Building the European Virtual Human Twin

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Advisory Group of Stakeholders Deep Dives Meeting Minutes (25, 26 & 28/6/2024)

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Executive summary

On June 25th, 26th and 28th, three EDITH Advisory Group of Stakeholders Deep Dives meetings took place online. This document contains the meeting agenda and the main discussion.

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Acronyms

Acronym	Full name
AGS	Advisory Group of Stakeholders
AI	Artificial Intelligence
CSA	Coordination and Support Action
EC	European Commission
ELSI	Ethical, Legal and Social Issues
EU	European Union
GDPR	General data protection regulation
HPC	High Performance Computing
HTA	Health technology assessment
MDR	Medical Device Regulation
MDSW	Medical device software
SaMD	Software as a medical device
SEEK	Web-based infrastructure to enable sharing and exchange in systems biology
WP	Work Package

1 Purpose of the meetings

1.1 Advisory Group of Stakeholders: goal & composition

The Advisory Group of Stakeholders (AGS) is one of the advisory boards of the EDITH Coordination and Support Action (CSA)[1]. The EDITH-CSA 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 (data, models, algorithms, computing power, storage *etc*.) to develop digital twins in healthcare, assess their credibility and facilitate their uptake in industry and clinical practice. It entails the development of a federated public infrastructure and the collection of appropriate resources, driven by the engagement of a collaborative ecosystem.

The AGS is an important component for strengthening the VHT ecosystem, providing high level feedback and validation, and supporting its further development going forward. The AGS members informed input to the VHT Roadmap, elaborated by the EDITH consortium and the wider ecosystem through public activities onsite and online, carries an important weight in its validation, wide dissemination, and acceptance. AGS members will then discuss orientations for future research beyond the EDITH CSA and ongoing initiatives. The AGS is composed of high level experts from academia, clinics, industry (large companies and start-ups), trade associations, regulatory agencies and notified bodies. The expertise of the AGS members covers the technological, ethical, legal and social (ELSI) aspects related to VHT.

1.2 Meeting objective

The European Virtual Human Twins (VHT) Initiative was officially launched by the European Commission on the 22 December 2023[2]. In 2024 the EU VHT Initiative activities kicked off with a core set of 12 ongoing actions supporting advanced VHT technology development, from foundational research through to evidence generation and deployment. A VHT Manifesto[3], summarizing the core elements and key challenges of the VHT was signed by over 90 organisations (academia, industry, hospitals, trade organisations, HPC centres, patient organisations and civil society organisations).

In the meantime, work on the EDITH-CSA led to the publication of the first draft of the VHT roadmap[4] in July 2023 and a further elaboration of its content since then, through a range of public activities and expert meetings. In light of the preparation of the final draft of the VHT roadmap, the AGS has been invited to meet and discuss the progress in first meeting that took place on May 13th. At the end of the meeting, it was agreed between all parties to organise 3 deep dives meetings to allow for more in-depth discussion on 3 main groups of topics (attended each time by those members of AGS with relevant expertise to the topic):

- VHT science, technology & infrastructure: 25th of June, 1 – 2.30 pm
- ELSI for VHT: 26th June, 11.30 am – 1 pm
- Uptake, users & sustainability: 28th June, 2.30 – 4 pm.

[1] www.edith-csa.eu (10/6/2024)
[2] https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins#:~:text=Launch%20of%20the%20Virtual%20Human,Human%20Twins%20(VHTs)%20Initiative.- (10/6/2024)
[3] www.virtualhumantwins.eu (10/6/2024)
[4] https://zenodo.org/records/8200955 (10/6/2024)

2 VHT science, technology & infrastructure

2.1 Agenda of the meeting

The "VHT science, technology & infrastructure" deep dive meeting took place online on Tuesday 25th June between 13.00 and 14:30 (CEST), with the following **agenda**:

- 13:00: Welcome & Introduction (Liesbet Geris)
- 13:05: Technology update (Amaryllis Raouzaiou, ATHENA)
- 13:45: Discussion

The meeting was **attended** by relevant members of the AGS members (representing academia, industry, notified bodies and patient organisations), as well as the members of the EDITH-CSA consortium (Amaryllis Raouzaiou, Edwin Morley-Fletcher, Artem Platonov, Bernd Schuller, Frederic Jung, Gerhard Mayer, Gökhan Ertaylan, Janaki Raman Rangarajan, Laura Bevis, Marek Kasztelnik, Sok Dim, Bernard Staumont, Valentina Huber, Elisa Rauseo, Vincent Uyttendaele, Liesbet Geris) and representatives of the European Commission (Kyriacos Hatzaras, Renata Palen and Konstantin Hypponen, DG CNECT H3 – eHealth, Wellbeing and Ageing).

2.2 Content of the meeting

The elements currently covered in the Technology chapter in the roadmap are the following.

