Building the European Virtual Human Twin

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Minutes of the Ecosystem Meeting Amsterdam, July 15th – 16th 2024

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Executive summary

On July 15th and 16th 2024, the EDITH consortium organised the final Ecosystem Meeting on the Virtual Human Twin in Amsterdam. This document contains the agenda and the notes from this meeting. It is complemented by the slides of the different plenary and break-out sessions. All presentations can be found in the following drive: https://shorturl.at/PSGhh.

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Acronyms

Acronym	Full name
1+MG	+1 million genome
AI	Artificial Intelligence
AMdEX	Amsterdam Data Exchange
API	Application programming interface
ASME	American Society of Mechanical Engineers
BBCT	Bologna Biomechanics Computer Tomography
CEN	European Committee for Standardization
CENELEC	European Committee for Electrotechnical Standardization
CSA	Coordination and Support Action
CWL	Common workflow language
DT	Digital Twin
DTH	Digital Twin in Healthcare
EC	European Commission
EHDS	European Health Data Space
EHR	Electronic healthcare record
EHR	Electronic health record
ELSI	Ethical legal and social issues
EM	Ecosystem Meeting
EMA	European Medicine Agency
EPF	European Patients' Forum
EU	European Union
EUCIAM	European Cancer Imaging
FAIR	Findable, accessible, interoperable, reusable
FHIR	Fast Healthcare Interoperability Resources
GDPR	General Data Protection Regulation
GUI	Graphical User Interface
HC	Healthcare
HPC	High performance Computing
HPC	Healthcare provider
ICU	Intensive care unit
ID	Identity
IEC	International Electrotechnical Commission
IPCEI	Important Projects of Common European Interest
ISO	International Organisation for Standardization
ISW_CoP	In Silico World Community of Practice
IVDR	In vitro medical device regulation
MDDT	Medical device development tool
MDR	Medical device regulation
NICU	Neonatal intensive care unit
OMOP	Observational Medical Outcomes Partnership (healthcare data standard)

PoC	Proof of concept
QA	Quality assessment
SaMD	Software as a Medical Device
SDO	Standards defining bodies
SSH	Social sciences and Humanities
TC	Technical committee
TRL	Technology Readiness Level
TS	Technical specification
USA	United States of America
VHT	Virtual Human Twin
WP	Work Package

1 Purpose of the meeting

1.1 Meeting objective

The EDITH coordination & support action is working on facilitating an ecosystem-driven creation of the roadmap for the Virtual Human Twin (VHT). The Virtual Human Twin (VHT) is envisioned as 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. With the help of the consortium, advisory boards, experts and the wider ecosystem (though public meetings and a public feedback phase), a draft of the VHT roadmap was created, discussed and extended.

This second and last EDITH ecosystem meeting has as its main purpose to inform the ecosystem of progress made on the Virtual Human Twin (VHT) roadmap and proof-of-concept EDITH infrastructure, to obtain input on the last open elements in the VHT roadmap and to start the process of ecosystem validation for the VHT roadmap and its final recommendations. The meeting will be the conclusion of the work performed by the EDITH consortium, expert advisors and the entire ecosystem in a range of activities including online meetings, surveys, online discussions, public writing and physical expert and ecosystem meetings. The meeting consisted of a mix of plenary sessions and breakouts. The strategic plenary sessions addressed several key challenges for the VHT related to infrastructure, regulatory, user uptake and embedding in society. Other plenary sessions showcased the proof-of-concept EDITH infrastructure and discussed and extended the final recommendations for the roadmap. The breakouts discussed both technical (infrastructure, use cases, user roles) and non-technical (collaboration, communication, health economics and standards) topics.

The meeting was hosted by EDITH partner UvA at the Royal Institute of the Tropics in Amsterdam. 222 people registered for the meeting, representing all aspects of the ecosystem: academia, industry, research institutes, hospitals, HPC centres, HTA agencies, legal offices, ethics societies, as well as policy makers, social sciences, and civil and patient organisations. The chart below shows the breakdown of the participants according to their affiliation and background. The ELSI category includes participants with backgrounds in ethics, law, social sciences and standards. Industry encompasses devices, pharma, modelling, software and consultancy. The infrastructure category refers to people working on simulation platforms and people working on compute infrastructure. Finally, the research category groups researchers active the following fields: AI, data, devices, imaging, modelling and omics.

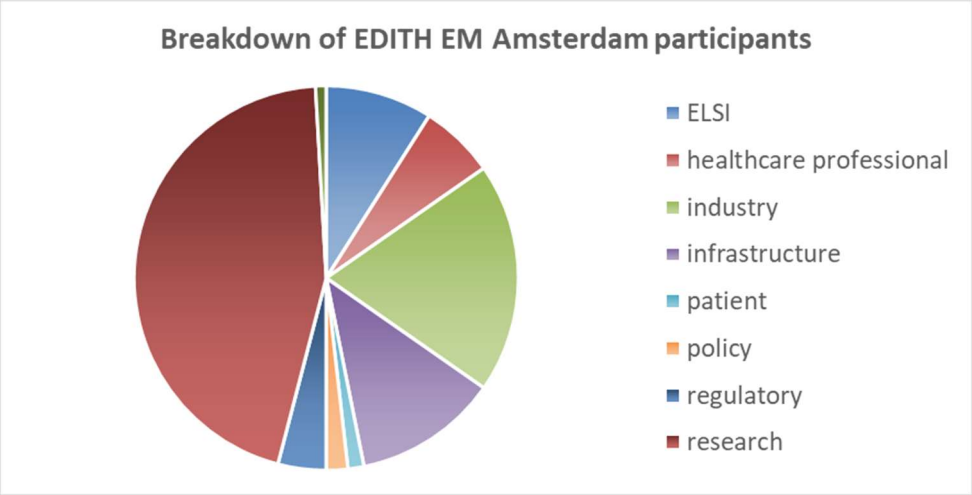


Figure 1: breakdown of the EDITH EM Amsterdam participants.

1.2 Agenda

Day 1: Monday 15/7/2024

12:00-13:00 *Lunch*

13:00-13:40 Plenary session: Welcome

- Introduction by the meeting host (*Barry Fitzgerald*)
- Welcome address by the local hosts (UvA rector *Peter Paul Verbeek,* host *Alfons Hoekstra*)
- Welcome address by the European Commission (*Margherita Fanos & Kyriacos Hatzaras*)
- Introduction to EDITH, VHT roadmap & purpose of the meeting (*Liesbet Geris*)

1.40-2.55 Strategic session 1: Healthcare-related infrastructures

- Keynote: *Jens Habermann* (BBMRI-ERIC and European Life Science Research Infrastructures)
- Other members of the panel:
    - *Kyriacos Hatzaras* (European Commission - DG CNECT)
    - *Jeroen Beliën* (Amsterdam UMC)
    - *Claire Biot* (Dassault Systèmes)
    - *Christopher Esterhuyse* (University of Amsterdam)

14:55-15:15 *Coffee break*

15.15-16.30 Plenary session: EDITH proof of concept infrastructure from user perspective

- Researchers : connecting resources in the VHT
    - User: *Caroline Roney, Laura Bevis* (Queen Mary University of London)
    - Developer: *Amaryllis Raouzaiou* (Athena Research and Innovation Center)
- Communities : federated nature of the VHT
    - User: *Martin Golebiewski* (Heidelberg Institute of Theoretical Studies)
    - Developer: *Sofia Karvounari* (Athena Research and Innovation Center)
- Industry : interactions of company services/activities with VHT (*ELEM - Athena*)
    - User: *Mariano Vázquez* (ELEM)
    - Developer: *Evita Mailli* (Athena Research and Innovation Center)
- Healthcare providers : deployment at bedside in clinical workflows
    - User: *Vincent Uyttendaele* (Insilicare)
    - Developer: *Konstantinos Triantos* (Athena Research and Innovation Center)
- Patient : functionality to upload own data in the VHT
    - User: *Sabato Mellone* (University of Bologna)
    - Developer: *Amaryllis Raouzaiou* (Athena Research and Innovation Center)

16.30-16.40 Introduction of the breakout sessions (*Liesbet Geris*)

16:40-17:00 *Coffee break*

17:00-19:00 Breakout sessions

- Digital health economics: *Edwin Morley-Fletcher* (Lynkeus); *Enzo Fabiani* (DigitalEurope)
- Use cases & proof-of-concept infrastructure: *Sabato Mellone* (University of Bologna)
- Standards: *Martin Golebiewski* and *Gerhard Mayer* (Heidelberg Institute of Theoretical Studies)
- Communication strategy & stakeholders: *Davide Montesarchio, Martina Contin, Goran Stanic and Zita Van Horenbeeck* (VPH institute)
- Balancing roles and responsibilities: how to define user profiles: *Gökhan Ertaylan*, *Simon Denil, Frederic Jung* (VITO); *Frank Rademakers* (UZ Leuven - KU Leuven)
- EU-AM-AP collaboration: *Liesbet Geris* (VPH institute), *Thiranja Prasad Babarenda Gamage* (AIB), Anna Niarakis (University of Toulouse), Gary An (University of Vermont Medical Center)
- Unlocking research infrastructures to broader community: *Marco Verdicchio, Sagar Dolas* (SURF); *Marian Bubak, Piotr Nowakowski* (Cyfronet)

19:00-22:00 Dinner

Tuesday 16/7/2024

8:30-9:30 Plenary session: reporting of breakouts + questions for entire audience (*breakout session chairs*)

9:30-10:45 Strategic session 2 : Regulatory science and policy update

- Keynote 1: *Aldo Badano* (USA-FDA)
- Keynote 2 : *Kelly Brown-Plueschke* (EMA)
- Keynote 3 : *Nada Alkhayat* (European Commission, DG SANTE)

10:45-11:15 *Coffee break*

11:15-12:30 Strategic session 3 : Healthcare professionals & patients

- Keynote: *Folkert W. Asselbergs* (Amsterdam UMC & University of Amsterdam)
- Other members of the panel:
  - *Gernot Marx* (Uniklinik Aachen)
  - *Job Leenen* (Isala Hospital)
  - *Valentina Strammiello* (European Patients' Forum)
  - *Frank Rademakers* (UZ Leuven – KU Leuven)

12:30-13:30 *Lunch*

13:30-14:45 Strategic session 4 : Bringing the VHT to society

- Keynote: *Signe Mežinska* (University of Latvia)
- Other members of the panel:
  - *Jolien Roovers* (Dept. Economy, Science& Innovation of the Flemish government)
  - *Rossana Alessandrello* (AQuAS)
  - *Frank van Praat* (KPMG-NL/AMdEX)
  - *Marco Verdicchio* (SURF)

14:45-15:45 Plenary session: recommendations & validation

Short presentations of different aspects, public discussion, active participation (*Liesbet Geris*)

15:45-16:00 Next steps & wrap-up (*Liesbet Geris & Barry Fitzgerald*)

2 Plenary Session: Welcome

Slides: EDITH_EM_Amsterdam_master file

Introduction by the meeting host (Barry Fitzgerald)

Welcome address by the local hosts

- UvA rector Peter Paul Verbeek evoked the 400 year history of University Amsterdam in bringing fields together and connecting them to society. The academic world is being inspired by what comes from outside. It is necessary to push the Academic world to find its way to the other aspects of life and take responsibilities for the societal implications. EDITH is doing this, changing the scientific world and society.

