ISW

In Silico World: Lowering barriers to ubiquitous adoption of In Silico Trials

Grant Agreement No. 101016503

Responsible Research and Innovation Workshop Report

Deliverable information	
WP number and title	WP5 Dissemination, Communication, and RRI
Lead beneficiary	VPHI
Dissemination level	Internal (Milestone)
Due date	
Actual date of delivery	November 2023
Author	Elisa Elhadj, Zita Van Horenbeeck, Elisa Lievevrouw, Liesbet Geris, Ine Van Hoyweghen
Contributors	

The following document reflects only the author's view. The Agency is not responsible for any use that may be made of the information it contains.

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101016503

ISW

In Silico World: Lowering barriers to ubiquitous adoption of In Silico Trials

Grant Agreement No. 101016503

Responsible Research and Innovation Workshop Report

(as part of WP5 - Task 5.3 - MS5.6)

This report presents the background, approach, and findings of the *Responsible Research and Innovation (RRI) Workshop* held on the 19th of April 2023 during the In Silico World General Assembly in Bologna, Italy.

Authors: Elhadj, E., Van Horenbeeck, Z., Lievevrouw E., Geris, L., & Van Howeghen, I.

Executive Summary

Responsible Research and Innovation is the approach that we have adopted throughout the stakeholder engagement activities as part of the ISW project. It emphasizes the continuous involvement of diverse stakeholders in all steps of research and innovation, to ensure inclusivity, anticipation, reflexivity, and responsiveness (Stilgoe et al., 2013). The workshop aimed to contribute to the design of a responsible research and innovation strategy for in silico medicine by discussing the ELSI findings based on our WP5 activities, considering social implications of in silico technologies, and prompting researchers and innovators to reflect and anticipate the governance of these social implications in their work.

Methods:

This report provides a detailed account of the RRI Workshop, which builds on the previous phases of the WP5 RRI trajectory; consisting of a desk review, Delphi survey, and focus groups. The workshop was held during the annual consortium meeting on the 19th of April 2023 in Bologna, Italy. By presenting the findings from each of these phases to the consortium, we provided a platform to discuss the following ELSI implications, informed by the previous focus group discussions (see 2.2): bias and responsibility, expertise, trust, 'holistic modeling' and representation, and lastly definitional issues. From this, we took the RRI approach a step further by co-creating possible governance solutions with the members of the consortium. This proactive approach underscores the importance of anticipating social challenges and collaboratively developing responsible governance mechanisms within the research community, putting a focus on the changes researchers can make in their daily work towards responsible innovation.

Findings:

ELSI topics at stake

The first step of our workshop focused on discussing the ELSI topics that were informed by our previous WP5 activities. An extensive overview of the discussed topics will be presented in this report.

- The workshop explored concerns related to **bias**, which were previously discussed in the focus groups. This led to new discussions on social exclusion and the responsibilities of engineers in minimizing bias. Participants recognized shared responsibility in model development but expressed uncertainty about the extent of individual responsibility. A suggestion was made to create an Ethical Manifesto to address these issues as a community as well as the role of synthetic data generation to minimize bias.
- Conversations surrounding **trust** focused on transparency in stakeholder engagement, encompassing researchers, regulatory agencies, future engineers, clinicians, and patients. This section highlights the significance of trust in shaping the future of in silico medicine.

- In silico medicine seems to challenge traditional understandings of **expertise**, reflecting the shifting landscape of medical expertise. The discussions focused on the expertise and roles of patients and clinicians. Opinions varied on the extent to which patients should be active agents in the process, and about how to account for the different ways of working of clinicians, as well as the perceived shortage of understanding of the field on the side of regulators.
- The concept of "**holistic modeling**" in in silico medicine, and what it entails was explored. Participants expressed differing opinions on whether building a comprehensive and integrated digital twin encompassing a wide range of parameters is achievable. Some saw it as a potential long-term goal requiring time and technological advancements, while others believed it was not realistic. Our report suggests that the discussions around 'holistic' and 'integrated' in silico modeling reflect to broader sociological **considerations of representation**, such as the desire to be as representative as possible, and encompasses social limitations and expectations related to representativeness, feasibility, and social exclusion.
- **Definitional issues** have been shown to be present at the intersection between in silico medicine and artificial intelligence. Discussions highlighted the need to overcome these definitional (and other) ambiguities and to increase awareness of in silico medicine with a broad range of stakeholders to address this and build trust. While some advocated for improved communication and standardized approaches to address these challenges, others noted that the inherent complexity in these definitions can be leveraged for collaboration with non-technical stakeholders.

Co-creating governance mechanisms for in silico medicine

The next step of the RRI workshop focused on governance solutions for discussed ELSI issues and prioritization. An examination of the discussed existing initiatives and the generation of new ideas is presented within this report.

- In terms of **standardization**, the need for a transversal adoption of V&V40, and the beneficial role of research communities in building such standards (e.g. on data collection) was raised.

- Interdisciplinary **training and education of all stakeholders** (regulators, clinicians, general public, engineers) have shown to be necessary for leveraging the awareness of the field, smoothening collaboration, and fostering the trust, all aspects that are crucial for the advancement of in silico medicine.
- The discussions highlighted the need for increased **patient and public involvement** in all steps of the research and innovation process, in order to build trust with the end users of the technologies.
- Participants of the workshop acknowledged the benefits of having a **public infrastructure**, an open-source data platform that, through open access, such as EDITH is working towards.
- Lastly, the suggestion to put together an **Ethical Manifesto** was suggested, serving as a compass for ethical decision-making and demonstrating the in silico community's commitment to RRI. The aim is to outline boundaries and guidelines for the responsible use of in silico models, addressing bias, the responsibility of engineers, and redlining potential malicious uses.
- This report concludes with preliminary policy recommendations, drawn from the discussed insights, as well as organizational takeaways for future similar RRI activities.

1. Introduction

The In Silico World project is geared towards lowering the barriers to the implementation of in silico medicine, by improving the responsiveness of these technologies to societal needs. To achieve this, work package 5 of the project has undertaken various stakeholder engagement initiatives over the course of the project: a desk review, a Delphi survey, three focus groups, and last but not least, an RRI workshop. This report will provide a comprehensive overview of the results from the RRI workshop, whose innovative advantage lies in anticipating the needs and expectations identified in the previous phases.

Background of studying the societal barriers to in silico medicine

Exploring ELSI in in silico medicine: an RRI approach

The incorporation of Responsible Research and Innovation (RRI) into the Horizon 2020 funding program marked a groundbreaking shift away from the well-known ELSI approach, emphasizing the importance of engaging with societal aspects of scientific research and development (Landeweerd et al., 2015). For background, ELSI, short for Ethical, Legal, and Social Implications, has been widely known in science and science policy since its inception in 1990 through the Human Genome Project in the US. It involves analyzing the societal repercussions of emerging scientific and technological advancements (Hartwig et al., 2022; Rosemann and Zhang, 2022). In this project, we adopted an RRI approach while pinpointing ELSI topics—specific themes that we aimed to explore with involved stakeholders to address societal concerns related to the emerging in silico technologies. It is crucial to emphasize the distinction between the ELSI approach and RRI: while the former primarily focuses on future consequences of technologies, researchers have argued the ELSI framework to fall short in actively addressing them (Rosemann and Zhang, 2022). In contrast, our RRI approach aimed not only to identify ELSI but also to respond to diverse needs, taking proactive steps to bridge the gap. This was done through consecutive activities, each assessing the social implications of in silico medicine. Introduced in European science policy about a decade ago, RRI aims to enhance inclusivity and transparency in research and innovation, emphasizing the integration of societal actors and addressing normative questions through co-creation (Felt, Öchsner, Rae, & Osipova, 2023; Von Schomberg, 2011). By including diverse knowledge, perspectives, and concerns from stakeholders, RRI aims to identify public expectations, respond to needs and values, and consider economic and ecological consequences throughout the science and technology lifecycle (L'Astorina and Di Fiore, 2017).

In the ISW project context, we employ an RRI approach that involves **anticipating** future scenarios in in silico medicine raising awareness, and encouraging social learning within the ISW consortium on the societal impacts of advancements in this field (**reflexiveness**). Through this approach, we aimed to include various stakeholders throughout various phases (**inclusion**), to enhance the overall capacity of the ISW research community to incorporate broader societal perspectives into ongoing research and development efforts (**responsiveness**). These four dimensions, crucial to the RRI framework, are expected to facilitate the responsible development of

these in silico technologies (Stilgoe et al., 2013; Van Oudheusden, Lesage, and Van Hoyweghen, 2022)[1].

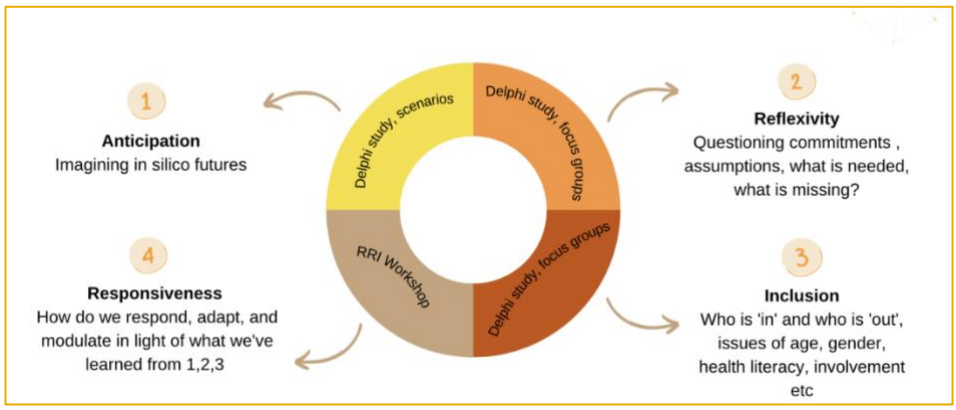


Figure 1: The ISW Co-creation cycle based on four key RRI dimensions (Stilgoe et al. 2013; Van Oudheusden, Lesage and Van Hoyweghen, 2022)

Through an **anticipatory RRI approach**, WP5 aimed to interact with a variety of stakeholders, including patients, patient organizations, clinicians, social scientists, legal experts, and innovators. Since the start of the project, we have organized several stakeholder engagement activities, with each phase oriented on understanding values, needs, and expectations in regard to in silico medicine[2].

The first phase involved a desk review, which is a literature mapping of the stakeholder networks and initiatives, and a review of ELSI topics in in silico medicine. This brought a scarcity of ELSI literature on in silico technologies to light. This then informed the next phase, the Delphi Survey, which gathered insights on the views, expectations, and concerns of an interdisciplinary panel of innovators working on in silico medicine. This survey illuminated various ELSI topics related to in silico medicine, encompassing areas such as technology optimization, fairness/justice, patient rights, ecological concerns, and global justice. These topics then functioned as input for the next phase: three focus groups, conducted in three different countries, to further discover the ELSI

[1-2] For additional information on the general RRI trajectory in ISW and the broader Delphi study approach please see ISW_T5.3_MS13_desk review (Van oudheusden, Lesage and Van Hoyweghen, 2022) and the Analysis Report of the Focus Groups (Elhadj et al., 2023). Both are available on the ISW SharePoint.

topics living with a broader array of stakeholders[3] (Van Oudheusden, Lesage and Van Hoyweghen, 2022). While literature on the Ethical, Legal and Social Implications of in silico technology addresses challenges like privacy, responsibility, data quality, bias, and accessibility in in silico medicine (Cordeiro, 2021; Leo et al., 2022; Shen et al., 2022), our focus group discussion findings delved into the risks, difficulties, and opportunities presented by in silico medicine, bringing other social implications to the foreground, such as questions around expertise, animal testing, and trust (Elhadj et al., 2023). Continuously exploring societal aspects through these phases deepened our understanding of the social implications of in silico medicine development for societal actors, and all these phases led up to the final round of our activities: the RRI workshop.

Aim of the RRI workshop

The RRI workshop represents the integration of the various stages of WP5 RRI initiatives, expanding upon the societal issues identified during the entire RRI process. As such, this RRI workshop functioned as the opportunity to present the gathered insights back to the ISW consortium[4]. Its aim, however, was not only to present the identified concerns but also to enable proactive discussions on the governance of these issues, aiming to anticipate legislation.

During the workshop, we delved deeper into themes such as representation, expertise, responsibility, and trust. We opted for these specific ELSI topics because they seemed to spark discussion among the stakeholders during the focus groups, and to fill the need to delve deeper into ELSI topics not currently covered in in silico medicine literature. This RRI workshop aligns with the responsiveness RRI dimension by tackling the insights from prior ethical, legal, and social implications assessments into the in silico innovation process, emphasizing a comprehensive and responsible perspective (Stilgoe et al., 2013).

[3] For additional information on the general RRI trajectory in ISW and the broader Delphi study approach please see ISW_T5.3_MS13_desk review (Van oudheusden, Lesage and Van Hoyweghen, 2022) and the Analysis Report of the Focus Groups (Elhadj, Van Horenbeeck and Lievevrouw, 2023). Both are available on the ISW SharePoint.

[4] See ISW proposal.

With the aim of contributing to the design of a responsible research and innovation strategy for in silico medicine, the RRI workshop focused on two main objectives. Firstly, it aimed at discussing the collected findings on ELSI issues through the WP5 RRI trajectory, considering social implications across its different aspects, applications, and developmental phases. Secondly from there, we took the RRI approach a step further by prompting researchers and innovators to reflect and anticipate on the governance of the social implications, rather than simply discussing the ELSI brought forward during the previous stages. The novelty of this approach lies in encouraging the researchers to move beyond the commonly emphasized legal implications of their work by providing them a dedicated space to critically reflect on the broader social implications (Ulnicane, Mahfoud, and Salles, 2022). As such, our RRI approach plays a vital role in anticipating the potential impacts of in silico medicine. It provides a platform to discuss possible governance solutions, offering valuable input for regulators and researchers in the field to create informed policies promoting responsible innovative advancements. Governance, in this context, refers to the structured framework through which the management and coordination of 'technology endeavors', such as research and innovation, are carried out (Landeweerd et al., 2015). Possible governance mechanisms entail regulations, principles, standards, securitization efforts, impact assessments, or value statements (Stark, Greene, and Hoffmann, 2020).

Particularly with emerging technologies like in silico medicine, a significant regulatory challenge lies in creating adaptive and comprehensive regulations that encourage innovation while ensuring safety, privacy, ethics, and societal impact are considered (Mandel, 2009). This is where RRI comes in, not just as a strategy to align innovation with societal needs, but also as a framework to consider potential governance solutions. This approach ensures all stakeholders are taken into account, with a particular emphasis on self-regulation mechanisms within the consortium. This proactive approach minimizes the necessity for regulators to intervene and underscores the importance of anticipating challenges and collaboratively developing responsible governance mechanisms within the research community. As a result, the in silico community stressed the significance of self-regulation mechanisms during the workshop.

Overview of the report

In what follows, we will elaborate on the reasoning behind the methodology for the RRI workshop, followed by a comprehensive overview of the main insights. Our findings delve into pivotal sociological themes of in silico medicine: addressing issues of representativity, expertise, responsibility, and trust are vital for ethical and collaborative progress in the field. From this, we then turn to governance solutions on how to tackle these key findings, which are the result of the two-way reflective dialogue with the innovators in the project, emphasizing, among others, the significance of ethical guidelines and the proposed ethical manifesto, a proactive measure addressing ethical, societal, and regulatory concerns. The synthesized action points will form the basis for practical policy recommendations. This will set the groundwork for our policy brief (D5.3-M36), which will be enriched by the broad range of perspectives and action points gathered throughout the different research phases in WP5. Finally, we will critically reflect on the limitations of our approach, to refine and enhance future endeavors, such as future similar workshops.

2. Methodology of the RRI Workshop

Practical information

For a more detailed description of the chosen approach for the RRI workshop, please refer to the handbook[5] (see Annex 1), which was written in preparation for the event.

When:	19th April 2023, 16:00-18:00
Where:	Bologna, Italy - Alma Mater Studiorum Università di Bologna
With whom:	ISW project members (in-person)
Organizers:	KU Leuven & VPHi

Data collection

We hosted a 2-hour workshop in Bologna in April 2023 with participants of the In Silico World (ISW) consortium. Given our aim to leverage the workshop as a collective

[5] An extensive handbook has been developed to serve as a comprehensive planning guide for moderators and observers, ensuring the smooth preparation and execution of the RRI Workshop. This handbook can be found in Annex 1 and is available on the ISW SharePoint.

moment to bring the findings of WP5 to the consortium and discuss the governance realm of in silico medicine, it made the most sense, at this stage, to exclusively include ISW consortium members. Reflecting on governance is an essential part of our RRI approach as its outcomes will guide and be used as a stepping stone in the next steps which include the policy brief and white paper.

The workshop was organized on the day preceding the ISW general assembly, taking advantage of the opportunity to have the consortium gathered in Bologna. For recruitment, participants were invited through email by WP5 members and supported with the attachment of a digital flyer (see Annex 6). Of the 41 participants invited, a total of 32 ISW members took part in the RRI workshop. Prior to the start of the workshop, a member of WP5 distributed consent forms and was made available to address any questions or concerns. Once participants were able to give their informed consent, their signed consent forms were collected[6].

