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Request for Information on the National Digital Twins R&D Strategic Plan

Center for Virtual Imaging Trials, Duke University

Future of Digital Twins and *In Silico* Trials in Medicine

Response to the National Academies report: National Digital Twins R&D Strategic Plan

Comments from Center for Virtual Imaging Trials, Duke University[1]

We have reviewed the National Academies report on Digital Twins with great interest and commend the committee for developing this comprehensive and invaluable document. The report effectively outlines foundational research gaps and future directions for digital twins across various domains, addresses practical concerns, and provides recommendations for program development and cross-agency collaboration. We believe that this document offers a thorough roadmap for advancing digital twin technology, enhancing scientific research, and industrial applications. We would like to share some complementary thoughts that may be considered for the Research & Development Strategic Plan in the context of biomedical sciences.

Moonshot for the future of digital twins and *in silico* trials in medicine

We believe that a strategic plan needs a "moonshot" goal, with identified gaps and prioritized areas. In April 2024, the Virtual Imaging Trials in Medicine (VITM) Summit at Duke University hosted a roundtable where thought leaders, developers, and regulators from academia, industry, government, and funding agencies gathered to chart a path forward for use of digital twins and *in silico* trials in medicine. The roundtable included leaders from the NIH, FDA, congressional offices, and leading experts of *in silico* methods. A white paper reflection of this roundtable is currently under peer review. The roundtable participants reached a consensus on an ambitious goal to drive the future of digital twins in medicine:

> ***Form and foster a digital twin of every individual, integrated into their medical record, owned by them, and continuously updated with new data. This twin will be used to deliver optimized personal care and, with the individual's permission, for technology assessment, real-world evidence, and population aggregate analysis.***

This moonshot envisions a future where every person has a digital twin that evolves over time, becoming more personalized with the integration of new data. This approach promises to revolutionize personal care across various medical priorities and conditions, including cancer, cardiovascular disease, diabetes, geriatrics, and obesity.

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Achieving this moonshot requires overcoming several critical gaps and obstacles identified during the discussions:

- Data access and privacy: Ensuring data accessibility while maintaining privacy and security, establishing an economical framework for data access and sharing, and emphasizing patient engagement in data sharing.
- Harmonization and standardization: Creating standardized resources and protocols.
- Educational and training gaps: Addressing educational deficits and skilled expertise in digital twin technologies, ensuring physicians have access to necessary technology, and providing more training to understand and use resources.
- Clarity of scope: Clarifying the complementary roles of regulators, industry, and academia.

These gaps are well articulated in the current National Academies report. Additionally, our roundtable discussions recognized two critical gaps when digital twins are used in biomedical applications:

- Individualized patient access and health equity: Tailoring access to technology for individual patients and ensuring equitable access for all, recognizing the willingness of individuals to share information if managed well.
- Regulation and reimbursement: Securing reimbursement from insurance companies, overcoming regulatory hurdles, and ensuring strong engagement of biomedical engineers at the Food and Drug Administration.

As rightfully mentioned in the National Academy report, "publicity around digital twins and digital twin solutions currently outweighs the evidence base of success." We agree with this sentiment and believe that priorities are needed to ensure credible advancement. Towards this, the VITM roundtable emphasized the need for national and global collaboration. Establishing a digital Contract Research Organization (CRO) framework is suggested to foster systematic trial development and build trust and awareness through transparent communication and early discussions. Additional advancement might be energized by

- Advocating with funding agencies
- Forming multi-disciplinary teams and initiating a regulatory science collaborative community
- Identifying and engaging standards communities for interoperability
- Harmonizing efforts across regulators and academics to devise good simulation practices
- Engaging the industry through regulatory affairs

We are pleased to see that the National Academy report has highlighted several of these priorities. An additional key priority recognized by us is:

- Engaging with patients and patient advocacy communities

We believe that patient engagement is crucial to ensure trust and their benefits since patient benefit and care is the ultimate goal in medicine. Advocacy communities are also needed to

ensure that patients have proper ownership of their digital twins, integrating them into their medical records, and updating them continuously with new data.

Four key priority area

In advancing the cause and potential of digital twins in medicine, the VITM summit further discussed and details four specific priority areas that we suggest to be incorporated in the deliberations of the National Digital Twins R&D Strategic Plans:

Real plus Virtual: Maximizing the complementary role of clinical and in-silico methods in medical evaluation

Proficient and efficient evaluation of medical products is a crucial need in medicine. The requisite proficiency and efficiency can be enabled by integration of diverse clinical trial methodologies, focusing on optimizing the complementary aspects of real and virtual methods. Common among all types of trials is the need and challenge of ensuring the diversity of studied population, addressing the needs of rare diseases focus, complexity of the research design and avoidance of bias, managing the open-source vs. proprietary nature of some tools, and lack of broad standards for trial design and execution. Within this landscape, real, virtual, and hybrid clinical trials, offer comparable advantages and disadvantages:

Real Clinical Studies:

- Advantages are well-detailed, reflecting standard clinical practices and educational alignment, and definitive clinical endpoints.
- Disadvantages accurately highlight the slow, costly nature and large sample size requirements.

