Federal Register Notice: 89 FR 51554, Federal Register :: Networking and Information Technology Research and Development Request for Information on Digital Twins Research and Development, June 18, 2024.

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

The Savic Laboratory at the University of California, San Francisco (UCSF)

Request for Information Response:

Networking and Information Technology Research and Development Request for Information on Digital Twins Research and Development

Submitted by members of the Dr. Rada Savic, PhD Laboratory, at the University of California, San Francisco

Contributing Members (Listed in alphabetical order)

Principal Investigator: Rada Savic, PhD

Postdoctoral Scholars / Clinical Fellows:
Eunsol Yang, PharmD, PhD; Maureen Shin, PharmD, MS; Sejung Hwang, PharmD, PhD; Tae Kyu Chung, PhD; Xujia Zhou, PhD; Ziran Li, PhD

Graduate Student:
Connie Silva, BS

The Savic Laboratory at the University of California, San Francisco (UCSF) offers the following submission for consideration in response to the Request for Information (RFI) by the Networking and Information Technology Research and Development (NITRD) National Coordination Office (NCO), National Science Foundation (NSF)

1. Introduction

From 2015 to 2017, an estimated median cost of $48 million was allocated for pivotal trials per approved drug.[1] Additionally, the average time for a drug candidate to receive regulatory approval is approximately 14 years.[1] Despite these efforts, roughly 90% of drug candidates fail to progress due to reasons such as inaccurate target selection, inaccurate patient recruitment, and unexpected adverse effects.[2] The traditional drug development process is lengthy and costly, encompassing several stages of clinical trials, from preclinical to human clinical trials. Although there have been numerous advancements in biomedical research and healthcare, with the increasing need for novel medications, modifications to the current bench-to-bedside methods of drug development should be considered from both a financial and practical standpoint.

Currently, randomized control trials (RCTs) remain the gold standard for evaluating efficacy and safety in humans. Despite providing rigorous scientific evidence to support approval from regulatory bodies, RCTs have drawbacks.[3] The logistical challenges and

high costs associated with these trials can lead to extended durations, hindering the development and dissemination of new therapeutics. There is an urgent need to develop innovative techniques that can make RCTs more efficient, reducing the cost and time required to bring a new therapeutic to market while maintaining the validity of trial outcomes. Notably, digital twin (DT) techniques present a viable option to achieve these goals.

This request for information aims to elucidate the potential benefits of integrating DTs in clinical trials, and how this can advance the field of biomedical sciences and improve patient care. To this end, we summarized DT in clinical trial design, potential applications of DTs to clinical trials, standard methods to develop DTs, and considerations for integration of DT.

1.1 Topics addressed:

Applications of digital twins:

- ***Clinical Trial Design:*** *Significance of clinical trial design in drug development and precision medicine; role of modeling in improving clinical trial design and improving patient outcomes; significance of equitable representation of individual variability and patient characteristics*

Standard methods:

- ***Standards:*** *Promote Development of Evaluation Tools, Methodologies and Consensus Standards for Digital Twin Development and Testing and Interoperability: Ontology and data exchange protocols; encryption standards; address challenges related to evaluation of data-driven Digital Twin components; personalized applications derived from Digital Twins*

Considerations:

- ***Regulatory****: Regulatory Science Challenges associated with the use of DTs*
- ***Data****: Governance methods for data collection, sharing and usage; shared public datasets and repositories*
- ***Responsible****: Ethical use of digital twins; identifying ethical issues, mitigating and biases with respect to data ownership*

2. DTs in Clinical Trial Design

2.1 Inherent limitations in current clinical trials

To understand the characteristics of a drug or a drug candidate, investigators strive to minimize bias and confounding variables in clinical trials by utilizing randomization and implementing strict criteria for patient inclusion and exclusion. Although RCTs are the accepted method to evaluate the safety and efficacy of a drug, they have limitations that must be acknowledged.

One of the primary challenges is ensuring adequate sample size. Larger sample sizes or long-term trial durations for statistical power may not always be feasible or cost-effective. In the case of rare diseases or vulnerable populations, participant enrollment may not be sufficient. In addition, the narrow inclusion and exclusion criteria and controlled conditions often result in trial populations that do not equitably represent different patient populations,[4] especially for smaller trials. Furthermore, there may be issues with patient compliance or adherence to treatment protocols, which can impact the validity of the results.[5] As a result, it may be challenging to generalize the results of RCTs to certain patient populations.