Layout of RRI workshop

In line with the objective of the project, as described under 1.1., the workshop was organized in the following manner.

The event commenced with welcoming words delivered by Prof. Dr. Ine Van Hoyweghen. This was followed by Elisa Elhadj and Zita Van Horenbeeck giving a brief presentation on Responsible Research and Innovation (RRI), emphasizing the significance of aligning research and innovation endeavors with the values, needs, and expectations of society. Additionally, and to set the stage for the next phase, the

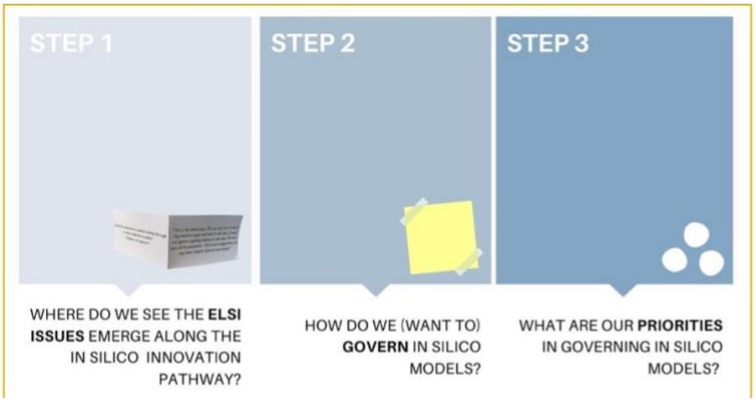


Figure 2: Group Conversations Steps Overview

[6] The consent forms are securely stored on a separate KU Leuven secured-drive, and a template of the consent form can be found on the ISW Sharepoint – "RRI Workshop".

findings derived from the focus groups were presented, offering valuable insights into the discussions held by diverse stakeholders.

The next phase of the workshop centred around group discussions (see Figure 2), which formed the crux of the event and included three distinctive steps. The aim was i) to discuss the ELSI findings derived from the previously conducted focus group, second, ii) to explore potential governance solutions for in silico medicine and iii) to reflect on the role of the consortium in overcoming potential societal barriers. Dr. Elisa Lievevrouw provided a detailed briefing on the structure and objectives of the group conversations. To allow the discussion to run as seamlessly as possible - ensuring enough time for each participant to share their views - we decided to break up the participants into five different discussion groups, each having its own moderator and observer. These groups were created in advance to ensure that the different groups were mixed up as much as possible.

	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**
M	Moderator KU Leuven Observer VPHI	Moderator KU Leuven Observer VPHI	Moderator KU Leuven Observer VPHI	Moderator KU Leuven Observer VPHI	Moderator KU Leuven Observer VPHI
P1	DIN - Deutsches Institut für Normung	University of Bologna	Erasmus MC	Instituto Ortopedico Rizzoli	In Silico Trials
P2	Materliaze Motion	Eindhoven University of Technology	Eindhoven University of Technology	KU Leuven	SANO Centre
P3	Eindhoven University of Technology	University of Bologna	University of Bologna	SANO Centre	University of Liège
P4	University of Bologna	University of Bologna	University of Bologna	University of Bologna	University of Bologna
P5	University of Bologna	Materliaze Motion	University of Bologna	University of Bologna	University of Bologna
P6	DIN - Deutsches Institut für Normung	KU Leuven	VPHI .	Budapest University of Technology and Economics	University of Bologna
P7		Unive,rsity of Catania			Mimesis

	Academia		Industry		Non-profit		Standard organizatio n		Clinical

Table 1: Overview Workshop participants and discussion groups

Within these groups, participants engaged in focused conversations that spanned within three distinct steps. Overall, the three steps involved productive discussions on ELSI concerns, opportunities, and governance solutions in the field of in silico

medicine. It is essential to emphasize here that the layout and topic selection of the workshop, ELSI and governance, are informed by preceding activities part of our RRI approach, such as the desk-review, the Delphi survey and the three focus groups. Each step within our RRI trajectory serves as a foundation for the subsequent one, with each informing and building upon the next, culminating in this workshop.

In collaboration with one of the in silico experts of the project, a visual representation of the innovation lifecycle of a computational model was developed based on Wender et al.'s (2014)[7] anticipatory life-cycle assessment (LCA) RRI tool to support the group discussions of this workshop (see Figure 3).

This division of the complex innovation lifecycle process into several delineated segments allows distinguishing between different phases of the development of an in silico model, which is an important contribution of our work to existing scholarly research on in silico medicine and RRI tools. Rather than merely identifying ELSI as they arise, our focus lies in anticipation, as we explore the potential ELSI which may emerge throughout the innovation lifecycle. This approach not only highlights the potential emergence of ELSI within specific segments of the innovation lifecycle, but also shows that certain ELSI can manifest in both the input and output phases of in silico models. This holds significance as it can facilitate the specific and more adequate tailoring of potential solutions to these implications of in silico models. We will present this important contribution in greater detail and what it means in terms of governance at the end of this section through Figure 4, which presents our RRI scheme.

We will now delve into a more detailed explanation of the three steps.

STEP 1 - The workshop was built on the ELSI insights from the focus groups[8], as the first part of the group discussions made use of actual quotes on ELSI issues from the focus group respondents. Due to limited time, not all ELSI issues that came up during the focus groups could be discussed during the workshop. Our selection was guided

[7] The RRI tool developed by Wender et al., (2014) is initiatlly thought of as a comprehensive framework which can be used to evaluate the environmental impacts of products, processes, and technologies. Their work inspired us to develop a similar tool adequate for the in silico medicine field and this workshop, which could lead to deliberations and reflections about the social aspects and implications of in silico medicine.

[8] An analysis report of the conducted focus groups is available on the ISW Sharepoint – WP5 folder.

by the previous activities, including the Delphi survey, and the pursuing of novel viewpoints which have not yet been discussed in the ELSI of in silico medicine literature[9].

The first step of the workshop served as a warm-up discussion on these different ELSI concerns, while respondents could place ELSI focus cards[10] (see Annex 3) along the in silico innovation lifecycle (displayed in Figure 3). For instance, one focus card would read "Complexities of the human body." On the flip side, a quote sourced directly from the focus groups accompanied it, *"We provide answers to the questions we ask. But what if a crucial parameter is overlooked, and we remain unaware of it?".* Another card highlighted "The right not to know & patient empowerment," with the following quote on the reverse: *"If we create a digital twin, we can employ it to predict a future disease. However, this closely intertwines with the realm of predictive genetic models. Do I truly want to glimpse into the future?".* In total, we assembled a set of 12 ELSI cards, each adhering to this template - one side featuring a specific ELSI issue in conjunction with a relevant quote from the focus groups.

[9]Our desk-review and in-depth exploration of biomedical and emerging technologies literature also played an important role in guiding our decisions on which ELSI should be prioritized in this report.

[10]The idea of utilizing focus cards stems from the Responsible Innovation Co-Creation Method Kit developed by Jegou et al. as part of the COMPASS project (www.innovation-compass.eu). For further information, a direct link to the method kit can be found in the References section.

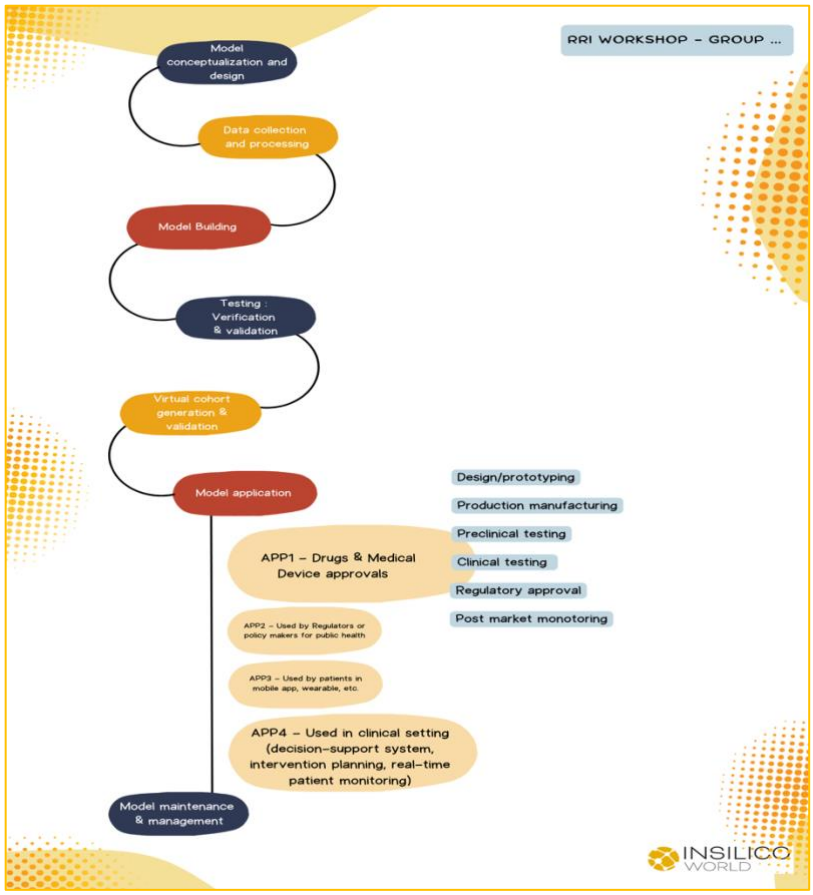


Figure 3: ELSI along the in silico model innovation lifecycle Poster Used for Group Discussions

As a conversation starter, each participant was engaged to share their two ELSI quote cards with the group and place them on the poster wherever participants deemed the ELSI issue the most appropriate in the innovation lifecycle. Participants also had the availability to make use of pink post-its if they would like to add additional ELSI concerns or themes to the poster.

The discussions were lively and constructive, with participants sharing their experiences and insights on the societal opportunities and challenges of in silico medicine. This was of particular relevance as it provided an invaluable opportunity for the experts involved in developing in silico models to gain insight into the perspectives of other participants.. This enabled the workshop participants to get an overview of different stakeholder's ELSI concerns.

STEP 2 - From this, we started discussion group conversations on the governance of in silico technologies. First, participants discussed existing governance initiatives

within the in silico medicine field, and considered its strengths and weaknesses. Secondly, participants were encouraged to explore and envision governance solutions that had not yet been discussed but held the potential to address pertinent ELSI. This approach was chosen as it was noticeable during the focus group discussions[11] that participants often highlighted governance issues but rarely proposed solutions.

This approach fostered a brainstorming session where participants actively imagined and proposed innovative solutions beyond the existing ones. By combining an examination of governance initiatives with the generation of new ideas, the conversation facilitated a comprehensive exploration of governance possibilities for in silico practices. To stimulate discussions, the moderators asked pertinent questions such as *"Where could the project come-in to support the governance-building for in silico?*" or *What could you do concretely to contribute to overcoming (specific barrier)?".* These questions not only stimulated participants to contemplate the role of the consortium but also prompted them to consider their individual roles as researchers and engineers, fostering a deeper level of engagement. Overall, some existing governance solutions (e.g. standardization of data collection and specific ISW public engagement efforts) were discussed, which could potentially **facilitate responsible development and adoption of IS technologies in society.** The valuable insights gathered within this workshop, will be integrated and used for the ISW policy brief and white paper.

STEP 3 - In the third and concluding step of this workshop, participants were asked to highlight their top three ethical, legal and social implications and governance priorities. The moderators handed out three dots to the participants to place next to the cards within the poster that they think is an absolute priority. This further helped identifying the most important ELIS topics that need to be tackled and the proposed governance solutions.

Data analysis

Each group discussion was audio-recorded with the help of voice recorders. Afterwards, the recordings were transcribed using the software Sonix, and each

[11] For more details, please refer to the preliminary focus groups analysis report available on the ISW Sharepoint.

transcript meticulously reviewed through a re-listening of the audio recording. All the transcripts were pseudo-anonymized to avoid any recognition of the speakers. These cleaned up transcripts were stored on the protected KUL shared drive, and the recordings got destroyed for privacy reasons.

Using the Atlas.ti software program, each discussion was coded iteratively for qualitative data analysis. First, the transcripts were analysed by every researcher separately and then discussed during a series of brainstorm sessions. Previously, while analyzing the focus group data, we developed a coding tree[12]. As this workshop builds on these focus groups within the In Silico World project, we used the same coding tree as a baseline. In accordance with the purpose of the workshop, new codeslaying out the governance solutions, were added. The final code tree for the RRI workshop can be consulted in Annex 2.

It is essential to note that in this report we also had to make informed decisions about what should be highlighted. These decisions were informed by the previous activities within our RRI trajectory as well as the objectives of this workshop, focusing on implications and their potential governance solutions. As will be noticeable, we went beyond discussing the classic ELSI issues (e.g. privacy, data protection, or animal testing) and instead focused on concrete social implications of in silico models that are identifiable along the innovation lifecycle. All the implications we explore in the following section have already been touched upon during the focus groups and/or the Delphi survey. Yet, during the workshop, we delved deeper into these implications and established a more profound understanding of what is truly at stake, concerning, for example, responsibility or social exclusion. Conversations on themes, such as animal testing for example, that remained superficial have been excluded from this report, as they did not yield any novel insights. Moreover, despite the prevalent discussion on algorithmic bias within social science literature[13], we chose to include this theme because we recognized that particularly intriguing and valuable discussions had taken place in the context of in silico technologies and modeling.

[12] For more details about the coding tree originally developed for the focus group analysis and its detailed process, please refer to the preliminary focus groups analysis report available on the ISW Sharepoint.

[13] For literature discussing (algorithmic) bias from a social science perspective please see: Crawford, 2021; Obermeyer al., 2019; Buolamwini & Gebru, 2018; Benjamin; 2019, O'Neil, 2016; Sharkey, 2018.

Before we dive into the findings, it is important to present our RRI scheme, which underlies our findings section.

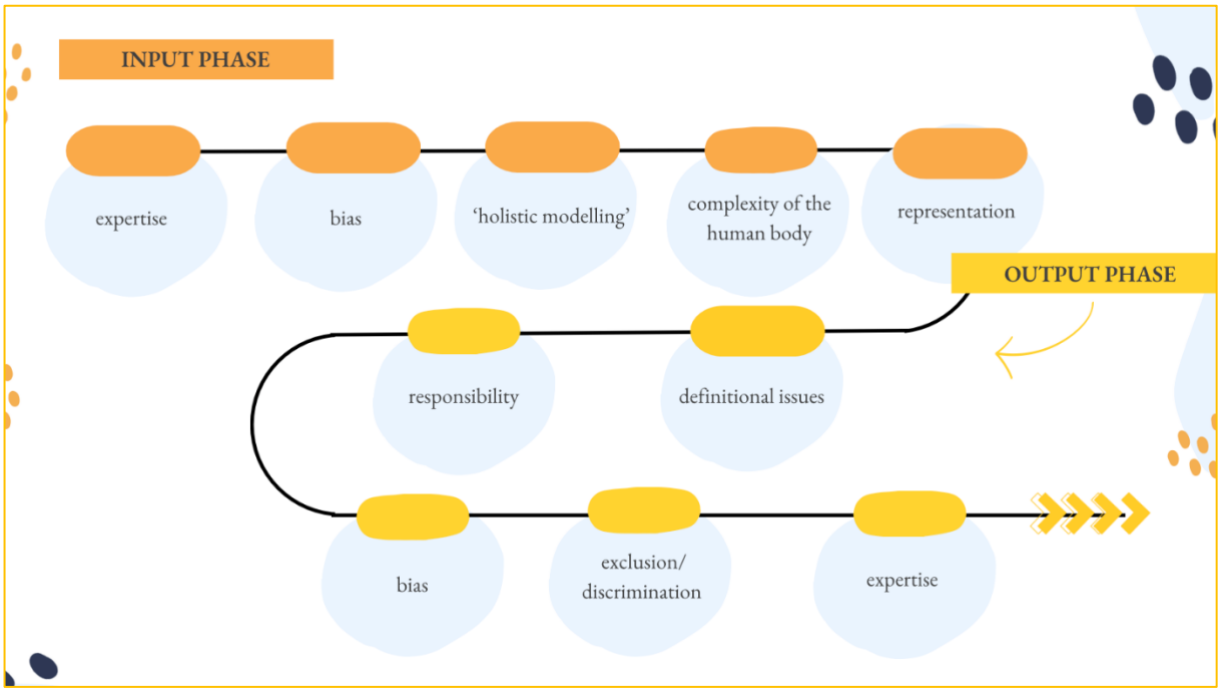


Figure 4: Overview of the addressed ELSI within the group discussions, showcasing where the focus cards were positioned by participants on the poster.

This RRI scheme is derived from the in silico model innovation lifecycle poster (see Figure 3) and informed by the focus cards placed by participants. It can be construed as an RRI scheme employed to elucidate the ELSI issues that (based on the RRI workshop) arose in the various stages of an in silico model's lifecycle. It simplifies this lifecycle into two distinct sections: input and output. The input phase refers to where the in silico model receives and processes input data and is in the design and development phase, while the output phase is where the in silico model generates results or predictions based on that input and is deployed. This division within the scheme helps highlight the ELSI issues that arise at different stages of the model's development. The task, within STEP 1, where participants positioned focus cards containing specific ELSI on the poster, unveiled that certain ELSI topics were discernible in both the input and output phases – a specific ELSI can manifest at various places within the innovation lifecycle. Besides showcasing the insights gained by putting ELSI next to the innovation lifecycle of emerging technologies, this scheme is also of significance as it gives an important hint to the in silico community. If the aim is to tackle these ELSI then the governance solutions need to be targeted at the

different segments of the innovation lifecycle where it surfaces. In other words, by highlighting these ELSI along the innovation lifecycle, clarity is gained about where and how this should be addressed in terms of governance mechanisms. Some proposed governance suggestions will be discussed below.