- Host Alfons Hoekstra took the audience back to the early days of the *in silico* medicine field, the VPH conference organized in the same venue. Over the past decades, research activities have focused on technology and infrastructure, now it is time for the societal impact.

Welcome address by the European Commission (Margherita Fanos & Kyriacos Hatzaras), providing overview of the VHT, showing the different initiatives and their main goals.

Introduction to the EDITH project, VHT roadmap & their status (Liesbet Geris), explaining the aim of the meeting (*cfr* Section 1), along with the goals of the different sessions.

3 Strategic sessions

3.1 Health-related infrastructure

Slides: EDITH_EM_Amsterdam_SS1
Video: https://www.youtube.com/watch?v=PCy_-U8JJXs

Keynote: Jens Habermann (BBMRI-ERIC and European Life Science Research Infrastructures)
Other members of the panel:

- *Kyriacos Hatzaras (European Commission - DG CNECT)*
- *Jeroen Beliën (Amsterdam UMC)*
- *Claire Biot (Dassault Systèmes)*
- *Christopher Esterhuyse (University of Amsterdam)*

This session included participants from academia, industry and EU infrastructures, as well as policy makers, discussing their perspective on health related research infrastructures, the vision, the requirements and possibilities for collaboration.

Presentations

- **Jens Habermann:** introduced BBMRI and the LSRI. Emphasized the importance of cooperation and avoid fragmentation, find interfaces and avoid gaps. Discussion on biobanking, data integration centres, co-creation, relevance of EHDS, federated infrastructure. Examples were from cancer.
- **Kyriacos Hatzaras**: reference to calls in GAP/evaluation phase (Digital-ICU, VHT platform). Synergies with other large-scale initiatives (*e.g.,* 1+MG, EUCIAM, Destination Earth)
- **Jeroen Beliën**: lead architect Health-RI. Discussed National nodes of European Infrastructures and possible links to (future) VHT.
- **Claire Biot**: VT for accelerating innovation and patients' centricity, importance for paediatrics and regulatory science. Trust comes through the platform.
- **Christopher Esterhuyse**: introduction to Amsterdam data exchange project (AMdEX).

Discussion

- Do we need a platform for research or should we go to one that includes industry, clinical practice and other collaborators?
  - From onset all possible users should be included
  - Importance of fitting into clinical workflow
  - Requires open mindedness, trust, equal partnership & co-creation
- Should we condense hardware or rather go for distributed data and compute solutions
  - Trust, economics of scale
  - Many research infrastructures work in a distributed manner, but sometimes centrally hosted repositories are necessary
  - Standards are necessary in order for federation to work
- Do all the acts (AI act, Data act,…) work?
  - Acts are challenges but also create conditions for trust

  - Data should be hosted on sovereign cloud so it cannot leave the EU
  - Sometimes data needs to stay with the controller but the learnings can travel.
  - Fundamental tension, needs to be looked at from design phase but will always require adaptation
- How can infrastructure help realize the regulatory approval: should we complement technology readiness levels with regulatory readiness levels?
  - Look at process and identify which thresholds you want to lower – not remove as checks are necessary - and focus on those.
  - EC as funder is funding best practices through projects (*e.g.,* TOOL-05-03 call) but also through horizon Europe analysis
- If we could start from a blank slate, would you go for 1 integrated research infrastructure or multiple ones?
  - Different platforms to cater to different needs (or changing needs)
  - If collaborative openness is there, multiple platforms is ok
  - Balancing threats: 1 platform might be too inflexible, but many (federated) platforms might make things messy.
- Joint controller units in federated structures
  - Possibility for speeding up process by semi-automation, provided there is a buy-in from lawyers
  - Drafting laws has similarities to programming (best practices, templating, …): systematic approaches can lead to automation and lowering the bar
  - Legal compliance is not only on GDPR but also IPR and other aspects

3.2 Regulatory science and policy update

Slides: EDITH_EM_Amsterdam_SS2
Video: https://www.youtube.com/watch?v=fhE_awzhJpg

Keynote 1: Aldo Badano (USA-FDA)
Keynote 2 : Kelly Brown-Plueschke (EMA)
Keynote 3 : Nada Alkhayat (European Commission, DG SANTE)

This session consisted of 3 keynote speakers from a regulatory and policy background, discussing various regulations and policies related to the VHT as well as tools and approaches to facilitate the credibility assessment and uptake of the VHT technologies.

Aldo Badano: Dr. Badano introduced regulatory science tools of FDA. The Catalogue of Regulatory Science Tools provides a peer-reviewed resource for medical device companies to use where standards and qualified Medical Device Development Tools (MDDTs) do not yet exist. These tools do not replace FDA-recognized standards or MDDTs. This catalogue collates a variety of regulatory science tools that the FDA's Center for Devices and Radiological Health's Office of Science and Engineering Labs developed. These tools use the most innovative science to support medical device development and patient access to safe and effective medical devices[1,2]. Dr. Badano showed several examples of the use of digital twins and the synergies between real models and digital models. Regulatory priorities in the area of DTs were underlined.

Kelly Brown-Plueschke: Dr. Brown-Plueschke introduced what EMA[3] is for human healthcare and veterinary science, and discussed the possibilities for partners (industry & academia) to interact with EMA across the medicine life cycle. She furthermore discussed different initiatives EMA is involved in in the context of big data and real world evidence (*e.g.,*

[1] https://www.fda.gov/medical-devices/science-and-research-medical-devices/catalog-regulatory-science-tools-help-assess-new-medical-devices
[2] https://cdrh-rst.fda.gov/
[3] https://www.ema.europa.eu/en/homepage

DARWIN) and outlined the involvement and developments related to the European Health Dataspace[4] and the AI act.

Nada Alkhayat: Dr. Alkhayat focused on 3 main regulatory/policy topics of relevance for the VHT: (1) EU medical device regulation (MDR) and *in vitro* medical device regulation (IVDR) – especially the impact on medical device software and the life-cycle approach; (2) Key MDCG Guidance for software and AI enabled medical devices (Qualification & Classification; Cybersecurity; Clinical Evaluation /Performance Evaluation); (3) Additional requirements from the AI Act (and its interplay with MDR/IVDR).

3.3 Healthcare professionals & patients

Slides: EDITH_EM_Amsterdam_SS3
Video: https://www.youtube.com/watch?v=6YXCOSPKVsA

Keynote: Folkert W. Asselbergs (Amsterdam UMC & University of Amsterdam)
Other members of the panel:

- *Gernot Marx (Uniklinik Aachen)*
- *Job Leenen (Isala Hospital)*
- *Valentina Strammiello (European Patients' Forum)*
- *Frank Rademakers (UZ Leuven – KU Leuven)*

This session included participants from various healthcare professions (medical doctors and nurses), representatives of patient organisations as well as a representation of the hospital innovation management. Key challenges were discussed related to trust, uptake, data, interoperability and capacity building.

Presentations

- **Folkert W. Asselbergs:** discussed existing risk predictors in cardiovascular diseases and their limitations. Showed examples of digital twins initiatives that aim to overcome these limitations and increase accessibility and participation.
- **Gernot Marx:** discussed challenges related to clinical practice, advocated for rapid uptake of new technologies, talked about the availability of high volume, diverse data. Explained the example of sepsis.
- **Job Leenen:** showed a tangible example of clinical reality (risk of alarm fatigue in NICU) and discussed added value of digital twins in that context.
- **Valentina Strammiello**: discussed EHDS and the patients' support for data sharing. Advocated for trust, transparency and patient control over their data. Discussed need for capacity building and digital health literacy.
- **Frank Rademakers :** discussed challenges of interoperability, automation and implementation in electronic health record (triggering analysis when relevant, not only when requested). Addressed the topic of informed consent and patient generated data.

Discussion

- How can we build trust?
  - Transparency, knowledge & education
  - User-friendliness, accessibility
  - Via networks, family, friends
  - Appropriate trials for evaluation of digital twin solutions
  - Patient trust via health-care providers
- Synthetic data
  - If synthetic data is validated, it will be used (*e.g.,* radiology)
  - Will speed up advances

[4] https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en

    - The quality of the data is key
- What happens when mistakes happen? (Knowledge on the legal possibilities lead to empowerment and trust)
    - Humans make mistakes – not intentional, caused by circumstances. Hospitals have insurance and no-fault claims for handling those. Should be the same for tech too. Claim should not go back to developers and builders of VHT.
    - Liability needs to be clear. Transparency is important.
    - Human will remain in the loop but needs to be trained to correctly use the predictions
    - Similar to any new developments & treatments > prospective trials
- Exposome – linking parameters of environmental records to health records
    - Location data: small particle pollution has been shown to be strongly linked to cardiac events. E.g. location data could be used to contact patients based on location basis and urge them to stay inside
    - Pollutants, noise, temperature.
    - Exposome shows correlation to health but within same regions, there are further important factors such as education and salary
- Education: who & when?
    - First HCP before (or at the same time) patients as they will need to work in tandem so without educated HPC this will work.
    - HPC and patients should receive the same information, perhaps in different format
    - Information should be offered so informed co-decision making is possible
    - Patients might not want to take up the information.
    - Patient in centre might give a wrong message that patient is the problem. Patient has a problem and is part of the solution.
- How can data that is not measurable ("human aspect" of) be included in VHT?
    - Not everything can be captured in data. The human aspect is task for the HCP, way to add value
    - Difficult to automate
    - Part of the conversation between patient and HPC – parts might actually be captured in the future.
    - Importance of human interaction. Should not necessarily be capture by AI or tools – even when it might become possible in the future.