- Organisation of resources
  - Multidimensional space as an organisational paradigm
  - Definitions
  - The data object
  - Annotation and annotation services
  - The model object
  - Execution, storage and networking services
  - Workflow objects
  - The credibility axis in the virtual human twin
- Data
  - Data generation
  - Data use and reuse
  - Data transformation services: harmonising and transcending boundaries
- Models
  - Models as data transformation services
  - Models as data generation services
  - Models as data flow orchestrations
  - Model classification by context of use
- Integration of resources
  - Identification of possibilities for integration
  - Integration of multiscale models
  - Workflows
  - Bidirectional communication with users (including knowledge generation)
- Infrastructure
  - Catalogue & repository
  - Simulation platform
  - Computational resources
  - Recommendations for VHT Infrastructure

The content was presented to the AGS members and followed by dedicated discussion.

2.3 Discussion points

- Curation: how will this be handled in the infrastructure?
  - For the moment, manual curation is foreseen, meaning that the inclusion of a curation team is a requirement for the operation of the VHT
  - For published resources, part of the curation might have been done by journals (or in future, journals might look at inclusion in VHT for this)
  - Context of use, question of interest and hypotheses made are important to be considered in this process
  - For certain groups (e.g. EC funded projects) the expectation should be to deliver resources requiring only a minimum of curation.
- Key role for interoperability and standards (further addressed in section 4)
- Strong opportunity for using platform to provide assistance to perform credibility assessment
- Users: there is a wide range of potential users so it will be a core challenge to address this through a single interface and triage information based on profile
  - This has indeed been thoroughly examined. The description of how to handle user profiles and user roles in the platform is included in the roadmap (see section 4)
- What is the intention of VHT with respect to medical devices and access to the market?
  - Assistance in credibility assessment and preparation of regulatory dossier for specific applications (not platform as a whole)
  - Data quality assessment is very important (provenance of data, metadata & certificate of birth of the information included as resource in VHT) > included in the proposed credibility axis
  - Focus will be mostly on pre-competitive aspects of building virtual twins.
- Incentives
  - Include a tool that aims to keep track of new resources added and provide overview (inventory)? > this will be covered (in part) by the catalogue.
  - Contractual engagement (e.g. for EC funded projects)
- How to handle commercial licenses?
  - Either restrict resources to those with open access or include them in repository while not facilitating their access? In case of the latter, information should be included to ask for access
  - This also includes commercial data included in the catalogue or data owned by others that are open to collaboration but not entirely free > cfr different models of open access
- Validation of the data. E.g. owner of data says accuracy is below 1 µm. This is impossible to verify, how to handle this?
  - Signed statement for those with submitted requesting the highest credibility: is this legally binding? What are the alternatives ?
  - Check similar issues from the biomedical sciences side. It is the responsibility of user of the data.
- Service to be included: data conversion / transformation tools
  - mapping tool that will convert data into available formats as well as make it correspond to other sets
  - Find adaptations for data sets to be able to correspond to or be combined with other data sets
  - Extract data sets from larger data sets
- How to combine data streams of different fidelity & frequency and do their credibility assessment? What are the implications when implementing this in hospital settings? What is the impact of this on the platform design?
  - start by combining a few bricks, facility the possibility
- Connection to other life sciences research infrastructures.

3 ELSI for VHT

3.1 Agenda of the meeting

The “ELSI for VHT” deep dive meeting took place online on Wednesday 26th June between 11.30 and 13:00 (CEST), with the following **agenda**:

- 11.30: Introduction (Liesbet Geris)
- 11.35: AI act & VHT (Lorenzo Cristofaro, LYNKEUS) + discussion
- 11.55: Reuse of health data for VHT (Francesca Conte, UNIBO) + discussion
- 12.15: Standards (prepared by Martin Golebiewski, HITS, presented by Liesbet Geris) + discussion
- 12.35: Social acceptance & trust (Zita Van Horenbeeck, VPHi) + discussion

Every topic consisted of a sort presentation, followed by a discussion on that particular aspect.

The meeting was **attended** by relevant members of the AGS members (representing academia, notified bodies and patient organisations), as well as the members of the EDITH-CSA consortium (Piotr Polec, Edwin Morley-Fletcher, Artem Platonov, Beatrice Bressan, Francesca Conte, Frederic Jung, Gökhan Ertaylan, Janaki Raman Rangarajan, Lorenzo Cristofaro, Marek Kasztelnik, Simon Denil, Sok Dim, Bernard Staumont, Valentina Huber, Wolfgang Müller, Vincent Uyttendaele, Zita Van Horenbeeck, Liesbet Geris) and representatives of the European Commission (Kyriacos Hatzaras, Renata Palen and Konstantin Hypponen, DG CNECT H3 – eHealth, Wellbeing and Ageing).

