EDITH
Deep Thinkers Meeting

Rome, 16-17/5/2023

EDITH

EDITH is a coordination and support action funded by the Digital Europe program of the European Commission under grant agreement n° 101083771.

TUESDAY 16TH AGENDA

12:30 - 13:30	**Welcome buffet lunch, networking**	*ALL*
13:30 - 14:00	**Welcome addresses by the Host (Translated and Pi School), the CSA Coordinator and the European Commission Representative**	*Sebastien Bratières (Pi School) Liesbet Geris (VPHi) Kyriacos Hatzaras & Margherita Fanos (DG-CNECT)*
14:00 - 15:45	**Presentation of vision and roadmap for the Virtual Human Twin**	*Liesbet Geris (VPHi)*
15:45 - 16:15	*Coffee break*	
16:15 - 18:15	**Breakout sessions**	
19:00 - 21:00	***Networking social dinner***	

BREAKOUT SESSION 1 *CAFETERIA ROOM*

Infrastructure

- A distributed/federated architecture: flexible, adaptable, scalable, deployable across multiple locations, interoperable between different systems
- What core elements need to be centralised
- General platform and scientific services to be provided to the end-users
- Domain-specific services ensuring easy onboarding for a variety of services and applications
- Interoperable access to HPC

Yannis Ioannidis (ATHENA)
Amaryllis Raouzaiou (ATHENA)
Sabato Mellone (UNIBO)

BREAKOUT SESSION 2 *GAZEBO ROOM*

Tech stack

- Data and Model objects within the six-dimensional VHT framework
- Collection from multiple sources, integration across different systems, interoperability
- Common Workflow Language
- Quality/credibility assessment

Liesbet Geris (VPHi)
Alfons Hoekstra (UvA)
Marco Viceconti (UNIBO)

BREAKOUT SESSION 3 *PERSUASION ROOM*

Data Privacy and Security regulatory landscape

- Legal scenario and regulatory boundaries
- Health data reuse
- Specificities of AI-driven approaches
- Privacy-enhancing technologies to foster data sharing in virtual twins
- Ways and recommendations to engage with regulatory bodies towards adoption

Edwin Morley-Fletcher (LYNKEUS)
Francesca Conte (UNIBO)
Lorenzo Cristofaro (LYNKEUS)

WEDNESDAY 17TH AGENDA

08:00 - 08:30	**Arrival, coffee**	*ALL*
08:30 - 08:45	**Welcome, purpose of the day, the process so far**	*Liesbet Geris (VPHi)*
08:45 - 10:45	**Breakout sessions**	
10.45 - 11:15	*Coffee Break*	
11.15 - 12:30	**Bringing breakout conclusions back to plenary**	*ALL*
12.30 - 13:30	*Buffet lunch*	
13.30 - 14:30	**World café sessions** ● Metaverse, AR/VR ● GPT ● Standardization of data, models, metadata and workflows ● Incentivization ● Worst case scenarios ● Training / retraining	*ALL*
14.30 - 15:30	**Lessons learned from other initiatives**	*Petra Ritter (Charité University Medicine Berlin)* *Gary Saunders (EATRIS)* *Niklas Blomberg (ELIXIR Europe)*
15:30 - 16.00	**Next steps, timeline & prioritization, wrapping up**	*Sabato Mellone (UNIBO)* *Liesbet Geris (VPHi)*

BREAKOUT SESSION 1 *BRENBACH ROOM*

Industry collaborations, Clinical partnerships — *Michael Strübin (DIGITALEUROPE), Liesbet Geris (VPHi)*

- Collaborations and partnerships between health technology companies, healthcare providers, and research institutions in the integration of multi-level and multi-organ models towards VHT
- VHT Manifesto
- Clinical uptake
- Recruitment of medical technology experts by healthcare providers and their professional recognition as co-decision makers

BREAKOUT SESSION 2 *GAZEBO ROOM*

User Experience and co-creation — *Amaryllis Raouzaiou (ATHENA), Sabato Mellone (UNIBO)*

- User-centred design
- User-friendly interfaces
- User engagement measurement
- Incentives for sharing data and models

BREAKOUT SESSION 3 *CAFETERIA ROOM*

Sustainability — *Edwin Morley-Fletcher (LYNKEUS), Minos Garofalakis (ATHENA), Sébastien Bratières (Pi School)*

- Pre-competitive to competitive transition
- Phases of Distributed Ledger Technology
- IPR and licensing
- Business cases
- Governance roles and responsibilities

BREAKOUT SESSION 4 *PERSUASION ROOM*

Communication and Dissemination

(Only D&C Team)

Household announcements

- Wifi: Translated, password: Hard2Forget!
- Dinner here on-site, taxis for after dinner arranged
- Transportation from hotel tomorrow morning or to airport > Mirko
- Filming:
  - Interviews (pre-arranged)
  - General images
- Recording/note-taking during sessions: for internal use only

Deep thinkers

- 60% consortium, 40% experts
- Mix of industry, academia, clinicians, research infrastructures, patient organisations
- Engineering, mathematics, medicine, biomedical sciences, social sciences, communication sciences, legal sciences
- Mostly EU-based but from around the world

Deep thinking

- Presentations are proposals to get discussion started
- Questions, comments, remarks welcome at any stage

- Aim is to ensure all elements relevant for the realisation of a succesfull VHT are captured into the roadmap
  - Research challenges (of any kind)
  - Infrastructure needs
  - Other requirements

Vision and Roadmap for the Virtual Human Twin

Presenting the work of the consortium M1-6

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Background

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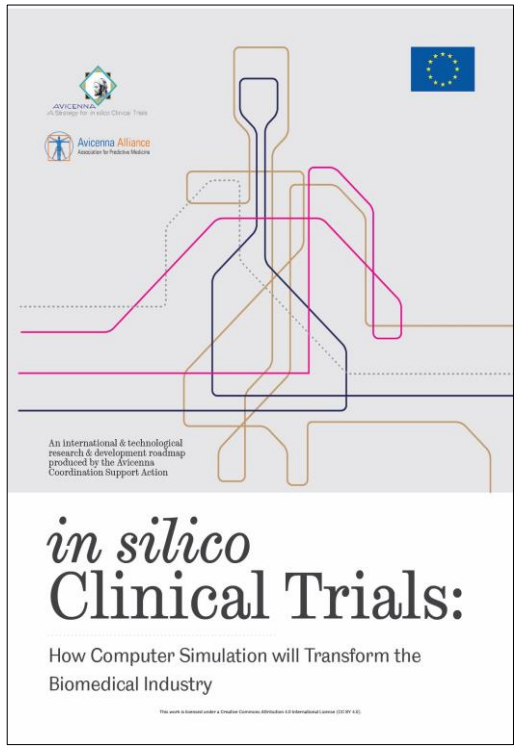
Background: EU investments



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

EDITH WP leaders

Edwin Morley-Fletcher
Lynkeus

Mapping / Ecosystem

Sabato Mellone
UNIBO

Repository

Amaryllis Raouzaiou
ATHENA

Simulation Platform

Sebastien Bratières
Pi School

Sustainability

Liesbet Geris
VPHi, U.Liège, KU Leuven

Vision

The Vision for the Virtual HumanTwin

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Vision for the Virtual Human Twin

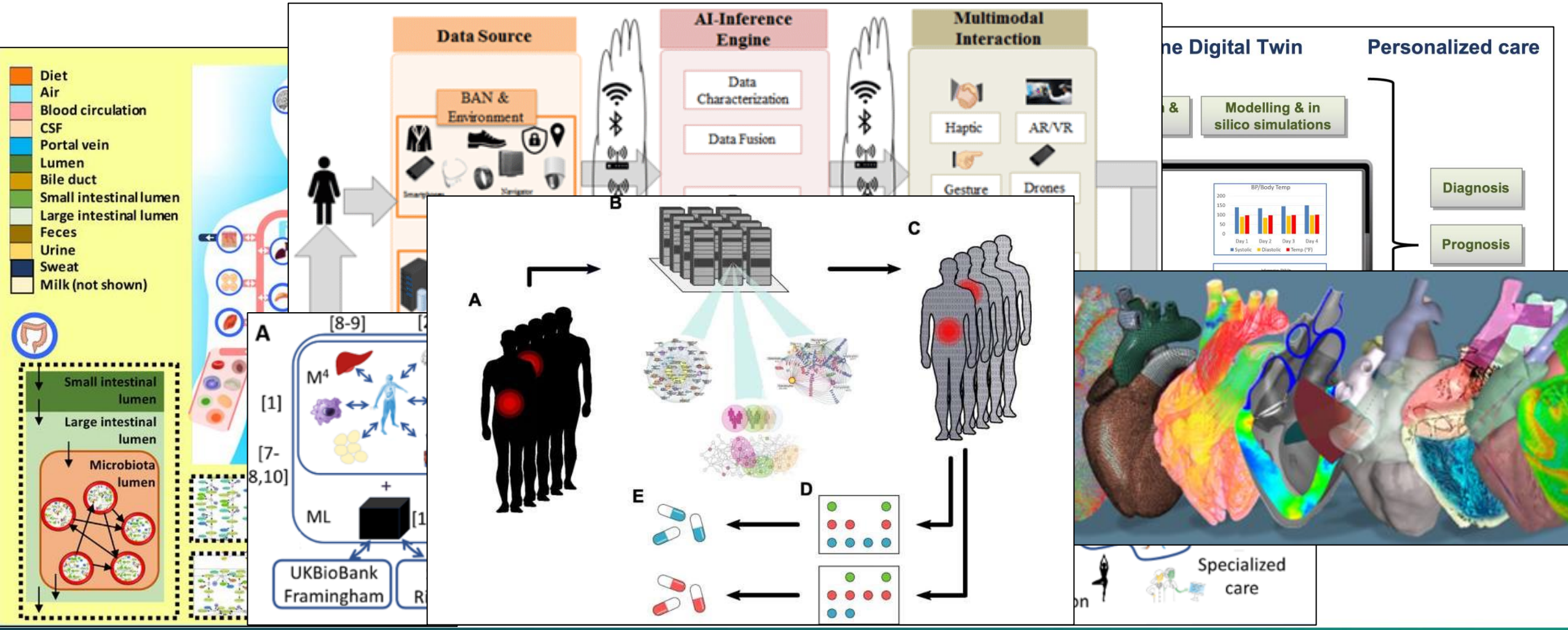
The Virtual human twin (VHT) is

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



Some tentative definitions /1

- The management of human health requires decision-makers to take **well-informed decisions**.
  - Clinicians making decisions on personalised therapeutic strategies for a patient;
  - Researchers making decisions on possible druggable targets to pursue in basic biomedical research;
  - Healthcare authority managers planning specific policies;
  - Biomedical companies seeking to refine, reduce and partially replace animal and human experimentation for the regulatory approval of new products;
  - …