3.4 Bringing the VHT to society

Slides: EDITH_EM_Amsterdam_SS4
Video: https://www.youtube.com/watch?v=OkGULwTy54E

Keynote: Signe Mežinska (University of Latvia)
Other members of the panel:

- *Jolien Roovers (Dept. Economy, Science& Innovation of the Flemish government)*
- *Rossana Alessandrello (AQuAS)*
- *Frank van Praat (KPMG-NL/AMdEX)*
- *Marco Verdicchio (SURF)*

This session discussed several key challenges related to the uptake of the VHT in society – from the perspective of social sciences, policy, procurement of innovation, health technology assessment, technology translation and community building.

Presentations

- **Signe Mežinska** : Discussed socio-ethical benefits and risks of digital twins in healthcare, using examples of informed consent, personal data protection, responsibility, liability and new questions coming up (in VHT) compared to previous situations. Talked about how to empower patients in the context of the VHT, how to address needs of different groups and ensure fair access to healthcare. Discussed Eurobarometer results.
- **Jolien Roovers** : Provided policy perspective from Flanders. Provided an overview of the Flemish ecosystem and its involvement in (pan)EU initiatives such as the Vanguard initiative on smart health.

- **Rossana Alessandrello** : Explained value-based procurement: value chain, innovation procurement as a risk-sharing approach, actors and activities needed to increase maturity levels of new products.
- **Frank van Praat** : Discussed compliance-by-design. Despite trustworthiness of platform, use can still go wrong. Audit looks at whole platform as well as use of it in the organization.
- **Marco Verdicchio** : Explained the activities of SURF, the Dutch ICT cooperative for education and research and capturing the complete e-infrastructure ecosystem. Discussed access, support and collaborations with (inter)national initiatives and organisations.

Discussion

- Are there surprises in the Eurobarometer results?
    - It is clear that science is still considered too complex to understand. Outreach and education should be part of the creation of the VHT from the get go.
        - A lot is already available in terms of GUIs, tools and communication material. It is important to not just inform but to provide tools.
    - Data and technologies, when not used in proper context, can lead to wrong conclusions - which than reflects badly on science in general (*cfr* child benefit scandal, 'kinderbijslagaffaire' in the Netherlands)
    - Power relationship that is experienced by many people (could be influenced by experiences during COVID?) can be altered by providing evidence-based solutions to empower patents and providing interfaces for increasing health literacy.
    - Environment is very important > include exposome in VHT
- Bringing VHT to society relies heavily on adoption by market – do we rely too much on market (stuck in growth paradigm) to deliver benefits to patients (needing a care paradigm)?
    - It should be a demand-driven process identifying unmet needs by public administration, not a technology-push from developers.
    - Explain what is the cost/opportunity – how to make this innovation viable, how does this investment lead to gain (savings, increased income).
    - Interest in VHT is there from organisations and institutions. We can improve on confidence by showing results and credibility.
    - Interoperability is a key concept, even if different organisations have different needs. Shift towards open science tools.
    - Market is a given and insurers have major power on HC market. For example, the Netherlands has a very cost-efficient HC system where technologies are only adopted if there is a benefit from a cost perspective.
    - Many lessons can be learned from access to medicines. Care must be taken that the market does not influence VHT development in the wrong way (*e.g.,* excluding patient groups, rare diseases *etc.*)
    - Collaboration in a public-private partnership bringing different players together. Pre-competitive procurement.
- What about the legacy value of my personal VHT after death?
    - Empowerment: patient can take decision with HCP on health status, patients decide if VHT dies with them.
    - From an implementation and technical perspective: this would be good data for validation and (re)training. However, this might lead to data explosion if everything is kept > data management tools to extract meaningful data based on metadata.
    - Ethical perspective:
        - your data might be relevant for your family members. Important to add protection to those data too – who will use it? for what purpose?
        - Information on family members might be used by insurers to calculate premiums (*e.g.,* in case of hereditary conditions)
    - There are discussion on this in the literature and solution put forward is autonomy and informed consent. But it means we need to ask and we ned to explain what the implications could be.

4 Plenary session: EDITH proof of concept infrastructure from user perspective

Slides: EDITH_EM_Amsterdam_PoC

This session showcased a number of features of the **EDITH proof of concept (PoC) infrastructure**. The aim of the PoC infrastructure is to **collect resources** (data sets, models, algorithms, *etc.*) and to identify developer and user needs and requirements to in**form the VHT roadmap**. This PoC infrastructure is fully independent from the official VHT infrastructure that will be built and for which the European Commission has launched the procurement process.
To illustrate the different aspects of the infrastructure, the session followed a **user-based approach**, where different user profiles first presented their own developments. These were then followed by a presentation from the EDITH PoC infrastructure developers showing how and where relevant features were included in the PoC infrastructure. The EDITH PoC infrastructure is undergoing final technical checks and will be released by early October.

Researchers : connecting resources in the VHT

- User: *Caroline Roney, Laura Bevis* (Queen Mary University of London)
  - Cardiovascular Use Case: Personalised Models for Atrial Fibrillation
- Developer: *Sofia Karvounari* (Athena Research and Innovation Center)
  - Working with CWL, User experience, collaborative research, incentives

Communities : federated nature of the VHT

- User: *Martin Golebiewski* (Heidelberg Institute of Theoretical Studies)
  - FAIRDOM SEEK: share your data and models FAIR
- Developer: *Sofia Karvounari* (Athena Research and Innovation Center)
  - Required adaptations, benefits

Industry : interactions of company services/activities with VHT (*ELEM - Athena*)

- User: *Mariano Vázquez* (ELEM)
  - Virtual Human Twins: the future of medicine now
- Developer: *Evita Mailli* (Athena Research and Innovation Center)
  - How to connect, what services are available

Healthcare providers : deployment at bedside in clinical workflows

- User: *Vincent Uyttendaele* (Insilicare)
  - Glucose control in the intensive care
- Developer: *Amaryllis Raouzaiou* & *Konstantinos Triantos* (Athena Research and Innovation Center)
  - Criteria for inclusion, services

Patient : functionality to upload own data in the VHT

- User: *Sabato Mellone* (University of Bologna)
  - Bone fracture risk prediction using the Bologna biomechanical computed tomography solution
- Developer: *Amaryllis Raouzaiou Konstantinos Triantos* (Athena Research and Innovation Center)
  - Process (registration, access, upload), benefits for patients

5 Breakout sessions

Slides of breakout reports session: EDITH_EM_Amsterdam_Breakout_report

5.1 Digital health economics

Slides: EDITH_EM_Amsterdam_Breakout_DHE
Breakout chairs: Edwin Morley-Fletcher (Lynkeus); Enzo Fabiani (DigitalEurope)

The session aimed at discussing principles from the field of digital health economics and investigate how they can be applied in the context of the VHT and support its sustainability.

5.1.1 Digital revolution

The expansion of digital technologies and the proliferation of modular production methods have unlocked opportunities for a completely different type of firm. In place of vertically and horizontally integrated corporate behemoths, or industrial conglomerates, there has been the **emergence of ecosystems orchestrators** with the ability of **collaborating** with a range of **interdependent complementors** to **create and capture value through the establishment of a specific structure of relationships and alignment**.

The digital revolution has given rise to economies of a different nature: it has made it possible to **identify and exploit complementarities** across users, machines, and sectors through the use of data, software, and networks. Digital technologies enable individuals to connect with other individuals and organisations with minimal friction. This **reduction of uncertainty** helps reduce the need for ownership of resources, which was previously compensating by hierarchical control excessive transaction costs.

5.1.2 Platform ecosystems

Platform ecosystems are **organisational structures** which are different from both hierarchies and markets. High transaction costs lead to hierarchies and command economies, low transaction costs lead to market solutions. Modularization and the subsequent reduction of frictional transaction costs are more likely to lead to the emergence of ecosystems, if there is at the same time a significant need for coordination that cannot be dealt with in markets, but which requires the non-hierarchical **alignment orchestration** provided by a platform.

Multi-sided platforms are ecosystems orchestrated by platforms which cumulate mutually reinforcing network effects through the implicit support derived by each of the sides served by the platform, often needing to subsize at least one side to overcome the "chicken and egg" problem and enable growth and subsequent adoption on the other side.
Digital platform firms and their ecosystems appear to be, for the time being, the organisation model showing the greatest capacity to scale, thanks to its capacity to internalise network effects by producing at loss on one side while eventually compensating it with profits on other sides. Digital platform firms thus **initially appear to go for growth, not for profits**, gathering this way huge amounts of equity from investors who value this approach, turning traditional industry dynamics on their head. This phenomenon is so quick and intense that it may drive unregulated competition to a "winner takes all" outcome.

All in all, ecosystems and platform seem to represent until now the emblematic organisational form of the digital age. **Platform ecosystems** have proved to be a powerful force in reshaping industries and, in all likelihood, they should show a comparable potential of disrupting innovation also in healthcare, eventually bringing about the **cost revolution** implied by prioritising predictive medicine through the growing adoption of Virtual Human Twins. Of course, such a transition risks to determine an immediate increase of costs while allowing for significant longer-term economies. This is another type of chicken and egg situation.

It is highly to be commended that the European Commission has engaged in initiating such an ambitious and far-reaching transformation of the EU healthcare systems as implied by the Virtual Human Twins by squarely facing the chicken and egg issue of fostering the VHT ecosystem while procuring a Platform for Advanced Virtual Human Twin Models, and showing all willingness of significantly funding new research and innovation initiatives in this crucial area. The expectation is therefore to trigger big changes in the next years, precisely leveraging the bold realisation of an essential precondition and strategic orchestration vantage-point as provided by this platform.

5.1.3 Business models for VHT

Various **business models** can be implemented by a variety of stakeholders within a mature sustainable VHT ecosystem, based on mutual incentives and advantages deriving from the interaction through the same platform. Different incentives and strategies can be explored to facilitate the adoption of VHT tools in the clinical practice, such as:

- **Assessing the economic** benefits of adopting VHT solutions compared to traditional ways of treating patients – on the basis of the known data about the costs of a given illness and of the relevant treatment; the target could be the payer of the health service (*e.g.,* insurance companies, public and private providers) with a patient-centric focus on outcome instead of established DRG performances
- **Experimenting new patient management and onboarding strategies**, so to offer incentives to care providers to adopt novel tools and technologies minimising costs and optimising treatment outcomes. The target could be decision makers managing the resources to be allotted to care providers for handling specific conditions (*e.g.,* chronic disease patients);
- **Demonstrate superior treatment outcomes** associated with the adoption of VHT tools if compared with standard practice; the target could be clinicians specialised in the area interested by the application of a given VHT approach.

