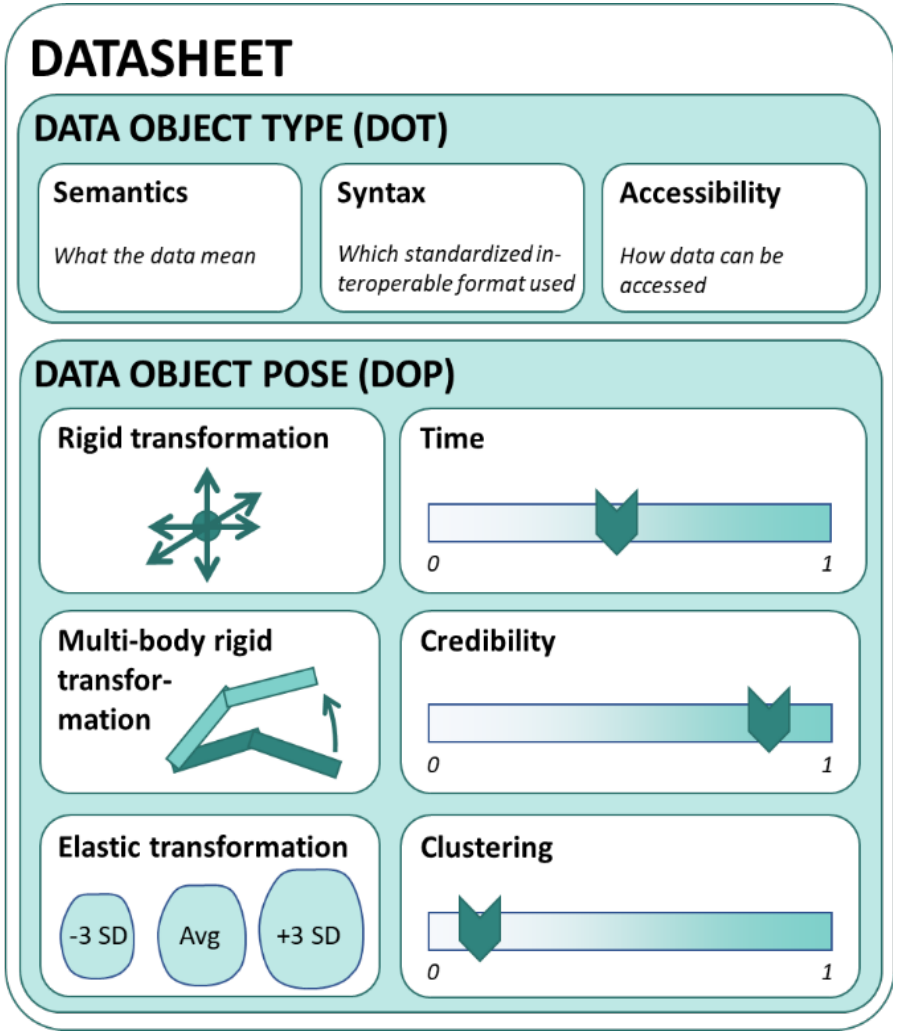


On the scaffold we store ….

- **Data objects**
  - Data Object Type: a dynamically expandible ontology of all data types supported by the VHT framework
  - Data Object Pose: the position and orientation of the data object in a 6D semantic space
- **Model objects**
  - Remote execution procedures that predict certain data objects when provided in input with some other data objects
  - Orchestrations
    - Strongly coupled orchestrations are exposed as new model objects
    - Weakly coupled orchestrations are exposed as data flows

