14/03/2025

'Call for MDR evaluation to leverage computer modelling and simulation methodologies including AI, to mitigate current challenges and prepare for future needs.'

Dear Commissioner Olivér Várhelyi,

As an international scientific society representing the professionals from academia, research institutes, hospitals and health technology assessment bodies with **expertise in *in silico* medicine,** we support the European Commission's consultation on the evaluation of Medical Device Regulation (MDR). In silico medicine refers to the **use of computer (*in silico*) modelling and simulations** in all aspects of prevention, diagnosis, prognostic assessments and treatment of diseases, as well the **development and de-risking medical products** (medicines, devices) and the **planning of interventions.**

While the current challenges in the regulatory landscape of medical devices are widely discussed, we assert that emerging computer modelling and simulation (CM&S) technologies, including artificial intelligence (AI), are ideally positioned to **address the pressing challenges and concerns surrounding device safety and the increasing costs** that impact the availability of novel treatments to wider segments of the European population.

As an academic not-for-profit scientific society with active engagement with other professional societies, such as the Avicenna Alliance, the European Patient's Forum etc., **we share the learnings from EC-funded policy initiatives, along with tangible scientific evidence** demonstrating how these *in silico* medicine technologies can be leveraged. We believe this will not only address the current bottlenecks of the EU health ecosystem but also act as an engine for competitiveness across the European healthcare sector. The VPH Institute, representing academic technology developers, users and assessors, has a longstanding history of partnering with health stakeholders, particularly key beneficiaries such as clinicians and patients, as well as governing actors: policymakers, regulators, HTA bodies, and ethical, legal, and social sciences scholars. We also foster innovation through pre-competitive collaboration with industrial actors.

Drawing upon learnings from EC-funded policy initiatives, including FP7, Horizon, and Digital Europe calls, we present our insights from numerous roadmaps, along with tangible recommendations on how CM&S technology can be an enabling paradigm across the entire lifecycle of medical devices, from ideation and design to deployment and post-market surveillance. A crucial elements in the successful deployment and uptake of this technology lies in its **comprehensive inclusion in the MDR** (extending beyond its currently assigned role in preclinical evidence generation). While this submission is a high-level report of the current state of challenges, **we look forward to constructively participating in stakeholder discussions reviewing the MDR** and stand ready to provide scientific insights from the academic community to best support the Commission's initiative.

Yours sincerely,

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VPH Institute; University of Liège, KU Leuven, Belgium.

Position statement

Observations and submissions in the context of MDR evaluation

1 Context of MDR evaluation

To begin with, we support the European Commission's initiative for public consultation on the EU-MDR[1] and align with the many key principles that the MDR evaluation process sets out to address. The Virtual Physiological Human scientific community's vision and mission is to *`act as a catalyst to bring together a variety of stakeholders to benefit from the understanding of human pathophysiology, to deliver the best possible treatment to patients and to drastically improve healthcare'*. This vision motivates us to proactively contribute to the following key aspects of the MDR evaluation:

- Protect patient safety and public health, while supporting innovation.
- Improve clinical safety and fair market access for manufacturers.
- Alignment with international practices.
- Foster European innovations, to achieve a competitive medical sector.

With regard to the principles and implementation of MDR, we broadly acknowledge that MDR includes stringent pre- and post-market requirements to reduce safety issues in the EU. Despite the criticism regarding increased scrutiny, we believe that the principles and measures introduced by the MDR, when pragmatically implemented, aim to deliver patient safety, transparency and remain the right direction to achieve clinical benefit and effectiveness for patients.

2 Current state of affairs

Drawing upon our community's extensive scientific contributions, we recognize and acknowledge the following challenges, their root causes, and possible solutions that are relevant to the MDR evaluation.

2.1 Challenges

Briefly, the key challenges of the medical device sector pertain to:

- Safety, Access & Availability of medical devices.
- Increased costs associated with manufacturing, regulatory compliance and patient access.
- Long delays in regulatory process, which rely on traditional, siloed sources of regulatory evidence that often result in evidence gaps.
- The fragmented MDR implementation structure, and the ad hoc guidance documents, leading to restrictive and conservative practices by the implementing organizations.

[1] EU-MDR – Medical Device Regulation - Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, http://data.europa.eu/eli/reg/2017/745/oj

We believe that some of the above challenges are directly related to the uncertainty of regulatory evidence and its oversight through the fragmented implementation of the MDR. They impact not only market approval decisions, but also funding decisions within national health systems, thereby increasing costs and delaying innovations that benefit patients.