Some tentative definitions /2

- **Reference Populations** are singles or groups of human beings whose health status can be affected by these decisions.
- **Quantities of Interest** (QoIs) are the quantification of constructs that represent the health status in the decision-making process.
- The **Context of Use** (CoU) defines how the QoI informs a specific decision-making process relevant to human health and under which specific conditions such process occurs.

- A **Digital Twin in Healthcare** (DTH) is a computer simulation that predicts (as opposed to measuring experimentally) QoIs necessary to support decision-making within a specific context of use in healthcare.

Some tentative definitions /3

- The most crucial feature of a DTH is their accuracy. We have:
  - **Generic DTH**, for which the expected accuracy is that the predicted value is within the range of the values measured experimentally in the reference population;
  - **Population-specific DTH**, for which the expected accuracy is that the predicted value is sufficiently close to some central property (typically mean or median) of the range of the values measured experimentally in the reference population;
  - **Subject-specific DTH**, for which the expected accuracy is that the predicted value is sufficiently close to the value measured experimentally in each individual in the reference population.
- By "sufficiently close", we mean that the predictive accuracy of the DTH is sufficient for its purpose as defined in the CoU.

Some tentative definitions /4

- Because of gaps in available knowledge and data, currently, we can develop DTHs designed to predict just one or a **small number of QoIs** with the necessary accuracy only in a **narrowly defined reference population**.

- The **Virtual Human Twin** is a framework to develop a new generation of DTHs, capable of predicting any QoI necessary for any CoU and reference population. This is achieved by:
  - Supporting the sharing of data and knowledge resources
  - Making easier the reuse of these resources
  - The collegial monitoring of resources' quality
  - Supporting the progression of technology readiness for DTHs

Some ground rules … (so far)

- **Only human data**, animal or in vitro data can be accepted as surrogates when human data are not accessible. Still, they have to be marked as surrogates in the provenance metadata.

- **Only for translational purposes**, either clinical or industrial. It is all about human health, not increasing fundamental biological knowledge per se. Fundamental research is fine when it has a "line of sight" with Human Health.

- **Methodologically inclusive**. From the atoms to the whole body (no preferential scale), from pure experimental to mechanistic modelling, passing through statistical and machine learning modelling.

The Virtual Human Twin

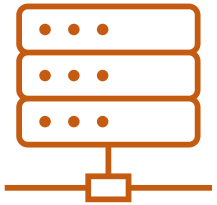
- The VHT will be:
  - A **community of practice** made of researchers and innovators from academia and the biomedical industry collaborate to accelerate the adoption of the Digital Twins in Healthcare
  - A **collection** of Good Simulation Practices and Standard Operating Procedures
  - A distributed collaborative **e-infrastructure**

- The e-infrastructure supports:
  - The sharing of data and knowledge resources
  - The reuse of these resources
  - The collegial monitoring of resources' quality
  - The progression of technology readiness for DTHs

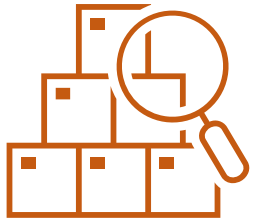
So what can the VHT look like?

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

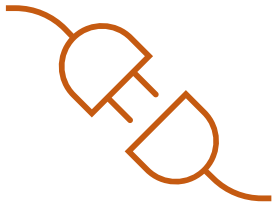
you can access every digital twin developed so far by anyone in Europe, including your own



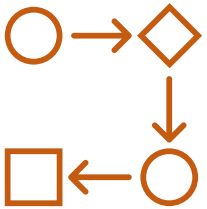
you can run all those models on every digital dataset available in Europe on human health



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
  - 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

Implementing the Vision for the Virtual HumanTwin

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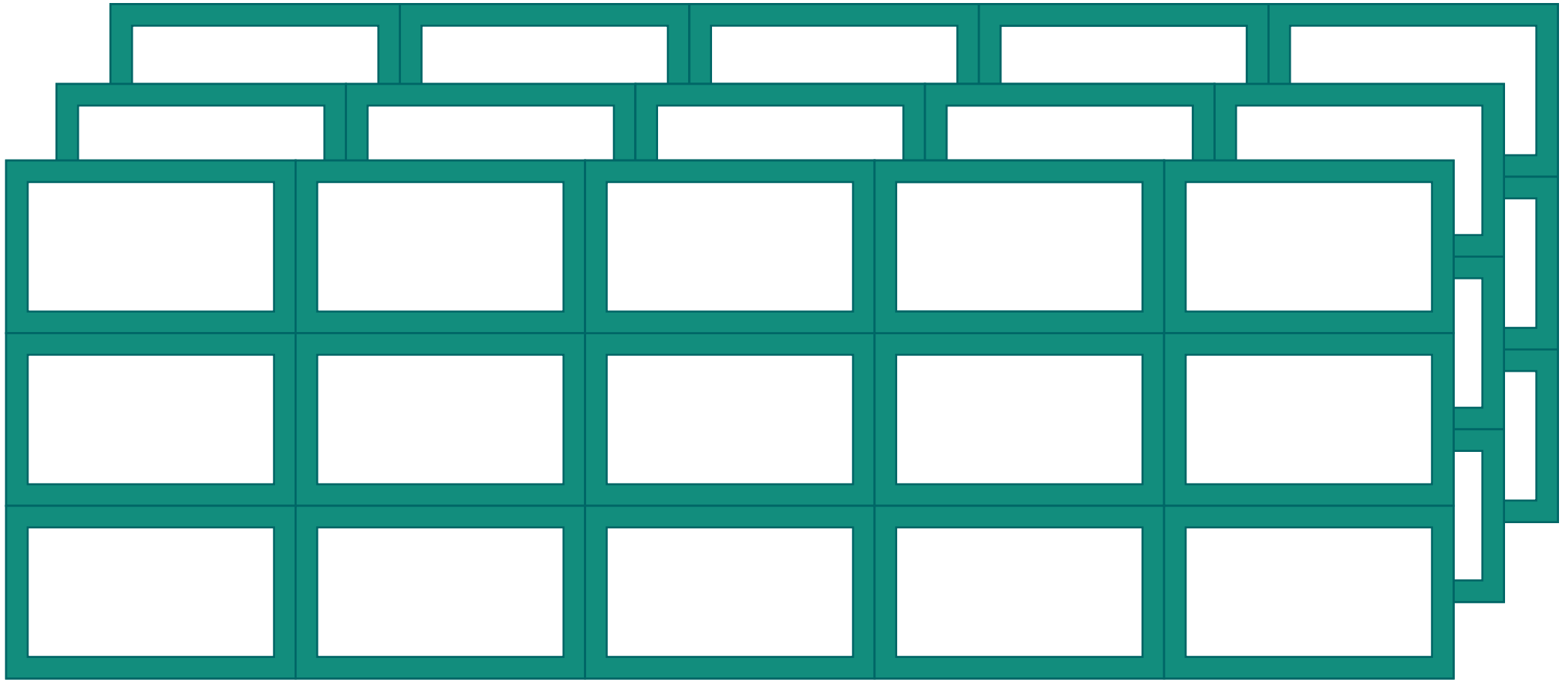
Vision for the VHT: a 6D scaffold