2.2 Utilization of DTs in in-silico trials

Emerging DT technologies are starting to make a significant impact on drug development. By leveraging advanced simulations, modeling, artificial intelligence, and big data, these technologies are transforming the drug development process. Particularly, an *in-silico trial*, also known as a virtual clinical trial, in drug development has garnered significant support. For example, the Model-informed drug development approach runs models on virtual patients with appropriate simulated scenarios, aiming to evaluate the efficacy and safety profiles in a larger population without the need for actual recruitment. Likewise, testing the drug characteristics *in-silico* is beneficial for understanding the characteristics of a drug in vulnerable populations, particularly those who are underrepresented in current clinical trials.[6,7]

To ensure the development of trustworthy DTs, cooperative research is necessary to establish shared metrics, test methodologies, quality and security standards, development practices, and standardized tools for designing, developing, and utilizing DTs effectively. To this end, various configurations and mechanisms for public-private partnerships have been developed over the past few decades for different DT applications, such as the Digital Twin Consortium,[8] the Virtual Physiological Human,[9] and the Living Heart Project.[10] Expanding the reach of these mechanisms, improving their functioning and outputs for a more diverse set of participants and application spaces, and creating new forms of public-private partnerships are significant and valuable endeavors.

3. Potential Applications of DT Technologies

3.1 Vulnerable populations

Inclusion of specific populations, such as pediatric or pregnant individuals in RCTs is a prominent need that comes with several challenges. Pediatric RCTs often face difficulties including small sample sizes and challenges in obtaining informed consent, in addition to ethical concerns to test interventions in children. It is well known that "children are not small adults", due to the differences in pharmacokinetics (PK) during their maturation.[11] As with pediatric populations, pregnant individuals have physiological changes which can affect the PK, potentially making treatment efficacy and safety different for pregnant individuals compared to non-pregnant individuals. The benefits and potential harm to both the mother and fetus must be rigorously evaluated to ensure ethical compliance. To ensure these steps, logistics to enroll pregnant individuals in clinical trials may be more rigorous. Obtaining informed consent from pregnant individuals is challenging due to their unique priorities and concerns. Regulatory bodies, such as the U.S. Food and Drug Administration (FDA), may have specific requirements for inclusion of such participants. For example, the FDA Guidance for Industry for PK studies state do not recommend inclusion of pregnant individuals, if the drug is not utilized in pregnancy or there is fetal-toxicity data.[12]

The integration of DTs may be a possible solution to model the complexity and time-dependent changes of the human body, those that occur in maturation of young children and in pregnancy. DTs can incorporate data on maternal and paternal risk factors, as well as environmental factors, to assess the overall risk to the mother and the newborn. Real-time data collection and analysis through DTs enable early detection of maternal and fetal health risks, allowing healthcare providers to intervene proactively and make informed decisions with their patients.[6,7] DTs may also provide insights on the long-term outcomes on pediatric patients. For example, researchers have been able to characterize infantile microbiome, create a DT, and subsequently utilize the DT to predict the probability of neurological deficits depending on the microbiome composition.[13,14] Similarly, the effect of pharmacological agents either exposed to the infant *in utero* or during breastfeeding may be studied with DT. Finally, DTs may provide benefit to pediatric populations in areas endemic to poverty-related diseases. Pediatric dosing often follows weight-based dosing for medications. Malnourished children, who are underweight for their age, are thus risk of being underdosed.[15] As RCTs may particularly be of a challenge in these populations, the utilization of DTs to simulate different dosing strategies may provide an economical solution for global and equitable medication utilization.

3.2 Precision medicine

In the realm of healthcare and therapy development, the concept of DTs has recently emerged, particularly in oncology. A DT of a cancer patient and their tumor could significantly inform clinical decisions such as treatment options and clinical assessments. The DT approach can be utilized for precision medicine, in which patient-specific therapies are designed based on the DTs' ability to predict treatment outcomes for real patients. One example is the development of patient-specific DTs using individual

quantitative MRI data from patients with triple-negative breast cancer.[16] A mechanism-based predictive model was applied to predict the DTs' response to neoadjuvant systemic therapy.

