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

UNLEARN

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Comment on "Networking and Information Technology Research and Development Request for Information on Digital Twins Research and Development" [Document No. 2024-13379]

Date:

July 24, 2024

By Electronic Delivery To:

Attn: Melissa Cornelius

[redacted]

[redacted]

To Whom It May Concern:

Unlearn.AI, Inc. (Unlearn) is submitting these comments in response to the June 18, 2024 Networking and Information Technology Research and Development (NITRD) Request for Information on Digital Twins Research and Development (R&D).

Unlearn is innovating advanced machine learning methods to leverage generative artificial intelligence (AI) in forecasting patient health outcomes, starting with the domain of randomized clinical trials. We produce a distribution of longitudinal forecasts for individual trial participants (i.e., their "digital twins"), enabling smaller and more efficient clinical trials to bring effective medicines to patients sooner.

We appreciate that the NITRD National Coordination Office (NCO), National Science Foundation is seeking information to assist in creating a National Digital Twins R&D Strategic Plan. In order to better understand how this document can serve as a national guide for government investments in digital twin research, it is important to align on a standard definition for "digital twin" and develop a shared vocabulary among stakeholders. This will promote a mutual understanding that facilitates collaboration rather than impeding innovation.

We believe that the definition of "digital twin" provided in The National Academies report is broad enough to encompass a variety of applications while also highlighting the term's key characteristics: digital twins 1) have predictive capabilities and 2) are bidirectionally interactive with their physical counterpart.[1] In the field of clinical trials and/or healthcare, a patient's digital twin can be defined as a virtual representation of that individual, typically built from physical theory, multimodal patient data, population data, and/or real-time updates on patient and environmental variables.[2] As stakeholders begin to rapidly develop their own field-specific terminology, it is clear that there also needs to be alignment on the methods used to evaluate digital twin models.

The digital twin's intended context of use is critical to determining the risk level associated with using the model. For this reason, it is imperative that these models are evaluated in a sector-specific manner, by experts in the field, rather than being subjected to sweeping federal regulations. Allocating federal funds to support the review of these technologies by the field's appropriate regulatory agency would accelerate the adoption of digital twin models to address national priorities and expedite agency missions.

Artificial Intelligence (AI): While there are many types of models that can successfully create digital twins of inanimate objects or processes, AI systems are especially suited for modeling the complexity of the human body. Deep learning models are able to take in vast amounts of data, learn from the relationships among variables, and become more precise in their predictions over time. Because of this, AI-generated digital twins of patients have immense potential for solving problems in healthcare that typically require months or even years of trial and error. We define an AI-generated digital twin of a patient as a virtual representation of that patient, created by modern AI methods applied to large clinical datasets, from which predicted trajectories that are statistically indistinguishable from the patient's real data can be generated.[3]

Data: The AICPA Trust Services Criteria[4] and the 2013 COSO Framework[5] have established data privacy and security trust criteria guidelines that can be utilized by stakeholders to encourage proper data management. These frameworks require companies to show that they have acceptable internal and external data protections, which include using secure servers, encryption techniques, access controls, and authentication mechanisms to safeguard stored data against unauthorized access, breaches, and cyber threats. This also includes using cloud computing and secure communication protocols, such as Secure Sockets Layer (SSL) or Transport Layer Security (TSL), for data transmission. In addition, employee training is required to ensure the efficacy of the appropriate structural controls.

Regulatory: The National Academies report recommends that federal agencies should "identify targeted areas relevant to their individual or collective missions where collaboration with industry would advance research and translation" (p. 120).[1] While we agree with this sentiment, the report lists the National Institutes of Health (NIH) as the federal agency for *in silico* drug discovery and clinical trials rather than the Food and Drug Administration (FDA). We endorse the FDA as the agency responsible for the review and regulation of AI technologies used in drug development, including digital twin models. The FDA released a discussion paper and request for comment in 2023 titled, *Using Artificial Intelligence and Machine Learning in the Development of Drug and Biological Products* that provides an overview of how digital twins can be used to make clinical research more efficient.[6] This discussion paper provides an introductory example of how regulatory frameworks should provide sector-specific guidance on the acceptable use of digital twin models according to the risk level associated with the context of use.

Standards and Trustworthiness: The following are practices currently used by Unlearn in model development and implementation to maintain standards and enhance trustworthiness:

- Description of the generative AI model, including summaries of the underlying architecture, data sourced, and training and validation procedures
- Analysis of model performance in a population similar to that of the planned trial
- Documented SOPs and controls
- Pre-specification of version-controlled model in Statistical Analysis Plan (SAP)

- Controlled and monitored secure cloud computing environment with automated version control, metadata, and audit trail
- Methods for probing model explainability include input sensitivity (measure of how much a given performance metric changes when a given feature is masked from input data) and SHAP (SHapley Additive exPlanations, which show how each feature contributes to individual predictions, regardless of how well that prediction matches to the data).[7]

Stakeholders can also consider the value of certifications and audit mechanisms, such as Service Organization Control Type 2 (SOC2) and frameworks from the National Institute of Standards and Technology (NIST), in both promoting trust and in improving internal processes.

VVUQ: When evaluating the validity of models, the paramount criterion should be performance in the specific context of use. This should be tested multiple times in a variety of scenarios that comprehensively address the breadth of situations that the model is likely to encounter with pre-established criteria for success. There are multiple types of validation approaches that can be used to understand different aspects of model performance, but specific choices should be justified. Cross-validation techniques are used to quantify model performance using available data, while external validation is conducted by testing the model on independent datasets or benchmarking against established methods. Model calibration and confidence estimation are used to assess reliability and uncertainty. Regardless of initial validation procedures, continuous monitoring of deployed models ensures the continued accuracy, reliability, and applicability of digital twins.

Rather than imposing broad federal regulations that align with the suggestions provided above, we believe that digital twin models should be evaluated by the appropriate regulatory body, according to the risk level associated with their context-of-use. Allocating federal funds to sector-specific experts, such as the FDA, for evaluating these models would accelerate the adoption of digital twin models and ensure their safe use.

Thank you for taking the time to review our response to the National Digital Twins R&D Strategic Plan Request for Information.

Best regards,

Jess Ross

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