Various models for applying VHT tools could be implemented, **both locally** (on premise at the hospital) **and as a service** – accessing the models directly within the platform.

The platform could **facilitate the validation** of novel tools and the **sharing** of relevant data by **incentivising** the offering of clinical expertise for validation, the availability of validated solutions and simulations to be accessed with appropriate IPR definition.

5.2 Use cases & proof-of-concept infrastructure

Slides: EDITH_EM_Amsterdam_Breakout_PoC
Breakout chair: Sabato Mellone (University of Bologna)

The aim of the session was to describe the purpose of the implementation of an EDITH PoC implementation of the infrastructure and show how to engage with it.

The session was a lively discussing around a few key questions from the ecosystem and meeting participants. Questions pertained to reasons for use of the EDITH PoC infrastructure

Reasons for using the repository and the possibilities this repository might provide that cannot be found elsewhere or in another way.
Clarifications were provided on these points. EDITH is releasing its own PoC infrastructure (catalogue, repository, platform) with as the strong underlying motivation to collect additional use cases and identify further technical, legal, or other specifications that would arise from the use of/interaction with the PoC infrastructure. All of this will therefore serve to inform the

roadmap and its finalization. The encouragement to the participants was to use the PoC with this spirit and especially to verify and possibly contribute to the text of the Roadmap.

Connection with VHT infrastructure under tender
There is no link between the EDITH project/consortium and the VHT tender. EDITH is a coordination and support action funded under the Digital Europe program that is building the ecosystem and coordinating the writing of the roadmap for the realisation of the Virtual Human Twin. The tender process is a completely separate process, managed by the European Commission. The roadmap, the collected uses cases and resources, as well as the lessons learned from the EDITH PoC implementation are shared publicly so that, at the very least, they can inform the implementation of the official VHT infrastructure.

Community and services for the community
The attendees expect a whole series of services, for those who use or develop Digital Twins, with a clear added value compared to the existing ones. Numerous examples were given during the discussion to illustrate the collaborative nature of the work on the VHT infrastructure, and identify conditions in which working together makes more than sense, such as reducing development times, accessing numerous resources simultaneously, consensus processes to validate the approach and/or the result, *etc.*
Next, clarification was provided on which community building, data curation, *etc.*, services were actually available. This discussion will be reflected in the Roadmap by specifically and explicitly including everything that was expected in terms of services. From this discussion, there was also a request from other Digital Twin projects funded by the EC, with explicit reference to EDITH and its repository, to establish a committee/coordination board that would apply the framework defined in the EDITH Roadmap regarding design and development choices for the models and choices related to standard formats. The idea was to establish this inter-project committee/coordination board in a workshop organized by EDITH before the end of the project.
Other topics of discussion included consent, synthetic data, anonymized data and permission for use of data by others and across different countries.

Timeline of release of the EDITH PoC infrastructure
The session concluded with the timeline for the public release of the PoC. At the time of the Amsterdam meeting, the PoC infrastructure was already online but limited to users from the EDITH consortium to allow for initial testing and debugging. After the conclusion of this phase, the infrastructure will be opened to the entire community. Those who have submitted a request as an external provider of use cases or resources will be informed personally, and a public announcement will be made to the entire community. In parallel, the EDITH consortium will draft a user manual to be made available on the website and/or within the repository

5.3 Standards

Slides: EDITH_EM_Amsterdam_Breakout_Standards
Breakout chairs: Martin Golebiewski and Gerhard Mayer (Heidelberg Institute of Theoretical Studies)

The session was composed of 2 parts. During the first half, the standardization landscape and available collections and overview documents were presented and discussed. The second half consisted of an open discussion on standardization needs and gaps.

Presentations with feedback and discussions

Introduction into the standardization landscape for the VHT (Martin Golebiewski)

- Standardization Requirements for the VHT
- COMBINE Community Standards for Computational Modelling in Biology[5]
- Standardized and Harmonized Data Sharing: ISO 20691:2022 Requirements for data formatting and description in the life sciences[6]
- ISO 23494 series: Provenance information model for biological specimen and data[7,8,9]
- Standards for model quality, verification and validation: ASME V&V 40[10], Good simulation practice guideline[11], ISO 9491 series (initiated by EU-STANDS4PM):
- Biotechnology — Recommendations and requirements for predictive computational models in personalised medicine research
    - Part 1: Guidelines for constructing, verifying and validating models (ISO TS 9491-1:2023)[12]
    - Part 2: Guidelines for implementing computational models in clinical integrated decision support systems (ISO TS 9491-2)[13]

Overview of EDITH documents and collections on standardization (Gerhard Mayer)

- EDITH Roadmap (comprises high-level recommendations on standardization and available standards)[14]
- Standardization landscape, needs and gaps for the virtual human twin (comprehensive 52 pages document)[15]
- EDITH standards implementation guide (practical guide for implementation of standards in VHTs and their parts, as well as construction, simulation and validation data and building approved models)[16]
- EDITH FAIRsharing standards collection for Virtual Human Twins in Health[17,18]

Discussions on standardization gaps and needs

- Need of long-term maintained standards that are drafted based on a broad consensus in the VHT communities
    - Technical committees of Standard Defining Organizations (SDOs) such as ISO (*e.g.,* ISO/TC 215 Health Informatics, ISO/TC 276 Biotechnology and ISO/TC 194 Biological and clinical evaluation of medical devices), CEN/CENELEC, IEC (*e.g.,* IEC/TC 62 Medical equipment, software, and systems) and national counterparts play a crucial role in collecting the expertise of experts from all different domains relevant for the VHT and in maintaining the standards on a long run, but scientific standardization initiatives needed as well to drive the standardization of novel VHT and modelling technologies and approaches
- Standardized assessment of model quality and credibility
    - Validation standard missing specifically for VHT
    - ASME V&V 40 currently transferred to an ISO/IEC standard[19] to fill this gap
- Standard for data quality (for construction, simulation and validation data) and for its assessment missing (partially already addressed by ISO/TS 9491-1 and 9491-2)
- Standards for granting and controlling access to data for model validation and instantiation missing
- Standards for modelling benchmarking missing
    - gold standards (model testing sets) needed for the different modelling and simulation approaches, as well as testing tools (see *e.g.,* SBML test suite[20])

[5] https://co.mbine.org
[6] https://www.iso.org/standard/68848.html
[7] https://www.iso.org/standard/80715.html
[8] https://www.iso.org/standard/87714.html
[9] https://www.iso.org/standard/89236.html
[10] V&V40, ASME. Assessing credibility of computational modeling through verification and validation: application to medical devices. *The American Society of Mechanical Engineers*, 2018.
[11] https://doi.org/10.1007/978-3-031-48284-7
[12] https://www.iso.org/standard/83516.html
[13] https://www.iso.org/standard/87403.html
[14] https://doi.org/10.5281/zenodo.8200955
[15] https://doi.org/10.5281/zenodo.10492796
[16] https://doi.org/10.5281/zenodo.10524795
[17] https://fairsharing.org/4787
[18] https://blog.fairsharing.org/?p=616
[19] https://www.iec.ch/ords/f?p=103:14:11832380161900::::FSP_ORG_ID,FSP_LANG_ID:51475,25
[20] https://sbml.org/software/sbml-test-suite/

- Standards for the lifecycle of the VHTs and their models and components missing (versioning standards)
- Another dimension: standardized recording and documentation of individuals/patients missing
- Standards for risk management needed

Several attendees volunteered and registered for the standardization work in ISO/TC 276 Biotechnology and IEC/TC 62 Medical equipment, software, and systems.

Question asked to all participants during breakout reporting session: **What are the gaps you still see in the standardization landscape?**

5.4 Communication strategy & stakeholders

Slides: EDITH_EM_Amsterdam_Breakout_Communication
Breakout chairs: Davide Montesarchio, Martina Contin, Goran Stanic and Zita Van Horenbeeck (VPH institute)

The first half of this breakout focused on stakeholder engagement. An interactive tool was used to draw on participants' own experience and opinions in this area, followed by a discussion on challenges and limitations. The discussion half of the session focused on communication strategies, using the tools developed by VPHi as example.

5.4.1 Stakeholder Engagement Strategy

Virtual Physiological Human Institut (VPHi) is developing an Info Kit containing best practices, lessons learned and tools developed linked to stakeholder engagement and interaction. By showcasing the tools (how to organize a focus group & how to design a survey) available in the soon-to-be disseminated Info Kit, we brainstormed about a possible stakeholder engagement strategy for the VHT ecosystem. The very lively discussion was facilitated by questions through Mentimeter.

1. What comes into mind when you think about effective stakeholder engagement?

33 responses

2. What are the most important stakeholder groups for the VHTs?

43 responses

4. What are the main challenges you face in communication and stakeholder engagement within VHT?

Technical aspects	Interest of clinical parties. Leading to poor/incomplete data, leading to poor model performance, leading to low interest of clinical parties.	Initial knowledge point	Misalignment of stakeholder needs and VHT objectives
Motivating stakeholders	misunderstanding, privacy, conflicts with medical staff	finding a broad diversity of stakeholders willing to engage	To make it not sound like science fiction for the patients

4. What are the main challenges you face in communication and stakeholder engagement within VHT?

Finding the relevant communities that could/should be interested	Realistic envision of outcomes.Depth and breath of validated results.Solid HURDLE analysis.	To really get everyone around the table (e.g. clinicians, notified bodies)	prejudices
Ensuring diversity of points of view	Clear representation of advantages	Conveying difficult concepts in an accessible and engaging way	lack of enough funding for engagement of some stakeholders

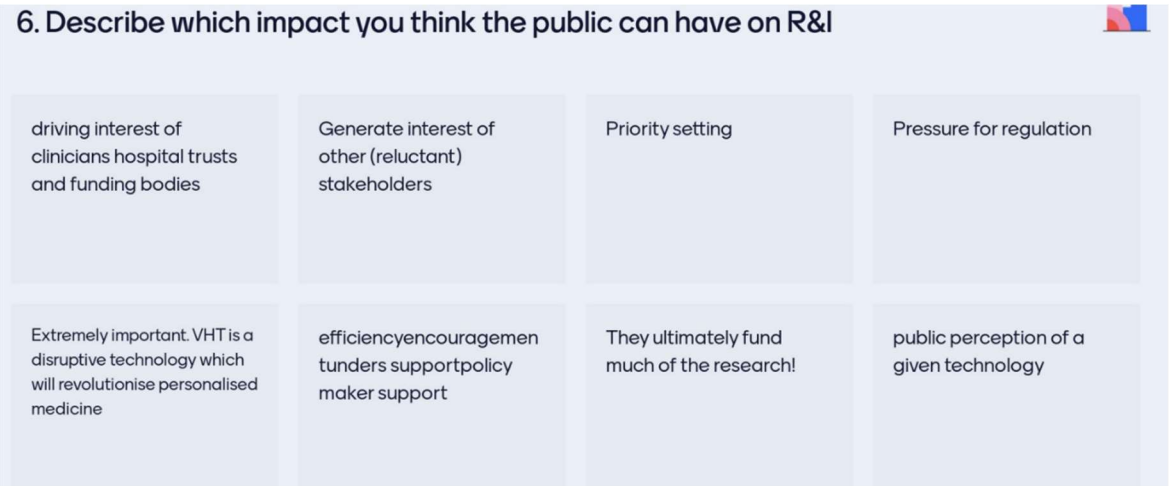


Figure 2: Examples of questions and answers related to stakeholder engagement

The main discussion points are reflected below.