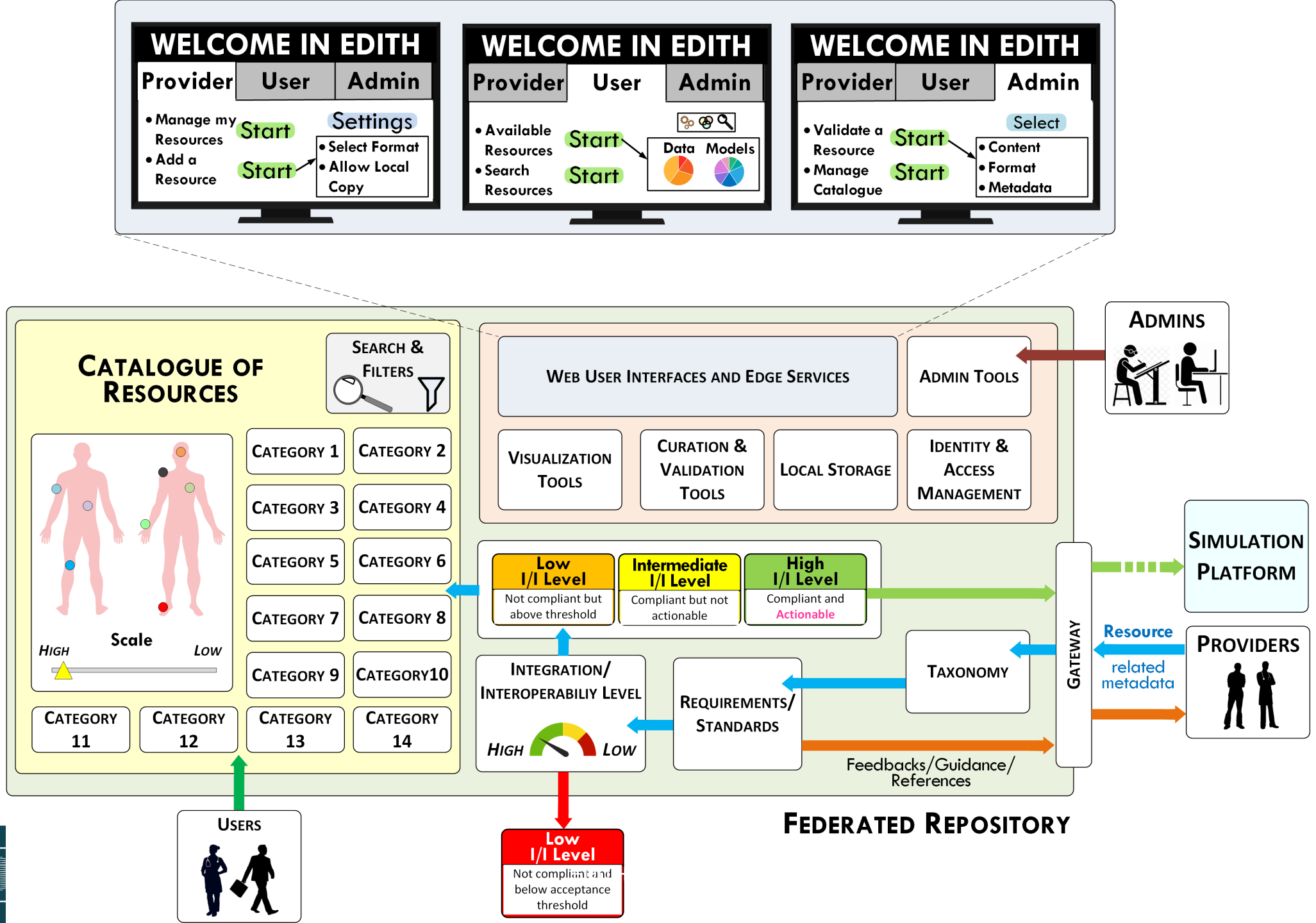
The six dimensions

- Every data object is annotated with a data object type (DOT) and a data object pose (DOP)
- DOT: makes possible the automatic association between model objects and data objects
- DOP: provide a standardised representation of the data objects over:
  - Space (anatomical space of the average human body)
  - Time (human life span from birth to death)
  - Clustering (from individual to average *Homo Sapiens Sapiens*
  - Credibility
- Credibility = 0 is a data object with evidence of credibility; credibility = 1 is a data object certified for medical use by a competent authority. The Community of Practice defines intermediate steps.
- All other info is added as optional metadata