3. Findings

3.1 ELSI issues and challenges

We will now dive deeper into specific ELSI challenges regarding bias and responsibility, trust, expertise, representation in 'holistic modeling' and integrated digital twins, and lastly, definitional issues as discussed during the RRI workshop.

Navigating bias & responsibility

In recent literature, it has been argued that the increasing use of technologies in medical research and healthcare brings up various societal challenges, one of which is bias (Wahl et al., 2018; Schönberger, 2019). Bias is not strictly limited to the input phase but can also be found in the access to the technologies (Zou & Schiebinger, 2018; Hooker, 2021). Moreover, this concern was previously addressed during the Delphi survey[14], where the experts raised preoccupations regarding the potential disparities in access to and benefits from in silico medicine, emphasizing the need to address issues of equity and global justice in its development and deployment. The next passage, stemming from the RRI workshop, discusses how this can lead to social exclusion.

> *Speaker 1: "I think the societal impact could be that only a couple of hospitals, for example, have access to this specific technology. In that way, you're biasing access to your in silico tool. For example, if they don't have private healthcare or something like this because of socioeconomic kind of problems or disadvantages, they then don't have access to be able to even be considered for the in-silico technique. They might have some kind of boundary or something that prevents them from actually getting access*

[14] For additional information please see Delphi Survey Analysis Group 1 (text and slides) available on the ISW SharePoint. ref

to what would be required for them to even be considered or to use this, which I think is a different way of looking at bias." (Group 2)

Within the same group, another participant pointed towards the idea that this concern of bias and social exclusion is, however, not limited to in silico medicine, as it also appears in other fields such as AI.

Speaker 3: "I guess we all agree that there are some problems of bias, social bias, which are not specific to in-silico as such, but they apply to any really innovative technology." (Group 2)

In the continuation of this conversation, which focused on discussing a potential solution to how bias can be minimized, two participants offered a (technical) solution to how in silico models can actually reduce bias: synthetic data. The following quotes describe how computer modeling and simulations could potentially be utilized to generate representative virtual cohorts, which they argue could lower the risk of bias in the output. According to these two participants, in silico medicine could in contrast have the potential to reduce bias, rather than to introduce it.

Speaker 5: "With making successful synthetic data you can overcome this bias very easily. [...]. It is possible to do something like a combination of artificial intelligence and modeling. In work package three we are working on the artificial intelligence-based data creation or data generation. It's more or less like a virtual cohort generation. We are trying to sort the issue of social exclusion of certain sample population by creating the virtual cohorts which represent the population." (Group 2)

What has made these conversations about bias particularly intriguing is that they have led us to interesting discussions about responsibility. This wasparticularly the case for the role of engineers vis-à-vis bias, errors, and malicious uses. The very notion of responsibility is at the heart of RRI and encourages researchers to contemplate the long-term impacts of their innovation and its value to society. Hence, having the participants, mostly engineers, reflect on their own responsibility is an important step within our RRI trajectory. It is gratifying that this occurred organically, which highlights our RRI activities as places for participants to reflect on their roles and responsibilities.

The following quotes provide some insights into the discussions regarding responsibility. They highlight that participants recognize a degree of responsibility when developing models, but there remains uncertainty regarding the extent of that responsibility, particularly in determining who bears the greatest 'share'.

> *Speaker 5: "I say that we make beautiful models, and we give them to clinicians and they could get X numbers of variables usable for the patients and they decide which one to give. I mean, it's not."*
> *Speaker3: "I understand. It's a shared responsibility, but you have to imagine the worst-case scenario and you have to warn the policymakers that we're giving you a new technology. It can do all these beautiful things, but be aware it can also do all these bad things. No, you disagree?"*
> *Speaker 5: "No, no, I don't disagree. But I mean, they should also know that it depends on the human and it's at the human level, you know, clinicians also should follow by some like or they have their principles they should be following. They should judge." (Group 2)*

> *Speaker 3: " [...]. You are responsible for your own. Of course, others have their share of responsibility, but you have your own." (Group 2)*

These quotes indicate that the understanding of the level of responsibility of in silico experts themselves is not self-evident. Reflecting on responsibility (and bias) marks an important initial step, yet its practical integration into the everyday practices of researchers presents a more complex challenge. On that point, one of the participants offered the suggestion to put together an Ethical Manifesto, which would discuss responsibility and how to minimize bias as a community. This suggestion will be explored in greater detail in the 'Governance Solutions' section.

Trust in in silico medicine: the foundation for progress and collaboration

An important prerequisite for the advancement of a new complex field such as that of in silico medicine is establishing trust and acceptability among different stakeholders, to ensure that the technologies are not only scientifically sound but also ethically and socially responsible (Leo et al., 2022). As such, in the realm of the In Silico World project, trust plays a pivotal role in shaping the future of in silico medicine. This ambitious research initiative, geared towards lowering the barriers to the implementation of in silico medicine, hinges on establishing trust among stakeholders.

Although not directly questioned using the focus cards, the topic of trust came up at several points during the group discussions, demonstrating its importance. The discussions underscore this critical need for trust, particularly in the delicate balance between regulators, researchers, and aspiring engineers.

In Group 3, an interesting conversation between professionals in industrial engineering and academia took place on the need for building trust between researchers and regulatory agencies regarding the use of in silico models. According to them, this trust is still lacking. As unanimously acknowledged by the participants in Group 3, they believe transparancy of data to be crucial in gaining the trust of regulators. In this discussion, the respondents emphasize the importance of validating a model's effectiveness and reliability for acceptance of the model. They suggest complementing the model with clinical trials to enhance its credibility and applicapility. The statement "putting a foot in the door" suggests taking a cautious and gradual approach to gain acceptance and trust in the new technologies on the side of the regulators. This resonates with the literature, which also highlights the importance of transparent, open, and prompt data disclosure in building public trust and confidence in computer modeling and simulations (Coveney and Highfield, 2021).

> *Speaker 2: "It's a matter of trusting the developers of the network, also a matter of resources as they have to evaluate your dossier because they can go check themselves what is inside. If you have provided everything, you can go check, what is inside and whether you have ethical use. [...] And that would be a validation."*
> *Speaker 7: "And then once it's good enough for them, then maybe the trust is, like, it's building trust."*
> *Speaker 6: "It's like putting a foot in the door."*
> *Speaker 7: "Yes, step by step." (Group 3)*

The participants in the same group realized that the need to establish trust in the data used for these simulations does not remain limited to the relationship with regulators, but that trust issues also arise internally during the training of future engineers, as students may hold skepticism about the accuracy of the data they use to build their models, or the effectiveness of the models. As such, the importance of teaching students how to work with in silico trials is highlighted, students often lack an

understanding of the complexities involved in these simulations. Therefore, expectation management is believed to reduce unrealistic anticipations, which will in turn foster openness to collaborate with engineers.

> *Speaker 5: "[...] the students need to learn how to deal with in silico trials because then they are more open to collaborating with engineers. So you notice sometimes they're (speaking about clinicians) a bit like who are you and what are you doing? And they also expect a lot immediately. If you tell us about a model they're like they think in two weeks it will be able to predict everything for them which is never the case because we need a lot of data for that and also it takes years."*
> *Speaker 1: "So to also make them trust the data?"*
> *Speaker 5: "Set their expectations right and also make them, yes build more trust. Yes."*
> *Speaker 2: "Oh right, the expectation management is a good point too." (Group 3)*

This embodiment of trust expands beyond the academic sphere. With the increasing integration of in silico application in clinical settings, the traditional relationships between doctors and patients are undergoing transformations. According to Cordeiro (2021), the shift towards in silico medicine potentially reduces face-to-face encounters, raising concerns about the altering dynamics and subsequent impact on trust between clinicians and patients. In this regard, research points towards the growing need for clear and transparent guidelines around stakeholder engagement during the entire process of research and innovation (Leo et al., 2022). As we navigate the pathway towards in silico medicine, understanding, managing, and fostering trust are not just prerequisites; they are keystones shaping the very foundation of the future of the field.

Unraveling the expertise

A significant proportion of the group discussions revolved around questions of expertise: who is and should be an expert when it comes to developing in silico models or devices? Literature suggests that in silico medicine has the potential to empower patients (Henney, 2012), but the question remains: how do in silico experts perceive patients as real active agents? Opinions seem to differ on this matter. For instance, in group two, a participant seemingly does not grasp what is meant by a patient's 'right not to know', to which he says that the future is not up to the patient.

Speaker 1: "The future is not up to the patient?" (Group 2)

In another instance, a participant expressed his doubt about patients currently having much of a "right to know". This right to be informed is a very hot topic in the ethical and legal debate in medicine, as it is part of the data protection rights of individuals. In debates surrounding medical ethics and policy, ensuring, and protecting a patient's "right to know" or the ethical principle allowing patients to choose not to receive specific medical information or test results. This principle is central to promoting individual autonomy and patient-centered care (Davies and Savulescu, 2021). In this, a parallel can be found with the Delphi survey, which also highlighted the importance of patient rights, obligations, and the ethical considerations surrounding these rights[15]. More specifically, respondents in the expert survey expressed uncertainty regarding their ability to predict whether a patient would want to be informed about the risks of a specific disease. This was also uttered during the RRI workshop:

Speaker 2: "But expertise. Yes, I see less of a role for the patient in making the models more correct. Maybe for the database of other risk factors, you need the patients for that, don't you? The knowledge that the doctor has, who has insight and expertise about others, but if the patient doesn't have them, the doctors, then he doesn't know" (Group 1)

Speaker 2: "I think it can cover kind of everything because the patient is at the core of building the model. So it's kind of the data collection. If you build the model based on the patient, but the patient is not giving his maximum or is not reflecting actually the population that you want to test, then you might have an issue. I think the doctor and the stakeholders should define which data you need and then you can ask the patient if they give their data. But I think the other way around is a little bit … I don't know if the patient really can see what is used at the end. So possibly the doctor a little bit more." (Group 1)

*

Speaker 6: "Yes, but let me ask you something. At this moment. Are the patients asked whether they agree with the way of treatment? I don't think they can get asked." (Group 4)

[15] For additional information on the broader RRI Approach please see Delphi Survey Analysis Group 1 (text and slides) available on the ISW SharePoint.

In addition, in silico medicine could impact the doctor-patient relationship by providing patients with more knowledge, altering once again the traditional notions of expertise (Cordeiro, 2021; Sauerbrei et al., 2023). Patients could gain a deeper understanding of their own health conditions, treatment options, and outcomes, making them more informed and engaged with the decisions concerning their healthcare. This is also a key goal of the Avicenna Alliance's patient and public involvement task force, which will be discussed later on. According to in silico experts, the field holds the promise that implementing in silico medicine will allow patients the opportunity to engage more actively in their healthcare journey. This increased knowledge could potentially foster a more collaborative relationship with healthcare professionals, enabling patients to actively participate in their own care and question traditional hierarchical models of expertise. In silico medicine is as such envisioned to contribute to a more inclusive and patient-centered future of healthcare (Levine et al., 2023). As patients become more invested in their health, they may contribute valuable insights and questions to the medical discourse, This shift in the dynamics of expertise highlights the evolving role of both patients and healthcare providers in the era of in silico medicine. Addressing the uncertainties surrounding patient rights and changes in patient empowerment is at stake for the very outcome of in silico medicine, a transformation towards more personalized healthcare. In silico medicine aims to pave a pathway to more personalized and effective treatments, a promise that can only become true by embracing this shift towards greater patient autonomy, allowing healthcare providers to build stronger, more collaborative relationships with their patients. As believed by the innovators in the field, the involvement of patients in their care would not only enhance their understanding but also promote a sense of empowerment and ownership over their health (Čartolovni, Tomičić and Lazić Mosler, 2022; Cordeiro, 2021).

On another note, attention was also given to the expertise and role attributions of clinicians. Nowadays, clinicians today are expected to balance traditional clinical skills with the ability to interpret huge amounts of research evidence, involve patients in decision-making, and navigate the complexities of presenting information effectively. All of these responsibilities make their role in healthcare highly multifaceted and challenging (Haynes, Dereveaux, and Gordon, 2002). How does machine learning impact the authority and sense of expertise of clinicians? Do medical doctors perceive

the implementation of in silico medicine as a threat to their own professional autonomy? In a study with radiologists, Lombi and Rossero (2023) emphasized the benefit of these techniques to support, and not replace, their expertise, a statement that resonates well with the findings from the focus groups[16]. On top of this, medical doctors all have different, unique ways of working, an observation drawn from the focus groups and confirmed by the participants (see below). But the question remains, can an in silico model even account for these differences? And if so, should it?

> *Speaker 2: "The solution for one surgeon, the best for one, doesn't need to be the best for the other surgeon. Because some surgeons cannot just proceed with something, so they choose another way and then what is better for the patients. The question is how can models account for different experts? I noticed, and that means that you have to put into the model also the one that has to carry out the procedure or whatever, which is something, something we thought about mental models we call this to take into account also the knowledge, but also the expertise of the manual." (Group 2)*
>
> *

> *Speaker 2: "If you use predictive models as a decision support, you come up with scenarios, different scenarios. These are the different scenarios. And then still a doctor can take the one that feels the best for him. But yeah, not, not not easy." (Group 4)*

Lastly, the majority of discussion on expertise revolved around the perceived lack of knowledge of regulators on in silico medicine, which suggests that this is a living concern on the side of the in silico experts. As such, regulators are on the sidelines during the developing phase and then are perceived to be a hurdle later in the innovation process. As a result, the participants argued that regulators oftentimes are not aware of the advancements of in silico medicine, and collaboration with these regulatory agencies is believed to be missing. In this context, participants have highlighted the goals of WP7, as they are preparing educational material to engage with, among others, regulatory bodies about in silico medicine.

> *Speaker 7: "And also, like the ones who make the regulations are not aware enough like that. They are not like, you know, experts as well. Like they don't use it or they are not in the development itself, so they are completely not aware." (Group 2)*

[16] For more details, please refer to the preliminary focus groups analysis report available on the ISW Sharepoint.

*

Speaker 3: "But I completely agree with you. I think it's a matter of education almost. (Group 1)

To conclude, the discussions highlighted divergent perspectives when it comes to different stakeholder's roles and expertise. We emphasized empowering patients and its impact on the relationship with medical professionals, potentially challenging traditional notions of expertise. On this note, the participants addressed clinicians' demanding workload and raised concerns about regulatory bodies' understanding of in silico technologies, emphasizing the need for ongoing education and interdisciplinary collaboration.

Representation in 'Holistic modeling' and the quest for an 'integrated digital twin'

At the outset of this section, it is essential to highlight that the conversations around 'holistic modeling', aspresented below, offer more than just reflections on the feasibility of digital twins and the complexity of the human body. They connect to sociological questions that extend beyond the initial appearance of these passages.

In literature, in silico medicine has been presented as the innovative pathway to holistic medicine, allowing for a more all-embracing view of modern medicine (van Sint and Geris, 2019). Such an integrative approach plays an important role in in silico medicine, as it tries to understand and capture the intricate interactions between, for example, different biological systems – moving away from a narrow and limited viewpoint. Discussions around this integrated and holistic approach to modeling surfaced in our project during the focus groups, where the inquiry into the holistic scope of in silico models intersected with the challenges of modeling the complex human body comprehensively and the potential for unrepresentativeness and exclusion[17]. These conversations raised interest, particularly in clinicians, regarding the necessary parameters that need to be taken into account (e.g. lifestyle data) and the

[17] For more details, please refer to the preliminary focus groups analysis report available on the ISW Sharepoint – WP5 – Data Analysis folder.

consequences of their omission[18]. Therefore, within the RRI workshop, we included focus cards that touched upon these themes of the complexity of the human body, "holistic modeling" and quotes stemming from the focus groups such as: "*We give answers to the questions that we ask. But what if a crucial parameter is neglected, and we do not know about it?"*

Contrary to the focus groups, the workshop conversations on an integrated and holistic approach to modeling pivoted towards the feasibility of a so-called integrated model that encompasses all possible parameters.

> *Speaker 3: regarding integrated digital twins*
> *"I talked to a researcher from [X] recently and he had a very nice image. He said it's the carrot that you dangle before yourself so you don't lose motivation. It's not something that's going to come in the next decade or two. It should be."*
> *(Group 1)*
>
> *
>
> *Speaker 7: "The point here is that we cannot have a unique model representing all the complexity of the human body. So my suggestion would be to combine different models to obtain a more general view of a specific disease because I don't think it's possible to have one only model, a holistic model representing all the features, and all the parameters. It's impossible, I think." (Group 5)*

From the quotes above, we observe that some participants expressed hope that 'holistic modeling', or an integrated digital twin is possible. However, they are aware that it would require time and technological advancements. As such, it is seen as a long-term goal that is not to be achieved during the beginning steps of in silico medicine. On the other hand, there also seems to be some disagreement that in silico models should be holistic at all. In this regard, one participant highlighted that it is never the intention of in silico to be 'holistic' (Group 5). These exchanges show us that the expectations around 'holistic modeling' are more multi-faceted than expected and not smooth. Particularly the last quote hints at something significant when it is mentioned

[18] See section "Towards 'holistic' or 'precision' medicine through In Silico Modeling?" of the preliminary focus groups analysis report.

that such models could not represent all the features, pointing to the limitations of representativeness.