- Participants highlighted the importance of **a feedback mechanism** when engaging with stakeholders. For instance, after conducting a focus group, we should aim to find a way to loop the results & impact made back to them. Sending them an extensive report is not the way to do this, there are tools out there to facilitate this feedback loop.
- Participants emphasized the importance of allocating **funds** for engaging with stakeholders from the proposal writing stage. Lately, there is a growing recognition of public involvement, which can lead to certain stakeholder groups (*e.g.,* patients) to be overburdened. Therefore, appropriate incentives should be provided. Foreseeing the budget for these important activities is a necessity, also acknowledging its importance.
- We discussed the different levels of intensity of stakeholder engagement (information-consultation-collaboration-empowerment) and we brainstormed about the **lack of empowering engagement** activities. Here, participants raised concerns about the conceptualization of empowerment, which can only happen when awareness is built to an adequate level. As such, the importance was placed on communication strategies to build literacy on VHTs, providing the public with more knowledge.
- Throughout the session, emphasis was placed on **balancing between overselling the technologies (to get people on board and thinking) and managing stakeholders' expectations (hopes vs fears)**, providing a clear picture of our ideas, proposals and the impact of our engagement efforts.
- Importance of **joining forces** between projects working on VHTs: VPHi can here be an intermediary facilitating these efforts; 'together we can get further'
- We also discussed the lecturing materials on *in silico* medicine as developed by the InSilicoWorld-project. Here, the suggestion was to create a **basic introductory course to VHTs that could be offered in all tracks** (from psychology, to medicine, engineering, to SSH). VHTs require an interdisciplinary approach, so we should not limit access to this information.

5.4.2 Communication strategy

The section dedicated to communication strategy started with the following questions:

- **How important is the communication of *in silico* medicine towards the lay publics?** On a scale from 1 to 10, the attendees voted with an average of 7,8
- **How much time do you dedicate to communication activities (hours/week)?** In this case, 7 attendees affirmed that they dedicate 1 hour of their work week to communication activities with the lay public. Then, three attendees indicated they dedicate 1-2 hours, and the other three indicated 8 or more.
- **Describe your reference public in terms of age.** The attendees indicate that their reference public is mainly composed of people aged at least 20, with the age range 30-39 being the most indicated.
- **Describe your reference public in terms of education level**. In this case, the answers were evenly distributed between the indicated answers, with a slight prevalence at the postgraduate level.
- **Do you use social media to communicate science towards the lay publics?** The attendees clearly indicated that they employ social media for communication activities.
- **If so, which is the main social media platform?** Most of the answers indicated LinkedIn, followed by X (formerly Twitter).

Figure 3: Examples of questions and answers related to Communication

The questions were then followed by a discussion on different ways to target different audiences, from the laymen who don't know about *in silico* medicine to the scientific community at large. The presented examples are the following.

- **Animated video series (Code & Cure)**: Short animated video pills, visually appealing and with simple language. Each video pill is seen from the perspective of a patient or a citizen who can benefit from *in silico* medicine. This series is intended as a brief introduction to *in silico* medicine for public who do not know of it.
- **Podcasts (The Digital Twin Theory)**: This podcast series is made of short episodes compared to other science-based podcasts of a maximum length of 15 minutes. In each episode, there is an interview with a scientist describing in easy terms her/his perspective on the topic. The topics include what a model is, AI in healthcare, how to manage health data, benefits of *in silico* clinical trials and so on. This product is intended for a science-enthusiast non-scientific public.
- **Characters of *in silico* medicine**: This is a graphic design product released each month on social media (Instagram, Facebook, Linkedin, X) about a person who has been relevant to the story of *in silico* medicine. This product is intended for science enthusiasts and the scientific community at large, as well as to create bonds and celebrate those incredible contributors. Characters include Ada Lovelace, Denis Noble, Regina Barzilay and Walter Pitts.
- **Success Stories**: Each month, a storytelling about a successful application of *in silico* medicine is published in the monthly newsletter of the VPHi. Such stories are intended to make the scientific community aware of successful real-world applications of *in silico* medicine, also from the perspective of creating bonds in the different sub-communities.

Two more questions then followed the discussion:

- Please indicate some examples of success stories;
- Are there any further suggestions for activities of interest to the public?

The last two questions and the final discussion provided some insights and suggestions from the attendees, including:

- Together with the icons from the past, also give visibility to the "icons of the future" to humanize *in silico* researchers of today;
- Success stories should also show the trials and errors of science, showing limitations as a way to achieve more ambitious goals;
- Create unique events to showcase the videos that we are producing (i.e. "Cinema event");
- Create short animated movies of 10-20' in length;
- Make longer podcast episodes.

General comments that apply to both parts.

- Patient and Clinicians are the number1 stakeholders
- Doctors are the centre
- Further simplify the language (image our target is 5 years old)
- Show results of our work in new creative ways

Question asked to all participants during breakout reporting session: **How can we effectively empower and engage clinicians and patients?**

5.5 Balancing roles and responsibilities: how to define user profiles

Slides: EDITH_EM_Amsterdam_Breakout_Users
Breakout chairs: Gökhan Ertaylan, Simon Denil, Frederic Jung (VITO); Frank Rademakers (UZ Leuven - KU Leuven)

The primary objective of this breakout session was to present the EDITH proposal on the management of data access and types of user roles. Current strategies and progress were discussed, seeking valuable feedback from the audience. The session aimed to ensure that the

proposed approach aligns seamlessly with the overall roadmap and integrates effectively with the progress of other ongoing tasks. By collaborating on the vision for profiles and roles, the session aimed to enhance the data management strategy and ensure comprehensive alignment across all partners.

5.5.1 Data Management in Healthcare: Legal Requirements

The first speaker, Frank Rademakers, professor emeritus at KU Leuven, medical doctor, and co-founder of MyNexusHealth, is a specialist in organizing patient data and analysis workflows. Professor Rademakers presented various types and sources of data from initiators and generators (Table 1), highlighting the legal requirements and approval processes needed in hospitals (Table 2). Dr. Rademakers' presentation covered a wide range of data types, including registry data, data from human experiments and trials, personal data generated by patients through commercial systems, and public or government data. He emphasized that all these data types are governed by GDPR guidelines, which ensure data protection.

Table 1: type/source data by initiator/generator

Clinical care Including prescribed wearables and questionnaires	**by HCP**	Clinical notes Labs, tests, genomics, ... Imaging Holter, BP 24hr Apps in EHR Social Biobank
Registries	**by scientific organisations, others**	Mostly linked to pathology ex ERN
Experiment Human	**by researcher**	Anything done xtra to normal clinical care (Cfr described in care program)
Personal	**by individual**	Data generated and stored by patient with own tool - weight, PoC data, ... - financial - social - economic - location information - diary - wellness apps
Personal	**by individual with use of a tool from a third party**	Data generated by patient with company tool - social media - wearables - financial - location information - diary - wellness apps
Employer	**by HR collaborator**	Personal - Social - Economic - Financial
Public	**by public entity**	General - Climate - Environment - Financial ...
Government	**by governmental entity**	General - Climate - Environment - Financial ...

A matrix illustrating the legal status of primary users was presented, raising important questions about data ownership and its implications. Dr. Rademakers clarified that there is no legally defined ownership of data, only stewardship. The legal basis for data usage is determined by its purpose, with two main categories: primary and secondary use of data.

Table 2: legal status of primary user

Legal Status of Primary User	**IP** **- database: structure and/or content** **- copyright (ex images)** **- patent right (if present)** **NOT for INDIVIDUAL DATA**		**Physically residing**	**Legal Basis**					
			(local or cloud)	**Primary use**	**Secondary use with Purpose Limitation** **Always Registration, Privacy conserving, Transparent, Possibility for Opt-Out when FP party involved**				
	Data creator unless contract = hospital or person	**Data user**	**with adequate safety precautions**	**Clinical care**	**Q-control, Q-improvement, Safety, managerial by UZ Leuven, KU Leuven**	**HTA, ZIV, Government and legally required reporting**	**Research NonForProfit by UZ Leuven, KU Leuven, entity with similar research goal policy**	**Research ForProfit**	**Use ForProfit (improvement product)**

The expansive exploration of these questions and concerns culminated in the development of a comprehensive spreadsheet, which took a year to compile. This spreadsheet provides an overview of data management responsibilities and public interest considerations, offering valuable insights into who manages the data and ensures its protection.

5.5.2 Advances in European Data Policy and Governance

The Evolution of European Data Policy

The second speaker, Dr. Gökhan Ertaylan, provided an insightful overview of the current status of multiple EU legislative acts affecting the VHT domain and data access. Particular attention was devoted to the European Health Data Space (EHDS) strategy and its data governance mechanisms. The EHDS aims to standardize data rules, empowering individuals to control their own data, which can be shared between member states for primary use. This strategy also seeks to establish a European-wide infrastructure and data catalogue to ensure secure data storage. Additionally, the secondary use of data is intended to support research and policy development. Although the language of the EHDS is still evolving, its current state is already influencing upcoming European projects.