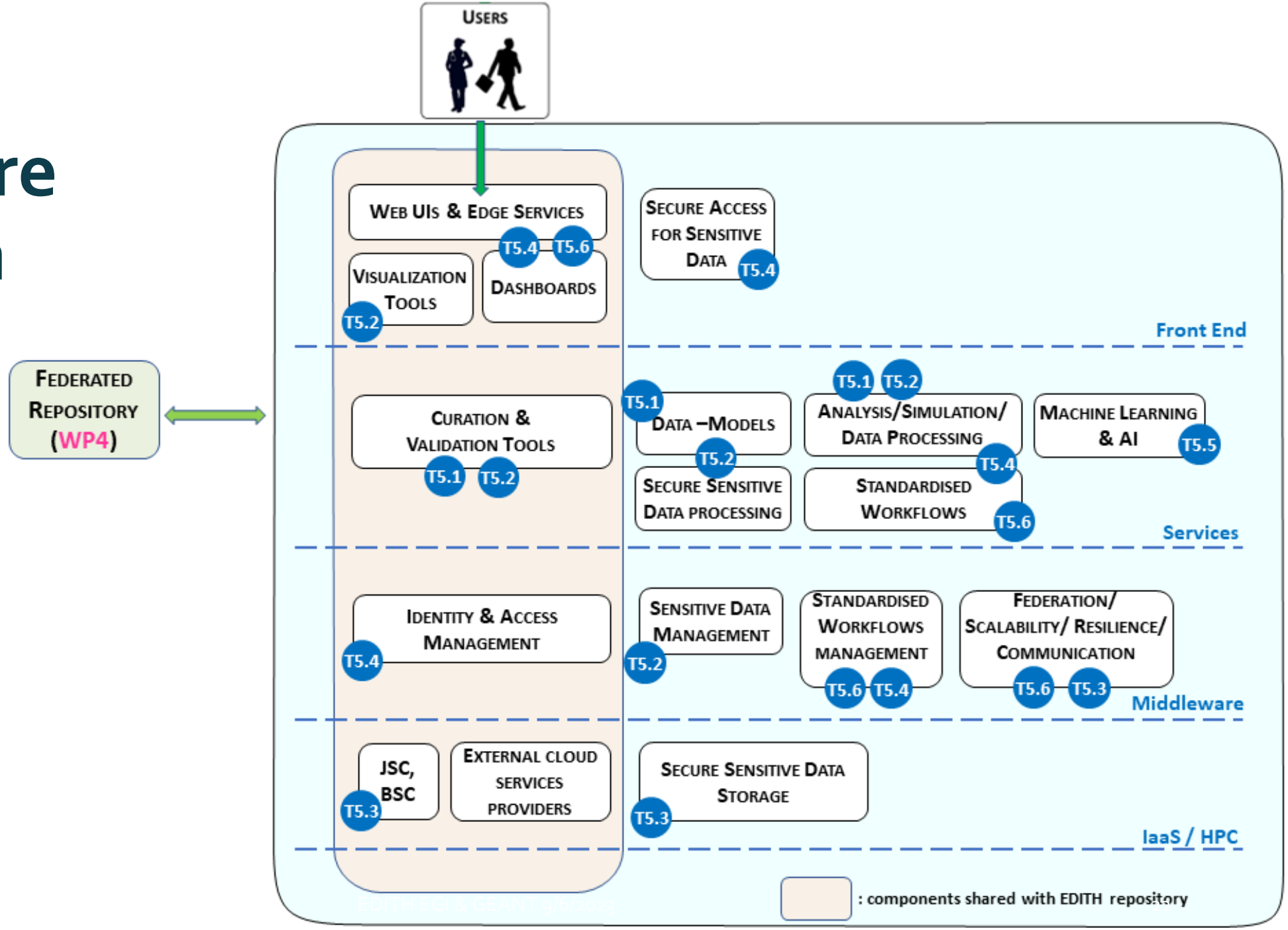


VHT infrastructure

- The core is a **repository of annotated data and annotated containerised models** supported by several data transformation services.
  - The data repository includes measured data (obtained experimentally) and predicted data (obtained computationally).
- Ideally, the data transformation services and the models should **run automatically** whenever a new valid input set is added to the data space.
  - So as models are added, the computational cost of adding new experimental datasets will increase exponentially.
  - Since the models' predictions are added to the data space, the data space will grow exponentially.
  - Eventually, the cost of storage and computations will have to be sustained by the end users (e.g. through model execution brokering software), but in the developing phase, it would be ideal to have a good fraction of it covered by grants.
- To increase the credibility of models VVUQ simulations will also be required.


