The Virtual Physiological Human Institute

Actions for Horizon Europe projects

28/2/2023

1. Introduction

The **Virtual Physiological Human institute** (Belgian non-for-profit, http://vph-institute.org) is an open community of scientists, clinicians and other healthcare professionals, focused on the development and uptake of computer modeling & simulation in healthcare. The VPHi represents many of the largest in silico medicine research groups worldwide. It has established collaborations with many sister societies and organizations (e.g. ESB (biomech), JRC, CAAT etc). Besides the organization of typical scientific society activities such as a bi-annual conference, summerschools, webinars and mentoring activities, the VPHi has also been very active in policy development and stakeholder interaction. These activities have been enhanced through the establishment of a formal collaboration in equal partnership with software, device and pharmaceutical industry called the Avicenna Alliance (also Belgian non-for-profit, http://avicenna-alliance.com). Additionally, the VPHi is actively interacting with members of the European Commission (DG CNECT & RTD) to provide state-of-the-art success stories on the use of computer modeling and simulation to advance healthcare and to discuss the challenges ahead to further facilitate in silico medicine.

Participation of the VPHi in any Horizon Europe consortium can be focused on one or more of the following core activities

- Communication & dissemination
- Stakeholder assessment & outreach
- Regulatory & Policy
- Connections with other in silico medicine (EU) projects

Below are the standard activities that we offer to all consortia equally, without restricting ourselves to one consortium per call - EC in fact explicitly asks for the creation of synergies between different projects awarded in the same call and having translational partners is an easy way to meet this demand. However, *if you want us to be involved for activities that are not these standard ones and are adapted/tailored specifically for your proposal, these will remain confidential to the consortium of course.*

2. Communication and dissemination

Currently established tools within the VPH institute are the following.

- The VPHi is the owner of the VPH conference brand. This biannual event has been running since 2010, and over the years has been growing its importance and outreach potentials. The last conferences were organized in Porto (300 delegates) and Paris (as an online event - 600 delegates). The upcoming VPH2024 conference will be organized in Stuttgart on 4-6 Sept 2024. More information can be found here: http://vph-conference.org/

- A monthly e-newsletter which reaches 7.000 unique contacts related to in silico medicine world
- A webinar series, organized since 2016 by the VPHi student committee that features prestigious keynote speakers on specific research topics related to in silico medicine.
- Social network presence: LinkedIn, Twitter, YouTube
- An established institutional website

The VPHi can take advantage of its pre-existing assets and (as already happened in the past with both Discipulus [1] and Avicenna [2] support actions as well as more recent projects InSilicoWorld [3], SimCor [4], SimCardiotest [5], EDITH [6] and REALM [7]) could join future funded EC projects taking care of dissemination activities and community engagement/building exercises. In particular, following dissemination activities can be handled:

- Production and distribution of the communication material through all its channels, such as news, events, press releases, brochures etc.
- Monthly e-newsletter
- Printed newsletter on regular bases (i.e. every 6 months)
- Project videos
- Organization of online webinars on project topics.

3. Stakeholder engagement and outreach

A number of important stakeholders are involved in the in silico medicine world:

- Clinical community (the actual end- user of VPH technologies)
- Industry (the producers of products that are based on VPH technologies)
- Health Technology Assessment organizations (assessing in silico medicine products)
- Payers & Insurance companies (possible reimbursement of in silico medicine related costs)
- Citizen and Patient organizations (who represents the patients that could (or already) benefit from the use and application of VPH technologies)
- Institutional community (funding bodies, regulators…), who regulates and shapes the future of in silico medicine

The VPHi is in contact with many of these stakeholders already – either through the engagement of thei representatives of these stakeholders within the institute itself, or through collaborations. Through these representatives and through the entire VPHi membership, contacts have been/can be made with larger organizations representing these categories on a higher level.