To evaluate the predictive capability of the generated DTs, patient-specific images from the first three visits were used to create the DTs and predict the treatment outcome. After obtaining the real treatment outcome, it was subsequently compared with the predicted outcome provided by the DT. Results showed that the DT approach significantly improved prediction performance compared to the machine learning model (AUROC increased from 0.78 to 0.89).[16]

The DT can also be utilized to explore the biological factors underlying a patient's response and associated biomarkers. In a previous study, virtual patients were generated in large numbers for each actual patient with non-Hodgkin's lymphoma, taking into account the patient's specific dose level and treatment schedule.[17] For each simulated virtual patient, the individual tumor profile was estimated using a quantitative systems pharmacology (QSP) model. The difference between the simulated tumor measurement of the virtual patient and the actual post-treatment tumor measurement of a real patient was then calculated. The top 25 virtual patients with the smallest error were selected as the DTs of each actual patient. With the use of these DTs, the QSP model was able to predict the efficacy of mosunetuzumab. Additionally, biomarkers that influenced the responsiveness of the DTs to mosunetuzumab were identified. Based on these identified biomarkers, patients that are more likely to get a response can be selected for further clinical trials. Therefore, the success rate of clinical trials will increase.[17]

4. The Development Process of DTs

The development of DTs can be divided into three primary stages, as follows:

(1) Creation of a data-driven or mechanism-based model, which is subsequently validated through predictive performance metrics.

(2) Collection of baseline data from the real patient and construction of the DT based on actual measurements.

(3) Utilization of the DT to simulate various "what if" scenarios and comparison of predicted outcomes with the actual outcomes from the real patient to assess the DT's performance. Once a validated DT has been created, it can be employed with real-time, real-world data from the actual patient to continuously monitor, diagnose, and forecast the patient's condition.[18]

Implementing DTs in healthcare presents several challenges, including data integration, privacy and accuracy, ethical considerations, and regulatory compliance. Standardized data formats and interoperability standards are necessary for seamless exchange and use of health data, which is stored in various formats across different systems. Ensuring data privacy and security is crucial as DTs rely on extensive patient data, including sensitive health information.

Strict adherence to regulations such as Health Insurance Portability and Accountability ACT (HIPAA) and General Data Protection Regulation (GDPR), along with robust measures for data encryption and secure storage, is required. The accuracy and quality of input health data is essential for creating reliable DTs, but it is often limited by fragmentation, noise, and biases. Longitudinal data, necessary for capturing changes in health over time, is frequently scarce and may have gaps, making accurate DT maintenance challenging. Ethical considerations, such as informed consent, data ownership, patient autonomy, and preventing healthcare disparities, must be addressed with specific guidelines for responsible data sharing and unbiased models.[19]

5. Considerations for DT Technologies

5.1 Data management and governance

Data generation for drug development and healthcare purposes is rapidly increasing due to advancements in technology for drug discovery and bioanalytical methods, as well as the collection of complex data such as genomic data and clinical information from hospitals.[20] However, managing this vast amount of data presents challenges for those in the field. Personalized medicine in drug development and healthcare is based on genetic, biochemical, physiological, and behavioral aspects of individuals.[21] As the use and application of personalized medicine increases, unmanaged data can result in low data quality and increased time and costs. Therefore, efficient data management is a crucial consideration for developers and organizations.[22]

The implementation of data governance is beneficial in respect to managing the data and minimizing the risks associated with the utilization of big data.[22] Data governance for DT comprises a comprehensive structure of policies, guidelines, and procedures designed to effectively manage and control massive data.[22,23] Data governance can encompass data protection, data classification, compliance, security, and privacy,[24] and it is applicable to DT in the healthcare sector.[25] The healthcare industry's data is diverse in form and lacks standardization, emphasizing the need for uniform data management.[22] Given that DT in healthcare primarily focuses on individual health-based information, data management must be closely monitored using tools or audits. Data governance for healthcare should concentrate on data management, security, privacy, and data depletion.[22] As data governance for DT in healthcare is not widely proposed, general guidelines for data governance should be followed.[23]

5.2 Guidelines for standardized analysis

DTs have vast potential in the realm of healthcare, extending beyond the boundaries of biomarker and drug discovery, design optimization, drug development, and personalized medicine.[19,26] Despite their advantages, the use of DTs remains fraught with challenges, mainly due to the absence of standardized documentation for each application, varied expectations for model assessments, and differing levels of understanding regarding the

principles and concepts. Comprehending the technological intricacies of artificial intelligence (AI) and DTs, as well as their interdependent and complementary relationship, is indispensable for the advancement of DTs in healthcare.