WELCOME IN EDITH
Provider
User
Admin
• Manage my Resources
• Add a Resource
Start
Start
Settings
• Select Format
• Allow Local Copy
WELCOME IN EDITH
Provider
User
Admin
• Available Resources
• Search Resources
Start
Start
Data
Models
WELCOME IN EDITH
Provider
User
Admin
• Validate a Resource
• Manage Catalogue
Start
Start
Select
• Content
• Format
• Metadata
CATALOGUE OF RESOURCES
SEARCH & FILTERS
Scale
HIGH
LOW
CATEGORY 1
CATEGORY 2
CATEGORY 3
CATEGORY 4
CATEGORY 5
CATEGORY 6
CATEGORY 7
CATEGORY 8
CATEGORY 9
CATEGORY10
CATEGORY 11
CATEGORY 12
CATEGORY 13
CATEGORY 14
WEB USER INTERFACES AND EDGE SERVICES
ADMIN TOOLS
VISUALIZATION TOOLS
CURATION & VALIDATION TOOLS
LOCAL STORAGE
IDENTITY & ACCESS MANAGEMENT
ADMINS
Low I/I Level
Not compliant but above threshold
Intermediate I/I Level
Compliant but not actionable
High I/I Level
Compliant and Actionable
SIMULATION PLATFORM
GATEWAY
Resource
related metadata
PROVIDERS
INTEGRATION/ INTEROPERABILIY LEVEL
HIGH
LOW
REQUIREMENTS/ STANDARDS
TAXONOMY
Feedbacks/Guidance/ References
USERS
Low I/I Level
Not compliant and below acceptance threshold
FEDERATED REPOSITORY

Possible architecture simulation platform



Questions related to tech stack

- Much work has already been done
  - Workflows, computational resources, knowledge graphs, networks
- Synergize with existing initiatives-organisations using similar/same technologies
  - Identify how needs of VHT community/infrastructure differ
  - Co-evolution?