3.2 Content of the meeting

The elements currently covered in the ELSI chapter in the roadmap are the following.

- 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 – semantic annotation and taxonomy
  - Semantic annotation & Taxonomy for VHT
- Health Technology Assessment and Payers
- Legal Aspects
  - Data privacy & protection
  - Data governance
  - Artificial Intelligence
  - Medical devices
  - Remarks and recommendations based on current EU policies
  - IPR management
- Ethical and Social Aspects

The content was presented to the AGS members and followed by dedicated discussion.

3.3 Discussion points

- Risk pyramid: if VHT can be considered a medical device, what measures have been taken to qualify it as such? Not the entire platform but rather tools developed through/with VHT will be considered as SaMD/MDSW and will have to be qualified as such.
- AI Act
  - Applications in health fall in the high risk category.
  - AI-based tools need to comply with both AI and MDR (with MDR being the dominant legislation)
- Trustworthiness is related to (amongst others) application of different legal principles in different applications. Stepping out of level of detail & showing more general ethics framework, including guidelines for trustworthy AI, vision creation & framework provision is required.
  - Development of a code of conduct as an example.
- Definition of AI and who decides what is what
  - Self-assessment by developer & deployer. Imposing decision by agency?
- Synthetic data: how can this replicate the real world? How can this be regulated (from perspective of Notified Body)?

    - Synthetic data comes from real world data & has been 'reprocessed'. Synthetic data now can still be connected to the RWD, which means GDPR might still be applicable.
    - 1+M genome data project is using synthetic data in the development of their (technical) platform
    - Data generator & discriminator, privacy-enhancing technologies
    - Context of use also important for synthetic data
- Are there additional topics of concern that need to be included (and were they already considered in the roadmap)?
    - Access: concerns related to access were focusing on reimbursement , but also general access for the non-first world countries needs to be included.
    - Gender: are there gender issues that might play? This topic did not come up during the focus groups but is important > females are less investigated and less involved in developments, leading to therapies less effective for females
    - What is different between digital twins and other new technologies > are there specific details that are uniquely related to VHT ?
        - There are unique challenges related to VHT, but it is hard to talk about specifics in the current situation where the level of knowledge/literacy is still insufficient to articulate this in patient/public focus groups.
- Clear instructions or a clear pathway should be included in the roadmap on how to bring successful applications towards the hospital patients via the regulatory agencies
- Additional sections in the roadmap to deal with
    - Vulnerable groups & individuals
    - Specific groups (e.g. minors)
    - Less developed countries
    - HTA & payers

4 Uptake, users & sustainability

4.1 Agenda of the meeting

The "Uptake, users & sustainability" deep dive meeting took place online on Friday 28th of June between 14:30-16:00 (CEST), with the following **agenda**:

- 14.30: Welcome & Introduction (Liesbet Geris)
- 14.35: user roles & responsibilities (Gökhan Ertaylan, VITO) + discussion
- 15.05: value proposition from the IAB (Liesbet Geris) + discussion
- 15.30: clinical perspective (Laura Bevis, QML) + discussion

Every topic consisted of a sort presentation, followed by a discussion on that particular aspect.

The meeting was **attended** by relevant members of the AGS members (representing industry, healthcare providers, notified bodies and patient organisations), as well as the members of the EDITH-CSA consortium (Enzo Fabiano, Evita Mailli, Artem Platonov, Frederic Jung, Gökhan Ertaylan, Janaki Raman Rangarajan, Maura Bevis, Nathan Carvalho, Simon Denil, Bernard Staumont, Sok Dim, Marian Bubak, Vincent Uyttendaele, Flaminia Malvezzi, Liesbet Geris).

4.2 Content of the meeting

The elements currently covered in the users, uptake & sustainability chapter in the roadmap are the following.

- Uptake
    - IAB, clinicians, other users
    - Analysis & implementation early prototype demonstrators
    - Incentivization
- Economics

  - VHT Value proposition for IAB & other stakeholders
  - Business model development
  - VHT Market place
  - Evolutionary Ecosystem Approach
  - Digital Health Economics
- Research infrastructure bench marks
- EU27 Member state strategy ongoing

The content was presented to the AGS members and followed by dedicated discussion.

4.3 Discussion points

- Dealing with individual patient data
  - Patient data pods, simulated data of patients goes back into the pod
  - Strong link to European Health Data Space > involvement with TEHDAS2
- Federated nature of the platform
  - Use case of SEEK platform will be included in proof of concept infrastructure to test the federation challenges
- Importance of education
- Activities on incentivization for uptake of VHT
  - Incentives for different stakeholders discussed in various EDTH public meetings

5 Next steps

The elements discussed during the deep dives meetings have been included in the draft of the VHT roadmap. One last meeting will be organised for the entire AGS to discuss the recommendations that will be included in the roadmap. This meeting will take place beginning of November 2024.