Virtual/In-silico Clinical Studies:

- Advantages include subject safety (e.g., no radiation exposure), long-term monitoring, rare disease study capabilities, testing of new concepts, reduction in animal testing, and providing quantitative endpoints.
- Disadvantages include needed validation for realism and credibility, as well as ease of implementation by users.

Hybrid Studies:

- Advantages includes potential balance between efficiency (of virtual) and accuracy (of clinical) methods.
- Disadvantages include certainty re the best integration strategy.

A key consideration for incorporating a virtual approach as a trial tool is its level of reliability and trustworthiness. These can be enhanced by combining the virtual approach with complementary physics experiments. This aligns with the need for quality metrics that closely reflect clinical outcomes, and in the same vein, clinical outcomes that should be expected and meaningful for virtual trials. Such goals, while worthwhile, are not absolute: striving for perfection can be counterproductive, as perfect is often the enemy of good.

Towards that goal, the FDA has recognized virtual diagnostic imaging tools as Medical Device Development Tools (MDDTs) in the Non-clinical Assessment Model category, indicating their acceptance for non-clinical evaluations of medical devices [1]. Future strategies should facilitate

uniform testing across imaging modalities and realistically optimize associated parameters through simulations followed by clinical validation. In that effort, the focus should extend from specific parameters to quantitative biomarkers to understand how simulation processes and accuracy impact imaging endpoints. Imaging and clinical and endpoints are certainly not necessarily identical either. They are distinct measures in medical research, each providing different information about treatment efficacy and patient outcomes. Understanding these distinctions is crucial for ensuring that research findings are relevant and applicable to broad patient populations.

Physics plus Biology: The intersection of physical and biological simulations impacts our understanding of metabolism, treatment, and disease progression

Real trials involve the entire complexity of reality, but they can only reveal a part of it due to practical limitations. Simulations focus on a limited aspect of reality, but within that scope, they can offer complete and detailed insights. These distinctions are important for understanding the strengths and limitations of different research approaches and methodologies.

Physics and biology take different approaches to simulation, each of which with their own assets and limits. Physical models tend to be more straightforward as physical approaches often involves well-defined laws and equations that can predict outcomes with high precision. In contrast, modeling biological systems is much more complex due to their high variability, numerous interacting components (genes, proteins, cells, etc.), and the influence of countless internal and external factors. This complexity makes it challenging to create simple models in biology such that they are accurate and predictive. However, this task can be a bit more manageable when the variabilities are captured for individual patients, as opposed to aggregates across patients which introduce additional sources of variability.

Utilizing digital twins to tailor treatments to the unique characteristics and requirements of an individual is an additional consideration. While clinical trials typically address the general population, evaluating utility across a population might disregard individual experiences. An “average” patient represents no single individual within a cohort of individuals. Consequently, although trials provide insights into broader trends for a given technology or intervention across a population, they naturally fall short of fully capturing what might be optimum for an individual patient.

Looking ahead, therapy and healthcare are becoming more personalized and responsive. Concepts like prospective adaptive therapy and response prediction are driving this shift. Additionally, individualized surveillance decisions are seeking to ensure monitoring strategies are customized for each person. These advancements promise more effective and precise care, better meeting the diverse needs of patients in the future. Towards that goal, there is need for the integration of physics- and biology-based models, as they not only invoke complementary mindsets, but together cover a broader swat of physical reality and offer different dimensions of phenotypes that are instrumental to personalized care.

Of course, as in any modeling effort, isolated or integrated, there is a need for a structured approach to validation of the models and processes. As integrated models are particularly complex, validation should begin with simpler, more fundamental aspects and progressively move to more complex and advanced components. This progressive approach ensures that each level of complexity is thoroughly tested and verified before moving on to the next, more

advanced level. This approach helps ensure that each stage is solidly built upon a verified foundation, reducing the risk of overlooking critical issues as complexity increases.

Virtual meets Diversity: Strategies to generate digital patient representations with enhanced diversity

Representing diversity is a key requirement of any clinical trial – recognizing that evaluation, claims, or solutions are only valid if generalized across a population. This need for diversity is also applicable to practitioners of medical interventions including image interpreters. While current imaging practice often assumes an "average" interpreter or observer, no single observer represents such a hypothetical average interpreter. Thus, there is a need to include diverse observers and incorporating their variability, which can be dataset-dependent, to assure generalizability.

This highlights the significance of virtual trials incorporating diversity in their constructs. In representing diversity, virtual trials provide unique opportunities. Virtual trials offer the capacity to represent a diverse patient population with fewer virtual patients compared to physical clinical trials. Instead of replicating the sampling of the data of clinical trials, the virtual trial can deploy differing distribution of configurations, including both uniform and skewed sampling towards "edge" cases, thus enabling a simpler and targeted trial design. An illustrative application of diversity in virtual trials involves simulating rare diseases across diverse patient cohorts to clarify disease responses and evaluate simulation boundaries. In the trial design for rare diseases where large-scale trials are impractical, Bayesian approaches are particularly beneficial. Such designs can provide evidence of efficacy and safety by integrating virtual and real data.