Amidst a fast-evolving technology landscape and the progression of research methods to regulatory science tools, the MDR continues to be interpreted only through conventional evidence bases, as well as a conservative mindset that stifles new innovations. In other words,

the **MDR has laid out future-looking guard rails for medical products**, and
the subsequent **digital technology decade has empowered a new generation of medical innovations** (next-generation trains), but
our signal systems (implementation challenges) remain outdated and sub-optimal,
reducing the speed, safety, and access (of trains) for citizens and patients.

2.2 Possible solutions

In this digital decade, the MDR is implemented with a siloed mindset. To best leverage the fast-evolving technological advancements, the regulation would benefit from dynamism that embraces new technologies and complementary **evidence sources across-all phases of the medical device lifecycle.**

To this end, we advocate for the broader use of evidence generated from **computer(*in silico*) modelling and simulation (CM&S) technologies, including Artificial Intelligence,** for regulatory decision-making. In particular as a substitute for conventional evidence, across the entire lifecycle of medical devices. However, current MDR clause (*Annex VII, section 4.5.2*) restrict use of CM&S methodologies to preclinical evidence, which does not reflect the latest evolutions of the domain.

Before detailing this further (in section 3), we first present the state of play of CM&S methodologies. Briefly, through the long-term vision and support **of European Commission's policy initiatives (see section 5.3)** and US FDA's CM&S program[2], ***in silico* technologies have substantially advanced in the last decade** (see Section 5.4 for details). The CM&S methodologies continue to become versatile and contribute to the safe design, testing, pre-clinical, clinical or post-market investigations (see section 5.3). CM&S-generated evidence demonstrates the potential to reduce or augment traditional laboratory, animal, or clinical studies, through virtual representation of animal models, patients, cohorts, and populations, whereby they steadily de-risk biomedical products throughout their lifecycle[3] (For details, see *'Roadmap for in silico trials[4] (2016)'*). To keep this submission concise, Section 5.4 present a comprehensive overview of roadmaps, position papers, and peer-reviewed publications substantiating the aforementioned potential of computer modelling and simulation.

[2] US FDA - Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices - https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/credibility-computational-models-program-research-computational-models-and-simulation-associated

[3] T. Morrisson - In Silico Technologies: A Strategic Imperative for Accelerating Breakthroughs and Market Leadership for FDA-Regulated Products – Reagan-Udall Foundation - https://reaganudall.org/sites/default/files/2024-06/In%20Silico%20Technologies_final_0.pdf

[4] 2016: Avicenna Alliance Roadmap: Viceconti, Marco & Henney, Adriano & Morley-Fletcher, Edwin. (2016). *in silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. https://doi.org/10.13140/RG.2.1.2756.6164.

3 Consideration of computer modelling & simulation methodologies in the MDR

3.1 Legislation: observations and reasoning

Broadly, **the MDR does not exclude the use of evidence produced using computer modelling and simulation**, rather, they **explicitly reference it under Annex I and Annex VII of the legislation** (for extracts from MDR – see section 6). Likewise, reference of computer modelling can be noted in MDCG guidance document **MDCG-2024-10-**Orphan devices (for extracts from MDCG – see section 7).

Limit disparities amongst evidence bases

In practice, the implementation organisations (Medical Device Coordination groups, Notified bodies), (inadvertently) limit the medical device assessment based on **CM&S evidence, as non-clinical data for use in preclinical phase**. This undermines the true value of *in silico* technology to de-risk human testing, unnecessarily exposing research subjects. Moreover, it leads to reference of evidence from modelling and simulation to be of low-quality or merely restricted to replacement of animal experiments.

The dilemma of quantifying uncertainties

In this context, we as a scientific community seek to clarify that **traditional evidence sources (including animal and clinical data) are accepted, as they have a long history of use** and "real-world testing". Conversely, **uncertainties of traditional evidence are even difficult to quantify and map with clinical endpoints or population level outcomes, objectively**. Emerging digital evidence paradigms, on the other hand, offer the potential of extensively quantifying the predictive evidence that they generate. **Ironically, the objective quantification of uncertainty itself seems to contribute to regulators' hesitation to embrace digital evidence**. As a result, guidance documents and regulatory practitioners **continue to rank *in silico* evidence as non-clinical data, as compared to human clinical data**.