When doing stakeholder engagement and outreach, an important pillar in the realization of Responsible Research & Innovation [8], specific programs should be set up, tailored to each of the stakeholder categories. For every stakeholder, a similar structure will be followed, although the specific implementation will differ for the different groups. First, a desk **review** will be conducted to get a good view on the state-of-the art of uptake and use of in silico medicine in a particular group as well as to identify possible partner organization for each stakeholder group (e.g. professional organizations, networks, existing event). This will be followed by an **assessment** where the stakeholder group will be interrogated to identify knowledge gaps, perceived risks and hurdles. This assessment can be done in the form of semi-structured

interviews, panels, focus groups or questionnaires. This information will be **analyzed** to distill key actions to be taken and discussed with the consortium in order to identify specific opportunities to link the identified actions to developments within the project. Subsequently these **actions** will be implemented in a format that is tailored to the specific target group which can include the creation of instructive video's, the development of a lecture series and the drafting of a (targeted) road map. Finally, the impact of the actions will be **evaluated** through another round of interviews, focus groups etc. and follow-up actions identified where necessary.

Through the actions in the currently ongoing projects, we have developed substantial expertise in the execution of surveys [9], panels and focus groups. The developed guidelines and information packages, implementation tools and scientific results will be made available to the entire community in 2023 as part of the current activities of the institute.

4. Regulatory & Policy

Policy

As mentioned previously, in collaboration with industry partners in the context of the Avicenna Alliance, the VPHi has had impact on the Medical Device Regulation and the current EMA legislation. Currently the pediatric and orphan medicine regulation are under review (or will be soon) and actions are being planned to lobby for the **inclusion of specific references to computer modeling & simulation in** those **regulations**. Inclusion of such explicit reference to CM&S will provide a mandate to companies, academics and all parties involved in the respective fields that are using CM&S in the search for safer and cheaper treatments for these categories of patients that are often overlooked by mainstream developments.

This process typically starts with the **formation of an expert working group** within a project or within the VPHi and/or Avicenna Alliance with representation from both academia, industry and other relevant stakeholders. This working group drafts a white paper, detailing the current state of the art as well as the possibilities that explicit inclusion of CM&S in the regulation can provide and listing a number of challenges (see [10-12] for examples). Specific training or information events can be provided to the relevant policy makers to suggest tangible actions and amendments to the regulations.

Regulatory & standardization

In order for digital evidence (evidence generated via the use of computer modeling & simulation) to be admitted as genuine evidence in a **regulatory submission**, or in order for computer models to obtain qualification as a tool, a thorough validation process needs to be followed. This can be summarized by VVUQ: verification, validation and uncertainty quantification [13]. Verification refers to the agreement between the mathematical model and the simulation results (both at the level of the model and the code). Validation refers to the agreement between the simulation results and the physical reality (impacted by the way the measures used to assess this agreement, as well as the quality of the physical data used as a comparator). Uncertainty Quantification relates to the assessment of the impact uncertainty on model assumptions and parameters has on the model's behavior, within the predefined context of use. A good overview of the history and relevant regulatory documents can be found in [14].

FDA has been very instrumental in driving the **inclusion of in silico models in regulatory** submissions for medical devices, starting with the publication of specific documentation guidelines [15]. After and thorough process with involvement of FDA and industrial partners, an ASME standard was released in 2018 (VV-40-2018 [16]) related to the verification and validation of computer models in the development of medical devices. The standard relates the amount of V&V that is required to pass regulatory scrutiny to the risk related to the use of the model (risk is defined as a combination of the influence the model has on the medical decision and the consequence of an error for the patient). At the European level, EMA regulations on physiology-based pharmacokinetic models used frequently in drug development [17], follow a comparable verification and validation strategy. The VPHi and EMA have joined forces to develop guidelines to go towards a validation strategy for all types of in silico medicine models [18]. Besides regulators and academia, the working group can count on the active participation of industry and other healthcare professionals. Once the general guidelines have been published, specific implementation of said guidelines in the application area of the project should be established. The VPHi will guide this process ensuring the engagement of the relevant stakeholders.

In terms of standardization efforts, the VPHi is involved with several ISO committees either directly or through the Avicenna Alliance with the aim of **establishing a coherent standardization framework for CM&S** in Europe, aligned with the ASME VV-40.