Ecosystem

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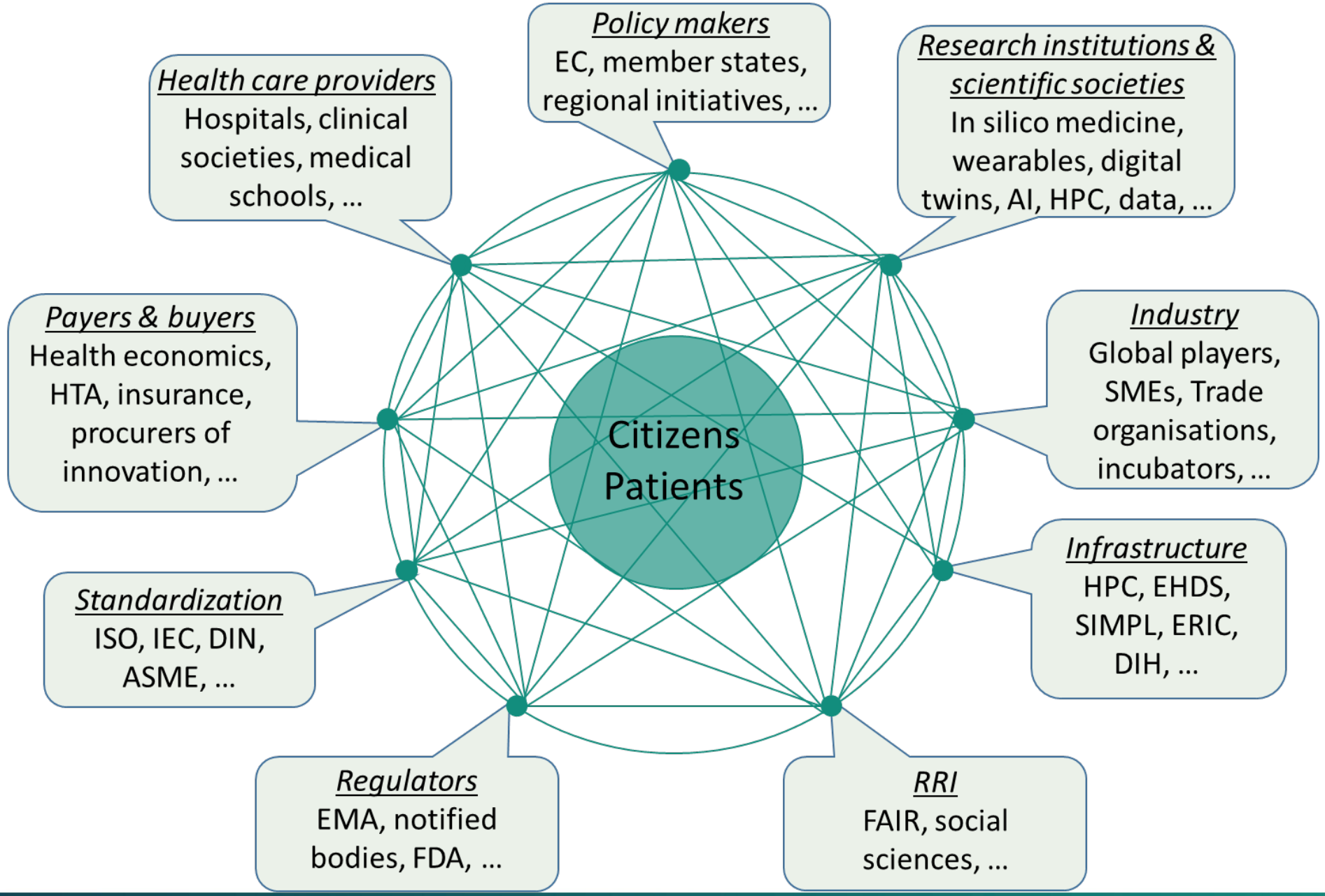
Policy makers
EC, member states, regional initiatives, …
Research institutions & scientific societies
In silico medicine, wearables, digital twins, AI, HPC, data, …
Health care providers
Hospitals, clinical societies, medical schools, …
Payers & buyers
Health economics, HTA, insurance, procurers of innovation, …
Industry
Global players, SMEs, Trade organisations, incubators, …
Citizens
Patients
Standardization
ISO, IEC, DIN, ASME, …
Infrastructure
HPC, EHDS, SIMPL, ERIC, DIH, …
Regulators
EMA, notified bodies, FDA, …
RRI
FAIR, social sciences, …

Industry uptake

- Use resources (data, models) available in the platform
- Use publicly available portion as sand box to test new developments
- Use as benchmark
- Benefit from supporting work on technology development
- Benefit from supporting work in establishing ELSI clarity & certainty
- Facilitate linking companies' own developments with other partners
- Facilitate finding new commercial opportunities

Clinical uptake

- Clinician – researcher
  - Clinical decision support
  - Investigate comorbidities
- Clinician in training
  - Train on virtual patients
  - Test hypotheses on pathologies
- AR/VR as technology to bridge to clinician-practitioner & patients

Exploitation and sustainability

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Approach

- **Early prototype demonstrators** of the simulation platform by means of the pre-selected use cases
- Develop **recommendations on regulatory, standards, ethical and legal elements**, in light of the future roll-out of the simulation platform. Develop code-of-conduct.
- EDITH **sustainability pathways** (evolutionary ecosystem)
  - exploration of business models
  - marketplace services
  - sustainability as research infrastructure

Ecosystem involvement

- **Promote buy-in** in the community, targeting resource developers (modellers, infrastructure providers, data collections) but also regional & national initiatives in EU27.
- Develop **incentive mechanisms** for developers/researchers for uploading and/or making their resources available on the federated cloud-based repository.
- Develops and promote specific **policy recommendations** to further the development of the VHT repository & simulation platform.

Manifesto

VIRTUAL HUMAN TWINS
A Statement of Intent on Development, Evidence, and Adoption in Healthcare Systems

Final Version *02 May 2023*

Virtual Human Twins (VHTs), digital representations of human physiology and pathology, have considerable potential for medical research and healthcare delivery, enhancing our understanding of human physiology, pathology, and disease aetiology, enabling personalised, patient-centred medicine.