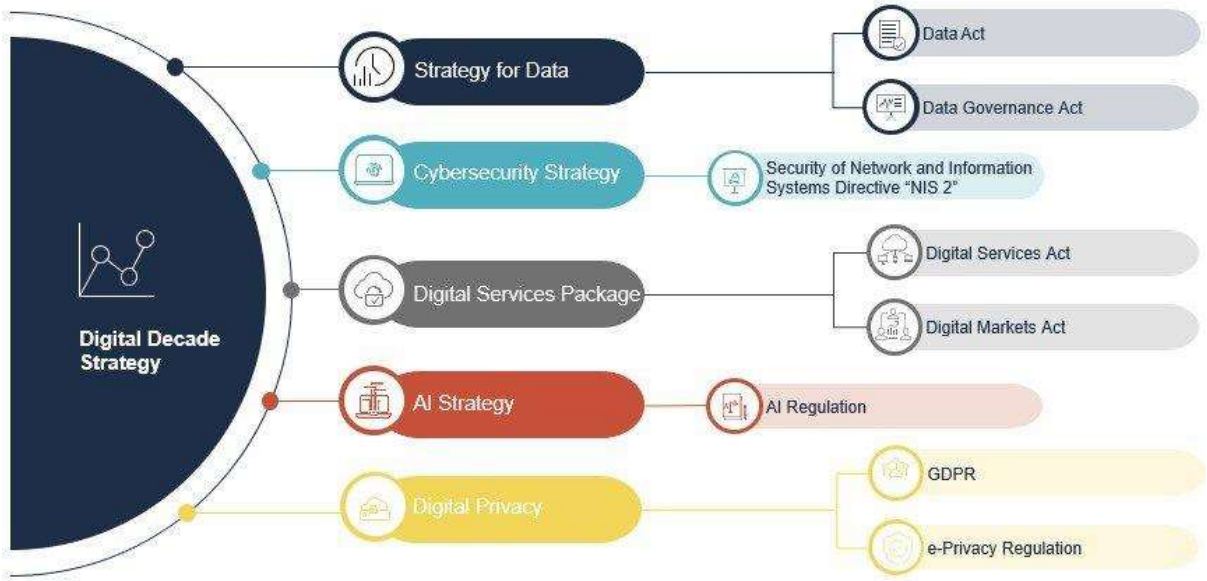


Figure 4: European Data Strategy & Legislation

Enhancing Authentication and Role Management

In this segment, we outlined enhancements to our proposed role systems, which include:

- **Grants**: Facilitates the dynamic allocation of resources (*e.g.,* HPC, data) to profiles based on agreements such as funded projects (EU/national/regional ...) or institutional agreements or affiliations.
- **Affiliations**: Identifies the profile's affiliation(s) with various institutions in the EU. Multiple affiliations are possible and can provide grants to user profiles for resource access.
- **Purpose**: Defines the explicit reason for using certain data in the system. The data descriptor (metadata) is machine-readable, which is essential as it outlines the workflow/pathway to access data resources.

These additions complement roles and profiles dynamically, enabling quicker and more flexible access without creating multiple roles.

We also discussed the envisioned login process for the VHT platform, which will initially rely on national identity providers. Each EU country has a national centralized identity system linked to a national identification number (*e.g.,* Belgium's "It's me"). We are aware of the

ongoing European effort to create a European Digital Identity Wallet, which will simplify many administrative procedures across domains such as education, payments, travel, and healthcare. If users do not utilize national identity providers, we plan to delegate this responsibility to the EU identity at the European level in the future.

This topic raises questions about linking roles with national identities. In some countries, a (health) authority registers (medical) experts and can verify affiliations (*e.g.,* systems for allocating Cyfronet HPC resources). It should be possible to link such roles and identities. But mapping/verifying roles such as patient advocate, developer or citizen scientist may present more challenges.

5.5.3 Defining and Discussing User Roles

Introduction to User Roles

In this section, we presented our defined roles as archetypes linked to a set of access features. This approach is closely tied to how we interface with other EU initiatives. The discussion emphasized the need for our role categories to align with those proposed in other EU projects. This topic was further explored in the second part of the breakout session to determine how best to integrate with other infrastructures.

The proposed and revised roles are as follow:

- Patients/Citizens Category
  - Patient
  - Patient Advocate
  - Citizen Scientist
- Healthcare Professional Category (Doctors, Specialists, *etc.*)
  - General Practitioner
  - Medical Specialist
  - Medical Researcher
  - Medical Educator
- Creator/Model Developer Category (can upload new model version, train the models)
  - Data Scientist
  - Simulation Engineer
  - Model Developer/Owner
- Platform Administrator Category
  - System Administrator
  - Data Curator
  - DevOps specialist
  - Software Developer

Overview of Profile Types

We introduced the four profile types we created, which started a discussion about the semantics of these different types. Feedback from the audience indicated that the term "healthcare professional" might be too broad. For example, in some countries, nurses are not classified as healthcare professionals but “clinical professional” which makes a significant difference in some institutes. Additionally, there were suggestions to separate the "patient/citizen" category into distinct groups. Patients and citizens have different interests and trajectories. Addressing them separately could lead to more tailored and effective data management strategies.

5.5.4 Addressing Key Questions and Discussion Topics

Anonymization of Data

The session included a robust discussion on the challenges and concerns related to data pseudonymization vs. anonymization. Anonymization of data must be handled with care, as

the process can hide relevant contextual information, reducing the data's utility. Additionally, the risk of re-identification of pseudonymized or even anonymized data is a growing concern, especially with the advent of AI technologies capable of re-identifying data under certain conditions.

Access to Raw Data

A significant topic was the determination of who should have access to raw data. Various data strategies are available, with the EU often favouring a federated approach. An alternative strategy is exemplified by Solid technology, which enables data to be stored in personal pods, keeping the data with the individual. The EDITH BBCT use case demonstrates the feasibility of using Solid pods in large-scale projects like EDITH, empowering patients in the management of their own data.

Quality Assessment and Security Roles

The discussion highlighted a potential oversight in our current role system: the absence of a dedicated role for Quality Assessment (QA) and Security. Involving patients actively in sharing their data through personal vaults necessitates a human in the loop to ensure the quality and accuracy of the uploaded data. While partial automation of this QA process could be integrated into the general data pipeline, it's crucial that data is properly annotated, particularly lifestyle data shared by patients, to maintain its reliability and accuracy.

This topic also raised concerns about the level of investment required from various stakeholders to ensure data quality. It may be challenging to engage individuals in this process, and further investigation is needed to define acceptable grey zones for data quality, where uncertainties can be addressed internally later. Additionally, the conversation returned to the issue of pseudonymization/anonymization, highlighting the need for a specific module within the VHT workflow to handle the trade-off between privacy and utility effectively.

5.5.5 VHT Platform Vision and User Input

Wireframe Demo

In this segment of the breakout session, we showcased the vision for the upcoming VHT platform. The focus was on illustrating the user journey and how different roles would interact with the platform through various scenarios. We demonstrated this vision using a wireframe, which has been updated since the Paris ecosystem meeting in January 2024.

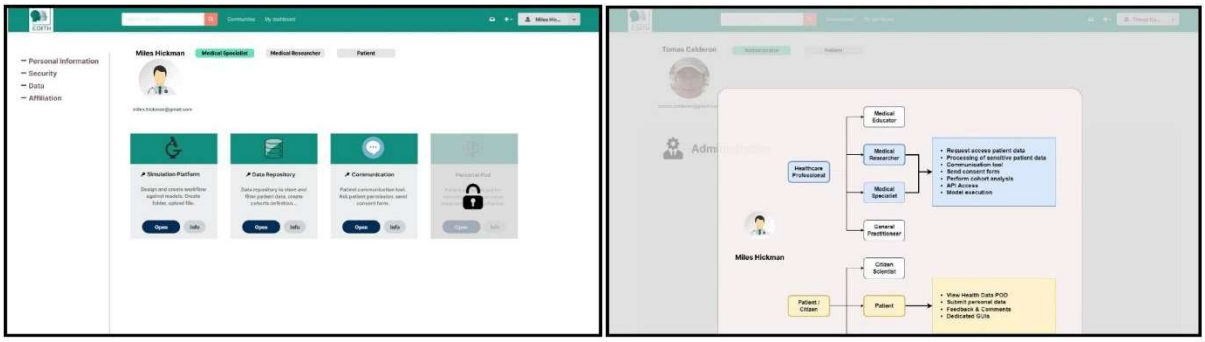


Figure 5 : demo wireframe of the vision of the VHT platform. This demo presents the story of a user identifying themselves through the Belgian national identity provider "It's me". The access summary can be visualized by the administrator.

User Questionnaire

Following the presentation of the vision, we aimed to gather feedback from the audience regarding their expectations, as they are potential future users of the VHT platform. This last version of the questionnaire has been refined since the Paris plenary meeting and has already been circulated in previous newsletters. The results will help identify any missing roles and map access features, ensuring the platform meets user needs effectively.