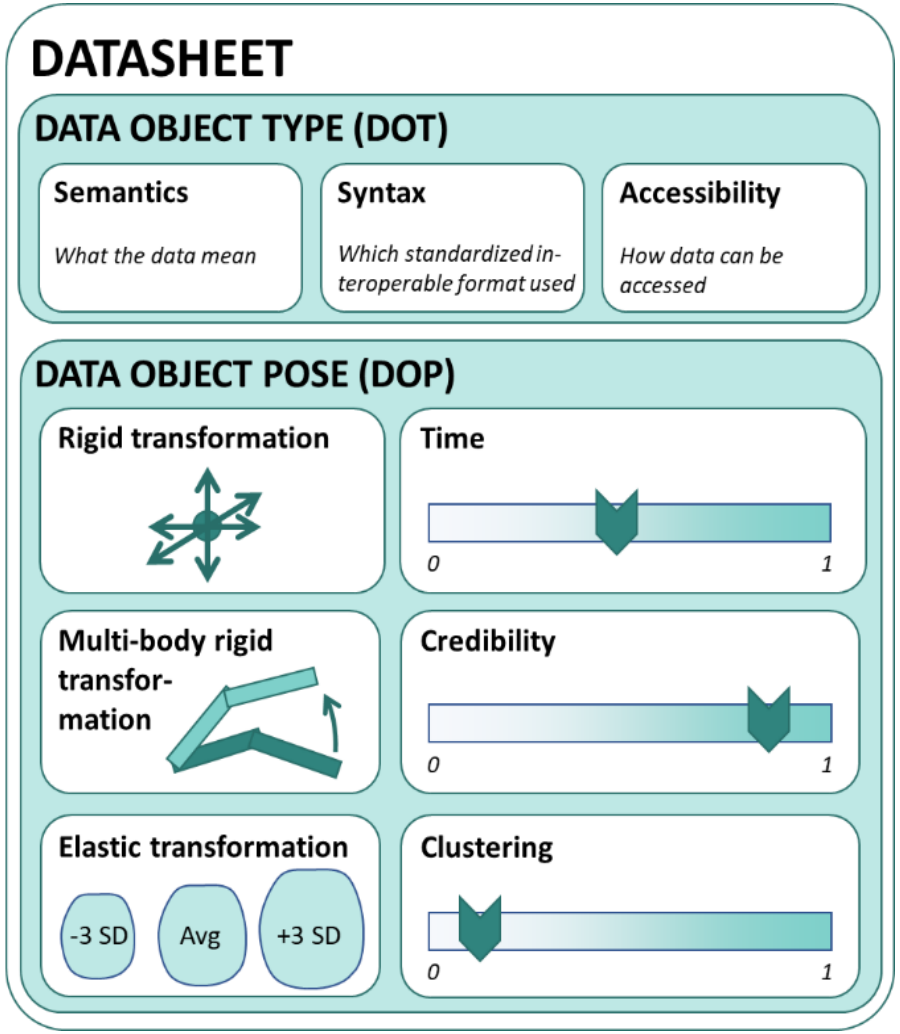


On the scaffold we store ….

- **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

- 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



Data transformation services

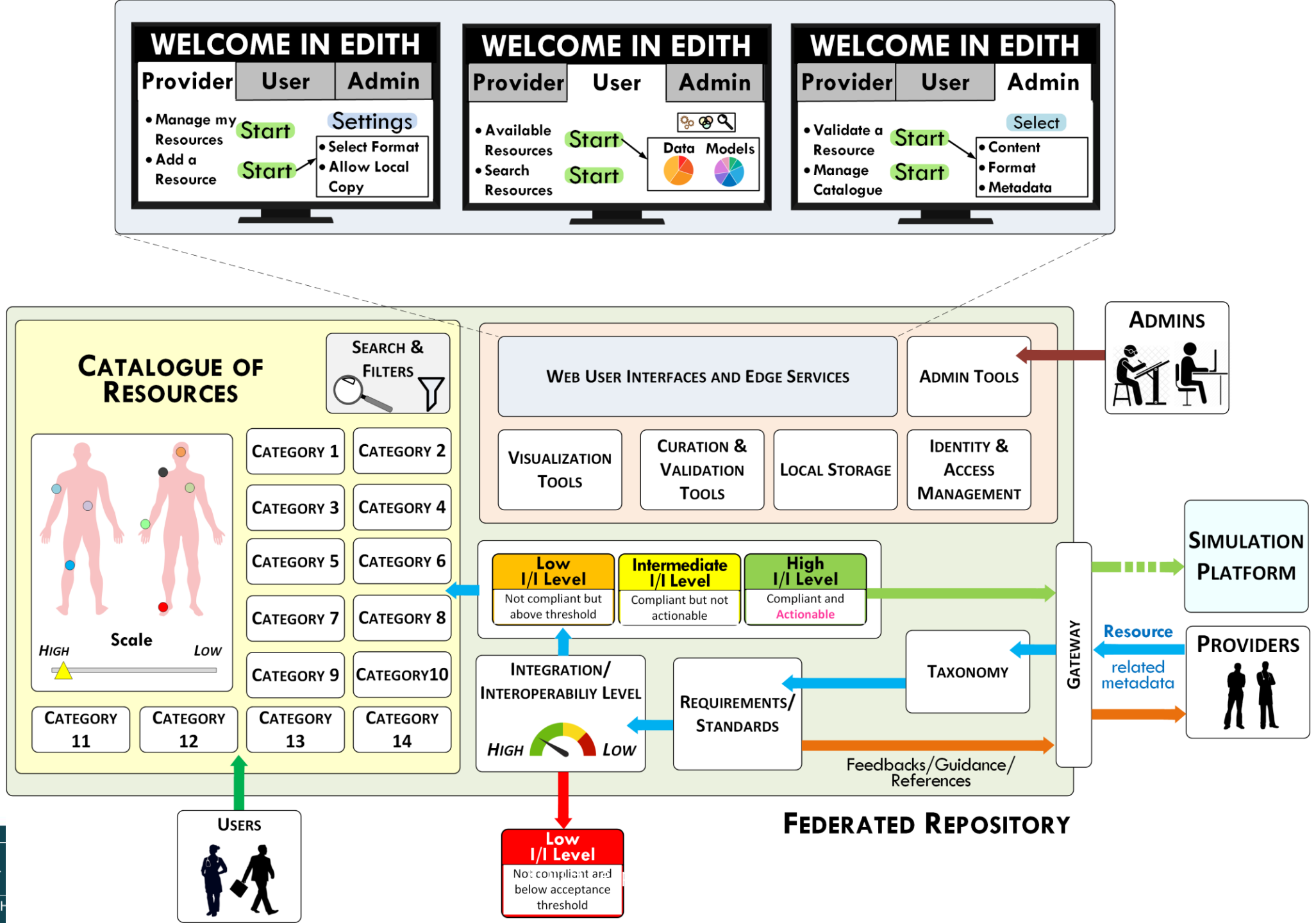
- Let us use the CT scan of the thigh of a 74 yrs woman as a guiding example.
  - ✓ The data object is stored in DICOM format in a compressed archive
  - ✓ The file must be annotated with nationality and age at scan. If the age at death is known, it translates on the Time axis; otherwise, the average 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

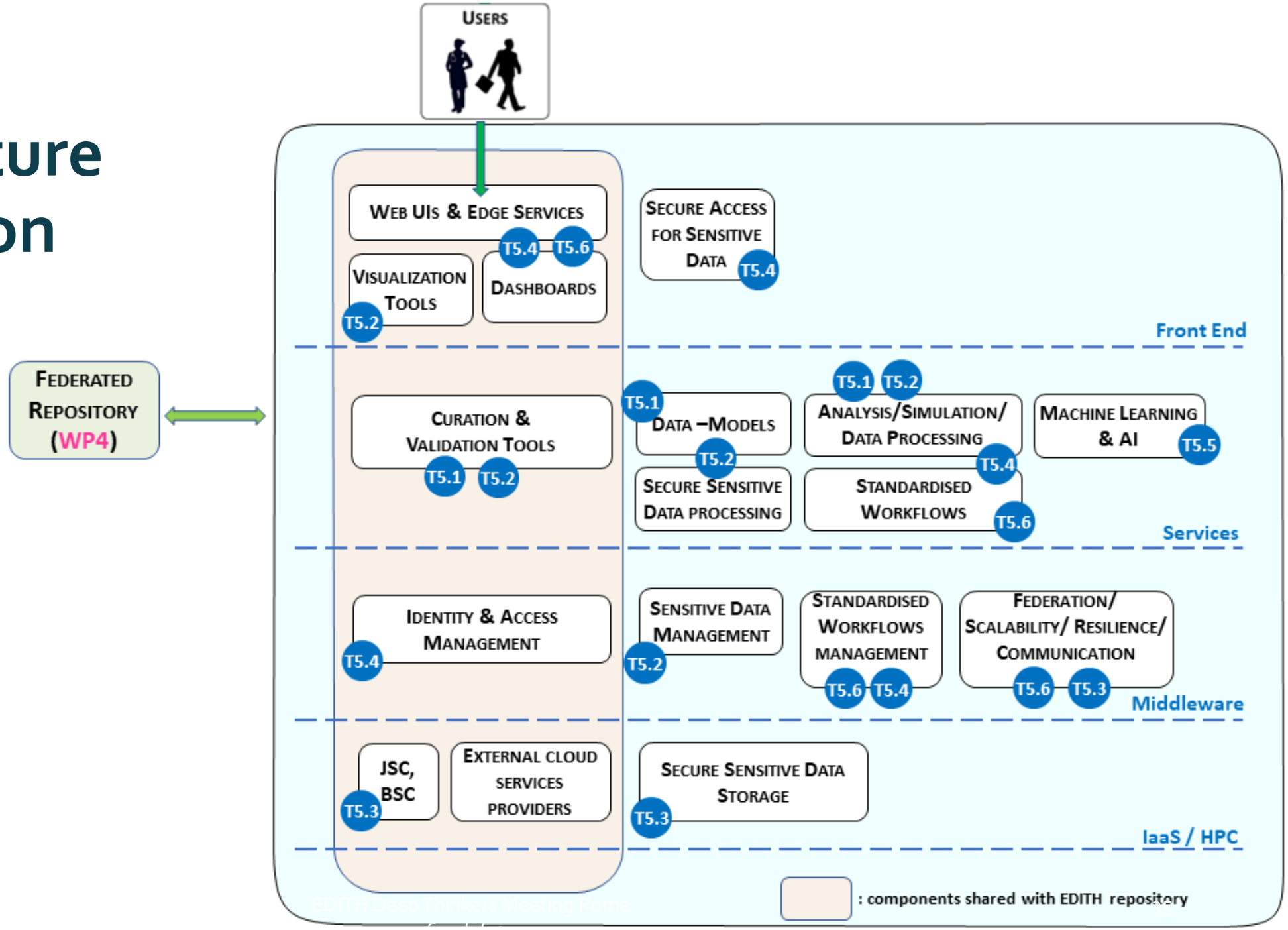
- **Models objects** are added as containerised remote procedure calls, annotated with all the DOTs that form a valid input set and the DOT that will be predicted.
- **Predicted data objects** are stored alongside the measured ones, but provenance metadata identifies them as such. They are processed 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.