In essence, DT technology leverages machine learning algorithms to process data and identify patterns. However, the complexity of DTs surpasses the capabilities of computational modeling and AI/ML algorithms alone, thereby complicating standardized analyses for DT studies.[19] Consequently, these obstacles hinder the evaluation of data quality, the robustness of analyses, the impact of modeling, and the credibility of applications. As a result, valuable opportunities for maximizing the benefits of DTs in various applications and improving decision-making have been missed. To overcome these challenges, it is crucial to establish detailed and standardized data formats and interoperability standards tailored to the specific purposes of DTs.[27] By doing so, consistency and reliability can be enhanced across regulatory assessments and applications, thereby unlocking the full potential of DTs in healthcare. Although a guideline specifically related to deep learning techniques (i.e., DTs) has not yet been released, the Good Machine Learning Practice (GMLP) guideline for Medical Device Development, which was issued in 2021 by the FDA, Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (HMRA), can be consulted for various applications of DTs.[28] This guideline was specifically designed for medical device development authorities. However, its message can also be applied to various applications of DTs, as computational modeling and AI/ML algorithms are widely used in the field of DTs. The ten principles emphasized in the GMLP guidelines are as follows:

- Multi-disciplinary expertise is leveraged throughout the total product life cycle
- Good software engineering and security practices are implemented
- Clinical study participants and datasets are representative of the intended patient populations
- Training datasets are independent of test sets
- Selected reference datasets are based upon best available methods
- Model design is tailored to the available data and reflects the intended use of the device
- Focus is placed on the performance of the Human-AI Team
- Testing demonstrates device performance during clinically relevant conditions
- Users are provided clear, essential information
- Deployed models are monitored for performance and re-training risks are managed

Therefore, it is imperative that guidelines be established to illustrate how physical entities can be described, as well as their corresponding virtual replicas, and the relationship between the two. Additionally, it is crucial to provide clarity on how to maintain the transparency of hypotheses and data utilized in developing DTs,[29] validate methods for verifying DT analysis results,[30] and establish ethical guidelines for trustworthy DTs.[21] Furthermore, an organization that can continuously provide feedback on DT applications is necessary. This organization can ensure that studies employing DT models are

accurate, reliable, and adhere to ethical standards. The formation of interdisciplinary review committees may be a viable approach to achieve this. Similar to pre-Investigational New Drug meetings, which can assist sponsors in addressing questions regarding their new drug candidate applications, meetings with interdisciplinary review committees can help sponsors prepare to submit applications for personalized medicines, for instance.

5.3 Ethical issues related to DTs

DTs are used in healthcare for diagnosis, prognosis, and personalized treatment based on health-related data. The data used to build DT ranges from general or specific genetic information to individual baseline lifestyle, health information, and disease status. Additionally, a large amount of data may be required to develop DT in healthcare, which is gathered from public sources.[31] However, the process of gathering and using this data raises ethical issues. The data collection is the first step in developing DT, and efforts to gather as much data as possible to create an appropriate model may result in the hypercollection of data, thereby compromising individual privacy.

After data collection, data management is carried out by developers according to their respective strategies, which can lead to barriers in accessing data.[32] If the provider fails to adjust the proper management of the model associated with DT, data accessibility can be disrupted. Outdated or disrupted data can make it difficult for individuals using healthcare services using DT to access health-related information, ultimately affecting the quality of healthcare services. Data brokerage is also a significant ethical issue in data management.[33] Before using data for DT development, data ownership should be characterized, and consensus on data ownership and informed consent from the provider should be established.

The process of data analysis using DT may inadvertently result in biased algorithms or biased training datasets, leading to unexpected discrimination.[31] To address this issue, developers must ensure that the algorithms use appropriate proxy or training datasets that are consistently labeled and accurately represented in the data features. The ultimate goal of implementing healthcare using DT is to provide prognosis of diseases and preventive healthcare. However, there are concerns about the use of DT in healthcare, particularly the risk of overdiagnosis.[31,32] In practice, early diagnosis and treatment can lead to overdiagnosis and overtreatment, resulting in increased individual and social costs. Therefore, organizations can encourage developers of healthcare using DT to collaborate with clinicians and researchers to ensure comprehensive interpretations.