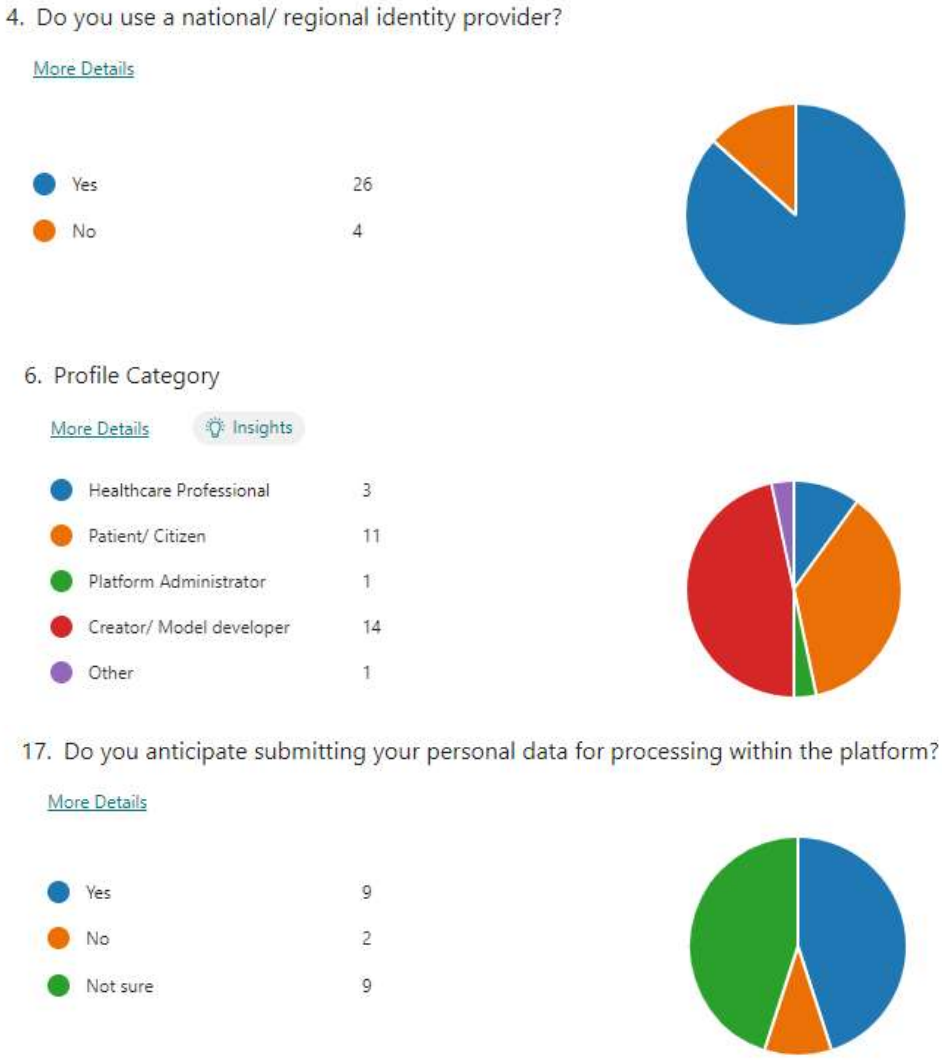


Figure 6 : Extract of user questionnaire

5.5.6 Discussion on Roadblocks

Defining Data Controllers and Access Procedures

A critical roadblock identified during the session is the need to define the role of data controller. This person or entity will be responsible for deciding on the secondary use of data. This issue mirrors the challenges faced by the access bodies of the EHDS, which also require clearly defined purposes and procedures for data access. Data controllers and access bodies will determine access through the EHDS, and a data access procedure and workflow independent of EDITH must be implemented. This external process should facilitate the pairing of data with their workflows, particularly for secondary use, where a clear purpose and decision-making authority are essential.

During the session, it was also noted that there should be distinct procedures for secondary use of healthcare data and data generated in the context of scientific research.

Challenges in Data Uniformity and Mapping

Another significant issue is the non-uniformity of data, which complicates the mapping of Electronic Health Records (EHR) and various registries. However, the situation is improving with the availability of more tools for automating structural and semantic data mapping. Many institutions are now adopting OMOP Common Data Models and structured EHR formats such as FHIR. Despite these efforts towards harmonization, implementing OMOP remains challenging due to a shortage of experts and the substantial time investment required to correctly input data.

Evolving Roles and Access

In light of these discussions, new roles and access protocols will need to be developed or updated. There is a need to create specific roles for groups such as healthcare representatives, patient associations and service providers. Additionally, we must consider how to interface these roles with other infrastructures to ensure seamless integration and functionality.

5.5.7 Summary

- **Overall**
  - National identity providers (later EU ID) are the preferred way for authentication in the VHT platform. This might leave some non-EU citizens out. A tailored strategy will need to be developed.
  - How do we interface with other health and research infrastructure? Is this a new role or a new function in an existing role?
  - Who assigns the roles initially?
  - How do we initialize and regularly synchronize in a federated infrastructure? Some professions have well organized national bodies, others not. Should there be a board for this purpose?
  - Should there be mandatory training to qualify for certain roles? If so, trained and certified by whom?
- **Quality assessment**
  - Who's job will it be to assess the quality of data? The role of Simulation Engineer or is this a missing role?
  - What about model credibility? What is the precise mechanism of keeping track of model credibility in relation to the roles?
  - Who evaluates the VHT platform? Should it be a combination of internal reviews and audits by independent agents/actors?
- **Roles missing or incomplete coverage**
  - Role of a data curator? – This role would require intimate understanding of the model requirements / underlying biology.
  - We need to be more sensitive and avoid use of umbrella terms – important to be aware of the semantic differences (*e.g.,* healthcare professional vs. clinical professional)

  - What is the intended purpose of giving citizens access? Clarify the suggested *evolution of these roles* in the roadmap.
  - The patient and citizen currently fall under the same category, which is ok in the early phase. Eventually these roles have different motivations, knowledge and interest. How does this translate to the level of access?
  - ELSI roles, where do they fit?
  - Can we have role categories for *Health Data Access agencies*, *healthcare representatives – Patient association*, *service providers …*
  - Industry related roles could be better fleshed out as their purpose of data access could be different from the equivalent academic roles. Have private industry actors with similar roles to academic users but with different levels of access? Through affiliations? Subset by purpose? (commercial vs. public vs. good/pre-competitive)
- **Data & Data-access procedure (Potential Road Block)**
  - Anonymization vs pseudonymization of data
  - Data access bodies – declared by EHDS to decide on access for secondary use, raises concerns about consistency across and within borders
  - Different from the DT/VHT simulation workflows – we need to create a data access procedure (we first need to know the purpose) to ask for permission. Create the workflow with a specific purpose and go through health data agencies to ask for the specific data.
  - Challenges are expected in data sharing & data-quality: even with considerable effort for the data access procedures, it will be difficult to ensure the data quality in this entire ecosystem.

5.6 EU-AM-AP collaboration

Slides: EDITH_EM_Amsterdam_Breakout_Collaboration
Breakout chair: Liesbet Geris (VPH institute), Thiranja Prasad Babarenda Gamage (AIB), Anna Niarakis (University of Toulouse), Gary An (University of Vermont Medical Center)

This session aimed to discuss the possibilities of collaboration across continents on VHT-related subjects. The session started with an overview of current funding possibilities from the EU side. This was followed by 2 testimonies showing the added value of global collaboration, i.e., the 12 Labours project of Auckland and the immune digital twin initiative.

5.6.1 Possibilities and examples of global collaboration

EU funding channels and possibilities for non-EU partners
Several funding options exist in the EU funding landscape for interdisciplinary and intersectoral collaborations. The horizon Europe framework (pillar II) and the Digital Europe programme were briefly presented, along with its focus on international collaboration and open science.

The 12 Labours project
The 12 Labours project was described in broad terms, emphasizing the role of synergistic international projects like SPARC (US-NIH) and VITAL (EC-Horizon Europe). The presentation went into more detail on data objects, standardising workflows, repositories and platforms.

The immune digital twin initiative
The use case of the immune digital twin shows how international collaborative efforts are starting up and trying to support their work through various channels. In particular, the immune digital twin organised a 3-week workshop at the Institut Pascal and has recently been accepted and endorsed as a Research Data Alliance working group, which will provide the community with a limited level of support (logistical, not financial) to realize its proposed activities (https://www.rd-alliance.org/groups/building-immune-digital-twins-wg/).

5.6.2 *Discussion*

- Sharing roadmaps & recommendations
  - Strategic documents
  - Key learnings, knowledge base, …
  - Aligning on vision & key-elements > interoperability-by-design
  - Mapping between standards
- For all stakeholders : Industry, academia, clinicians, patients, policy makers, regulatory, HTA, payers
  - Patients as drivers? Rare diseases, paediatrics,…
  - Inter sectoral collaboration
- Communication
  - Success stories to help show progress: IDT
  - failures & lessons learnt
  - Find relevant project calls > overview?
- Facilitate collaborations across continents
  - Find relevant partners across the globe
  - find collaboration opportunities
  - Find collaborative platform
- VHT ecosystem is a success story: keep it alive!

Question asked to all participants during breakout reporting session: **What is the biggest challenge in collaborating with partners/organisations?**

5.7 Unlocking research infrastructures to broader community

Slides: EDITH_EM_Amsterdam_Breakout_RI4community
Breakout chairs: Marco Verdicchio, Sagar Dolas, Ivar Janmaat (SURF); Marian Bubak, Marek Kasztelnik, Piotr Nowakowski (Cyfronet)

During this session, an interactive approach was followed to discover barriers and opportunities for bringing research infrastructures to the broader communities. The session included an overview of existing European HPC infrastructures as well as an overview of benefits and challenges of accessing HPC resources for research. This was followed by a structured discussion based on pre-defined questions.

Main barriers related to performing research on EU funded infrastructures:

- There is insufficient dissemination of information regarding the available infrastructures ("we don't know about these possibilities")
- There should be a well-defined outreach methodology, with KPIs - benchmarking - otherwise most infrastructures are used only internally

- "Proposal within a proposal" - the process of applying for access to infrastructure is tedious; perhaps the grant agency could apply to the infrastructure provider on our behalf while deciding to fund your proposal?
- Unclear if research infrastructure is certified for medical research
- Physicists/astronomers know how to apply for/use HPC because they tend to have longstanding experience - this is less true for life science researchers. Funding is biased towards established communities.