From the workshop, we have gathered that the term ‘holistic modeling’ can be perplexing, meaning different things to different participants. Yet, through further analysis, we realized that the discussions around ‘holistic’ and ‘integrated’ in silico modeling connect to a broader sociological reflection on representation (e.g. the desire to be as representative as possible) and in how far a digital twin can represent a person (Braun, 2021). Whilst at first and at the surface, it might seem that the conversations around “holistic modeling” are focused on the technical capabilities of in silico models and a shifted approach to the human body, it also encompasses the social limitations and expectations around representativeness, feasibility, and social exclusion (see Ankeny & Leonelli, 2011; Leonelli & Ankeny, 2013). In other words, ‘holistic modeling’ and the quest for an integrated digital twin do not just raise technical aspects and debates but also bear social implications.

Definitional issues on the intersection of in silico medicine and artificial intelligence

As the upcoming field of in silico medicine is trying to establish itself, we observed during our workshop that the field is trying to distinguish itself from other already established fields of study. Establishing clear boundaries can help to better grasp the challenges and benefits that are peculiar to in silico medicine. In this regard, during the discussions, it was noticed that often confusion arises for participants as to the different in silico terms and applications, but also as to what in silico medicine is and what it can do, and how it differs from, for instance, artificial intelligence (AI).

> *Speaker 7: “Artificial intelligence can be a part of an in silico model. It depends on the in silico model. That's the question. I feel that only representing a mechanical model is like finite element, method, or something like that. Then it's not artificial intelligence normally, but you can use processes of artificial intelligence to build a new model and to widen the application. But then this uncertainty about definitions, is it something that needs to be taken into account really at the beginning just to ensure that all stakeholders are aware of the process of?*”

Speaker 3: "Of course we need to find a better way. We need to continue to explain that AI is a broad family of methodologies that can be used to do a lot of things. And there are some AI techniques that can be used to do in silico medicine. Thus some in silico medicine technology can be based on AI methods, some other are not, it depends. The two things are not the same and they are not different. They are two overlapping sets." (Group 2)

A general comment came up among the participants in Group 2 regarding non-technical stakeholders assuming all in silico medicine applications involve AI when this relationship is way more nuanced according to them. One of the respondents said to have given up on clarifying the difference between the two constantly. The perceived lack of clarity is believed by the in silico experts to hamper effective communication, particularly when explaining the intricate technical aspects to non-technical stakeholders. To overcome this challenge, several participants suggested that clarity in the communication with stakeholders and standardized approaches could help address these definitional challenges surrounding the integration of AI into in silico modeling.

Speaker 2: "And does it mean that it's rather an issue of communication towards stakeholders then?"
Speaker 3: "I think so. And standards can help in that. If there are standards, communities can agree on what to do, which is the whole point of it." (Group 1)

Speaker 4: "It's the same way when we when we talk about these in silico medicine in general, people not coming from specific topics usually think about that all is AI, AI based." (Group 2)

A possible consequence of these discussiona round boundary-making is that they could sometimes lead to unrealistic expectations of the capabilities of in silico models and the field in general. Additionally, this ambiguity carries substantial regulatory implications, particularly within the realm of AI regulations. These uncertainties in categorization may also have profound impacts on the field itself, necessitating careful consideration and clear boundaries to navigate the regulatory landscape of in silico medicine. This shows that the social implications of these definitional struggles, when left unclear or misrepresented, are profound, emphasizing the importance of ongoing dialogue and collaboration to navigate the intricate landscape of in silico medicine and artificial intelligence. These unclarities around where the data for the in silico models

come from can have some unwanted consequences, as they can lead to friction between the involved stakeholders. This oftentimes stems from limited awareness of knowledge of the complex elements that make the field (Bensaude Vincent, 2014).

From a sociological point of view, these definitional unclarities are inherent and complex elements of the field of in silico medicine, and, although regarded as a hurdle by the experts of the consortium, there can also be some value in embracing this ambiguity (Kuiper et al, 2022). These struggles highlight the urge of the experts to establish clear boundaries within this multidisciplinary field, where different domains are brought together. In this specific case, the concept of artificial intelligence is a buzzword and functions as a so-called “boundary object” in the field of in silico medicine, meaning that it holds a certain flexibility to be understood in a broader context (Bensaude Vincent, 2014). AI is widely known by a variety of stakeholders, making it a valuable tool for collaboration, whilst in silico medicine is still innovative, and unknown to many. Consequently, the lack of definitional clarity in both in silico medicine and AI could be utilized for collaboration with non-technical stakeholders, rather than disadvantageous. The openness provides room for various stakeholders to potentially shape the field's trajectory, influencing its direction and development (Kuiper et al., 2022). It is beneficial to allow continuous questioning and refinement of these definitions. because by actively engaging in boundary work, stakeholders can contribute to a clearer understanding of in silico medicine, ensuring that the nuances and complexities inherent in the field are appropriately represented (Bensaude Vincent, 2014; Gieryn, 1983). Within the scope of the In Silico World project, this means acknowledging and navigating these uncertainties collectively, by engaging multiple stakeholders throughout the whole research and innovation process. Therefore, the in silico field might benefit from boundary work by examining how professionals, researchers, and non-technical stakeholders define the scope of in silico practices. This includes understanding and continuously negotiating the contested definitions, and the integration, but also limits, of various technologies. To come back to the statement discussed at the beginning of this section, it is important for the in silico expert to ‘not just give up’ and actively participate in addressing and representing the nuances of the field appropriately.

3.2 Proposed governance solutions

In the introduction of this report, we clarified what is meant by 'governance' and explained why we placed particular emphasis on discussing governance solutions within Step 2 and 3 of the RRI workshop group discussions. The added value that we, as the ISW project, bring to the table is our anticipatory approach to governance ahead of the widespread adoption of in silico models. We explore the potential ELSI at an early stage to address uncertainties that often underlie governance debates. Ensuring effective technology governance is a challenging endeavor, particularly when people's health is at stake. What is crucial to mention is that governance does not solely encompass regulations, it consists of a variety of mechanisms that guide technology development such as: soft laws (e.g. ethical guidelines), self-regulation (codes of conduct, standards), R&D agenda-setting, public engagement and science communication (Stark, Greene and Hoffmann, 2020).

Due to the extensive and lengthy discussions on establishing a regulatory framework within (and promoted by) the in silico field as well as the dedicated Work Package 9 (WP9) addressing 'hard' regulatory aspects in our ISW project, we aimed to shift our attention towards alternative governance mechanisms: What can we, as a community, do ourselves to governing in silico? Therefore, we used the RRI workshop to discuss self-regulation, which can complement 'hard' regulations, including standards, ethical committes and the role of research communities, training and education, patient and public involvement, an ethical manifesto and lastly, public infrastructures.

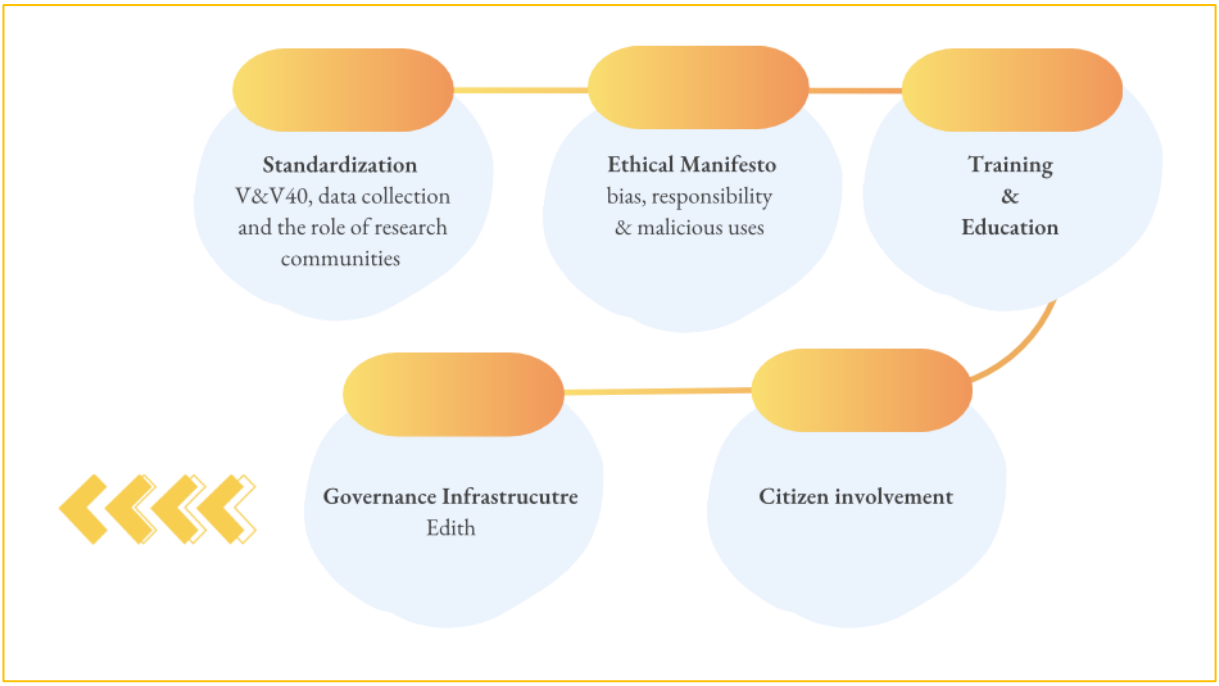


Figure 5: Proposed governance solutions by participants during the workshop

Standardization, Ethical Committees & Research Communities

With the current absence of a clear regulatory pathway for in silico models, the flexibility of self-regulation particularly in terms of the in silico community being able to initiate such governance mechanisms themselves is a huge plus by the in silico community. Self-regulation is not a magical one-size-fits-all solution for every issue in the in silico medicine context, but it offers some much needed guidance. Self-regulation is not limited to the industry, as think tanks, standard-setting organizations or research centers can also have a substantial impact.

One example of such is the American's Society of Mechanical Engineers (ASME) V&V40[19]. This standard provides a framework for assessing the relevance and adequacy of completed Verification and Validation (V&V) activities in establishing the credibility of a computational model. In the workshop, V&V40 was mentioned on different occasions by participants, to indicate its usefulness, but to also highlight the need for a transversal adoption of it in Europe (which ISW is working on), and the benefit globally accepted standards would have.

[19] For an overview about V&V40 see this resource of the VPHI: http://www.vph-institute.org/upload/presentation-v-v40training-fullslidedeck-vph2022-final_635f9a37849ad.pdf

Speaker 3: (regarding V&V40) "Manufacturers can maybe tell if it works, but people who I talk to, they told me it's pretty good and it works quite well to do that for medical devices." (Group 1)

*

Speaker 7: "Actually, the In Silico World Project is working very hard towards this direction and we are trying to create a new European standard, specific for medical devices. And it's very difficult, of course, because in the USA, I guess it already exists, but here we don't have anything like that. (...)So the only possibility I see, is to extend the applicability of the existing standard." (Group 4)

Adapting V&V40 is not a new governance solution, it is worth mentioning it here, as the ISW project is actively working on its implementation (Pappalardo, 2022). It ties to a discussion, which occurred within Group 1 on standardizing data collection. There, participants highlighted the need for standardized data collection in in silico medicine to overcome the current lack of consistency in data collection, which leads to comparability and reliability issues.

Speaker 3: "[...] If you think about clinical trials that are happening today, I think every publication has different factors, different parameters they use to collect data. I mean, you have some reliance that the data is okay, but you have no standardization on what to collect, how to collect it."

Speaker 7: "So, the standard should be regarding more what needs to be written in the how, it was collected and everything so it can be repeated."

Speaker 2: "Or maybe it is just about the aim that for similar model designs you have a standardized way of collecting the data so you can use existing models here because the data collection was done in the same way." (Group 1)

As noticeable from the passages above, the governance suggestion here is to standardize data collection processes, however, there seems to be uncertainty about responsibility for setting and maintaining these standards.

Speaker 3: "But I don't think it necessarily needs to be a technical standard in the sense of it being ISO or whatever way. it's almost a question to the medical societies and ethical boards on how to how to do that. But that's really beyond my expertise. But that's what I think about it." (Group 1)

Speaker 1: "But would that technically be feasible If you always have, I mean, have to iterate again and change the standards?"
[...]
But maybe that's the solution for in silico. So maybe that's what we should aim for."

Speaker 6: "I mean technical standards are usually updated every few years, right? So I think something similar could happen for data collection as well." (Group 1)

While Group 1 discussed the role of ethical committees in standardization, it needs to be pointed out that existing research community initiatives have been launched on standardizing data collection and testing protocols. The C4Bio Community Challenge Towards Consensus on Characterization of Biological Tissue organized by FIBEr (KU Leuven), the Avicenna Alliance and the VPHI is a good example of that. The goal of this challenge is to achieve community consensus on testing protocols for biological tissue characterization, including different aspects of the entire testing process such as sample collection, and data processing. While positive outcomes have not emerged from this challenge (yet)[20], it is an important demonstration of community-led governance initiatives. This is also the case of the forthcoming book "Toward Good Simulation Practice: best practices for the use of computational modelling & simulation in the Regulatory process of biomedical products" (Ref). In the last two years, a group of 144 experts from academia, industry, and regulatory agencies including members of the ISW project condensed their expertise into this book to establish best practices. Overall, within the workshop and beyond it, we can observe increased efforts in developing standards and best practices within the in silico medicine field, including within our ISW project – demonstrating the utility of self-regulation.

Training and education

As touched upon in the previous section, there appear to be ambiguities between different stakeholders regarding terminology, as well as notions of expertise and responsibility. These issues point to an increasing importance for interdisciplinary collaboration among different stakeholders. In addition, a significant portion of the discussions centered around the imperative need for comprehensive training and

[20] More information on the results of the C4Bio Community Challenge can be found on their website: https://c4bio.eu

education for all involved stakeholders involved in in silico field, underscoring its critical role in addressing the challenges and fostering effective collaboration. For clinicians, continuous training in computer modeling and simulation is deemed necessary, during the medical education as well as after, to stay updated on the advances in the field.

Noteworthy, the discussion mainly revolved around familiarizing clinicians with the technical aspects and practical applications of in silico methods, rather than delving deeply into the broader social and ethical considerations related to their implementation. However, the Delphi survey did highlight the importance of providing adequate training and education for professionals and stakeholders in the field of in silico medicine to address the discussed ELSI challenges in an effective manner. Nonetheless, during the workshop, a participant from Group 3 questioned as to whether this is the right approach, since the curriculum of a clinician in training is already very demanding, and they already have a broad range of responsibilities and trainings on their plate. Despite these concerns, preference seems to be given to training on the technical over the societal dimensions, highlighting a focus on equipping clinicians with the necessary technical skills related to in silico techniques rather than delving extensively into the broader societal implications during their training. One of the participants here substantiates the argument with stressing it is not fair to put a higher pressure on the clinicians, as well as researchers in general on this matter, as shown in the following quote:

> *Speaker 2: "But for clinicians I would find it tricky because it's like researchers they have more and more responsibilities. I have the impression coming on the researchers back at the end of the day they can't do everything. They cannot be researcher, communicator, IP manager, human manager, during the research teaching it's too much. And knowing the legal aspect. So same for the clinician, I think at some point you need to have specialists and they cannot know everything about everything." (Group 3)*

On this same topic, the lack of knowledge of regulatory bodies of in silico medicine comes up as a challenge, as hinted on previously. In this context, another approach that comes up quite a few times is close and continuous collaboration between the different involved parties (e.g. regulators, clinicians, in silico experts, social scientists, etc.). As such, it is believed that their unique expertise, when combined in

transdisciplinary training, enriches the field and addresses the lack of awareness effectively. This is shown in the following discussion.

> *Speaker 2: "But I think a major issue to do that in Europe at least there are not very open ways to interact with regulators. It's very difficult. There is no mechanisms or processes where there is good interaction. If you compare with like in the US where they have a lot of research and development at FDA and they have a lot of mechanisms where you can have like open discussion and build regulatory science to get scientists, regulators and all the stuff. And in Europe, much less, they are really close on their daily duties and not really exploring."*
>
> *Moderator: "And how do you see that could improve?"*
>
> *Speaker 2: "But I think it has to come from regulators because scientists are constantly trying to reach out. So it has to come from them to open and find solutions".*
>
> *Speaker 5: "And one problem is also that there are not many people in the regulatory body that can understand every type of qualification. Because of the different type of model that we can develop. So it's also a matter of training."*
>
> *Speaker 2: "So you need a starting point, it should be collaboration between the regulatory office and the scientists and then see from there."*
>
> *Speaker 5: "And training of regulators." (Group 3)*

To solve the need for proper education, the Work Package 7 of the ISW project is currently focused on addressing the need for training in the field of in silico medicine. They are actively developing courses and educational materials to provide comprehensive training on in silico methodologies and techniques. To conclude, participants agree that trainings for clinician and regulators are a must, in order to increase the awareness and knowledge of in silico medicine, which will prove beneficial for the uptake. One participant even suggested that the European Medicines Agency (EMA) should consider building a special 'in silico unit', which would have the necessary skills to comprehend the nitty-gritty of in silico models. Once again here, the need for training on the societal considerations of in silico medicine does not seem to be prioritized by the participants.