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.
- To increase the credibility of models VVUQ simulations will also be required.
- Eventually, the cost of storage and computations will have to be sustained by the end users, but in the developing phase, it would be ideal to have a good fraction of it covered by grants.


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
Low I/I Level
Not compliant but above threshold
Intermediate I/I Level
Compliant but not actionable
High I/I Level
Compliant and Actionable
INTEGRATION/ INTEROPERABILIY LEVEL
HIGH
LOW
REQUIREMENTS/ STANDARDS
TAXONOMY
GATEWAY
Feedbacks/Guidance/ References
ADMINS
SIMULATION PLATFORM
Resource
related metadata
PROVIDERS
USERS
Low I/I Level
Not compliant and below acceptance threshold
FEDERATED REPOSITORY

Possible architecture simulation platform



Ecosystem

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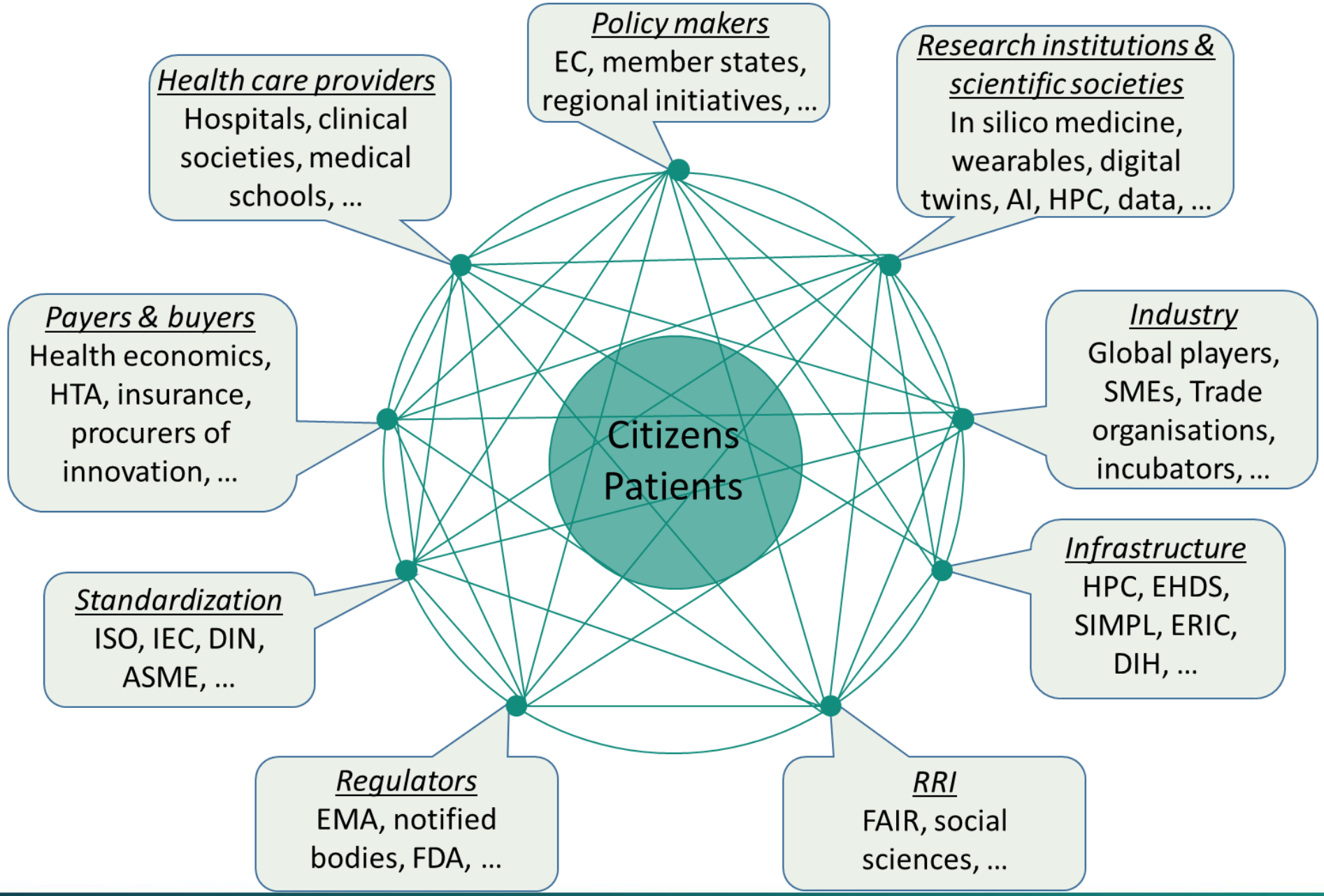
Policy makers
EC, member states, regional initiatives, …
Health care providers
Hospitals, clinical societies, medical schools, …
Research institutions & scientific societies
In silico medicine, wearables, digital twins, AI, HPC, data, …
Payers & buyers
Health economics, HTA, insurance, procurers of innovation,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

Industry uptake - IAB

- 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

Exploitation and sustainability

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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.

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

Roadmap & project timeline

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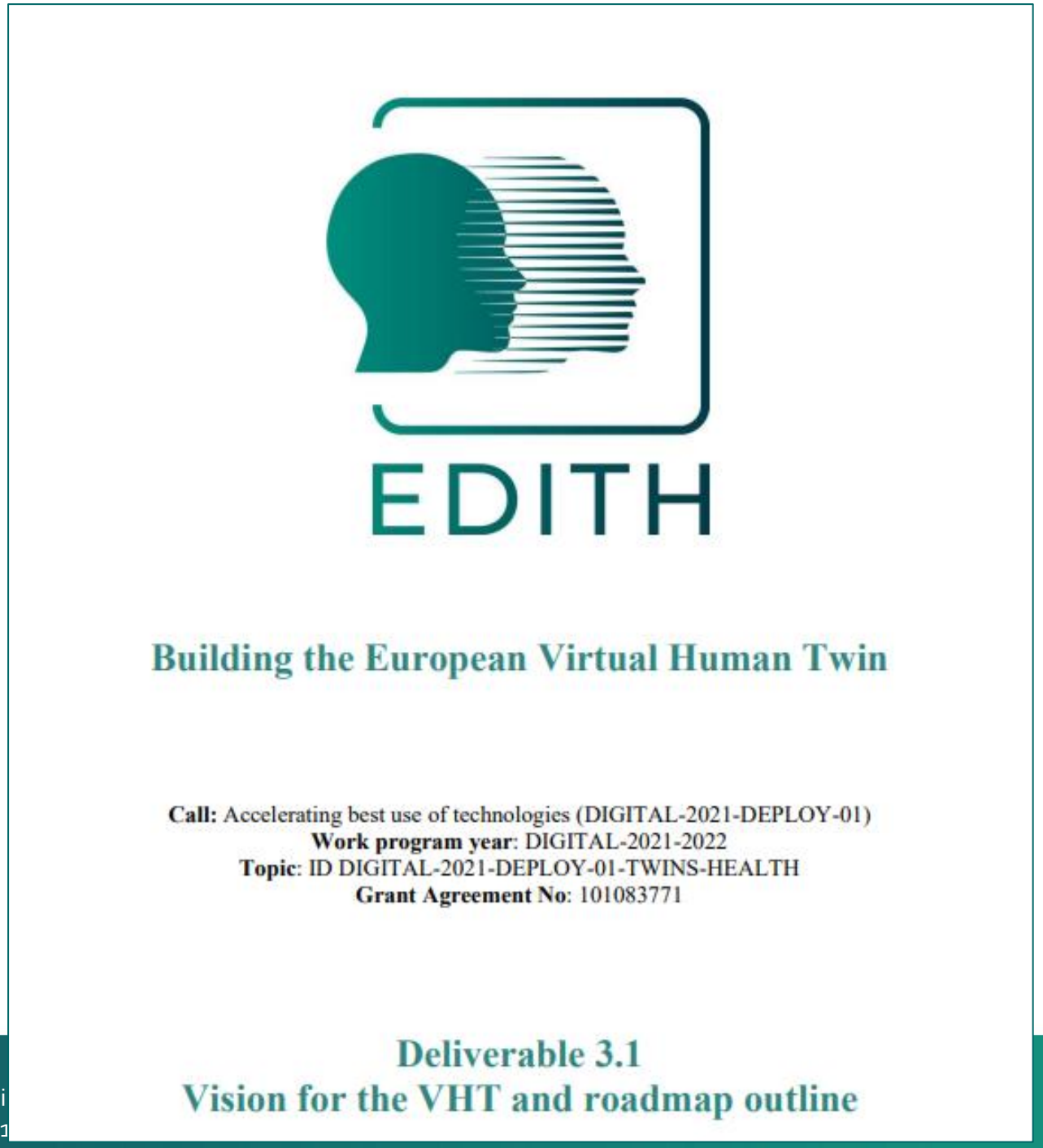
EDITH crucial first steps

- **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

EDITH vision

- http://www.edith-csa.eu
- Deliverables available under tab 'dissemination/material'
- Feedback form



Plenary Discussion

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12.30 - 13:30	*Buffet lunch*	
13.30 - 14:30	**World café sessions** ● Metaverse, AR/VR ● GPT ● Standardization of data, models, metadata and workflows ● Incentivization ● Worst case scenarios ● Training / retraining	*ALL*
14.30 - 15:30	**Lessons learned from other initiatives**	*Petra Ritter (Charité University Medicine Berlin)* *Gary Saunders (EATRIS)* *Niklas Blomberg (ELIXIR Europe)*
15:30 - 16.00	**Next steps, timeline & prioritization, wrapping up**	*Sabato Mellone (UNIBO)* *Liesbet Geris (VPHi)*