Recognizing the importance of diversity in trials highlights the need to create a "science of diversity" to understand the complex factors that influence imaging examinations and trial outcomes. Often diversity is targeted by using large datasets, assuming that higher numbers translate to higher diversity. Typically, diversity is characterized by generic attributes such as age, sex, race, etc. However, these broad representations rarely capture all attributes that influence the outcome. There is a need for a systematic of diversity at multiple scales. Virtual trials offer a controlled way to do so, with its inherent unique advantage of defining and controlling for the ground truth of the subjects and the interventions. Such a control also offers an opportunity to consider matching the data and interpretations so as to optimize or fine-tune the intervention for specific subpopulations. This is a unique asset to balance generalizability (ensured by population statistics) with personalized care, recognizing that while models must account for diverse populations, individual patient needs should not be overlooked.

Addressing diversity gaps in clinical trials requires a multi-layered approach. Options include generating numerous digital phantoms based on real data, manual modifications using 3D modeling, leveraging deep learning methods such as generative AI, and exploring other strategies. While digital phantoms offer flexibility in simulating diverse scenarios, they may still follow a distribution, limiting their effectiveness in truly addressing diversity. However, incorporating interpolation techniques can mitigate this limitation. Diversity in virtual trials is also crucial when dealing with underrepresented groups or when real data collection is challenging. It is essential to recognize biases and actively pursue inclusivity in trial design and data representation, ensuring that virtual trials reflect the diverse global population accurately.

Virtual meets Reality: Overcoming barriers to accessibility and widespread implementation

To take advantage of what virtual trials can offer, we need to have reliable and easy to use tools and resources. These resources are currently not where they need to be. There are various challenges and opportunities towards such readiness and confidence. Those includes factors related to the validation and realism of simulation methods, as well as transparency associated with 'black box' AI systems. There is a significant need for openness, transparency, and collaboration to address these challenges and fully capitalize on the opportunities within medical imaging research to synergistically integrate experimental and modeling aspects to enhance healthcare outcomes.

This level of confidence is essential, especially when virtual trials are planned to address the needs in regulatory science. The regulatory evidence has a pivotal role as the cornerstone of scientific validation, going towards controlled trials, prioritizing simulation to adhere to the principle of "first do no harm". In that regard, we emphasize the distinctions and interconnections between basic science, regulatory science, and translational science in the development and evaluation of products, post-market surveillance, and public health preparedness through multiple programs include the Centers of Excellence in Regulatory Science and Innovation (CERSI) program [2]. Pertinent to virtual trials is the establishment of Good Simulation Practices (GSP), which build upon other established Good Practices, setting the level of needed details and credibility assessment guidelines [3].

In terms of availability of tools and resources, current offerings range from independently developed tools to FDA-provided and FDA-approved programs [4-7]. Those include Monte Carlo packages like PENELOPE [8] and GEANT4 [9], demonstrating a balance between open-source software and self-developed technologies. Key factors to consider include accessibility, quality, and regulatory compliance. There is a dynamic tension between making open-source software widely accessible, ensuring high quality, and meeting regulatory requirements. Balancing these factors is challenging because increasing one aspect (e.g., accessibility) might impact the others (e.g., quality or regulatory compliance).

Currently, there exists a prevalent uncertainty within the community regarding the reliability of virtual imaging trials which underscores the need for improvement in robust validation of simulation technologies. Further, there is a deficiency in the lack of crucial biological data which hinders the accuracy and reliability of virtual trials, contributing to widespread skepticism regarding their predictive capabilities. To build trustworthiness encompassing credibility, reproducibility, and accessibility, it is essential to address these data gaps, thereby enhancing the validity of virtual trials and fostering greater confidence in their outcomes. Towards that goal, several actions may be considered:

- Developing a quality for the quality of simulation studies, similar to the AAPM Task Group 268 report [10].
- Consider establishing certification standards or good simulation practices to increase trust in *in silico* results submitted for regulatory review.
- Explore a neutral third-party validation mechanism to validate proprietary simulation aspects from manufacturers, ensuring protection of intellectual property while encouraging collaboration.
- Requiring manufacturers to provide research access to reconstruction algorithms and data through contractual agreements or incentives from regulators.

- Continuously monitor clinical reports for changes in disease detection correlated with imaging protocols to help validate virtual results.
- Establish a community of stakeholders (e.g., The Regulatory Science In-Silico X Collaborator Community – ISXCC) to coordinate and facilitate efforts across stakeholders.
- Clarify designations and terminology within this space, which can offer consistent and clear definition of terms such as digital twins, in-silico, and virtual.
- Develop stages for granularity and quality of digital data.
- Ensure the context of use for an in-silico tool is always noted to ensure relevance to regulatory practices and beyond.

By implementing these action items, the medical imaging community can improve the credibility, reproducibility, and accessibility of virtual trials, thereby enhancing their overall trustworthiness and effectiveness. Equally important is the need to effectively incorporate patient perspectives into the prospects of using virtual trials for evidence generation including AI-driven medical research. Patients are the ultimate recipient of the "good" that virtual trials would offer and thus their voice and agency should be respected.

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