Impeding MDR clause and MDCG guidance

On contrary, restricting CM&S evidence to the preclinical phase, based on the MDR's reference to 'computer models' in **MDR Annex VII 4.5.4(e)** (see section 6.2), **undermines the full leverage of *in silico* technologies to de-risk medical device experimentation in humans**. This considerations has further been propagated to the MDCG guidance **MDCG -2024-10** (see section 7.1).

Our submission is that the governing actors, whether regulators or HTA organizations, do acknowledge the existing evidence gaps across all evidence sources, including those from human RCTs. This evidence conundrum is where **CM&S methodologies can complement and/or substitute one or multiple of the traditional models (bench, animal, human) across the entire lifecycle, rather than merely being restricted to the preclinical phase**.

Emerging needs – digital twins in healthcare

With advanced CM&S representations of human pathophysiology, one can simulate real-world clinical and post-market scenarios on personalised digital representations of organs, devices, and pathologies of individual patients. Thus **pave way to potentially reduce the risk of exposing humans to unsafe or unethical clinical investigations**, as well as capture adverse reactions ahead of time, saving lives, time, and money. Moreover, with the advent of CM&S powered **digital twins in healthcare**, multi-scale modelling of organs and human

pathophysiology are starting to emerge[5,6]. On this note, consider the EC's vision and policy initiatives to foster digital twins in healthcare through the **European Virtual Human Twin initiative**[7]. It is imperative that the MDR remains relevant to these new technologies. Crucially, anticipate and shape regulatory science such that MDR evaluation sets the direction to transform the current stagnation of regulatory pathways. Only then can **publicly funded European innovation reach patients**, which, in turn would **enhance the competitiveness of the EU healthcare sector.**

3.2 Governance: lack of progressive frameworks and guidance

Beyond the specific contentious references in MDR and emerging needs, the current regulatory landscape within the European Union also faces significant other practical governance challenges for the adoption of CM&S methodologies in medical device development. **Europe currently lacks ISO-IEC standards** (like ASME V&V40[8]), **CM&S guidance documents for medical devices** (like US FDA CM&S guidance[9,10]), and recognised regulatory programs (like FDA CM&S program[11]) for evaluating *in silico* methodologies, creating uncertainty for health technology developers and also challenging for Notified Bodies.

Notified Bodies under the oversight of National Competent Authorities (NCA), often limit their scope to explicit references within the EU-MDR[12] and Medical Device Coordination Group's (MDCG) guidance. While the MDCG has clarified the use of structured dialogue for pre-submission to reduce ambiguities for developers, **cautious approach among Notified Bodies in using structure dialogues for new methodologies like *in silico* technologies**[13], limit its effectiveness. Furthermore, as explained in previous section, existing guidance documents, such as **MDCG 2020-6[14] and MDCG 2024-10[15], either do not explicitly list modelling data as a valid data source or restrict its use to non-clinical evidence.**

[5] Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform. 2023 Oct 11;PP. doi: 10.1109/JBHI.2023.3323688

[6] HORIZON-HEALTH-2023-TOOL-05-03: Integrated, multi-scale computational models of patient patho-physiology ('virtual twins') for personalised disease management

[7] European Virtual Human Twin Initiative - The European Virtual Human Twins Initiative is an EU framework supporting the emergence and adoption of the next generation of virtual human twins solutions in health and care. https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins

[8] Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices V&V 40 – 2018. American Society of Mechanical Engineer ASME, 2018. 60p. ISBN: 9780791872048.

[9] 2023 -US FDA - Guidance for Industry and Food and Drug Administration Staff; Docket Number: FDA-2021-D-0980; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions

10 2016 - US FDA - Reporting of Computational Modeling Studies in Medical Device Submissions – Guidance FDA-2013-D-1530 - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/reporting-computational-modeling-studies-medical-device-submissions

[11] US FDA - Credibility of Computational Models Program: Research on Computational Models and Simulation Associated with Medical Devices - https://www.fda.gov/medical-devices/medical-device-regulatory-science-research-programs-conducted-osel/credibility-computational-models-program-research-computational-models-and-simulation-associated

[12] EU-MDR – Medical Device Regulation - Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, http://data.europa.eu/eli/reg/2017/745/oj

[13] A recent public webinar ('Structured Dialogue – How to Engage with Notified Bodies? – dt. 4 October, 2024 by RQM+') - with Notified Body representatives indicated that in silico trial evidence is considered an 'emerging technology' outside their current scope.