Several people from the ISW consortium have been given the opportunity to spread the word on in silico medicine to regulatory bodies, as can be seen by the following points. It is also important to note that in addition to these instances, significant efforts have been invested by various key actors to establish communication channels with EU regulators and policymakers. These efforts are ongoing, both within and beyond the ISW project.

- Marco Viceconti training workshop to EMA (September 2022)
- Marco Viceconti giving a presentation at EFPIA (December 2022)
- Cristina Curelli giving a talk to HTA (Australia) on in silico medicine (June 2023)

Public and patient involvement (PPI)

> *Speaker7: "For that application because it's extra expertise outside of a normal clinical procedure, the patient participation is critical, I think". (Group 1)*

As shown in the quote above, the significance of the inclusion of patients and citizens was not forgotten and was brought up on multiple occasions, sometimes indirectly and not always as explicit. Another suggestion emphasized the importance of **science communication and outreach activities** to build trust with the general public through various channels, including social media. In order to create more awareness around in silico medicine for the general public the project continuously works on communication activities for society. Currently, WP5 is working on promotional videos which explain what in silico medicine is and introduces some concrete examples stemming from the consortium. These videos aim to explain complex concepts, ensuring accessibility for the general public by utilizing layman terminologies. The so-called glossary videos will be readily accessible for a wide audience, enabling easy understanding of in silico medicine and its applications.

Overall, the discussions highlighted the need for better education and inclusion of all involved parties (e.g. regulators, scientists, clinicians, citizens) to address the challenges associated with in silico technologies. Enhancing awareness, expanding the education on in silico medicine, and collaboration among stakeholders, with the inclusion of the broader public, can bolster research endeavors and cultivate trust,

constituting essential components of the responsible research and innovation approach, that was discussed in detail above. Citizen involvement in in silico medicine could empower individuals, enabling them to make informed healthcare decisions and fostering collaborative discussions with professionals in the field. Public and patient engagement in the research and innovation process could not only benefit them but is also essential for the progress of the field itself, fostering a mutual relationship that guarantees that innovations resonate with societal values and drive ethical, patient-centered healthcare outcomes. Embodying the essence of the "nothing about me without me" ethos, this collaborative approach could ensure that the voices and needs of the individuals the innovations aim to serve remain at the core of the research and innovation process. In summary, citizen involvement is not just a necessary ethical consideration; it is a cornerstone for building trust, fostering transparency, and ensuring the responsible advancement of in silico medicine. Allocating resources within research projects for robust stakeholder engagement and outreach activities is not only recommended but essential for the responsible development of this field, aligning it with societal needs and expectations (Jackson et al., 2020; Price et al., 2022).

Currently, there are several initiatives in place that try to enhance this public and patient involvement in the realm of in silico medicine. For instance, the Avicenna Alliance established a dedicated Public & Patient Involvement (PPI) Task Force[21]. This task force empowers the public by conducting stakeholder engagement activities, enhancing public awareness through digital platforms, building trust in technology through relevant case studies, and offering guidance for effectively representing public and patients' interests in digital evidence submissions to competent authorities, thereby fostering a deeper understanding of in silico medicine. In the same line, the previously mentioned VPHi functions as an international society for in silico medicine, by bringing together a variety of stakeholders, and providing them a platform and a voice. As an explicit example, this not-for profit is currently working on establishing an info kit to support innovators in engaging with different stakeholders, including the public[22]. Another initiative is EUPATI, the European Patients' Academy on Therapeutic

[21] For more information on the mission and goals of the Avicenna Alliance, please refer to their website https://www.avicenna-alliance.com

[22] This information package is a deliverable for the ISW project and will be available from M42.

Innovation, that educates patients and the public about the drug development process, to enable them to contribute effectively to medical research and development, ensuring patient involvement in research and innovation[23]. Clearly, several efforts are in place to promote public and patient involvement in the scope of in silico medicine. However, the question remains: to what extent does the public's voice really count? Nevertheless, the remaining shortage of public and patient involvement in project's Advisory Boards underscores a critical area for improvement, highlighting the necessity to address this shortage for the future advancement of in silico medicine.

Ethical Manifesto: Addressing Bias and Responsibility

As discussed within this workshop, bias in in silico models could arise from various sources, which can perpetuate existing inequalities and those responsible for building the models have an important role to play in minimizing it. In the regulatory landscape, the EU Artificial Intelligence Act (AI Act) addresses these concerns. The European Union's AI Act is a proposed legal framework aimed at regulating AI systems to ensure that AI systems are developed and deployed in a way that respects fundamental rights of citizens. As laid out by Biasin (2022), medical device software could be categorized as a high-risk AI system under the AI Act (AIA), potentially making it applicable to in silico-developed technologies. With regards to bias, the AIA mandates that AI system developers must actively prevent bias and provide clear evidence of their efforts to avoid bias and related risks at every step of the AI lifecycle. Whilst this regulation addresses bias to some extent[24], there are additional mechanism available to address bias arising from emerging technologies. A proposed solution within the workshop is the development of a so-called ethical manifesto by the ISW consortium. One of the participants in group 2 considers it to be the responsibility of the in silico experts to be aware of and try to minimize bias as well as condemn and anticipate possible malicious uses of the applications. It is deemed crucial to take these worst-case scenarios into account when developing the technologies and outline the responsibility that those behind the models have. An ethical manifesto could help here by outlining usage boundaries and guidelines.

[23] For more information on EUPATI, please refer to their website https://eupati.eu.
[24] This is also supported by existing literature, see, for example, Kalluri, 2020 and Benjamin, 2019.

Speaker3: "Let me table something. I was thinking during the plenary while you and your colleagues were talking some of the questions that are being raised in this exercise goes back to the old discussion, I made a technology. How you use it is your responsibility. Yeah, I make a model to predict something. Whether you use it to help the people or to make them miserable is not my responsibility. Now, this is being debated by ethicists from the Second World War and after. And we know that it is not that easy. So we also have a responsibility on the possible use of of our technology. When we develop a technology, we also need to think about the evil way that one could could use those technologies, which doesn't mean that we don't develop them. So shouldn't we produce a sort of an ethical manifesto where we say the things that we should not do within in silico trials..

(…) (…)

We can make a public statement saying we acknowledge that our technology could be used, for example, by evil insurance to do profiling, to refuse to insure people who have a higher risk than average of developing certain diseases and so on. We could make a list of all these things that could go wrong in the use of in silico trials." (Group 2)

According to Group 2, this manifesto could thus serve as a compass, guiding decisions and actions to ensure the ethical and responsible use of in silico medicine. In addition, it was suggested that it would also be an opportunity to showcase to regulators and policymakers that the in silico community takes the ethical and social dimensions of their technology seriously. This governance solution has been taken up within the ISW project following the workshop and WP5 is currently brainstorming on how this ethical manifesto could look like in practice.

The need for a public infrastructure

When discussing the last step of the in silico model's lifecycle, namely model maintenance and management, another important governance mechanism was brought up by multiple groups: the need to establish a dedicated governance infrastructure for the in silico community. Participants pointed out the need for better access to more data, through for instance a database, an open-source data platform. Such a well-structured governance infrastructure would help maintain transparency,

accountability, and responsible innovation within the in silico community, while fostering trust and confidence in the field's contributions to various industries and domains. The following conversation from group 3 shows this perfectly.

> *Speaker5: "Then sort of governance needed here is an infrastructure where these results are shared. So at the moment I don't think we have anything for that."*
> *Speaker3: "I think they are working on it in the EDITH project, the project we just started, which is aiming to build a ecosystem, but also an infrastructure that can well make the whole data integrated together, the data and the models. And there at the moment discussing that. But, I don't know if it can answer this issue, but, kind of a bit, yeah." (Group 5)*

In this fragment, they refer to EDITH, a Coordination and Support Action (CSA), which mission it is to build a roadmap to realize the 'virtual human twin', a concept that was also brought up during the discussions[25]. The goal of EDITH is to establish an evolving ecosystem, including a data/model repository and a simulation platform, to support the transition toward an integrated Virtual Human Twin (VHT) system. This repository will be made available as a public infrastructure, serving as a central hub for designing, developing, testing, and validating digital replicas. This effort represents a crucial advancement in the domain of in silico modeling, signifying a significant stride toward open science. As such, EDITH aims at establishing a collaborative research platform, prioritizing the sharing of research data, models, and methods. EDITH's objective to create a federated and cloud-based repository also aligns with the idea open science principles by providing a virtual collaboration environment for multiple users and organizations. This emphasis on data sharing enhances research and innovation, ensuring more dependable outcomes. Ultimately, this collaborative endeavor paves the way for the development of a virtual human twin (EDITH, n.d.). EDITH will be publicly launching a manifesto[26] soon at a high-level event, with the main goal to gather diverse organizations in healthcare, research, and education to endorse the VHT initiative. The ISW consortium has endorsed this manifesto.

[25] More information on EDITH's objectives can be found on the website: https://www.edith-csa.eu
[26] http://www.vph-institute.org/upload/virtual-human-twins-statement-vf--02-05-23_6477526f710ba.pdf

4 Conclusions

The main takeaway from the RRI workshop on the current state of in silico governance:

- With the development of in silico medicine, establishing a regulatory pathway is essential, particularly for incorporating in silico trials in the CE marking process for medical devices, a central aspect of our ISW project. Unlike previous debates with novel technologies such as AI for example[27], where discussions have focused on the need for either self-regulation or 'hard' regulation in the past, our focus here is not on the necessity of hard law - it is clear for in silico experts that regulatory adjustments are needed. While the in silico community awaits regulatory changes, it is important to note that they are not limited to inaction; our workshop has emphasized the value of self-regulation mechanisms in this field. There is an opportunity to contribute to these mechanisms, which ultimately will complement the regulatory framework. This workshop served as a space for anticipation and reflexiveness on potential governance solutions which deserve further attention. To conclude, tangible steps are being taken within the ISW project toward specific governance mechanisms – on various fronts.

Several general conclusions from the presented findings:

- From the provided quotes, it is evident that participants actively interacted with the focus cards and displayed a keen interest in understanding the perspectives of various stakeholders. Nevertheless, it is notable that the translation to how such social implications can be considered within their everyday practices still requires further discussions and efforts. This is where RRI and its co-creation cycle is of great help.
- ELSI can come up at various stages of the lifecycle of an in silico model and requires different governance solutions. It is essential to emphasize that participants did **not** consistently **agree** on the **placement of specific cards**, indicating that a definitive connection to a particular stage of the model could not be established within this workshop. This underscores the **fluid nature of implications**, which highlights the importance of establishing robust governance solutions. The policy brief will be a great opportunity to take this a step further.

[27] See Taeihagh, 2021 for an overview of AI governance and regulatory challenges around it.

- The **definitional unclarities** among stakeholders have shown to go beyond the distinction between AI and in silico. Examples are the different interpretations and understandings of the term "bias", a concept that will be discussed in the next part, or the need for clarifications when reading out the different focus cards, laying out the different ELSI. As such, this shows that different stakeholders are used to different jargon, it is not to be assumed that concepts, obvious to some, will be understood in the same way by others. This calls for interdisciplinary collaboration and clear science communication initiatives.
- Several participants have pointed out that the ELSI that were raised within the focus groups and workshop are the same ones that are commonly raised concerning AI. Further research should explore this remark and the **potential differences in implications.** Is there a specific layer to in silico, which has not been discussed yet?
- Participants engaged in productive discussions regarding potential governance solutions and suggested interesting solutions. In some ways, it illustrated that the **challenge** within the governance landscape does not lie in the shortage of solutions, but rather in the **realization and implementation.**

5. Preliminary policy recommendations

Overall, some existing governance solutions were discussed, but also potential ones that could facilitate responsible development and adoption of IST technologies in society and these enable us to suggest some **preliminary policy recommendations:**

- **Promote and build awareness** on in silico medicine and **engage** through **science communication** and **outreach activities** to a wide range of stakeholders.
- Continue to foster **collaborations** with EU regulators and policymakers.

- **Educate and train all stakeholders**. Particular attention should also be given about the impact that the uptake of such models can have on clinicians. Furthermore, training on ethical and societal considerations for engineers is necessary to foster inter-disciplinary collaboration, in order to foster trust in the field. And the same goes for non-technical stakeholders, such as the public, who would greatly benefit from gaining more knowledge on the technical aspects of in silico medicine.
- Measures should be taken to **ensure that underrepresented populations are not excluded** from benefiting from in silico medicine. This needs to be addressed both during the input and output phase. This may involve collaborations with healthcare providers, regulatory bodies, and policymakers to develop strategies for improving access to in silico technologies and services.
- **Develop manifestos/letters/code of conducts** should not only discuss malicious uses or ethical responsibilities of researchers, but also acknowledge the limitations of in silico models and the potential risks. This should be as detailed as a context-of-use and would enable to foster trust.
- **Continue to promote** a transitional adoption of VV-40 in Europe as well as the development of an EU harmonized **standard** – a core element of the ISW project.
- **Recognize and involve patient expertise**. Patients should be recognized as active agents in the development and use of in silico models. As such, it is to be adviced to include patients and patient organizations (eg. EUPATI) in advisory boards of different in silico projects. Policies should support patient empowerment by ensuring their right to access and control their health data, as well as their right to be informed and engaged in decisions related to in silico medicine.

- **Encourage collaboration** and **interdisciplinary research** between experts in in silico medicine. Integrating a wide range of disciplines in research and innovation, including social sciences and humanities (SSH) is an integral commitment of the Horizon 2020 funded program. This interdisciplinary approach, by bringing in different perspectives, ensures a comprehensive understanding of the complex ethical, legal, and social concerns associated with in silico modeling and facilitate the development of models that incorporate diverse perspectives. Research on stakeholder's experiences with in silico medicine (from success stories to concerns) is adviced to gain deeper understanding of the present needs, expectations and values.

5. Organizational Takeaways

This RRI workshop marked the inaugural event of its kind. As with any novel endeavor, it served as a **learning process**, enabling us to identify aspects that worked well and areas that require improvement. One of our key observations was that Step 1 consumed a disproportionate amount of time. Although this made some groups exceeded the scheduled time substantially for that step, which is not ideal, it was justified as it did yield substantial content. We might deduct from this that participants were eager to discuss the focus cards and ELSI. Some participants gave us the feedback that some of the conversations were very insightful as usually they (IS experts) do not have a space in which they discuss in-depth the social implications of in silico medicine and that it was also interesting to read direct quotes from different stakeholders.

During Step 2, we observed that engaging in specific and situated discussions about governance solutions, rather than abstract ones, was a **refreshing and novel experience for participants**. This validated and affirmed our decision to prioritize governance solutions as the focal point. Moving forward, it might make more sense to focus on very specific topics within Step 1 (e.g. standardization or expertise) instead of a broad range of topics as was done within this workshop. It might also **help** to share an **infographic with some background information on potential ELSI** of in silico

medicine to already have participants reflect a bit beforehand, and this would also enable to shorten up some other parts such as the “presentation of the findings”.

It is important to keep in mind that **RRI** is an **ongoing and iterative process**, and organizing this RRI workshop was just one aspect of it, it is by no means the terminus. Continuously involving a diverse group of stakeholders and fostering open and inclusive dialogue are essential elements throughout the entire project. To **maintain** this **collaboration and reflexivity**, we plan to present the discussed results of the various stakeholder outreach activities (including the Delphi survey, focus groups and RRI workshop) to the whole consortium, complemented by a conversation on next steps to tackle the concerns in a responsible manner. This way, consortium members can also contribute to the delivery of the policy brief, which is foreseen by the end of the year.

Finally, we intend to **organize** similar Responsible Research and Innovation (RRI) **workshops beyond the scope of the ISW project**, demonstrating our **commitment** to **promoting ethical and socially responsible practices** in various research and innovation initiatives. Furthermore, we are actively working towards the **publication** on the protocol of this RRI trajectory, including the workshop and the focus groups, and a publication of the findings of the RRI approach in general, aiming to share our approach and experience with a wider audience. By doing so, we aim to establish a lasting legacy and contribute to the ongoing promotion of RRI principles across diverse projects and institutions (e.g. universities).

6. References

Ankeny, R. A., & Leonelli, S. (2011). What’s so special about model organisms?. *Studies in History and Philosophy of Science Part A*, *42*(2), 313-323.

Belenguer, L. (2022). AI bias: exploring discriminatory algorithmic decision-making models and the application of possible machine-centric solutions adapted from the pharmaceutical industry. *AI and Ethics*, *2*(4), 771-787.

Benjamin, R. (2019). Assessing risk, automating racism. *Science*, *366*(6464), 421-422.