In healthcare, VHTs can enable enhanced diagnosis and personalised interventions of higher efficacy and safety a
can also dra
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as a whole.
instrumental in unleashing investment supporting innovation.

We are ready to be part of these advanced solutions led and facilitated by the European Commission. Working with all stakeholders across the ecosystem, we will contribute to the further development of VHT technologies and its ecosystem in Europe by actively contributing to the following actions:

- **Attaining excellence in European research and innovation** in the development, testing, validation, and verification of advanced VHT technologies, making use of digital services and capabilities available at European level, e.g. EuroHPC, SIMPL, and others where appropriate.
- **Identifying high-impact clinical use cases** that stand to benefit from the adoption and use of VHT technologies, products and services, including diagnostics, medical education, training, decision support, intervention planning.
- **Designing, building, and enhancing the EU VHT data and models repository** with expertise and resources in full compliance with applicable laws and regulations in Europe.

of citizens, patients, and healthcare professionals are proactively captured and addressed as part of the development, testing, verification, and validation of VHT technologies.

- **Ensuring that VHT technology benefits people of all ages, genders, ethnicities, socioeconomic statuses, and physiological disabilities, fostering equitable and universal access** to high-quality healthcare across Europe.

Roadmap & project timeline

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EDITH crucial first steps

- **Roadmap** (M10 first official draft, intermediate updates)
  - Vision for integrated VHT
  - Discussion of issues with recommendations for funding and policy instruments, areas in need of intervention
- **Use cases**
  - Concrete, mature & supporting the EDITH goals (integration)
- Building **ecosystem**
  - Make sure roadmap represents all EDITH communities
- Establishing basis for repository, platform & sustainability

Public consultation

- Mid June -July 15: public comments on overview of the first RM draft
  - via shared google doc & discussions via ISW-CoP slack

- *Deliverable: first draft of roadmap (31/7/2023)*

- Public meetings (Q4 2023/Q1 2024 & Q2/Q3 2024)
- Community phase
  - Writing of full version of the roadmap
  - Contribution of use cases & upload into repository

http://www.edith-csa.eu

Deliverables available under tab ‘dissemination/material’

Indication of interest via de contact form on site

info@edith-csa.eu

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Data transformation services

- Let us use the CT scan of the thigh of a 74 yrs woman as a guiding example.
  - ✓ The data object is stored in DICOM format in a compressed archive
  - ✓ The file must be annotated with nationality and age at scan. If the age at death is known, it translates on the Time axis; otherwise, the average life span for women in that country is used to normalise on the Time axis.
  - ✓ The file must be annotated with the anatomical location: thigh, and with the organ of interest, the femur, which is segmented and stored in a separate file in STL format.
  - ✓ A 3D rigid transformation is calculated to align the femur surface with the average human template. Then, an affine transformation scales the femur surface to that of the template. Last, an elastic registration is performed between the femur surface and the template. The same operators are also applied to the CT scan raw data using appropriate voxel value interpolators.
  - ✓ Now we can average the femur geometry and the CT voxel values with all clustering groups that include CT scans of the thigh. We can get the average femur shape for all women, for all 74 yrs women, up to the average for *homo sapiens sapiens*.
  - ✓ When uploaded data objects have credibility = 0. The CoP defines how CT scan increases their credibility (e.g. by adding metrology data on the accuracy of the spatial and densitometric information).

Data prediction services

- **Models objects** are added as containerised remote procedure calls, annotated with all the DOTs that form a valid input set and the DOT that will be predicted.
  - **Predicted data objects** are stored alongside the measured ones, but provenance metadata identifies them as such. They are processed with all data transformation services and annotated accordingly.
  - Ideally, as soon as a new valid input set appears in the data space, the associated model object should be run, and the predicted data objects added to the data space.
- Population-specific models will add a data object directly to the appropriate clustering group, as no individual predicted values are available. Subject-specific models predict data objects with clustering zero; their values can be clustered only if predicted by the same model.
- **Data validation services** may automatically compare the predicted values to measured values if available and use this predictive accuracy information to annotate the credibility axis of the predicted data objects.