Making research results sustainable on EU funded infrastructures

- What is needed is some kind of instrument for upkeep of research services.
- A standard to describe infrastructural requirements would be useful.
- The way forward for advanced platforms is to work towards a higher level of engagement of member state actors (ministries, *etc.*) to promote sustainability beyond the nominal end of EU support.
- Important Projects of Common European Interest (IPCEI) - funding instrument, incl. for cloud services (quite high on the EC's agenda)

Interoperability, data sharing and usage of commercial resources for scientific research

- Nowadays, we have catalogues, marketplace, containers *etc.* - technical challenges are going away
- On the other hand, platforms do not share authentication mechanisms and have few infrastructural commonalities (unlike commercial platforms – *e.g.,* Azure, where you can deploy services all around the world under a single contract with Microsoft) - no shared APIs/billing systems/accountability in EU systems
- Legal issues (including data privacy and IPR)
- Incentivization is key - it cannot just be red tape and responsibility for the data provider
- Need a clear path for individual researchers/clinicians on how to become involved with EU infrastructures (EHDS, *etc.*)

Question asked to all participants during breakout reporting session: **How can we engage the VHT ecosystem in the communication process (related to infrastructures)?**

6 Plenary session: recommendations & validation

Slides: EDITH_EM_Amsterdam_masterfile

The plenary session discussed the recommendations that will be included in the EDITH roadmap. The were broken down into 5 categories: (i) Research & use cases; (ii) Infrastructure; (iii) ELSI, standards & regulatory; (iv) Users & inclusiveness; (v) Sustainability. A public

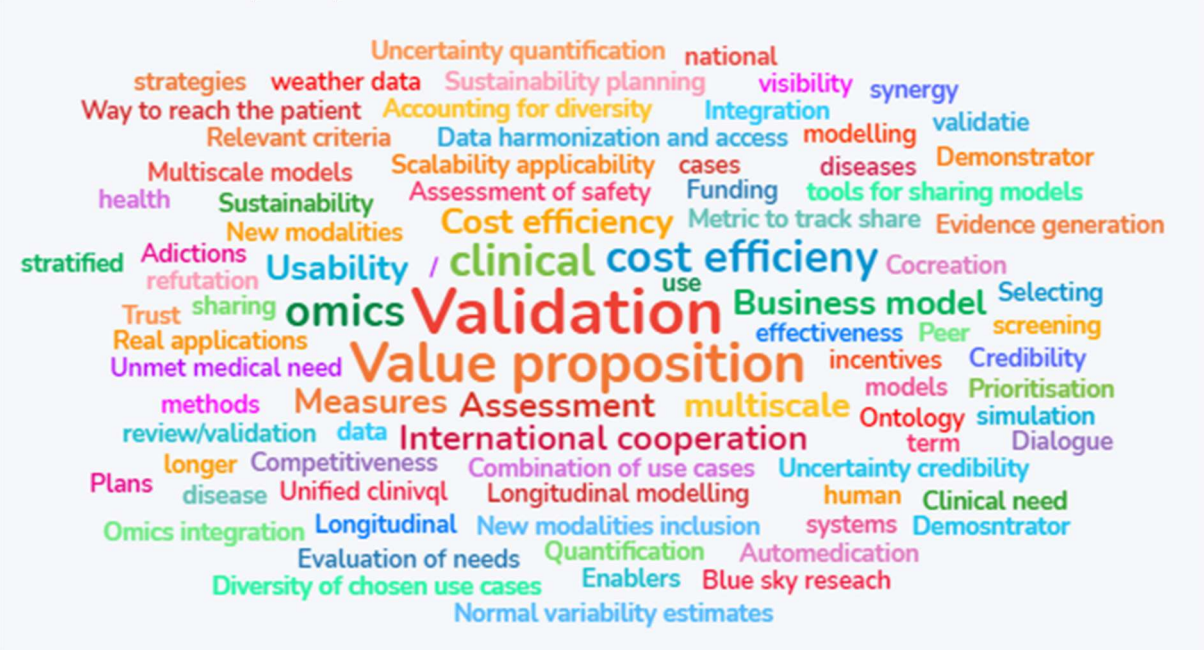
voting system was used to provide all participants with the opportunity to add missing items and a short discussion followed the voting to further elaborate points when necessary.

6.1 Research & use cases

Proposed recommendations

- R&I in the **development, testing, validation, and verification of advanced VHT technologies**
  - In synergy with existing digital services and capabilities
  - Basic research defined on identified knowledge gaps
  - Continuum of basic to translational research
  - Includes lower TRL work
  - Covering generic / population-specific and personalized digital twins
- Advancing the understanding of how VHT solutions, products, and services can be used **across the disease continuum**
  - Prevention, treatment and follow-up
  - Biomedical studies, clinical studies
  - Therapy development, diagnostics, remote care and self-care
- **Generation of clinical, experimental and digital evidence** for the (future) development of VHT solutions, methods, and tools and technologies.
- Identification, development and delivery of **high-impact clinical and scientific use cases**
  - Diagnostics, medical education, training, decision support, therapy development and intervention planning.
  - Credibility / risk-informed credibility

Additions from the participants



6.2 Infrastructure

Proposed recommendations

- Designing, building, and enhancing the **VHT resource repository and simulation platform**
  - In full compliance with applicable laws and regulations in Europe
  - Incentivize adoption of VHT in new developments
- **Support development, testing and implementation of advanced and interoperable IT platform architectures** combining technology advances
  - Computational infrastructure, cybersecurity, HPC, cloud services and edge infrastructure
- Advancing the **availability of and access to high quality, annotated and interoperable digital health data**

  - Standardized in terms of format and semantics
  - Safeguarding patients' privacy, personal data, health and safety.
- Include **co-evolution with other initiatives**
  - Global vision for (life sciences) research infrastructures
  - Links to existing platforms
  - Longevity of support

Additions from the participants

6.3 ELSI, standards & regulatory

Proposed recommendations

- Development of **common ground, trust**, agreement and certainty on **IPR management, and protection of Trade Secrets**
  - Forms basis for partner collaborations among stakeholders
  - [harmonization or at least] monitoring national laws
- HTA: analysing effectiveness & efficiency
  - Analyse impact , harmonize approaches
- Identification of opportunities, approaches, standards, tools, and techniques that **enhance clarity of the regulatory landscape**
  - To enable efficacy, safety, trustworthiness, performance and risk management, from early stages of development
  - Evolutionary framework
  - Standards-based interoperability
  - Credibility-by-design
  - Best practices, community-driven standards, consensus procedures, link to credibility & interoperability

Additions from the participants

6.4 Users & inclusiveness

Proposed recommendations

- Ensuring the contributions, feedback, priorities, requirements, views, concerns and interests of citizens, patients, industry, healthcare professionals, and scientists are **proactively captured and addressed**
  - As part of the development, testing, verification, and validation of VHT tech
  - Active & outgoing ecosystem & user community
- **Building trust** amongst users of the VHT & its developments
  - Trustworthiness vs trust
  - Responsible research & innovation
- Ensuring that VHT technology **benefits people** of all ages, genders, ethnicities, socioeconomic statuses, and disabilities
  - Fostering equitable and universal access to high-quality healthcare
  - Access to VHT: manage own health, personal health forecasting
- **Education & training** on use and developments of VHT
  - For all stakeholders
  - Training & re-training
  - Use of VHT as training platform

Additions from the participants

6.5 Sustainability

Proposed recommendations

- Realising the embedding of the VHT as a European Digital Research Infrastructure
  - Co-evolution of existing infrastructure
  - Interoperable, federated, distributed
- Continuous source of support and ecosystem development
  - Top-down
  - Bottom-up
  - Incentivize adoption
  - Ecosystem & technology

Additions from the participants

6.6 Others

As can be appreciated from the above sections, oftentimes specific elements appear under different sections as they are impacted by many factors. One example is health data that is required for building the VHT where pertinent elements include (but are not limited to): access to patient-specific data; data pods; link and access to EHDS; federated nature of the infrastructure; cases where consent is there & data can be harvested; synthetic data and its status across EU Member States.

7 Plenary session: next steps & wrap-up

Slides: EDITH_EM_Amsterdam_masterfile

The end of the Amsterdam meeting marked the start of the final phase of public discussion & collaborative writing of the roadmap, facilitated through online meetings and the InSilicoWorld Community of Practice slack channels. All of this work will be brought together and included in the final draft of the VHT roadmap.

7.1 General observations of the meeting

- There is a very strong basis for the realisation of the VHT, in terms of technologies, budding infrastructure, community and other key drivers and facilitators.
- The VHT ecosystem is growing rapidly & thriving. This will be a key element for the success of the VHT infrastructure and the uptake of VHT technology in clinics.
- There is a strong collaborative mindset that is crucial for the further development of integrated digital twins in health and care.
- All stakeholders are represented in the ecosystem and there are a lot of cross-disciplinary and cross-sectoral activities taking place that further solidify and strengthen the ecosystem.

7.2 Roadmap writing and validation timeline

The Amsterdam meeting marked the start of the final phase of the EDITH roadmapping activities, the deliver phase.

- Design phase (1/10/2023-31/7/2023)
  - Consortium, industry advisory board, expert meetings (covering all elements of ecosystem)
  - Public writing 1st draft
- Develop phase (1/8/2023-16/7/2024)
  - Manifesto, boards, expert meetings, ecosystem meeting
  - Public writing 2nd draft
- **Deliver phase (17/7/2024-31/12/2024)**
  - **Ecosystem**: public endorsement
  - **Advisory boards**: expert / political endorsement
  - **EPF**: patient endorsement

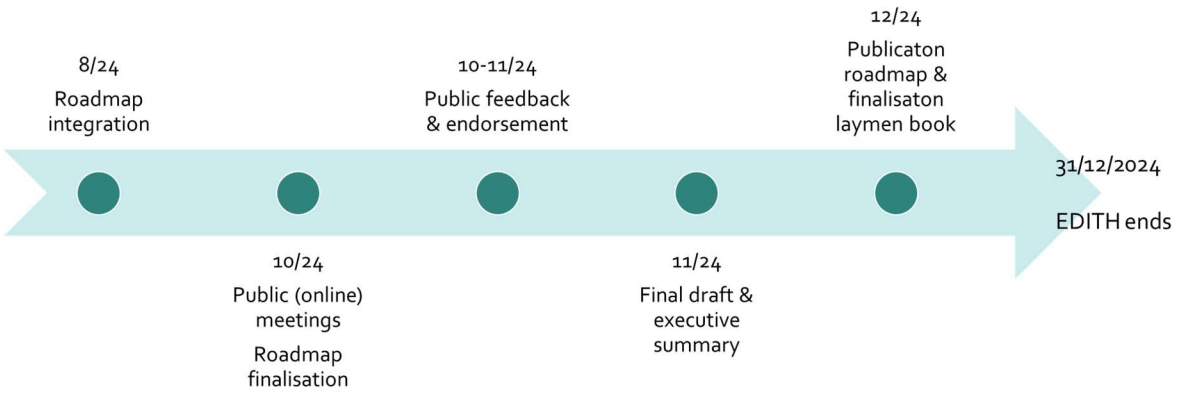


Figure 7 : Timeline of roadmapping activities in 2024

7.3 Practical requests

Several activities are currently ongoing that will strengthen the ecosystem and the development and realization of the Virtual Human Twin.

- Adding input, comments, feedback to the roadmap: www.edith-csa.org/roadmap
- Signing the manifesto www.virtualhumantwins.eu
- Contributing use cases, resources : www.edith-csa.org/call-for-use-cases
- Spreading the word about EDITH and the VHT: www.edith-csa.org/contact