Bensaude Vincent, B. (2014). The politics of buzzwords at the interface of technoscience, market and society: The case of "public engagement in science." *Public Understanding of Science*, *23*(3). https://doi.org/10.1177/0963662513515371

Buolamwini, J., & Gebru, T. (2018, January). Gender shades: Intersectional accuracy disparities in commercial gender classification. In *Conference on fairness, accountability and transparency* (pp. 77-91). PMLR.

Čartolovni, A., Tomičić, A., & Lazić Mosler, E. (2022). Ethical, legal, and social considerations of AI-based medical decision-support tools: A scoping review. In International Journal of Medical Informatics (Vol. 161). https://doi.org/10.1016/j.ijmedinf.2022.104738

Cordeiro, J. v. (2021). Digital Technologies and Data Science as Health Enablers: An Outline of Appealing Promises and Compelling Ethical, Legal, and Social Challenges. In *Frontiers in Medicine* (Vol. 8). https://doi.org/10.3389/fmed.2021.647897

Coveney, P. v., & Highfield, R. R. (2021). When we can trust computers (and when we can't). In *Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences* (Vol. 379, Issue 2197). https://doi.org/10.1098/rsta.2020.0067

Crawford, K. (2021). *The atlas of AI: Power, politics, and the planetary costs of artificial intelligence*. Yale University Press.

Danks, D., & London, A. J. (2017). Algorithmic Bias in Autonomous Systems. In *IJCAI* (Vol. 17, pp. 4691-4697).

Davies, B., & Savulescu, J. (2021). The Right Not to Know: some Steps towards a Compromise. *Ethical Theory and Moral Practice*, *24*(1). https://doi.org/10.1007/s10677-020-10133-9

EDITH (n.d.). https://www.edith-csa.eu

Felt, U., Öchsner, S., Rae, R., & Osipova, E. (2023). Doing co-creation: power and critique in the development of a European health data infrastructure. Journal of Responsible Innovation, 10(1). https://doi.org/10.1080/23299460.2023.2235931

Genus, A., & Stirling, A. (2018). Collingridge and the dilemma of control: Towards responsible and accountable innovation. *Research policy*, *47*(1), 61-69.

Giantini, G. (2023). The sophistry of the neutral tool. Weaponizing artificial intelligence and big data into threats toward social exclusion. *AI and Ethics*, 1-13.

Gieryn, T. F. (1983). Boundary-Work and the Demarcation of Science from Non-Science: Strains and Interests in Professional Ideologies of Scientists. *American Sociological Review*, *48*(6). https://doi.org/10.2307/2095325

Haynes, R. B., Devereaux, P. J., & Guyatt, G. H. (2002). Clinical expertise in the era of evidence-based medicine and patient choice. *Evidence-Based Medicine*, *7*(2). https://doi.org/10.1136/ebm.7.2.36

Hartwig, T., Ikkatai, Y., Takanashi, N., & Yokoyama, H. M. (2022). Artificial intelligence ELSI score for science and technology: a comparison between Japan and the US. *AI and Society*. https://doi.org/10.1007/s00146-021-01323-9

Hoeyer, K. (2023). *Data Paradoxes: The Politics of Intensified Data Sourcing in Contemporary Healthcare*. MIT Press.

Hooker, S. (2021). Moving beyond “algorithmic bias is a data problem”. *Patterns*, *2*(4).

Jackson, T., Pinnock, H., Liew, S. M., Horne, E., Ehrlich, E., Fulton, O., Worth, A., Sheikh, A., & de Simoni, A. (2020). Patient and public involvement in research: From tokenistic box ticking to valued team members. In *BMC Medicine* (Vol. 18, Issue 1). https://doi.org/10.1186/s12916-020-01544-7

Kalluri, P. (2020). Don't ask if artificial intelligence is good or fair, ask how it shifts power. *Nature*, *583*(7815), 169-169.

Kuiper, J. M. L., Borry, P., Vears, D. F., van Esch, H., & Van Hoyweghen, I. (2023). Navigating the uncertainties of next-generation sequencing in the genetics clinic. Sociology of Health and Illness, 45(3). https://doi.org/10.1111/1467-9566.13533

Landeweerd, L., Townend, D., Mesman, J., & Van Hoyweghen, I. (2015). Reflections on different governance styles in regulating science: a contribution to 'Responsible Research and Innovation'. *Life sciences, society and policy*, *11*, 1-22.

L'Astorina, A., & di Fiore, M. (2017). A new bet for scientists?: Implementing the Responsible Research and Innovation (RRI) approach in the research practices. Relations, 5(2). https://doi.org/10.7358/rela-2017-002-last

Leo, C. G., Tumolo, M. R., Sabina, S., Colella, R., Recchia, V., Ponzini, G., Fotiadis, D. I., Bodini, A., & Mincarone, P. (2022). Health Technology Assessment for In Silico Medicine: Social, Ethical and Legal Aspects. In *International Journal of Environmental Research and Public Health* (Vol. 19, Issue 3). MDPI. https://doi.org/10.3390/ijerph19031510

Leonelli, S., & Ankeny, R. A. (2013). What makes a model organism?. *Endeavour*, *37*(4), 209-212.

Levine, De Cunha-Burgman, Geris, Lesage, Marchal, Mengoni, Rousseau, Serigado, Staumont, Thorez, Voisin, & Thinnes. (2023). A snapshot of current practices and perceptions of Public & Patient Involvement (PPI) within the Avicenna Alliance. Zenodo. https://doi.org/10.5281/zenodo.7987038

Lombi, L., & Rossero, E. (2023). How artificial intelligence is reshaping the autonomy and boundary work of radiologists. A qualitative study. *Sociology of Health and Illness*. https://doi.org/10.1111/1467-9566.13702

Mandel, Gregory N. "Regulating emerging technologies." In *Emerging Technologies*, pp. 361-378. Routledge, 2020.

Obermeyer, Z., Powers, B., Vogeli, C., & Mullainathan, S. (2019). Dissecting racial bias in an algorithm used to manage the health of populations. *Science*, *366*(6464), 447-453.

O'neil, C. (2016). Weapons of math destruction: How big data increases inequality and threatens democracy. Crown.

Pappalardo, F., Wilkinson, J., Busquet, F., Bril, A., Palmer, M., Walker, B., ... & Viceconti, M. (2022). Toward a regulatory pathway for the use of in silico trials in the CE marking of medical devices. *IEEE Journal of Biomedical and Health Informatics*, *26*(11), 5282-5286.

Price, A., Clarke, M., Staniszewska, S., Chu, L., Tembo, D., Kirkpatrick, M., & Nelken, Y. (2022). Patient and Public Involvement in research: A journey to co-production. *Patient Education and Counseling*, *105*(4). https://doi.org/10.1016/j.pec.2021.07.021

Princen, S. (2007). Agenda-setting in the European Union: a theoretical exploration and agenda for research. *Journal of European public policy*, *14*(1), 21-38.

Rosemann, A., & Zhang, X. (2022). Exploring the social, ethical, legal, and responsibility dimensions of artificial intelligence for health – a new column in Intelligent Medicine. In *Intelligent Medicine* (Vol. 2, Issue 2). https://doi.org/10.1016/j.imed.2021.12.002

Sarewitz, D. (2011). Anticipatory governance of emerging technologies. *The growing gap between emerging technologies and legal-ethical oversight: The pacing problem*, 95-105.

Sauerbrei, A., Kerasidou, A., Lucivero, F., & Hallowell, N. (2023). The impact of artificial intelligence on the person-centred, doctor-patient relationship: some problems and solutions. In BMC Medical Informatics and Decision Making(Vol. 23, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12911-023-02162-y

Schönberger, D. (2019). Artificial intelligence in healthcare: a critical analysis of the legal and ethical implications. *International Journal of Law and Information Technology*, *27*(2), 171-203.

Sharkey, N. (2018). The impact of gender and race bias in AI. *Humanitarian Law and Policy*.

Shen, F. X., Silverman, B. C., Monette, P., Kimble, S., Rauch, S. L., & Baker, J. T. (2022). An Ethics Checklist for Digital Health Research in Psychiatry: Viewpoint. *Journal of Medical Internet Research*, *24*(2). https://doi.org/10.2196/31146

Stark, L., Greene, D., & Hoffmann, A. L. (2020). Critical perspectives on governance mechanisms for AI/ML systems. In *The Cultural Life of Machine Learning: An Incursion into Critical AI Studies*. https://doi.org/10.1007/978-3-030-56286-1_9

Stilgoe, J., Owen, R., & Macnagthen, P. (2013). Developing a framework for responsible innovation. 42(9), 1568-1580. https://doi.org/10.1016/j.respol.2013.05.008

Taeihagh, A. (2021). Governance of artificial intelligence. *Policy and society*, *40*(2), 137-157.

van Sint Jan, S., & Geris, L. (2019). Modelling towards a more holistic medicine: The Virtual Physiological Human (VPH). *Morphologie*, *103*(343), 127–130. https://doi.org/10.1016/J.MORPHO.2019.10.044

von Schomberg, R. (2014). Towards Responsible Research and Innovation in the Information and Communication Technologies and Security Technologies Fields. *SSRN Electronic Journal*. https://doi.org/10.2139/ssrn.2436399

Wahl, B., Cossy-Gantner, A., Germann, S., & Schwalbe, N. R. (2018). Artificial intelligence (AI) and global health: how can AI contribute to health in resource-poor settings?. *BMJ global health*, *3*(4), e000798.

Watson, W., & Marsch, C. (2020). *Artificial Intelligence Bias in Healthcare*. Booz Allen Hamilton. Retrieved December 11, 2021, from https://www.boozallen.com/c/insight/blog/ai-bias-in- healthcare.html.

Wender, B. A., Foley, R. W., Hottle, T. A., Sadowski, J., Prado-Lopez, V., Eisenberg, D. A., ... & Seager, T. P. (2014). Anticipatory life-cycle assessment for responsible research and innovation. *Journal of Responsible Innovation*, *1*(2), 200-207

Zou, J., & Schiebinger, L. (2018). AI can be sexist and racist—it's time to make it fair. xxx

Annex 1. Guiding Handbook for RRI Workshop

The following annex showcases the shared handbook, a comprehensive planning guide that provided direction for the preparation and smooth execution of the RRI Workshop organized in Bologna on April 19, 2023 by WP5.

1. **Workshop Layout**

Duration: 2 hours, 16:00-18:00 – April 19th, 2023

16:00-16:05 - Welcome - *Prof. Ine Van Hoyweghen*

16:05-16:20 - Introduction to RRI Approach & Presentation of the Findings – *Elisa Elhadj & Zita Van Horenbeeck*

16:20-16:25 - Q&A Session - *Elisa Elhadj & Zita Van Horenbeeck*

16:25-16:30 - Aims of the Workshop - *Dr. Elisa Lievevrouw*

16:35-17:50 - Group discussions with moderation + conclusion

→ last 5 minutes should be used for the summary of the group discussions

17:50-18:00 - Concluding Remarks – *Dr. Elisa Lievevrouw*

2. **General Protocol for moderators & observers**

The moderator's role:

- The moderator's job is **to progress and facilitate the group discussion**, not to participate in the discussion itself.
- The moderator may **probe for understanding** if they feel that someone is on the verge of an important insight. We have added additional questions in the protocol below that could the moderator.
- The moderator is responsible to **keep an eye on the timing**, and if necessary direct the conversations accordingly.

- If a participant or participants begins to dominate proceedings – the moderator should gently encourage others to get involved and rein in the dominant participant(s).
- The moderator and observer should try to **establish a permissive and safe environment** in which everyone feels free to contribute.

The observer's role:

- The observer's main task is to **make detailed notes** about the actual content of the discussion. These notes may include: interesting quotes, key points & themes, follow-up questions, ideas & insights, keywords and anything else that they deemed as noteworthy.
- The observer is **responsible for the recording** of the discussion.
- The observer can **assist the moderator** with the following:
  - If a participant or participants begins to dominate proceedings – the observer can assist the moderator in encouraging others to get involved and rein in the dominant participant(s).
  - Keeping an eye on the timing.
  - summarizing key themes and sharing observations at the end of the discussion.

3. **Protocol break-out discussions**

The group discussions will be organized in the following way:

- The cards used for the first phase will be handed out to the participants at the beginning of the workshop. Each participant should get two cards. During the presentation on ''Introduction to RRI Approach & Presentation of the Findings'', the speakers will hint that these cards will be used for the workshop.
- Participants will be seated in their respective groups at the beginning of the workshop.

Phase 1 - Discussing ELSI

16:35-17:05 - Duration: 30 minutes

Key goal: warm-up group discussion on the ELSI concerns raised during the focus groups and delphi study

- Each group is set-up with a poster on which the innovation cycle of in silico modeling is represented.
- Each group receives a set of cards, to start the discussion on the ethical, legal and social barriers to the uptake of in silico. Participants should be handed 2 cards. The moderator will engage the participants to discuss the card and is then responsible to place the card on the poster wherever participants deemed it the most appropriate.
- Participants also have the availability to make use of pink post-its if they would like to add another 'concern; or theme to the poster.

Script for the moderator:

- Once everyone is settled down, the moderator begins with disclosing that the session will be recorded. The observer then starts the recording.
- 5 minutes>: The moderator will start by introducing themselves (as short as possible: name, position & WP5) and their role during this group conversation. The word is then given to the observer, who follows the same format. Each participant is then asked to do the same and reminded to keep it brief. Everyone will be wearing a badge with their name and affiliation.
- The moderator will state the aim of this first phase, which is to discuss some of the ELSI that came to the foreground in the focus groups and Delphi survey. This is also a great opportunity to re-state that today we will focus on the concerns so that we can enter discussions about how to govern in silico and this does not undermine the many advantages that in silico has.
- The moderator then introduces the practicalities of this first phase: a poster, which represents the innovation cycle of an in silico model, will be used together with the cards that each participant received at the beginning. The aim is to

place each card where they deem it the most fit and to discuss it. An important component here is to use the cards as conversation starters. The moderator needs to make sure that the cards are not only placed, but also discussed within the group. The moderator may probe for understanding if they feel that someone is on the verge of an important insight or re-direct the conversation.

- The moderator should also point out that there are pink post-its available in case someone wants to add anything to the poster or if something comes up during the discussion that should be placed on the poster.
- The cards contain both a question and/or quotes, if the moderator feels that the topic was not discussed enough or if participants are stuck, his/her role is to initiate the conversation. A great option is to re-read the quote or question to see if anyone has any remarks and if needed a follow-up question can be added.
- It is crucial to remember that the moderator should only facilitate this discussion, and not participate in it actively. The moderator is responsible to make sure that everyone has the opportunity to share their thoughts and is responsible for placing the cards on the poster wherever participants deemed it the most appropriate.
- Once all the cards are placed and discussed, the group can move to Phase 2. If the discussions took longer, then the moderator still concludes this phase and moves on. Participants can then keep the cards in their hands, and might have the opportunity to re-discuss them at a later stage. However, this should be avoided with good time management.

Card examples:

How can you ensure the quality of the parameters in the model?	*"We give answers to the questions that we ask. But what if a crucial parameter is neglected, and we do not know about it?"*

Could the reduction to animal testing	*"This is the ethical way. We can only trust IS data if they match or agree well*

through in silico trials be a reality? Replace or support?	*with in vivo data. I would not approve anything without in vivo data. We don't have all the parameters. The in vivo configurations are way more complex than we have thought."*

Phase 2 - Towards Governing In Silico

17:05 - 17:45 - Duration: 40 minutes

Key goal: To gain an overview of In Silico's existing governance initiatives and to understand their strengths & limitations

- The first questions posed by the observer to start this phase should be: How could we tackle the concerns raised within phase 1? What governance initiatives already exist to solve some of these concerns? Are they working, (if not) what needs to change? What are you doing in your own daily work to tackle these concerns?
- This will enable it to flow into a conversation where participants discuss governance examples and suggestions across the in silico lifecycle.
- If the participants get stuck, the moderator can jump in and ask questions such as:
  - What could you do concretely to contribute to overcoming (specific barrier)?
  - What can be done short-term vs. long-term?
  - What is not taken into consideration?
  - Where could the project come-in to support the governance-building for In Silico?
  - What do you consider is your role in the development of guidelines for regulating in silico medicine tools, and how can your expertise be leveraged effectively?

- ❖ Governance suggestions should be written down on post-its by the participants and sticked on the poster in proximity of the card that it is relevant to.

Script for the moderator:

- The moderator announces that phase 2 will now start and **discloses the motivation behind it:** during the focus groups, it was noticeable that participants often discussed concerns or ambiguities, but rarely concrete governance practices/solutions were proposed. Therefore, we want to have a discussion about in silico governance, as WP5 is interested in proposing concrete actions to the identified barriers to the uptake of in silico.
- The moderator uses his/her first input within this phase to also inform the participants that **governance suggestions** that surface during the discussion should be written down on yellow post-its by the participants and sticked on the poster in proximity of the card that it is relevant to.
- The moderator invites the participants to have a look at the poster and asks the first question: How could we tackle the concerns raised within phase 1?
- Once that discussion has run its course and this topic has not been brought up yet, the moderator follows up with: What governance initiatives already exist to solve some of these concerns? Are they working, (if not) what needs to change?
- Within these discussions, the moderator should also divert the conversation to what are the participants doing in their own daily work to tackle these concerns?
- The moderator is free to decide which of the additional questions should be asked. This truly depends on the flow of the conversation.
    - What could you do concretely to contribute to overcoming (specific barrier)?
    - What can be done short-term vs. long-term?
    - What is not taken into consideration?