[14] MDCG 2020-6 (April 2020) – MDCG - Clinical evidence needed for medical devices previously CE marked under Directives 93/42/EEC or 90/385/EEC – lists a summary of considerations related to use of clinical and non-clinical data sources in Appendix II, which noticeably does not list modelling data, but even more indicates simulated user as not clinical data.

[15] 'MDCG 2024-10 (June 2024) - MDCG Guidance on Clinical Evaluation of orphan medical devices –– page 10 – 'Useful source of non-clinical data can include - Results of laboratory and animal tests; Data from computer modelling and simulated use testing, including software-based

The above constraints, coupled with a lack of visibility and acknowledgment of these critical implementation gaps related to MDR, significantly hinder the progression of *in silico* technology to be considered as a viable source of regulatory evidence for evaluating the safety and effectiveness of medical devices, in Europe.

3.3 Need for change

Wait-and-see approach amidst changing times

While the regulatory evidence gap and uncertainty of traditional evidence are typically acknowledged by regulatory and HTA decision-makers, they **have historically followed the "wait-and-see" doctrine, expecting "perfect evidence" to emerge over time**. While this approach is conceived in the best interest of public health and well-being, it is becoming increasingly impractical due to not only economic (increased costs) and time (for parallel evidence generation) constraints, but also its **detrimental impact on healthcare systems, the care provided to the patients and competitiveness of the EU medical innovation ecosystem.** This approach delays access to potentially safer medical products that could improve health and move us beyond simply treating diseases.

Another reason why the wait-and-see approach is unwise is that it relies on the presumption that the underlying healthcare provision models are and will remain stable in the near future. This is not the case, **due to the ageing of the EU population, and the associated growing demand for care; there is a desperate need to reduce the unit cost of care if we want to protect the universal healthcare model** that has historically contributed to the social justice model of the union. We need innovative medical products, and one effective way to achieve this is more "intelligent" pathways for regulatory derisking of medical products and more personalised provision of care. So there is no time to waste, **we need the type of innovation *In silico* Methodologies promises today, not tomorrow.**

4 Potential way forward

As the EU pharmaceutical strategy report highlights[16], today's reality is one of increasing health emergencies, including pandemics, anti-microbial resistance, and a barrage of comorbid chronic conditions. **Moving from "reactive" to "preventive" health systems**, offering more "health" than "care", and paving the way for "healthy ageing" are now indispensable, as outlined in the OECD-EU-Health at a Glance report 2024[17]. To achieve this vision**, recognising that digital evidence generated from computer (*in silico*) modelling and simulation, including AI predictors, has the potential to act as a replacement for traditional physical experiments is paramount**. Subsequently, accelerating the integration of computer modelling and simulation evidence can facilitate the technology developers to **generate evidence relevant to both regulatory evaluation on safety and efficacy and HTA's emphasis on relative effectiveness,** which are both critical to get the patient's safe and better cures.

This submission presents a few confounding factors (MDR clauses, MDCG guidance documents) and the needs of emerging technologies. These are conversational starters, while **we do anticipate broader questions,**

models, 3D printed models, and other physical models;…' citing Non-clinical data' is understood as any relevant data that does not meet the MDR definition of clinical data Per MDR Article 2(48)

[16] A pharmaceutical strategy for Europe, adopted 25, November 2020 - European Commission communication - https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52020DC0761

[17] OECD/European Commission (2024), Health at a Glance: Europe 2024: State of Health in the EU Cycle, OECD Publishing, Paris, https://doi.org/10.1787/b3704e14-en

detailed deliberations, and constructive discussions related to the consideration of *in silico* evidence, within the oversight of MDR. The aforementioned considerations serve only to draw your attention and to initiate dialogue regarding the gaps and challenges, which need critical consideration during the evaluation of the MDR. On this note, we have already identified additional MDR clauses, articles, definitions that needs consistent reference to CM&S in the entire regulatory process. Such amendments are need of the hour to streamline the admission of *in silico* evidence into regulatory pathways.