6. References

1. Moore TJ, Heyward J, Anderson G, Alexander GC. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015–2017: a cross-sectional study. *BMJ Open*. 2020;10(6):e038863. doi:10.1136/bmjopen-2020-038863
2. Sun D, Gao W, Hu H, Zhou S. Why 90% of clinical drug development fails and how to improve it? *Acta Pharm Sin B*. 2022;12(7):3049-3062. doi:10.1016/j.apsb.2022.02.002
3. Hariton E, Locascio JJ. Randomised controlled trials – the gold standard for effectiveness research. *BJOG Int J Obstet Gynaecol*. 2018;125(13):1716-1716. doi:10.1111/1471-0528.15199
4. Blonde L, Khunti K, Harris SB, Meizinger C, Skolnik NS. Interpretation and Impact of Real-World Clinical Data for the Practicing Clinician. *Adv Ther*. 2018;35(11):1763-1774. doi:10.1007/s12325-018-0805-y
5. Saldanha IJ, Skelly AC, Ley KV, et al. Strengths and Limitations of RCTs. In: *Inclusion of Nonrandomized Studies of Interventions in Systematic Reviews of Intervention Effectiveness: An Update [Internet]*. Agency for Healthcare Research and Quality (US); 2022. Accessed July 23, 2024. https://www.ncbi.nlm.nih.gov/books/NBK584466/
6. Scott AK, Oyen ML. Virtual pregnancies: predicting and preventing pregnancy complications with digital twins. *Lancet Digit Health*. 2024;6(7):e436-e437. doi:10.1016/S2589-7500(24)00086-4
7. Calcaterra V, Pagani V, Zuccotti G. Maternal and fetal health in the digital twin era. *Front Pediatr*. 2023;11:1251427. doi:10.3389/fped.2023.1251427
8. Home. Digital Twin Consortium. Accessed July 22, 2024. https://www.digitaltwinconsortium.org/
9. The Virtual Physiological Human – a “digital twin” for patients. Accessed July 22, 2024. https://www.vph-institute.org/news/the-virtual-physiological-human-%E2%80%93-a-digital-twin-for-patients.html
10. Living Heart Project | SIMULIA™ - Dassault Systèmes®. Accessed July 22, 2024. https://www.3ds.com/products-services/simulia/solutions/life-sciences-healthcare/the-living-heart-project/
11. Krekels E, Neely M, Panoilia E, et al. From Pediatric Covariate Model to Semiphysiological Function for Maturation: Part I–Extrapolation of a Covariate Model From Morphine to Zidovudine. *CPT Pharmacomet Syst Pharmacol*. 2012;1(10):1-9. doi:10.1038/psp.2012.11
12. Research C for DE and. Pharmacokinetics in Pregnancy — Study Design, Data Analysis, and Impact on Dosing and Labeling. Published April 27, 2020. Accessed July 23, 2024. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacokinetics-pregnancy-study-design-data-analysis-and-impact-dosing-and-labeling
13. Sizemore N, Oliphant K, Zheng R, Martin CR, Claud EC, Chattopadhyay I. A digital twin of the infant microbiome to predict neurodevelopmental deficits. *Sci Adv*. 2024;10(15):eadj0400. doi:10.1126/sciadv.adj0400
14. Field MJ, Behrman RE, Children I of M (US) C on CRI. The Necessity and Challenges of Clinical Research Involving Children. In: *Ethical Conduct of Clinical Research Involving Children*. National Academies Press (US); 2004. Accessed July 23, 2024. https://www.ncbi.nlm.nih.gov/books/NBK25553/
15. Radtke KK, Dooley KE, Dodd PJ, et al. Alternative dosing guidelines to improve outcomes in childhood tuberculosis: a mathematical modelling study. *Lancet Child Adolesc Health*. 2019;3(9):636-645. doi:10.1016/S2352-4642(19)30196-8
16. Wu C, Jarrett AM, Zhou Z, et al. MRI-based digital models forecast patient-specific treatment responses to neoadjuvant chemotherapy in triple-negative breast cancer. *Cancer Res*. Published online August 1, 2022:CAN-22-1329. doi:10.1158/0008-5472.CAN-22-1329
17. Susilo ME, Li C, Gadkar K, et al. Systems-based digital twins to help characterize clinical dose–response and propose predictive biomarkers in a Phase I study of bispecific antibody, mosunetuzumab, in NHL. *Clin Transl Sci*. 2023;16(7):1134-1148. doi:10.1111/cts.13501