- Where could the project come-in to support the governance-building for In Silico?
- What do you consider is your role in the development of guidelines for regulating in silico medicine tools, and how can your expertise be leveraged effectively?

- In this phase, it is once again crucial that the moderator makes sure that everyone has the opportunity to discuss.
- Once the time is over, the moderator gently concludes this phase.

Phase 3 - Conclusion

17:45 - 17:55 - Duration: 10 minutes

Key goal: gain a more comprehensive insight into what the participants' top ELSI/governance priorities might be

- The **moderator** (with the **observer**) will conduct a summary exercise at the end to summarize key themes and share observations.
- In this phase, the moderator can also raise a question about an **overlooked ELSI** or anything that might have fallen into the background of the conversation.
- If time permits, the moderator hands out three dots to the participants to place next to the focus card/post-it that they think is an absolute priority. This can help identify the most important topics for further discussion.
- The participants will be asked if they agree or disagree with this summary and if they have anything to add.

Script for the moderator:

- To begin the last phase, the moderator will point out that despite the fruitful conversations, it is now time to wrap-up. This will be done through a summary exercise.
- The moderator begins with briefly summarizing some of the key points made during phase 1 & 2, and asks the participants if they would like to add something.
- The moderator then hands out three dots (stickers) to each participant and asks them to place them next to the focus card/post-it that they think is an absolute priority. Here, the moderator explains that this is done to help identify the most important topics for further discussion.
- If there is the need to and there is time left, the moderator can also raise a question about an overlooked ELSI or anything that might have fallen into the background of the conversation.
- During the last minute of the conclusion, the moderator warmly thanks the participants for their participation and the observer for their support.

4. **Participant Groupings**

Group 1 - moderator: Elisa Lievevrouw, observer: Davide Montesarchio

Group 2 - moderator: Elisa Elhadj, observer: Goran Stanic

Group 3 - moderator: Zita Van Horenbeek, observer: Janaki Raman Rangrajan

Group 4 - moderator: Ine Van Hoyweghen, observer: Roberta De Michele

Group 5 - moderator: Elisabetta Biasin, observer: Martina Contin

5. Required material

- Laptop with slides (including opening slide/general slides)
- Audio recording devices (x5)
- 5x download of recording app as a safety measure if the recordings would not work
- Water for workshop participants
- Technical set-up for the presentation (microphone, projector for the slides, etc)
- Paper and pens for observers & moderators

- ➢ 5x post-its yellow for action points
- ➢ 5x post-its pink for extra concern-suggestions of participants
- ➢ 5x dot-stickers for priorities

❖ Badges with name & group number (and badges for moderators & notetakers)
❖ Chairs (already in the room)
❖ room dividers (if possible)
❖ Tesa tape

6. Task distribution

Task	**Responsability**
Sending out a reminder for the workshop with additional information (e.g. room) + requesting participants to arrive within a time frame 15:30-16:00	Goran & Martina
Room preparations & testing technical set-up	Goran & Elisa E./Elisa L. & Zita
Prepare slides	Elisa E./Zita
Print posters (x5)	tbd
Tessa tape	Elisa L.
Print and prepare focus cards	Elisa E.
Bring stickers/dots	Elisa E.
Borrow 5 audio recording devices (KUL)	Elisa E.
Badges, water, etc	Goran & Roberta
Bring recording device VPHi	Raphie
Prepare material for group discussions	Elisa E, Zita, Elisa L.
Setting-up the room on Wednesday (group groupings)	Elisa E./Elisa L. & Goran/Martina (tbd)
Welcoming participants and direct them to their groups	tbd
Prepare and collect consent forms	Elisa E./Zita

Annex 2. Coding Tree for Analysis

#INPUT

- **input_ISM_ClinicalTrials**

This code is to differentiate within discussions between In Silico trials and In Silico models for clinical practice. It should be used when participants implicitly or explicitly refer to In Silico trials.

- **input_ISM_ClinicalPractice**

This code is to differentiate within discussions between In Silico trials and In Silico models for clinical practice. It should be used when participants implicitly or explicitly refer to In Silico models for clinical practice.

- **input_bias**

What is meant here is the different types of biases that can flow into the input phase. A good example would be selection bias, or unrepresentative datasets that can impact the accuracy of the models.

- **input_holisticview**

The purpose of this code is to capture this notion of taking a holistic point of view of the human body (e.g. accounting for variations between patients) within In Silico. In silico models are said to be designed to capture the complex and interconnected nature of biological systems, rather than focusing on isolated components or factors in isolation, this means that these models also take into account lifestyle and environmental factors that can influence disease development/progression.

- **input_holisiticview_epigenetics**

This sub-code should be used when participants refer to epigenetics

- **input_holisiticview_socialdeterminants**

This sub-code should be used when there are discussions around social determinants of health such as obesity.

- **input_roleattribution**

This code captures role attributions for different stakeholders by participants. It also includes expectations that are attributed to individuals during conversations for the role they should play in the input phase. Role attributions can take a variety of forms, including explicit statements or descriptions of roles, as well as more subtle cues.

- **input_roleattribution_responsability**

Use this code if within the role attributions there is this element of responsibility. An example would be conversations around who is responsible for a certain task, a certain decision or if there are any harms resulting from the use of an In Silico model.

- **input_roleattribution_responsability_clinicians**

This sub-code should be used when the responsibility of clinicians is discussed.

- **input_roleattribution_responsability_patients**

This sub-code should be used when the responsibility of patients is discussed.

- **input_roleattribution_responsability_regulators**

This sub-code should be used when the responsibility of regulators is discussed.

- **input_roleattribution_responsability_companies**

This sub-code should be used when the responsibility of companies is discussed.

- **input_decisionauthority**

When participants express their views on decision authority; this refers to the level of decision-making that an individual has within the input phase. An example of this would be, who makes the decision about which patient data should be included in a model (target group).

- **input_cost**

Captures discussions around the costs that go into the input phase of an In Silico model. An example might be the costs of setting-up clinical trials.

- **input_socialsorting**

Use this code when tracking conversations about social sorting; decisions within the input phase that may result in the exclusion of certain patient groups. In other words, social sorting in the case of In Silico medicine refers to the use of computational modeling and simulations to group people based on their health information or certain characteristics - which leads to certain 'prioritizations'.

#OUTPUT

- **output_uniqueness_of_patients**

This code captures the statements of participants on the notion of uniqueness of the human body and particularities of patients within the output phase of the In Silico model. An example of this would be when clinicians discuss if a model is capable of integrating the complexities of a specific case as there can be specific needs and circumstances that must be considered.

- **output_decisionauthority**

When participants express their views on decision authority; this refers to the level of decision-making that an individual has within the output phase of the model. An example of this would be, when a doctor makes the decision to be supported by an In Silico model, or to go against its suggestions.

- **output_accesibility**

Use this code when tracking conversations about the accessibility of these models for patients. Who has access and who doesn't?

- **output_socialexclusion**

Use this code when tracking conversations about the exclusion of certain patient groups. This can happen on various levels and can raise questions such as who can/is excluded from being able to benefit from In Silico models.

- **output_cost**

Captures discussions around the cost effectiveness of integrating In Silico models for healthcare systems.

- **out_technicalfesability vs societal benefits**

Use this code when tracking conversations concerning an existing tension between technical feasibility and societal benefits. This is particularly relevant for conversations around the proportionality of a model and in which sector it makes most sense to be

deployed. Another example would be conversations that discuss how it might not be because we can develop a model that we necessarily should – if we think in terms of beneficence for society.

#REFERRING to

- **ref_ISM_for_prediction**

Use this code when tracking conversations about the use of In Silico models for prediction purposes.

- **ref_privacy**

Use this code when tracking conversations about privacy. This can be the privacy of patients, but also of other stakeholders. It can also be used when participants discuss specific regulatory frameworks such as the GDPR, which tend to bring up discussions about privacy.

- **ref_definition**

The purpose of this code is to capture the element of definitions in the In Silico field.

- **ref_definition_unclarities**

Use this code when noticing that there are definition unclarities between participants. It might be that a participant is discussing potential barriers relating to In Silico trials, whilst the other participant might be discussing In Silico models for clinical practice. This code should also be used for instances where participants have difficulties with comprehending what In Silico is, or difficulties with understanding the scenarios.

- **ref_definition_discussion**

Use this code when participants explicitly mention that there are definition issues in In Silico medicine

- **ref_animaltesting**

Use this code when participants refer to animal testing. This is usually done when discussing how In Silico trials can replace the need for animal testing through simulations.

- **ref_doctorpatient_relationship**

Captures discussions about the patient-doctor relationship, and how In Silico models might change certain dynamics.

- **ref_datamanagement**

Use this code when participants refer in a broad sense to data management. An example would be: how should patients manage their data.

- **ref_perceivedrisks**

Use this code when participants discuss perceived risks that can arise with In Silico models. This can be both within In Silico trials and in clinical practice, through the input and output phase.

- **ref_trade-offs**

Use this code when participants refer implicitly or explicitly to trade-offs. A trade-off involves making a decision between two or more options, where each option has its own advantages and disadvantages, and choosing one option means giving up some benefits of the other options.

- **ref_synthetic data**

Use this code to follow conversations on the use of synthetic data, e.g. to map discussions around its use to minimize bias

- **ref_artificial intelligence**

Use this code when participants refer to any type of AI

- **ref_collaboration with regulatory bodies**

Use this code to map discussions on the collaboration with regulatory bodies on in silico

- **ref_digital twin**

Use this code when participants refer to digital twins

- **ref_ethical committee**

Use this code when participants discuss the role of ethical committees in, for example, 'regulating' the quality of the input of the model.

- **ref_transparancy**

Use this code when participants raise the importance of transparency or being able to explain what data was used in the model.

- **ref_VV-40**

Use this code when participants refer to this specific standard.

- **ref_complexities model**

Use this code when participants refer to the shortcoming/limits of the model when it comes to input of parameters

- **ref_expectations vs reality**

Use this code when respondents discuss the limits of in silico medicine in relation to the ideal/expectations of it.

- **ref_Lack Harmonization EU**

Use this code when participants refer to inter-country differences when it comes to standards and regulations (leading to inequalities between member states), and a lack of harmonization

#VIEW

- **view_ISWtool_deterministicview**

The purpose of this code is to capture what we would call a deterministic view towards In Silico medicine. It encompasses the assumption that these models can predict the behavior of a biological system accurately and with certainty, and they therefore can replace clinicians, … in care practices.

- **view_ISWtool_humaninvolvement**

The purpose of this code is to capture discourses which highlight the importance of keeping a human in the loop, and who portray In Silico as a tool to support clinicians, and not as a replacement.

#CONTESTED KNOWLEGDES

Contested knowledges is about frictions between knowledges and how different knowledges interact with each other.

- **ck_patient vs clinician**

Use this code when tracking conversations about knowledge tensions between patients and clinicians or notions of non-knowledge or knowledge asymmetries between these two actors.

- **ck_human vs tech**

Use this code when tracking conversations regarding tensions between humans and technology. This also encompasses (among others) the feasibility and accuracy of a model compared to a clinician, proportionality of technological use, invasiveness of a treatment based on a model and technological dependance of clinicians.

#AUTONOMY

- **aut_patients**

Captures discussions on the autonomy of patients. This, for example, includes the right not to know by patients when it comes to genetic determinants of their health. In the clinical setting, patient autonomy is a crucial concept that is supported by ethical (principle of respect for autonomy) and legal principles.

- **aut_clinicians_discretion**

Captures discussions on the autonomy of clinicians in their professional setting. This, for example, includes their freedom of decision-making. Despite what a model might tell him, a clinician has decision authority.

#EXPERTISE

- **expertise_companies**

The purpose of this code is to capture viewpoints on the expertise of companies. Where should they come in, and what is considered as within the realm of their expertise?

- **lack_expertise_companies**

Use this code to capture viewpoints on the lack of expertise of companies. What is outside of the competences and expertise of companies?

- **expertise_regulators**

The purpose of this code is to capture viewpoints on the expertise of regulators. Where should they come in, and what is considered as within the realm of their expertise?

- **lack_expertise_regulators**

Use this code to capture viewpoints on the lack of expertise of regulators. What is outside of the competences and expertise of regulators ?

- **expertise_patients**

The purpose of this code is to capture viewpoints on the expertise of patients. Where should they come in, and what is considered as within the realm of their expertise?

- **lack_expertise_patients**

Use this code to capture viewpoints on the lack of expertise of patients. What is outside of the competences and expertise of patients?

- **expertise_clinicians**

The purpose of this code is to capture viewpoints on the expertise of clinicians. Where should they come in, and what is considered as within the realm of their expertise?

- **lack_expertise_clinicians**

Use this code to capture viewpoints on the lack of expertise of clinicians. What is outside of the competences and expertise of clinicians?

- **expertise_engineers**

The purpose of this code is to capture viewpoints on the expertise of engineers. Where should they come in, and what is considered as within the realm of their expertise?

- **lack_expertise_engineers**

Use this code to capture viewpoints on the lack of expertise of engineers. What is outside of the competences and expertise of engineers?

#STANDARDS

- **standards_validity**

Captures discussions around validity by the different stakeholders. These conversations can be layered and need to be given particular attention. An example would be discussions around how to establish guidelines for validity, and the issues of demonstrating validity.

- **standards_accuracy**

Use this code to capture discussions on the accuracy of the models. Accuracy in In Silico medicine refers to the degree to which computer-based simulations and models are able to predict and simulate real-world biological processes and medical outcomes. Conversations around accuracy (among others) can be around how variable is the prediction of a model, but also how can a model move towards better accuracy, or what do we deem as sufficiently accurate.

- **standards_methods**

Use this code when participants discuss methods relating to In Silico medicine. The term methods and methodology seems to be used interchangeably within the discussions. Therefore, this code also relates to discussions on how to overcome methodological challenges and how to develop common methods, also for regulatory approval purposes.

- **standards_monitoring_expost**

Captures discussions around the monitoring of models after its uptake.

- **standards_EUvsUS**

Captures discussions around the difference between guidelines/standards in Europe and the United States.

#ROLES

- **role_patient**

Captures discussions on the role of patients.

- **role_patient_ trust**

Use this code when participants discuss the role of patients in building trust in In Silico models.

- **role_patient_uptake**

Use this code when participants discuss the role of patients in supporting the implementation of In Silico models.

- **role_citizen_uptake**

Use this code when participants discuss explicitly the role of citizens in supporting the implementation of In Silico models.

- **role_clinician**

- **role_clinician_trust**

Use this code when participants discuss the role of doctors in building trust in In Silico models.

- **role_clinician_uptake**

Use this code when participants discuss the role of patients in supporting the implementation of In Silico models.

- **role_clinician_training**

Use this code when participants discuss the role of clinicians in getting a better understanding of how In Silico models work and the training they might need to undergo.

- **role_regulators**

- **role_regulators_innovation**

Use this code when participants discuss the role of regulatory agencies in enabling/challenging the emergence of In Silico medicine.

- **role_regulators_trust**

Use this code when participants discuss the role of doctors in building trust in In Silico models.

role_regulators_training

Use this code when participants discuss how regulators need training as well as clinicians.

- **role_engineers**

Use this code when participants discuss the role of engineers within within the different lifecycles of In Silico medicine.

- **role_companies**

Use this code when participants discuss the role of companies within the different lifecycles of In Silico medicine.

#GENERAL

- **gen_advantages**

Captures general discussions around the advantages of making use of In Silico medicine for the healthcare sector.

- **gen_complexities**

Captures general discussions around complexities that arise within In Silico medicine and its uptake. This includes conversations on challenges, hurdles, or barriers as some participants might call it.

- **gen_personalization**

Captures general discussions around the notion of personalization of medicine. In silico is a good example of an approach to medicine which is personalized (also precision medicine), therefore it comes up frequently within the discussions.

#REGULATORY AGENCY

- **reg_roleofcompanies**

The purpose of this code is to capture viewpoints referring to the role of companies within regulatory approval.

- **reg_EUvsUS**

The purpose of this code is to map comments on the regulatory agency of the European Union compared to the United States. This also related to discussions around guidelines set by the EMA or the FDA.