While we seek changes, we do fully acknowledge the need for caution and careful consideration of the implications. We look forward to constructive engagement with stakeholder groups, to present evidence, address concerns and support the EC's collaborative efforts, during the consultation process. Our learned academic colleagues look forward to share our academic stakeholder-informed insight and learnings from numerous EC-funded policy initiatives, Research & Innovation projects, stakeholder engagement, ecosystem activities, CSA actions and peer-reviewed scientific evidence, and stand ready to leverage CM&S technology as an enabler to mitigate the overarching challenges addressed in this MDR evaluation process.

Annex

5 Annex 1 - Potential of computer (*in silico*) modelling & simulation

5.1 Definitions

In silico, a term widely recognized in mission-critical sectors like aerospace, automotive, manufacturing, climate modelling and healthcare, involves creating **digital representations of physical objects, processes, or situations,** in order to analyse and predict their behaviour in real-world settings.

- The term *"in silico"* here refers to the digital representation ('computer model') and experimentation ('simulation') of biological systems in computers. This is analogous to the physical studies that use benchtop models (*"in vitro") or* living organisms/animals/humans (*"in vivo"*) or *"ex vivo"* methodologies conducted outside the living organism.
- The field of ***In silico Medicine*** more broadly encompasses the use of ***in silico*** **technologies within the entire healthcare continuum,** starting with understanding the (patho-) physiology and disease mechanisms of biological systems and including all aspects of prevention, diagnosis, follow-up, prognostic assessment and treatment of patients, as well as derisking development and evaluation of biomedical products.
- The underlying ***In silico Medicine*** **methodologies** help create *in silico* models using computer modelling and simulation (CM&S) techniques, including Artificial intelligence. The *in silico* models replicate real-world phenomena or systems by creating **digital representations of physical objects, processes, or situations** to analyse and predict their behaviour. *In silico* models can be built based on their reliance on data and prior knowledge. Since most computational models require a combination of both, they exist on a spectrum. At one end lie **purely phenomenological or data-driven models, like AI**, which rely on the availability of high-volume, high-quality datasets. On the other hand are **knowledge-driven models, such as physics-based or mechanistic models,** primarily built on established scientific principles and expert knowledge[18,19].

5.2 Background & relevance to medical device regulation

Briefly, computer (*in silico*) modelling and simulation (CM&S) methodologies can be used throughout the entire lifecycle of medical products, be it for design, development, testing, assessment or post-market surveillance. Likewise, *in silico* methodologies may reduce, refine or replace diverse evidence sources, be it biophysical test, simulated tests, animal test as well as human testing. These CM&S technologies continue to advance and establish themselves **from being research methods to regulatory science tools**, thus becoming versatile for use in design, testing, pre-clinical, clinical or post-market phases.

[18] Viceconti M, Juarez MA, Curreli C, Pennisi M, Russo G, Pappalardo F. Credibility of *In silico* Trial Technologies-A Theoretical Framing. *IEEE J Biomed Health Inform*. 2020;24(1):4-13. doi:10.1109/JBHI.2019.2949888
[19] Viceconti M, De Vos M, Mellone S, Geris L. Position paper From the digital twins in healthcare to the Virtual Human Twin: a moon-shot project for digital health research. IEEE J Biomed Health Inform. 2023 Oct 11;PP. doi: 10.1109/JBHI.2023.3323688

Though limited, the use of computer modelling and simulation in healthcare products have historic precedence. For example, CM&S methodologies already function as CE approved standalone medical device[20,21,22,23]. Likewise, they are also being considered for 'Qualification as drug-development tools', by European Medicines Agency, for use in clinical trial design, patient stratification, paediatric dose determination etc[24,25].

CM&S methodologies are used in the pre-regulatory phase, to reduce, refine or replace bench or animal tests for medical products (medicines, devices), in Europe. In addition, virtual human subject based on CM&S models have been used to conduct safety testing of imaging systems (e.g. MRI 7 Tesla scanner). Regulatory approval based on *in silico* modelling has allowed the approval of cardiac pacemaker leads compatible with MRI scanners, thereby safeguarding human exposure[26]. In such cases, CM&S evidence has helped avoid long and large clinical investigations, while still yielding safe and early access of innovative technology to patients[27,28].