BREAKOUT SESSION 1 *BRENBACH ROOM*

Industry collaborations, Clinical partnerships — *Michael Strübin (DIGITALEUROPE), Liesbet Geris (VPHi)*

- Collaborations and partnerships between health technology companies, healthcare providers, and research institutions in the integration of multi-level and multi-organ models towards VHT
- VHT Manifesto
- Clinical uptake
- Recruitment of medical technology experts by healthcare providers and their professional recognition as co-decision makers

BREAKOUT SESSION 2 *GAZEBO ROOM*

User Experience and co-creation — *Amaryllis Raouzaiou (ATHENA), Sabato Mellone (UNIBO)*

- User-centred design
- User-friendly interfaces
- User engagement measurement
- Incentives for sharing data and models

BREAKOUT SESSION 3 *CAFETERIA ROOM*

Sustainability — *Edwin Morley-Fletcher (LYNKEUS), Minos Garofalakis (ATHENA), Sébastien Bratières (Pi School)*

- Pre-competitive to competitive transition
- Phases of Distributed Ledger Technology
- IPR and licensing
- Business cases
- Governance roles and responsibilities

BREAKOUT SESSION 4 *PERSUASION ROOM*

Communication and Dissemination

(Only D&C Team)

Reports Breakout Sessions

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Infrastructure

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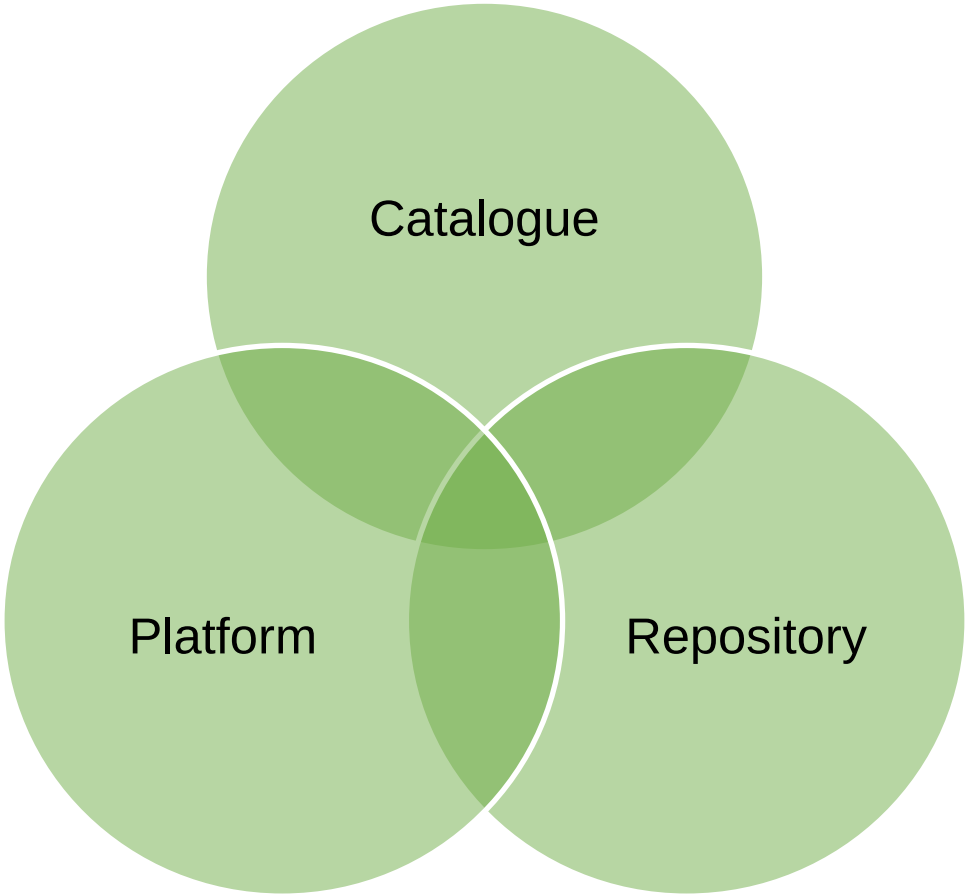
EDITH Infrastructure /1

- EDITH Ecosystem: Catalogue, Repository, Platform
- Catalogue: no storage, basic automated “validation”
- Repository: storage, services
- Platform: standard workflows (CWL), interactive computing, remote desktop



EDITH Infrastructure /2

- Data Quality (and model validity): automatic VS manual. Who does the data curation? What type of documentation/guarantees do we want to request? E.g. research protocol with details about how the data was collected/verified. Adopt a rating model?
- Data Standardization: converters as a service? Who does it, the user (community) or the provider? Harmonization and mapping cannot be automatized in most of the cases.
- Versioning as a service. Notify when a new version of a VHT resource is released.
- Visualization tools should be included
- Knowledge base/graphs for indexing, query, etc.
- Licenses: types and management. Contribute agreement to be included for composite workflows?
- Information about authorized uses and documentation associated with a VHT resources as part of the metadata
- Central role of the Community

Tech stack

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Tech Stack /1

- Focus on determining points requiring further discussion
  - Clarification VHT vs DTH
  - Influence of environment: exchange, exposome, risk profile
  - Time: normalized, years, dates
  - Individuality: moving quantities, anatomical.functional partitions, metadata
  - Disease axis: disease vs illness, no axis but annotation
  - Model object type: where to put in 6D space? Models are operators, crediblity different depending on location
  - Eager computing: why (not) > model brokering
  - Trust: credibility > trueness & precision, discrete values, influence of CoU

Tech Stack /2

- Focus on determining points requiring further discussion
  - Validation: measurement chain or validation experiment, quality of data, calculation of trueness/precision in VHT
  - Data provenance: learn from others (ELIXIR), curation-standardization-annotation
  - Categories of resources: (1) model, (2) data, (3) data transformation services
  - Additional resources: compute, storage & network (geant)
  - Integration: inside & between resource categories
  - Workflows: managers, knowledge graphs, specificity of VHT vs other communities
  - UQ campaigns
  - Include clinical applications in VHT itself: technologically possible

Data Privacy and Security regulatory landscape

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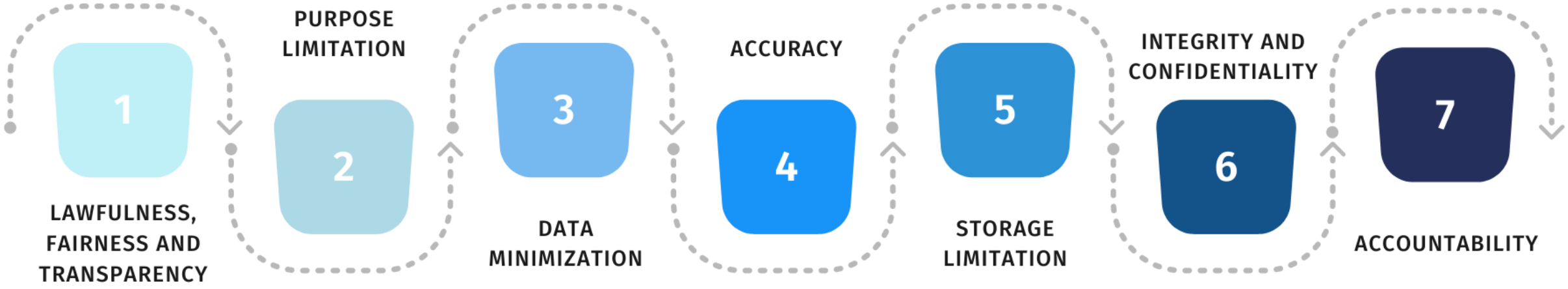
Data Privacy and Security regulatory landscape

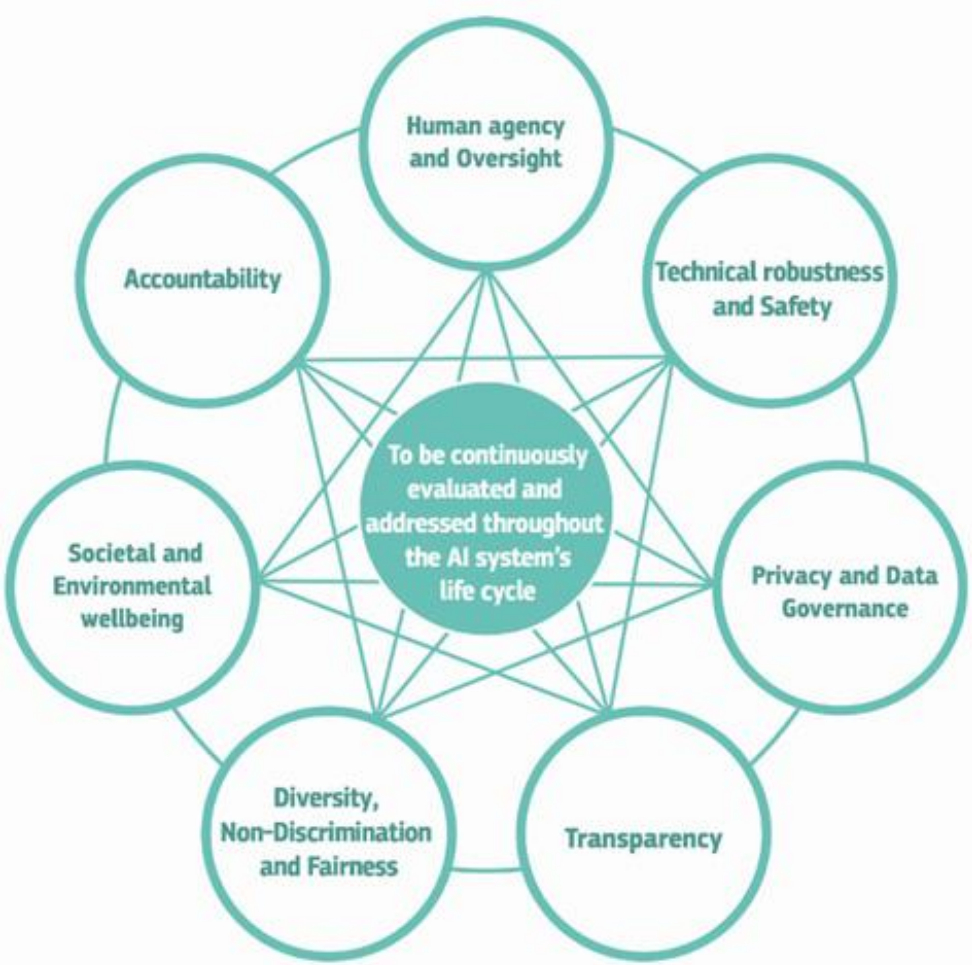
In the light of the currently applicable legislation, there are a number of gaps which need to be filled and issues that must be addressed. The debate started from 6 macro-questions:

1. ***which are the privacy conditions and safeguards that must be fulfilled so that personal data can be lawfully used in the context of VHT?***

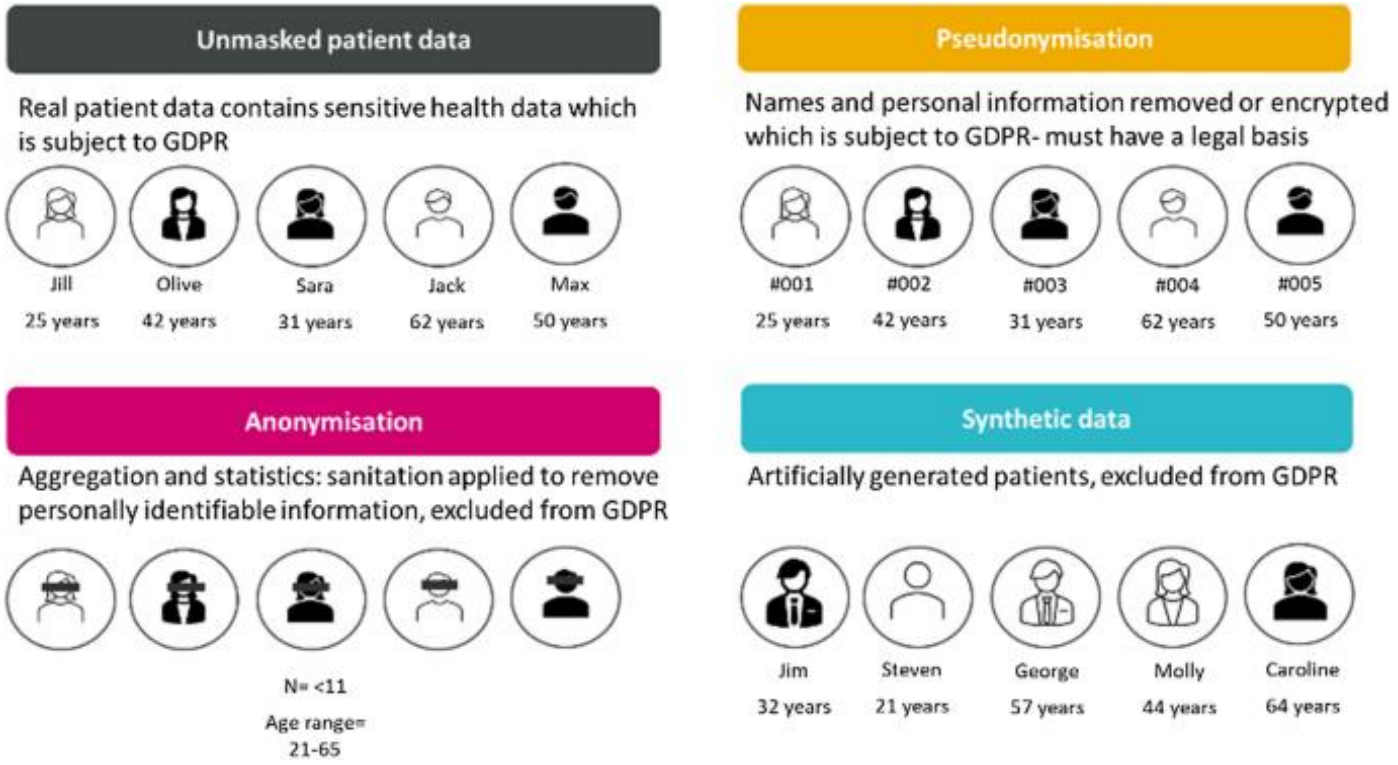


Data Privacy and Security regulatory landscape

2. *is the reuse of health data permitted in the EU for the purpose of delivering Artificial Intelligence-driven medical solutions?*
3. *which obligations apply to the developers and the users of AI-based models necessary to elaborate VHT and relevant ecosystems?*



Data Privacy and Security regulatory landscape



4. ***Can specific Privacy-Enhancing Technologies help ensuring safe and compliant processing for the purpose of* in silico *medicine?***

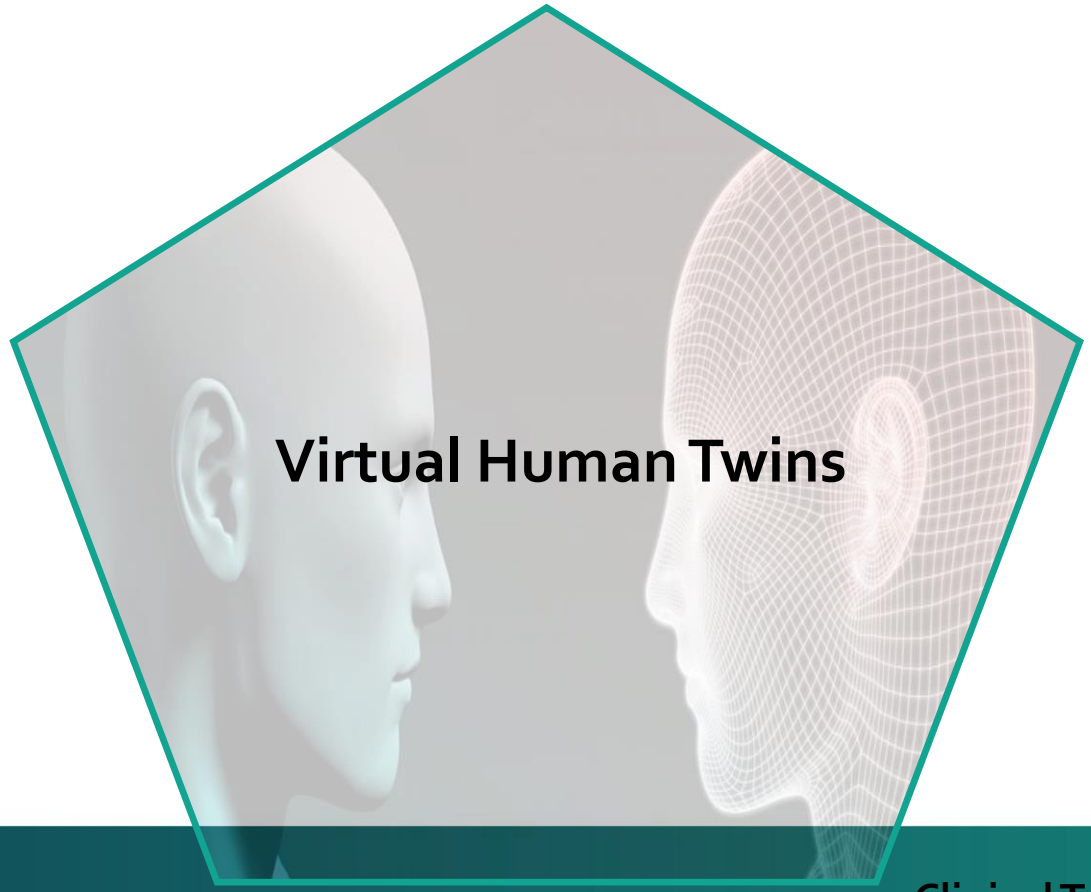
5. ***Can clinically reliable VHT be generated thanks to anonymous, pseudonymous or synthetic data?***

Data Privacy and Security regulatory landscape

6. ***Which regulatory recommendations can be made to policy-makers to ensure that the EU will soon be at the global forefront of the VHT sector?***

Data Privacy and Security regulatory landscape

The main areas of legislation which are relevant to *In Silico* Medicine and so to Virtual Human Twins ('VHT') are to date:



Data Privacy and Security regulatory landscape

EUROPEAN LEVEL

The secondary processing of data is strongly limited in the GDPR (Article 6.4 states that personal data can only be further processed for a purpose other than that identified and communicated to the individuals at the time when their data were collected, if the the secondary use is compatible with the initial purpose). However, ***re-use is permitted by default for scientific research purposes, provided that security and data minimization measures are applied to the data*** (Articles 5(1)(b) and 89 GDPR).