Annex 3. Focus cards used during RRI workshop

• Which factors should be included in the models ? • 'Holistic' modelling	*"I see it as much more complicated because in predicting the response to a treatment, the efficacy of a therapy, multiple factors come into play, as I said before, that are individual genetics, are the person's living conditions, are "comorbidities", a lot of other factors that have to be taken into account when we try to set up an in silico trial."*
• Complexities of the human body	*"We give answers to the questions that we ask. But what if a crucial parameter is neglected, and we do not know about it?"*

• Reduction of animal testing through in silico trials • Replace or support?	*"This is the ethical way. We can only trust IS data if they match or agree well with in vivo data. I would not approve anything without in vivo data. We don't have all the parameters. The in vivo configurations are way more complex than we have thought."*
• Where does the risk of bias surface in the in silico lifecycle? Does it differ from bias issues that we see in artificial intelligence?	*"Yes, but if that other group of patients might also benefit from that anyway [...] then you block off a group of patients from that, who maybe in eighty per cent of the cases might also have the treatment with that kind of valve."*
• Definition uncertainties	*"Another thing that I want to ask because in my opinion there is a "definition" problem that however is quite important: are we talking about in silico but thinking also at the digital approach? Because the data analysis through artificial intelligence is something in my opinion different from in silico model (doctors and ISW experts agrees)."*

• What are some of the potential factors that can contribute to social exclusion in the context of in silico?	*"We create a model and train it with data. We can use it other than the initial focus. Besides medical device development, it can also be used by insurance companies for filtering which patients should be insured. This can be published scientifically for a completely other reason. These accidental outcomes are hard to predict."*
• Where and how can clinicians or other stakeholders be included in the input phase of the models?	*"ISW expert 1: But to expertise then. yes, I see less a role for the patient in making your models more correct.* *ISW expert 2: Maybe [for] that database of other risk factors? You need the patients for that, don't you?* *ISW expert 1: Yes, I think [so], but that's in my view the knowledge that a doctor has. Who has insight.* *ISW expert 2: But if the patient doesn't tell then the doctor doesn't know, no?"*
• The right not to know • Patient empowerment	*"If we create a digital twin, we can run it to have a prediction of a given disease. But it shares a lot with the topic of predictive genetic models. Do I want to know the future?"?"*

• How can models account for different experts and ‘knowledges’?	*“If you're going to do that, you're going to have to take different surgeons side by side, you're going to have to include people in that study, because every surgeon has his own way of working [...]”.*
• Technological dependance & oversight	*“The next big step will be the adaptation of robotic surgeries, where we don’t have the human oversight, since it will be executed automatically.”*
• How can we ensure that the regulatory process for in silico is flexible enough to adapt to new developments?	Anticipation

• What are the potential challenges for monitoring in silico tools ex post ?	*"I work in the other field, so the challenges that my field is facing right now are to keep the model monitored once it is used in clinical practice. I monitor the model and monitor it with the data that feed this model. This is the biggest challenge because there is no standardization, because there are no guidelines established yet by either FDA or EMA."*

Annex 4. List of values

Public values and their definitions
Derived from the Delphi survey (first participation round) [ref]

On this sheet you will find an overview of the values (guiding principles) that ISW experts (researchers) raised in the first of two ISW "participation rounds," also called the Delphi study round (ref). These values indicate what experts consider important ////, for example, privacy, autonomy, and equity. The list is not exhaustive but intended to guide further reflection and discussion.

As a reminder, in silico medicine (also known as "computational medicine") involves the modeling, simulation and visualization of biological and medical processes, from the cellular and molecular level to specific organ systems and disease states. Computer simulation is used in the diagnosis, treatment or prevention of disease with the goal of simulating real biological processes in a virtual environment. Applications of this new technology can be found in cancer research, vascular and heart disease treatment or diabetes, among others. The ultimate goal is to make healthcare more efficient and improve patient outcomes, preferably at a lower cost.

Autonomy
In our health care system, citizens and patients are supposed to make their own choices about their health. So they are (or will be) in control of their healthcare process. But what if a patient does not wish to be informed about a prognosis, for example? Or what if he refrains from further medical treatment? Does that choice affect his right to medical assistance? If so, how voluntary is that choice?

Data privacy and management
Data from hospitals, general practitioners, medical labs and from patients themselves, can contribute to "tailored" care and better prevention of health problems. But in a system of digital health care, it is not always clear how and for what such data is used.

The experts in the ISW project recognize the need to balance the benefits of in silico medicine (e.g., reducing collective health care costs) with applicable privacy rights, such as the patient's right to access their own health data and control over what happens to their data.

Efficiency
Efficiency or effectiveness is the rate at which a service delivers as much as possible at the lowest possible cost. In silico medicine, enabled by digital technologies, would contribute to more efficient health care because it increases the quality of care and leads to cost savings, for example, by testing virtual patients.

'Do no harm' (non-maleficence)
New medical technologies and interventions raise questions about the non-maleficence of harming patients. In medical ethics, the principle of "do no harm" (non-maleficence) requires that any medical treatment be first weighed against its potential benefits, risks and consequences. But sometimes no treatment is found to be the best treatment, making it difficult to balance the benefits and risks of an intervention. How is this balancing act guided in part by the introduction of in silico technologies?

Informed Consent
In informed consent, a person receives information from a medical professional (e.g., a physician) about the potential benefits and harms of a medical treatment in order to decide whether to undergo the treatment based on that information. ISW experts are eager to make this type of decision with patients. But they also recognize the difficulties: sometimes patients find it difficult to understand all the information given to them. Sometimes a doctor or practitioner is better positioned than a patient to make a decision. Sometimes even the practitioner does not have all the information necessary to make a judicious decision.

Environmental considerations
The explosion in the use of digital technology in health care has implications for our environmental footprint. Some ISW experts point out that more "computing power" and the generation of ever more digital data could increase global CO2 emissions unless we find ways to use digitization to devise climate-efficient solutions.

Independence from technology
The rising influence of digital technology in the health sector significantly facilitates the work of doctors, practitioners and researchers but also makes them more dependent on those same technologies. One question ISW experts are asking in this regard is whether experts can still diagnose without technology. Can and dare they still make decisions based on their own judgment and experience? Are they gradually losing their judgment to machines and algorithms?

Inequality
In silico medicine can contribute to improved quality of care, reduced costs and improved access to that care, albeit especially for individuals with digital knowledge and skills. Moreover, digital and medical technologies and data are not available in all countries. In other words, in silico medicine can both narrow and widen the digital care gap.

Prevention
In silico medicine aims to prevent disease (prevention). By screening people early, it is possible to better predict which treatments and lifestyle interventions can help prevent or make certain diseases more favorable. A question that arises here is whether preventive measures are always desirable: do they effectively lead to a better quality of life for every patient? And does preventive screening make sense if we do not improve the living conditions of vulnerable groups?

Equity
In principle, everyone has equal access to care. But what if citizens are denied access to certain drugs or services because of their medical history or risk profile? And what if conditions are imposed by third parties to take out insurance or take out a mortgage on housing, for example? In these cases there is discrimination, and therefore injustice.

Solidarity
In order to keep health care affordable and accessible, citizens are supposed to take control of their own health, for example by exercising regularly and getting screened for health risks. This personalized approach stands alongside impersonal organized solidarity: in a welfare state, all citizens have access to care regardless of income, education or background. The Delphi survey shows that ISW experts consider both approaches (the personal and impersonal) important. The question, however, is whether digitally-driven medicine allows for both personal and organized solidarity.

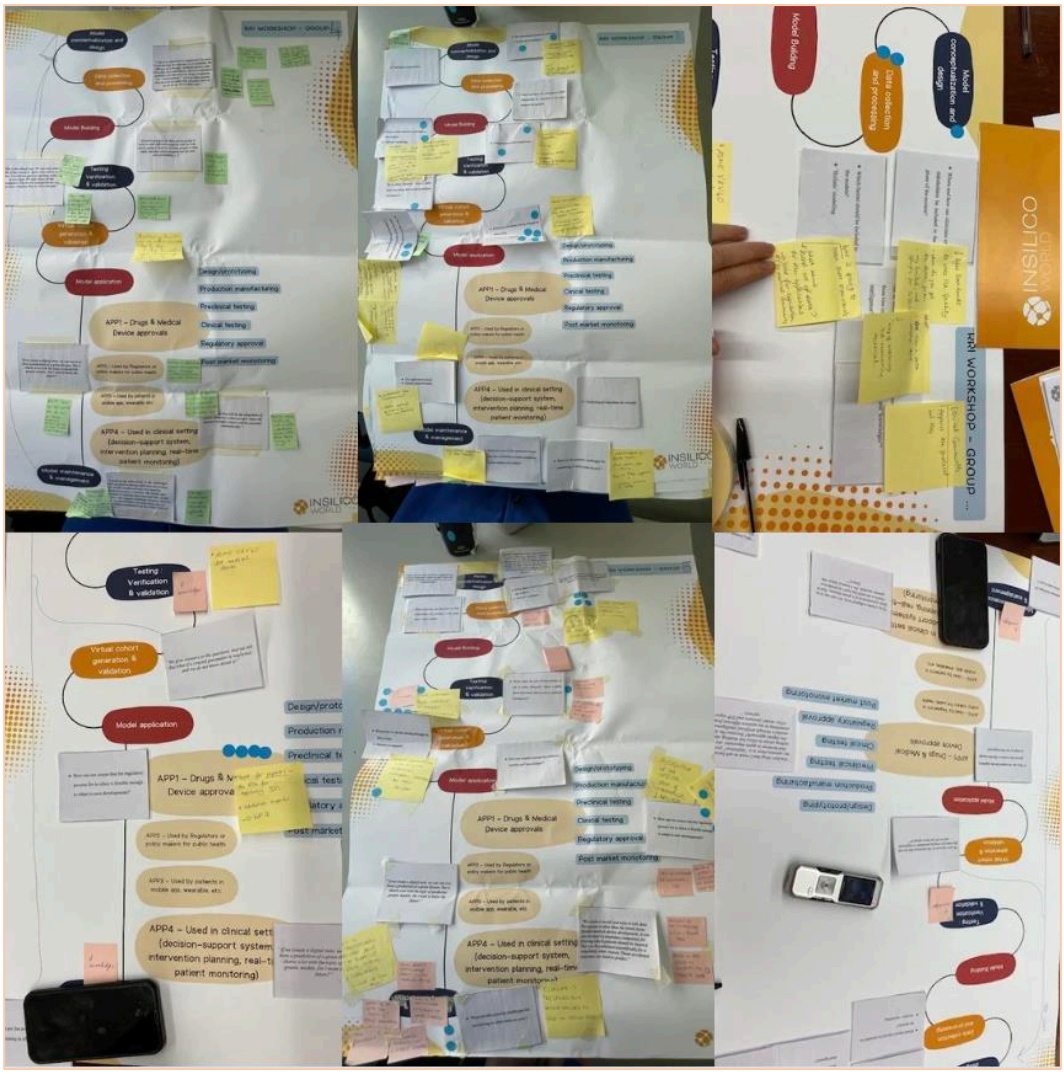
Accountability/Responsibility
There is a chance that a medical or regulatory decision based on computer predictions may turn out to be wrong in practice. In that case, who is responsible for the outcome? How is responsibility determined? How can the risk be mitigated? ISW experts recognize that these are relevant questions that deserve attention in the development of in silico medicine.

Trust in technology
Trust in a technology includes two questions: can we trust the technology (rely on the technology without having a firm proof or guarantee) and is the technology reliable (does the technology work as it is supposed to work)? In silico experts are asking: at what point is an in silico model for medical applications sufficiently trustworthy? What kind of evidence do we need for this?

Human and animal welfare
Thanks to in silico medicine, the use of laboratory animals in clinical trials can be drastically reduced, as well as the number of test subjects. More so, according to ISW experts, in silico technologies can provide more and better scientific evidence (proof) than would be the case with animal testing.

'Customized' care
In silico technologies should lead to higher quality healthcare and better and safer treatments for patients. ISW experts are thinking especially about personalized medicine in the form of treatments "tailored to your needs. These treatments meet the specific needs and characteristics of each individual patient. According to ISW experts, this is one of the most important benefits that in silico medicine has to offer.

Annex 5: Pictures of the posters during and after the workshop



Annex 6: Digital flyer used for participant recruitment (3 pages)


IN SILICO WORLD
GENERAL ASSEMBLY
19th-20th April 2023
Università di Bologna - Accademia delle Scienze - Via Zamboni 33
•19th April
h16:00-18:00
RRI WORKSHOP
Mandatory for all modelling track developers
h19:30
DINNER
•20th April
20th April h8:30-17:00
CONSORTIUM MEETING
h19:00
DINNER
FOR THE DETAILED PROGRAMME PLEASE CHECK THE FULL AGENDA
INSILICO WORLD

INSILICO WORLD

RESPONSIBLE RESEARCH & INNOVATION (RRI) WORKSHOP

Mandatory for all modelling track developers

The goal is to further discuss the ethical, legal and social implications of in silico medicine with stakeholders.



Wednesday
April 19 2023
16:00 - 18:00

Università di Bologna
Accademia delle Scienze
Via Zamboni, 33

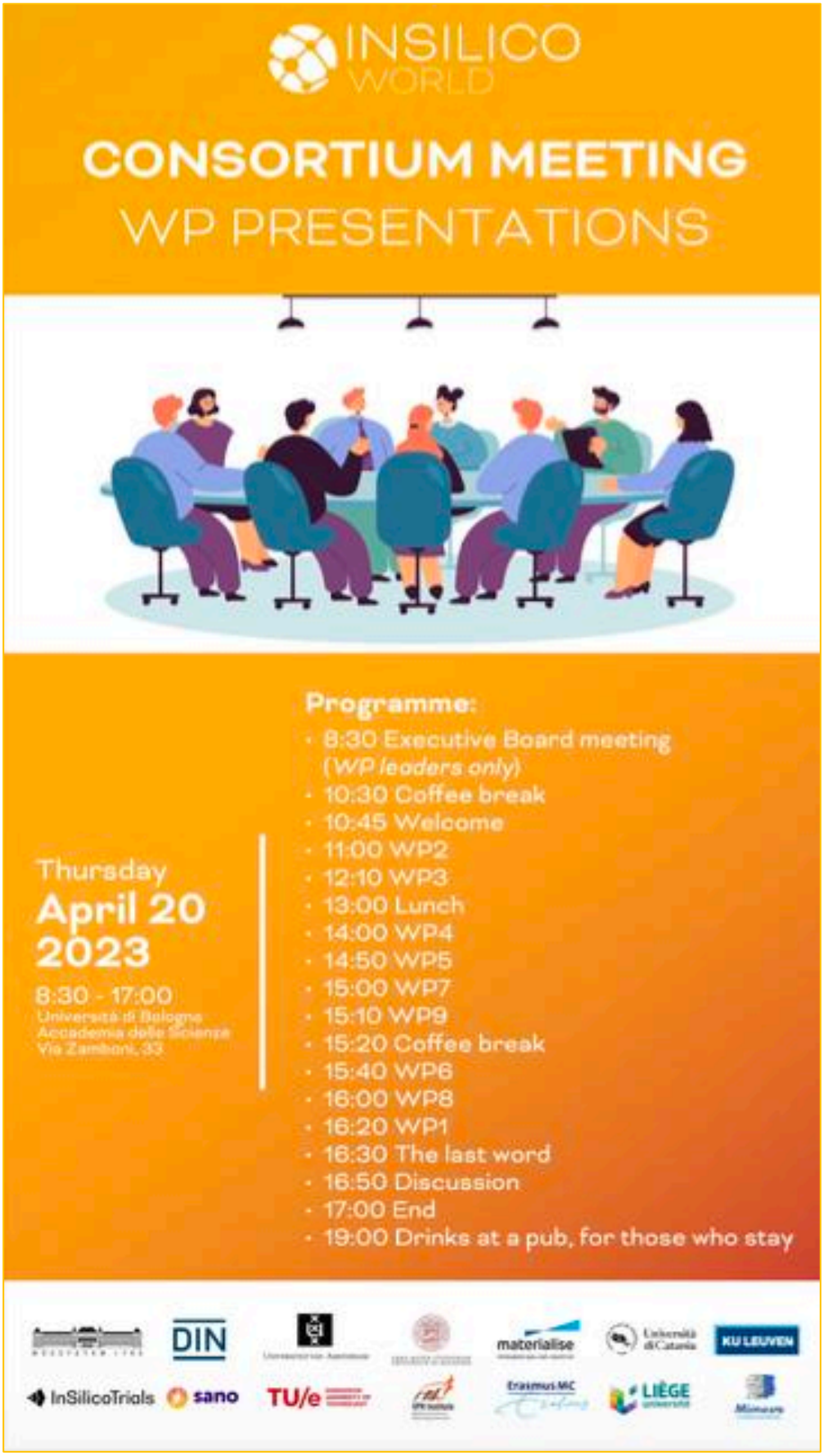
Programme:

- 16:00-16:10 Welcome, brief intro to RRI | *Prof. Ine Van Hoyweghen*
- 16:10-16:35 Presentation on Qualitative Research Findings | *Elisa Elhadj & Zita Van Horenbeeck*
- 16:35-17:45 Group Discussion with moderation | *Dr. Elisa Lievevrouw*
- 17:45-18:00 Wrap-up

KU LEUVEN

ALMA MATER STUDIORUM UNIVERSITÀ DI BOLOGNA

VPH Institute


INSILICO WORLD
CONSORTIUM MEETING
WP PRESENTATIONS
Thursday
April 20
2023
8:30 - 17:00
Università di Bologna
Accademia delle Scienze
Via Zamboni, 33
Programme:
· 8:30 Executive Board meeting (WP leaders only)
· 10:30 Coffee break
· 10:45 Welcome
· 11:00 WP2
· 12:10 WP3
· 13:00 Lunch
· 14:00 WP4
· 14:50 WP5
· 15:00 WP7
· 15:10 WP9
· 15:20 Coffee break
· 15:40 WP6
· 16:00 WP8
· 16:20 WP1
· 16:30 The last word
· 16:50 Discussion
· 17:00 End
· 19:00 Drinks at a pub, for those who stay
DIN
materialise
KU LEUVEN
InSilicoTrials
sano
TU/e
LIÈGE

***