5.3 Policy initiatives supporting the advancement of CM&S for regulatory process

Research efforts, funding opportunities, and collaboration between different organisations have propelled the growth of *in silico* trials. The European Commission (EC) continues to support *in silico* trials with programs like Horizon 2020, Horizon Europe and Digital Europe. These programs fund research in areas including:

- *In silico* trials for developing and assessing biomedical products[29], leading to projects[30]
- Accelerating the uptake of computer simulations for testing medicines and medical devices[31], leading to several EU-funded projects, including *In silico* World[32], SIMcor[33] and SimCardioTest[34], in which VPH Institute has been part of and played the ecosystem organisation role.

[20] Diabeloop DBLG1 - a self-learning algorithm that automates and personalizes the treatment of Type 1 diabetes - https://www.diabeloop.com/
[21] HeartFlow (U.S.A) - HeartFlow FFRCT - Fractional Flow Reserve CT Analysis - for evaluating and managing coronary artery disease - https://www.heartflow.com/heartflow-ffrct-analysis/
[22] inHeart™ (France) - inHEART deliver AI-enabled, digital twin of the heart to advance the care of patients living with cardiac disease. The digital twin of the heart for image guided ablations - https://www.inheartmedical.com/
[23] FeOps HeartGuide (Belgium) - FEops is a recognized pioneer in the field of physics-based simulations for minimally invasive cardiovascular devices and procedures. https://www.feops.com/product/healthcare-professionals
[24] EMA Qualification opinion for Prognostic Covariate Adjustment (PROCOVA) - 2022 https://www.ema.europa.eu/en/human-regulatory-overview/research-development/scientific-advice-protocol-assistance/opinions-letters-support-qualification-novel-methodologies-medicine-development#prognostic-covariate-adjustment-procova-8081
[25] EMA Letter of support for Universal Immune System Simulator – Tuberculosis disease model - https://www.ema.europa.eu/en/documents/other/letter-support-universal-immune-system-simulator-tuberculosis-disease-model-uiss-tb-dr_en.pdf
[26] FDA - MDDT Summary of evidence and basis of qualification decision for Virtual MRI Safety Evaluations of Medical Devices - 2021 - https://www.fda.gov/media/154181/download?attachment
[27] VICTRE: *In silico* Breast Imaging Pipeline - The regulatory science tool is a set of computer models that allow for the generation of *in silico* breast radiographic images for the evaluation of digital mammography (DM) and digital breast tomosynthesis (DBT) devices. Accessed via: https://cdrh-rst.fda.gov/victre-silico-breast-imaging-pipeline
[28] Sharma D, Graff CG, Badal A, Zeng R, Sawant P, Sengupta A, Dahal E, Badano A. Technical Note: *In silico* imaging tools from the VICTRE clinical trial. Med Phys. 2019 Sep;46(9):3924-3928. doi: 10.1002/mp.13674. Epub 2019 Jul 17. PMID: 31228352
[29] H2020 – 2016-17 - In-silico trials for developing and assessing biomedical products - https://cordis.europa.eu/programme/id/H2020_SC1-PM-16-2017
[30] STriTuVaD In Silico Trial for Tuberculosis Vaccine Development, INSIST IN-Silico trials for treatment of acute Ischemic STroke,
[31] H2020 -2020 - Accelerating the uptake of computer simulations for testing medicines and medical devices - https://cordis.europa.eu/programme/id/H2020_SC1-DTH-06-2020
[32] https://insilico.world/
[33] https://www.simcor-h2020.eu/
[34] https://www.simcardiotest.eu/wordpress/

- Developing an ecosystem for digital twins in healthcare[35].
- Personalised disease prediction and management using computational models[36].

5.4 Scientific evidence supporting the use of CM&S in regulatory pathway

Building upon years of dedicated efforts by the *In silico* Medicine community to overcome barriers to the widespread adoption of *in silico* methodologies, the members of the VPH scientific society have published a series of comprehensive position papers in recent years, including: *'Roadmap for in silico trials[37] (2016)', 'Concept and early adoption of in silico trials[38] (2018)', 'Regulatory pathway of in silico methods for medicinal products[39,40] (2020)', 'Possible Contexts of Use for In silico trials[41] (2021)', 'Regulatory pathway for devices[42] (2022)', and a most recent one (November 2024) titled 'Advancing In silico Clinical Trials for Regulatory Adoption (2024)[43]*'. Finally, a "moonshot vision" paper was published in 2024, summarising decades of achievements and outlining the path forward[44], alongside a open-access community-driven Good Simulation Practise book[45,46].