NATIONAL LEVEL

Notwithstanding the above simplification, Art. 9.4 of GDPR provides that member States can "*maintain or introduce further conditions, including limitations, with regard to the processing of (…) data concerning health*". As it was likely, national legislators have not implemented this delegation in a homogenous way, «***resulting in a complex and fragmented landscape for researchers to navigate***. *Consequently, differences between member States in the way the GDPR is implemented and interpreted in the area of scientific research has made data exchange between Member State and EU bodies for research purposes difficult and in some cases highly technical*» **(EU Commission – DG Health and Food Safety, '*Assessment of the EU Member States' rules on health data in the light of GDPR*')**

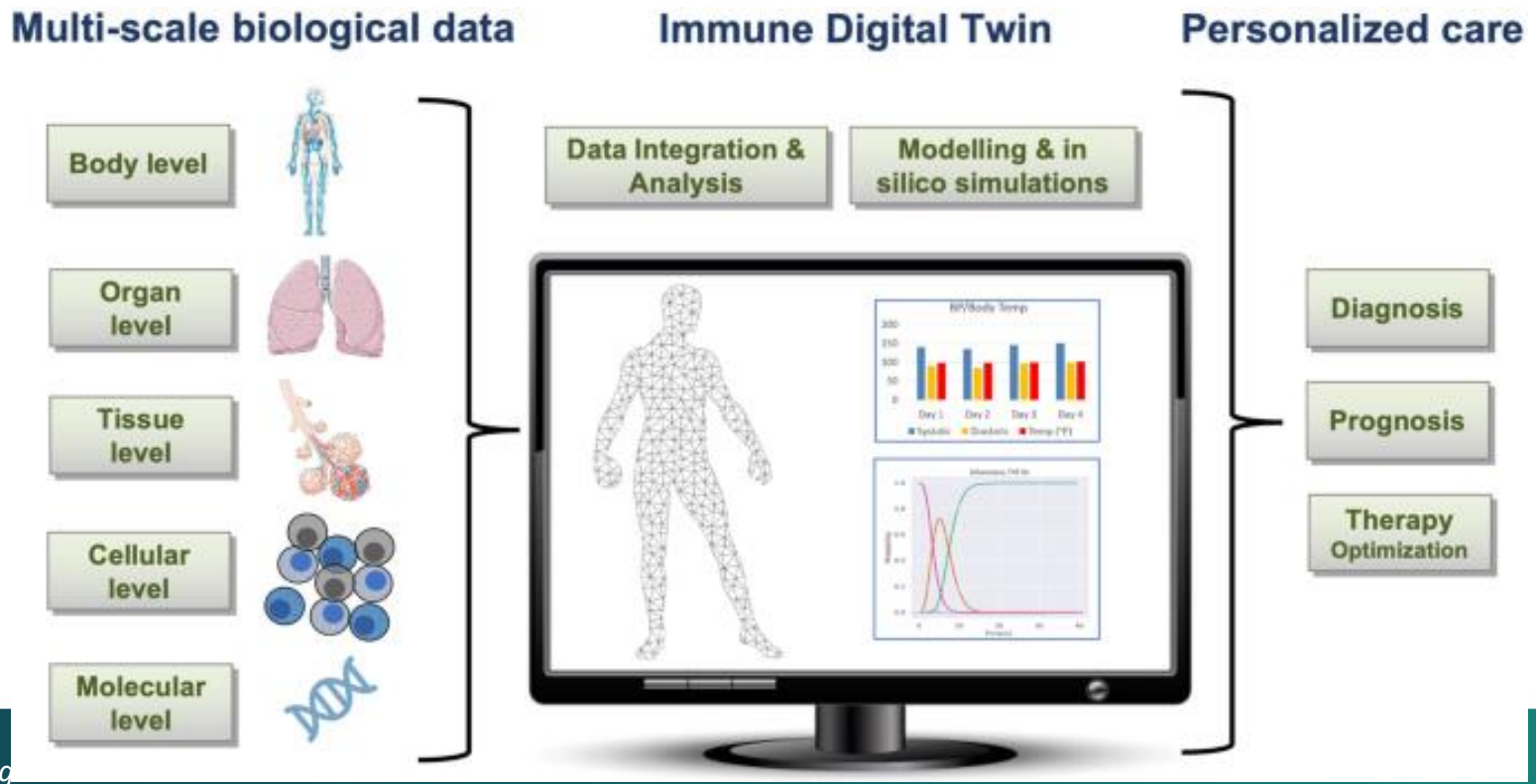
Data Privacy and Security regulatory landscape

After having assessed in-depth this fragmentation, the main novelties of the **Data Governance Act**, the **Data Act**, the **Artificial Intelligence Act** and the **European Health Data Space** were analysed in the Breakout session, with a special focus on the roles and responsibilities of the parties involved in the reuse and/or sharing of personal and health data.

Data Privacy and Security regulatory landscape

VHT will always configure 'high-risk systems' under the AI Act, whenever they will qualify as *Medical Devices* (or SaMD, *Software as Medical Devices*).

In other cases, a case-by-case assessment must be carried out to ascertain whether the VHT amount or not to an AI high-risk system.



Data Privacy and Security regulatory landscape

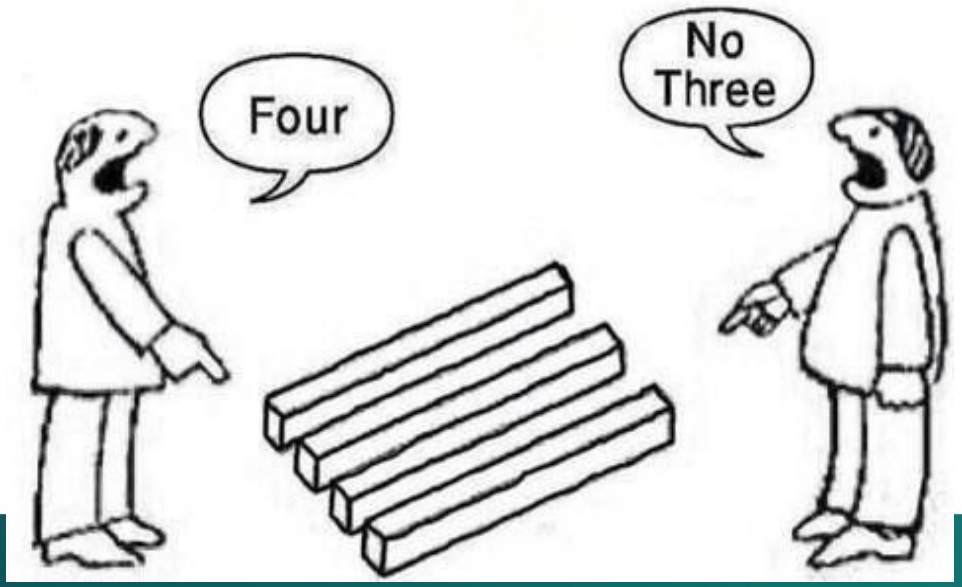
Special attention was then paid to anonymisation and pseudonymisation, comparing the very complex scenario and operational uncertainties deriving from the strict interpretation of these concepts provided by the Article 29 Working Party (now renamed as European Data Protection Board) in its – still fully applicable – Opinion 05/2014 on Anonymisation Techniques, and the novel perspective offered by EU Court of Justice in a very recent landmark ruling (dated 26 April 2023, in Case T 557/20).

TEHDAS

There is no common European interpretation of what constitutes 'sufficient anonymisation' to transform personal data to non-personal data. Researchers, stakeholders and policymakers reported a lack of guidance on anonymisation at national and international level as a key barrier to data reuse and sharing. In particular, a lack of clarity between "absolute" and "relative" anonymisation has been identified as a key issue, as well as a lack of guidance in relation to anonymization of medical images, genomic data, longitudinal data and rare diseases.

Data Privacy and Security regulatory landscape

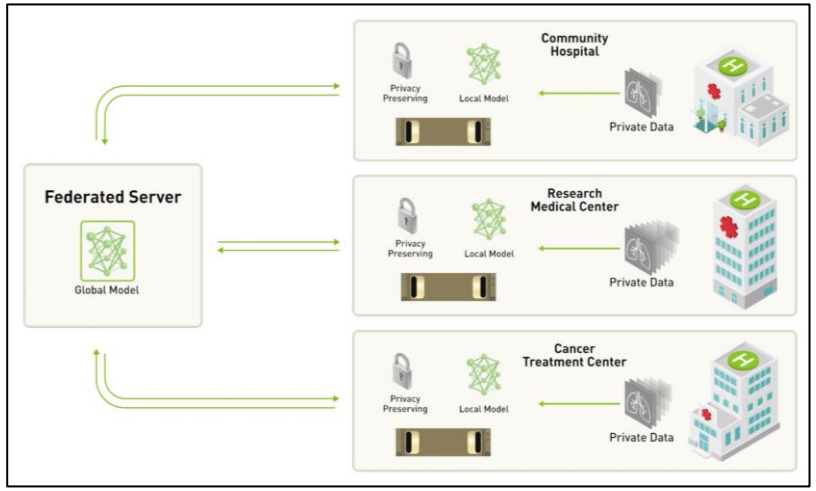
In brief, the CJEU highlighted that in order to determine whether pseudonymised information transmitted to a data recipient constitutes personal data, it is necessary to consider the latter's standpoint: **if the data recipient does not have any additional information (or other tools) enabling it to re-identify the data subjects and has no legal means available to access such information, the transmitted data can be considered anonymized and, therefore, not personal data**. The fact that the controller transmitting the data still has the means to re-identify the individuals is irrelevant and does not mean that the transmitted data is automatically also personal data for the recipient.