5. Interaction with EDITH-CSA

EDITH is the Coordination Support Action (2022-2024) funded under the Digital Europe Program (DIGITAL-2021-DEPLOY-01-TWINS-HEALTH), coordinated by the VPHi, that aims to build the Ecosystem for DIgital Twin in Healthcare, equipping all European stakeholders with the right infrastructure and tools to develop the so-called **Integrated Virtual Human Twin**. The Integrated Virtual Human Twin is to be an integrated multiscale, multi-time, and multi-disciple representation of quantitative human physiology and pathology. As the question of interest will determine what features are useful to include in a model, the Virtual Human Twin will create a 'level playing field' where all available resources (models, data, algorithms) can be combined if and when needed. Its realization through a collaborative distributed knowledge and resource platform is specifically designed to accelerate the development, integration and adoption of patient-specific predictive computer models. These models can be knowledge-driven, data-driven or both and the interaction with their physical counterpart (the patient) can be real-time (as in the classical engineering definition of the digital twin) or not. This includes models to be used as clinical decision support systems, for personal health forecasting or as methodologies for the development and de-risking of personalized medical products. This CSA should provide a **general vision and a roadmap** for deploying the Integrated Virtual Human Twin, including the establishment of a **federated cloud-based repository** for sharing of resources between stakeholders as well as the design of a **simulation platform** where all stakeholders can actively interact with and integrate the aforementioned resources and link directly to the appropriate compute infrastructure (cloud, edge, high performance computing).

EDITH has brought together the entire **ecosystem**, i.e., academia, industry, healthcare professionals, regulatory agencies, policy makers, HTA, patients and payers, from software, hard-

ware, devices and pharma backgrounds. The ecosystem is leveraged through expert meetings, online working groups, community meetings, surveys etc. to identify the research challenges and required infrastructure that will facilitate the integration of different models, algorithms and data sets across different organ systems and spatio-temporal scales. Several **use cases** will be developed as early-stage demonstrators of the range and potential of the simulation platform. In the second year of the project (2023-2024), we will launch a call for new demonstrators, allowing all researchers, companies and stakeholders to actively engage with the CSA project and align with the technological, ethical and legal concepts that would allow for a seamless integration in the future platform. *It is through participation in the meetings and inclusion of project-specific use cases as demonstrators that ongoing and new project will be able to actively engage with the EDITH project.*

The required efforts will include substantial developments on the technological side, **supported by linked initiatives** such as the European Health Data Space [19], FAIRDOM-SEEK [20] or the EBRAINS project [21]. Additionally, there is a strong focus on ensuring the appropriated ethical, social and legal frameworks by **influencing the future European policies** on the use of in silico methods in healthcare. The first version of the roadmap, developed by the EDITH ecosystem with the close support and collaboration of the European Commission DG-CNECT and several advisory boards (clinical, industrial, regulatory, etc.) can be accessed through our website and via Zenodo from August 2023.

6. Budget & Contact

In general terms, EC funded projects allocate a 10-15% of their total budget to dissemination and exploitation activities. Given the synergy that the VPHi can create with other ongoing projects, we can be more efficient in our budgeting. The VPH can be a partner in C&D activities or be the lead of the entire work package. Depending on the size of the activities covered and the responsibilities, we will need to assign up to 2 FTE for the duration of the project, spread over multiple people working on several projects to ensure coverage of the entire skill set. The **VPHi team consists of biomedical engineers, a social scientist, communication specialists and a graphic designer** to ensure this aforementioned work is done in a scientifically correct manner.

If you want to discuss a possible involvement of the VPH institute in your project proposal, please feel free to reach out via the following email addresses:

- Manager Martina Contin: manager@vph-institute.org
- Executive Director Liesbet Geris: director@vph-institute.org.

Also if you have questions on any of the aforementioned subjects, are looking for partners within the in silico community that can provide a specific technological expertise, if you want to include the VPHi in an advisory board member capacity or write a letter of support for your project, you are welcome to contact us.

References

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