18. Coorey G, Figtree GA, Fletcher DF, et al. The health digital twin to tackle cardiovascular disease—a review of an emerging interdisciplinary field. *NPJ Digit Med*. 2022;5:126. doi:10.1038/s41746-022-00640-7
19. Katsoulakis E, Wang Q, Wu H, et al. Digital twins for health: a scoping review. *Npj Digit Med*. 2024;7(1):1-11. doi:10.1038/s41746-024-01073-0
20. McComb M, Bies R, Ramanathan M. Machine learning in pharmacometrics: Opportunities and challenges. *Br J Clin Pharmacol*. 2022;88(4):1482-1499. doi:10.1111/bcp.14801
21. Bruynseels K, Santoni de Sio F, van den Hoven J. Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm. *Front Genet*. 2018;9:31. doi:10.3389/fgene.2018.00031
22. Rahmadian E, Feitosa D, Virantina Y. Digital twins, big data governance, and sustainable tourism. *Ethics Inf Technol*. 2023;25(4):61. doi:10.1007/s10676-023-09730-w
23. Arundel ST, McKeehan KG, Campbell BB, Bulen AN, Thiem PT. A guide to creating an effective big data management framework. *J Big Data*. 2023;10(1):146. doi:10.1186/s40537-023-00801-9
24. Ghavami P. *Big Data Management: Data Governance Principles for Big Data Analytics*. Walter de Gruyter GmbH & Co KG; 2020.
25. Wan L, Nochta T, Schooling JM. Developing a City-Level Digital Twin ?Propositions and a Case Study. In: *International Conference on Smart Infrastructure and Construction 2019 (ICSIC)*. Cambridge Centre for Smart Infrastructure & Construction. ICE Publishing; 2019:187-194. doi:10.1680/icsic.64669.187
26. Research C for DE and. Artificial Intelligence and Machine Learning (AI/ML) for Drug Development. FDA. Published March 18, 2024. Accessed July 22, 2024. https://www.fda.gov/science-research/science-and-research-special-topics/artificial-intelligence-and-machine-learning-aiml-drug-development
27. Botín-Sanabria DM, Mihaita AS, Peimbert-García RE, Ramírez-Moreno MA, Ramírez-Mendoza RA, Lozoya-Santos J de J. Digital Twin Technology Challenges and Applications: A Comprehensive Review. *Remote Sens*. 2022;14(6):1335. doi:10.3390/rs14061335
28. Health C for D and R. Good Machine Learning Practice for Medical Device Development: Guiding Principles. *FDA*. Published online October 20, 2023. Accessed July 22, 2024. https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles
29. Chang KC, Shao SC, Chen HY, Chan YY, Fang YF. Comparative Effectiveness and Safety of Standard-Dose and Low-Dose Pembrolizumab in Patients with Non-Small-Cell Lung Cancer: A Multi-Institutional Cohort Study in Taiwan. *Cancers*. 2022;14(5):1157. doi:10.3390/cancers14051157
30. Moingeon P, Chenel M, Rousseau C, Voisin E, Guedj M. Virtual patients, digital twins and causal disease models: Paving the ground for *in silico* clinical trials. *Drug Discov Today*. 2023;28(7):103605. doi:10.1016/j.drudis.2023.103605
31. Huang P hua, Kim K hun, Schermer M. Ethical Issues of Digital Twins for Personalized Health Care Service: Preliminary Mapping Study. *J Med Internet Res*. 2022;24(1):e33081. doi:10.2196/33081
32. Ahmadi-Assalemi G, Al-Khateeb H, Maple C, et al. Digital Twins for Precision Healthcare. In: Jahankhani H, Kendzierskyj S, Chelvachandran N, Ibarra J, eds. *Cyber Defence in the Age of AI, Smart Societies and Augmented Humanity*. Springer International Publishing; 2020:133-158. doi:10.1007/978-3-030-35746-7_8
33. Huckvale K, Torous J, Larsen ME. Assessment of the Data Sharing and Privacy Practices of Smartphone Apps for Depression and Smoking Cessation. *JAMA Netw Open*. 2019;2(4):e192542. doi:10.1001/jamanetworkopen.2019.2542