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EDITOR'S PAGE

# The Use of Digital Healthcare Twins in Early-Phase Clinical Trials

## Opportunities, Challenges, and Applications

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The advent of digital health technologies has ushered in a new era of personalized medicine, potentially revolutionizing the way that clinical trials are conducted. Among these innovations, the emergence of the digital health twin (DHT) represents a disruptive technology that may transform the conduct of clinical trials, especially phase I and II trials. Digital twins are virtual representations of physical objects, acting as their digital counterparts. The concept of digital twins was initially applied to manufacturing equipment in 2002. Virtual manufacturing models allowed iterative processes to model, test, and improve manufacturing products within a digital environment. With time, this technology spread to various sectors in manufacturing, supply chain management, plant operations, civil engineering, and all modes of transportation. By 2010, the concept of a "digital twin" was formally recognized during a NASA initiative designed to create digital simulations of spacecraft for testing purposes.[1] Recently, this technology has been adapted to health care within the realm of precision medicine. In this context, the digital twin represents the digital counterpart of the patient. The DHT is synthesized using integrated data streams from individual patients, population data sets, and real-time inputs from patient and environmental factors (Figure 1).

**FIGURE 1** Digital Healthcare Twin Concept (Illustration by Dalle2)


DHTs are becoming increasingly important in personalized medicine by combining epidemiologic data with real-time patient-specific information. The growing use of wearables, environmental sensors, and smartphone apps that track physical activity, diet, and mental health generates continuous streams of physiologic and environmental data. When combined with electronic health record data, such as laboratory results, imaging, examinations, and genomic information, these data can be used to create synthetic data sets that inform generative AI models capable of predicting health care outcomes and clinical patient trajectories. Importantly, the effectiveness of these projections can be measured and fed back to the DHT model to further enhance future

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predictions.[2] As discussed below, DHTs are now being used to facilitate early-phase clinical trials.

Phase I clinical trials are primarily concerned with assessing the safety of a new drug or device. Traditionally, these trials involve a small group of healthy volunteers and focus on determining the appropriate dosage range and identifying any side effects. However, studies in healthy volunteers may not accurately predict drug or device safety in patients with the target disease, because the disease itself, along with the patient's underlying health conditions and concurrent medications, can significantly alter the body's response, leading to different safety profiles. A DHT be used in conjunction with traditional studies in healthy volunteers by simulating patient responses to a new drug, using virtual models to predict potential side-effects and to help optimize dosing. This helps refine safety assessments before administering the drug to actual participants.

Phase II clinical trials are designed to evaluate the dose and potential efficacy of a drug, as well as further assess its safety, usually in a larger group of patients who have the medical condition that the drug is intended to treat. Here the use of DHTs offers several unique benefits. First, around 80% of all clinical trials are delayed or prolonged due to slow patient enrollment.[3] As further discussed below, the use of DHTs can reduce the number of patients needed to assess a drug/device, which is critically important to accelerating drug development at lower cost and patient burden. DHTs can also accelerate the development of novel new therapies for orphan diseases, which are often hampered by the limited number of patients that can be recruited.

Several companies are pioneering the use of digital twins in clinical trials. Unlearn.AI[4] has developed a platform called TwinRCTs, which creates digital twins (ie, virtual synthetic models of patients) based on historical clinical trial data. PROCOVA (Prognostic Covariate Adjustment) is a proprietary method developed by Unlearn.AI to enhance the statistical power of clinical trials. PROCOVA uses advanced algorithms to adjust for prognostic covariates, which are baseline characteristics of patients that can influence the outcome of a trial. By accounting for these covariates, PROCOVA helps to reduce variability in the data, making it easier to detect true treatment effects. One of the core features of PROCOVA is the use of DHTs to simulate the control group. These twins are virtual representations of control patients enrolled in the trial, generated based on real-world data and existing clinical trial information. This allows for a more robust and accurate comparisons between the treatment group and the synthetic control group. By generating additional synthetic control data, Unlearn.AI can reduce the number of actual patients who are needed to be enrolled in the actual control group, thereby enhancing the statistical power of the trial while potentially reducing costs and ethical concerns. Unlearn.AI's TwinRCTs technology has already been qualified by the EMA (European Medicines Agency) for use as the primary analysis in phase 2 and 3 clinical trials with continuous outcomes. Recently, Unlearn.AI received feedback from the U.S. Food and Drug Administration's Center for Drug Evaluation and Research, which confirmed alignment with the EMA assessment. The FDA agreed that PROCOVA adheres to current guidelines, recognizing it as an accepted statistical methodology under both EMA and FDA standards.

Despite their potential, the use of DHTs in clinical trials also presents several challenges, some of which are generic to AI prediction models and some that are unique to this particular application of AI. First, the accuracy of DHTs depends on the quality and comprehensiveness of the data used to create them. Incomplete databases or biased databases can lead to inaccurate predictions, which could compromise the validity of the trial results. Second, DHTs, like other AI models, are "black boxes" wherein the decision-making process is not transparent. This lack of interpretability can lead to skepticism among researchers, clinicians, and regulators, potentially hindering the acceptance and use of DHTs in clinical trials. Third, all current generative DHT models are restricted to a single therapeutic target, resulting in DHTs that are highly specialized for that specific target but lack generalizability across other therapeutic areas. Although this might seem easily surmountable, it's important to recognize that most methodologies used to train DHT models rely on data from fewer than 5,000 patients. This is considered a small data set for deep learning models, which could potentially limit the generalizability of these models in more heterogeneous patient populations.

DHTs represent a promising innovation in the field of early and late phase clinical trials, and offer the potential to improve efficiency, cost, precision, and ethical standards in cardiovascular drug/device development. Although there are still challenges to overcome, including issues related to data quality and the complexity of implementation, the potential benefits of digital twins in phase I and II clinical trials are significant. As the technology continues to evolve, DHTs are likely to play an increasingly

important role in the future of clinical research, supporting the development of safer, more effective, and personalized treatments for patients afflicted with cardiovascular disease. As always, we welcome your thoughts on the DHTs, either through social media (#JACCBTS) or by e-mail (jaccbts@acc.org).

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