Successful use of *in silico* modelling in regulatory assessment:

In the light of ageing and comorbid population, CM&S technology facilitated safe-testing and faster- access to new generation of MRI-compatible pacemaker[47]. This enabled reduce costs, reliable regulatory decision, leading to early-access of life-saving MRI scans for patients with pacemaker[48].
Key benefits through in silico solution facilitated[49]:

- 2 years – The product was released 2 years earlier.
- 256 – reduction in the number of patients involved in the clinical trials.
- $10 million – cost reduction due to the reduced number of patients

[35] DIGITAL -2021 - An ecosystem for digital twins in healthcare - https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/digital-2021-deploy-01-twins-health
[36] Horizon -2023 - Integrated, multi-scale computational models of patient patho-physiology ('virtual twins') for personalised disease management - https://ec.europa.eu/info/funding-tenders/opportunities/portal/screen/opportunities/topic-details/horizon-hlth-2023-tool-05-03
[37] 2016: Avicenna Alliance Roadmap: Viceconti, Marco & Henney, Adriano & Morley-Fletcher, Edwin. (2016). *in silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. https://doi.org/10.13140/RG.2.1.2756.6164.
[38] 2018: Francesco Pappalardo, Giulia Russo, Flora Musuamba Tshinanu, Marco Viceconti, *In silico* clinical trials: concepts and early adoptions, *Briefings in Bioinformatics*, Volume 20, Issue 5, September 2019, Pages 1699–1708, https://doi.org/10.1093/bib/bby043
[39] Musuamba Tshinanu, F., Bursi, R., Manolis, E., Karlsson, K., Kulesza, A., Courcelles, E., Boissel, J. P., Lesage, R., Crozatier, C., Voisin, E. M., Rousseau, C. F., Marchal, T., Alessandrello, R., & Geris, L. (2020). Verifying and Validating Quantitative Systems Pharmacology and *In silico* Models in Drug Development: Current Needs, Gaps, and Challenges. *CPT: Pharmacometrics and Systems Pharmacology*, *9*(4), 195-197. https://doi.org/10.1002/psp4.12504
[40] Musuamba FT, Skottheim, Rusten I, Lesage R, et al. Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:804–825. https://doi.org/10.1002/psp4.12669
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[45] Viceconti, M., Luca, & Editors, E. (n.d.). Synthesis Lectures on Biomedical Engineering Toward Good Simulation Practice Best Practices for the Use of Computational Modelling and Simulation in the Regulatory Process of Biomedical Products.
[46] Viceconti, M. *In silico* World Online Community of Practice and GSP Consensus. Zenodo, 23 Dec. 2024, doi:10.5281/zenodo.14548377.
[47] Safe magnetic resonance imaging scanning of patients with cardiac rhythm devices: A role for computer modeling Wilkoff, Bruce L. et al. Heart Rhythm, Volume 10, Issue 12, 1815 - 1821
[48] https://www.dicardiology.com/product/medtronic-gets-ce-mark-mri-compatible-pacemaker
[49] https://www.avicenna-alliance.com/application-brief/in-silico-trials.html

- 10000 patients – number of patients treated during these two years with the product.

Roadmap and position papers, from academics and regulators are summarised below:

1. Avicenna Alliance Roadmap: Viceconti, Marco & Henney, Adriano & Morley-Fletcher, Edwin. (2016). *in silico* Clinical Trials: How Computer Simulation will Transform the Biomedical Industry. https://doi.org/10.13140/RG.2.1.2756.6164.
2. Viceconti, M. Cobelli, C., Haddad, T. et al. (2017) *In silico* assessment of biomedical products: the conundrum of rare but not so rare events in two case studies. Proceedings of the Institution of Mechanical Engineers. Part H: Journal of Engineering in Medicine, 231 (5). pp. 455-466
3. Sharma D, Graff CG, Badal A, Zeng R, Sawant P, Sengupta A, Dahal E, Badano A. Technical Note: *In silico* imaging tools from the VICTRE clinical trial. Med Phys. 2019 Sep;46(9):3924-3928. doi: 10.1002/mp.13674. Epub 2019 Jul 17. PMID: 31228352
4. Pappalardo F, Wilkinson J, Busquet F, et al. Toward A Regulatory Pathway for the Use of *in silico* Trials in the CE Marking of Medical Devices. *IEEE J Biomed Health Inform*. 2022;26(11):5282-5286. doi:10.1109/JBHI.2022.3198145
5. Lesage R, Van Oudheusden M, Schievano S, Van Hoyweghen I, Geris L, Capelli C. Mapping the use of computational modelling and simulation in clinics: A survey. Front Med Technol. 2023 Apr 17;5:1125524. doi: 10.3389/fmedt.2023.1125524.
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7. Favre P, Bischoff J. Identifying the patient harms to include in an *in silico* clinical trial. Comput Methods Programs Biomed. 2023 Nov;241:107735. doi: 10.1016/j.cmpb.2023.107735.
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9. Elhadj, E., Van Horenbeeck, Z., Lievevrouw, E., & Van Hoyweghen, I. (2024) Brokering responsible research and innovation in in silico medicine, Journal of Responsible Innovation, 11:1, DOI: 10.1080/23299460.2024.2414484
10. Alessandra Aldieri, Thiranja Prasad Babarenda Gamage, Antonino Amedeo La Mattina, Axel Loewe, Francesco Pappalardo, Marco Viceconti, Consensus statement on the credibility assessment of machine learning predictors, *Briefings in Bioinformatics*, Volume 26, Issue 2, March 2025, bbaf100, https://doi.org/10.1093/bib/bbaf100
11. Faris, Owen, and Jeffrey Shuren. "An FDA Viewpoint on Unique Considerations for Medical-Device Clinical Trials." The New England journal of medicine vol. 376,14 (2017): 1350-1357. doi:10.1056/NEJMra1512592
12. Morrison TM, Pathmanathan P, Adwan M and Margerrison E (2018) Advancing Regulatory Science With Computational Modeling for Medical Devices at the FDA's Office of Science and Engineering Laboratories. Front. Med. 5:241.doi: 10.3389/fmed.2018.00241
13. US FDA - Guidance for Industry and Food and Drug Administration Staff; Docket Number: FDA-2021-D-0980; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-credibility-computational-modeling-and-simulation-medical-device-submissions
14. T. Morrisson - In Silico Technologies: A Strategic Imperative for Accelerating Breakthroughs and Market Leadership for FDA-Regulated Products – Reagan-Udall Foundation - https://reaganudall.org/sites/default/files/2024-06/In%20Silico%20Technologies_final_0.pdf
15. Pathmanathan, Pras et al. "Credibility assessment of in silico clinical trials for medical devices." *PLoS computational biology* vol. 20,8 e1012289. 8 Aug. 2024, doi:10.1371/journal.pcbi.1012289
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6 Annex 2 – Reference of computer modelling in MDR

6.1 Annex I – GSPR chapter II – Design and manufacture - Item 10.1 (e)

- "where appropriate, the **results of biophysical or modelling research** the validity of which has been demonstrated beforehand;"

Observation: MDR allows consideration of biophysical or modelling evidence in relation to the device requirements regarding design and manufacture, is enshrined in MDR[50].

6.2 Annex VII – Conformity assessment activities for Notified Bodies – section 4.5

- Section 4.5.4: "The notified body shall examine, validate and verify that the manufacturer's procedures and documentation adequately address:
  (a) the planning, conduct, assessment, reporting and, where appropriate, updating of the pre-clinical evaluation, in particular of
  — the scientific pre-clinical literature search, and
  — the pre-clinical testing, for example laboratory testing, simulated use testing, **computer modelling**, the use of animal models,"

Observation: Consideration of evidence from "computer modelling", while assessing pre-clinical evaluations submitted by manufacturer, is enshrined in MDR[42].

7 Annex 3 – Reference of computer modelling in MDCG guidance

7.1 MDCG 2024-10 Clinical evaluation of orphan medical devices - June 2024

"Under Part A clinical evaluation considerations - Section 6: The role of non-clinical data

- Useful sources of non-clinical data can include:
  - Results of laboratory and animal tests;
  - **Data from computer modelling and simulated use testing, including software-based models**, 3D printed models, and other physical models;
  - Data from ex vivo studies and cadaveric studies;
  - …"

Observation: Consideration of evidence from "computer modelling", as part of non-clinical data[42].

[50] Pappalardo F, Wilkinson J, Busquet F, et al. Toward A Regulatory Pathway for the Use of *in silico* Trials in the CE Marking of Medical Devices. *IEEE J Biomed Health Inform*. 2022;26(11):5282-5286. doi:10.1109/JBHI.2022.3198145