It's always a matter of perspective…

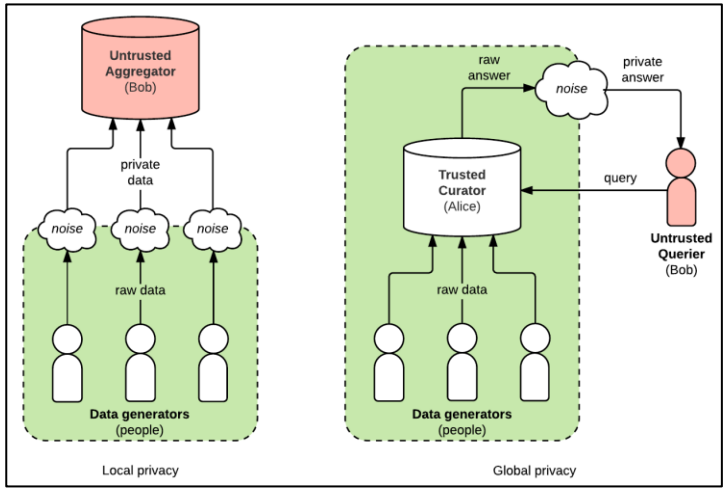
Data Privacy and Security regulatory landscape

All the hurdles and negative effects – also in terms of competitive disadvantages between member States – deriving from the lack of uniform approach in the EU regarding reuse of personal data in the healthcare sector and application of anonymization must be addressed by policy-makers, by examining more in depth the **benefits and opportunities of Privacy Enhancing Technologies, with particular reference to *Federated Learning*, *Differential Privacy* and *Data Synthesis*, also combined together**.



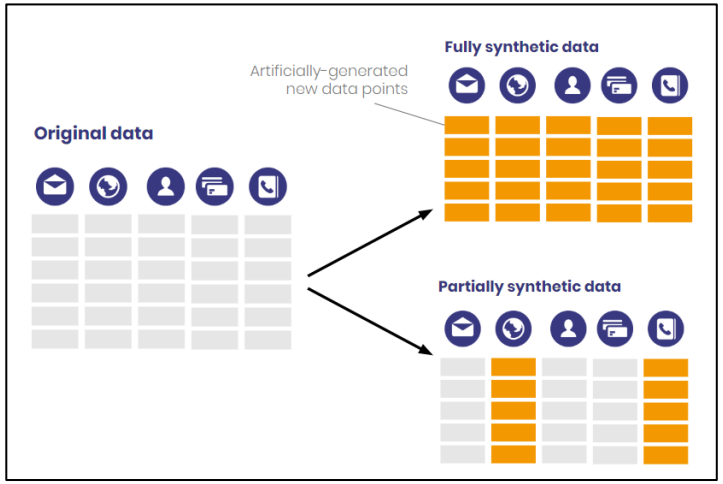
FEDERATED LEARNING

To implement data minimization and security



DIFFERENTIAL PRIVACY

To prevent re-identification and reduce the risk of data breach



DATA SYNTHESIS

To enhance minimization and safely train AI models and reduce bias without need for big data

Data Privacy and Security regulatory landscape

The attempt made by the EU to attain simplification for health data sharing and reuse (especially through the EHDS and the Data Act) must further evolve, since **the EDPS and EDPB have questioned how all these data flows and processing «*may be reconciled with Article 9(4) GDPR and the possibility for Member State law to introduce further conditions, including limitations with regard to the processing of genetic data, biometric data or data concerning health*»** (Par. 89 of the EDPB-EDPS 'Joint Opinion 03/2022 on the Proposal for a Regulation on the European Health Data Space' adopted on 12 July 2022).

In light of all these considerations, we concluded that in order to foster clinical research, *in silico* medicine and so the uptake of VHT in the EU, **all data flows between (i) Data Holders (namely data controller, *eg.* clinical institutions), (ii) Data Access Bodies and (iii) Data Users, should be built as an explicit derogation of Art. 9.4 GDPR, meaning that any eventual limitation or stricter condition for accessing and reusing health data laid down by member States at national level must not apply, being overridden by the obligations posed by the EHDS (and the Data Act)**.

Industrial collaboration & clinical partnerships

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Industrial collaboration & clinical partnerships

- Industry & clinical testimonies
- Key-points
  - Different outlooks & perspectives (patients, HCP, industry,…)
  - Hybridization of people/profiles, shadowing
  - Collaboration from the get-go
  - Monetization
  - Open science
  - VHT uptake in whole ecosystem
  - Reimbursement
  - Regulatory - MDR

User experience & co-creation

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User experience & co-creation

Sustainability

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Sustainability

World Café

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Instructions

- Format:
  - Discussions in smaller groups
  - All participants can choose in what discussions to participate.
  - Focus is on interactions, not on presentations
- Scenario
  - 3’-5’ to introduce the topic
  - 11’-13’ for free discussion or live polls
  - 2’ to wrap up with main conclusions for further development in VHT/roadmap
  - 2’ to move from one space to another

Topics & spaces world café

- **Metaverse & AR/VR** (Bernbach): Claudio Capelli
- **GPT** (Gazebo): Sanjay Pant & Sébastien Bratières
- **Standardization of data, models** (Cafeteria): Martin Golebiewski & Gerhard Mayer
- **Incentivization** (small room next to Bernbach): Liesbet Geris
- **Worst case scenarios** (Persuasion - upstairs): Raphaëlle Lesage
- **Training / retraining** (library downstairs): Bernard Staumont

Lessons learned from other initiatives

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Next steps, timeline & prioritization

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Meeting follow-up

- Minutes & slides will be shared
- Any additional thoughts, inputs, links are most welcome!

EDITH next steps

- Presentation AR/VR community: May 22nd
- Public discussion session: June 1: 12-1pm
- *Deliverable: first draft of roadmap (31/7/2023)*
- Public meetings (Q4 2023 & Q2 2024)
- Community phase
  - Writing phase via shared documents & discussions via ISW_CoP slack
  - Contribution of use cases & upload into repository
- Manifesto

EDITH use case contributions

- The EDITH repository proof of concept implementation will include selected use cases from consortium partners: from the integration with other platform to the interconnection between models developed by different research groups

- External contributors are expected too and will be reached through Advisory Board Members, synergies with the ongoing research projects, coordinated activities with relevant stakeholders, and other EU networking initiatives.

- To invite in external contributors, we will release a structured form and procedure by the end of summer.

EDITH use case contributions

- The external use cases will require:

1. **a narrative description**, e.g. intended use of the model, users involved, brief description of inputs/outputs of the model.
2. **the full dataflow**: the flow of information for any process/step in the pipeline.
3. **a detailed description and a sample of input/output data** for each computational block.
4. **a detailed description of each single computational block** in the pipeline, models and tools.
5. **the computational requirements** for each block in the pipeline.
6. **the additional functional requirements**; e.g. the need for dedicated user interfaces.
7. **the legal requirements** for both models and data; e.g. who is the data controller, the lawful basis for the processing, the need for an ISO certified data hosing service, etc.

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

VHT research and innovation, building upon current achievements, must be oriented towards establishing VHTs as a platform technology, generating evidence and value for healthcare and society as a whole. An ecosystem ensuring incentives for excellence, regulatory certainty and trust will be 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,

development, validation and adoption.

- **Ensuring the contributions, feedback, priorities, requirements, views, concerns and interests 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.

Pre-Market Consultation VHT

Priorities

- Ecosystem & roadmap
  - Large-scale initiatives (data, incentives, …)
  - International leading examples: 12 labours
  - Evolutionary ecosystem endpoint
  - Clinicians & hospitals
  - …
- Repository
- Use cases: prototypes
- Platform: outline

Priorities

- Roadmap
  - First draft

PART 1: State of the Art

- Maturity
  - In silico medicine
  - AI in health
  - Wearables & data-driven twins
- VHT initiatives & actors in Europe, identifying trends & game-changers
  - Scientific, clinical & industrial organisations
  - Infrastructures & platforms
  - Standardisation, Regulatory & HTA actors
  - Public policy at EU and member state level

PART 2 - VISION: Set the stage for the virtual human twin

- The VHT vision and barriers
  - Introduction
  - Digital Twins in Healthcare: from generic to subject-specific
  - Digital Twins in Healthcare: the life cycle
  - Barriers to the development of Digital Twins in Healthcare
  - Vision for the virtual human twin
- The VHT ecosystem
  - The VHT community of practice
  - The VHT infrastructure
  - The VHT Standards
  - The VHT Long-term sustainability
- Vision and mission of the VHT initiative and of the EDITH action

PART 3: Technology for the virtual human twin

- Organisation of resources
  - 6-dimensional framework as a backbone
  - Semantic annotation & Taxonomy
- Data
  - Data sources
  - Data management
  - Data reuse
  - Data transformation services
- Models
  - Model's exposure as data transformation services
  - Model's exposure as data generation services
  - Models' classification as data flow orchestrations
  - Models' classification by context of use
- Integration of resources
  - Workflows
  - Identification of possibilities for integration
  - Bidirectional communication with users (including knowledge generation)
- Infrastructure
  - Repository
  - Simulation platform
  - Computational resources
  - Standard Operating procedures, algorithms

PART 4: Responsible Research & Innovation related to the virtual human twin

- Regulatory science and Standards
  - Standards for data formats, data integration and data input into models
  - Standardisation of modelling
  - Standards for metadata of data and models
- Health Technology Assessment and Payers
- Ethical, legal and social aspects
- Legal aspects
  - Data privacy & protection
  - IPR management

PART 5: Uptake of the virtual human twin

- Users
  - user profiles
  - Clinical users
  - Industrial users
  - Academic users
  - Individual users
- Evolutionary Ecosystem
- Sustainability
  - Business models
  - European infrastructure

PART 6: Conclusions & recommendations

Priorities

- Roadmap
  - First draft
  - Focus on identification of
    - Topics/questions
    - Research challenges
    - Infrastructure need
    - Additional needs

Comments, questions?

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