

Digital Twins in Clinical Development: A Technical Review of In Silico Trials, Virtual Control Arms, and Hybrid Mechanistic-AI Architectures (2025–2026)

Harsh Mahesh Sonavaane

Student, SMES's Mahavir Institute of Pharmacy, Varvandi, Nashik

Date of Submission: 15-04-2026

Date of Acceptance: 25-04-2026

ABSTRACT: Digital twin technology is revolutionizing the paradigm of clinical development with its ability to generate realistic, data-driven simulations of the patient's physiological system. Contrary to conventional simulation approaches, digital twins are capable of incorporating real-time data and mechanistic modeling alongside artificial intelligence, thus allowing for more accurate simulations of physiological responses. Review literature from the period between 2025 and 2026 illustrates the expanding use of digital twins for in silico trials, virtual control arms, and mechanistic–AI hybrid models.

Specifically, in silico trials enable the testing of novel therapies on simulated patient populations, thus mitigating ethical concerns while decreasing the reliance on costly human trials. Similarly, the implementation of virtual control arms facilitates more efficient study designs by introducing computational alternatives to the standard placebo treatment groups. Lastly, hybrid mechanistic-AI models offer the advantages of both mechanistic modelling and machine learning to generate highly reliable predictions.

However, several issues still exist regarding data integration, regulatory approval, validation of models, and ethics. The current review aims to discuss recent advances in the application of digital twin technology within clinical development (2025-2026), highlighting their technical underpinnings, practical utility, limitations, and potential.

KEYWORDS: Digital Twin; In Silico Trials; Virtual Control Arms; Hybrid Modelling; Mechanistic Models; Artificial Intelligence; Clinical Development; Precision Medicine; Computational Pharmacology; Digital Health

I. INTRODUCTION

Clinical development has been considered a lengthy, expensive, and risky process due to a

variety of factors such as high attrition rates and poor predictability of preclinical models. However, the synergy between computational modelling, artificial intelligence, and live data collection techniques has provided an impetus for the emergence of innovative digital twin technology.

To begin with, a digital twin is a dynamic virtual image of an organism or a medical subject that incorporates all sorts of physiological, clinical, and behavioral features in order to predict real-world outcomes. Unlike static computer models, a digital twin is capable of updating itself based on incoming data, thus providing accurate predictions and recommendations for personalized treatment options.

Perhaps the greatest potential application of the technology lies in the emergence of in silico trials, in which virtual human populations are being utilized to test drug efficacy and safety before moving to clinical trials on humans. In addition, the development of a virtual arm allows using past data for computational modelling to avoid employing placebo groups and eliminate ethical risks associated with clinical research.

In addition, new technologies have been introduced into the development of hybrid mechanisms of artificial intelligence (AI), which unite the advantages of classical mechanistic models (based on biological principles) and machine learning technologies. Hybridization improves the interpretability and predictive accuracy of the models, which makes it especially beneficial for modelling diseases and personalized medicine.

However, despite the numerous promising advances, the use of digital twins in the development of clinical research is still in its infancy. The main problems associated with it are data heterogeneity, lack of standardization, regulatory issues, and data privacy and ethical concerns. In this regard, an in-depth knowledge of

the latest advances and limitations is necessary to continue further scientific research.

This review will provide a critical analysis of recent studies (2025-2026) dedicated to digital twins in clinical development, paying special attention to in silico trials and virtual control arms, as well as to hybrid modelling approaches and their current limitations.

II. DIGITAL TWIN

Digital twins can be defined as digital replicas that accurately reflect the structure, operation, and lifecycle of physical objects through data exchange between both systems.

Based on literature review, digital twins leverage the use of real-time data streams and computation models to predict the states of physical objects both currently and in the near future.

This way, digital twins differ from simulation models since they provide an adaptive platform where the state of the system evolves according to the data gathered from the external environment.

▪ Core Components of Digital Twin

The typical architecture of digital twins consists of three major elements: the physical object, a digital representation, and data exchange infrastructure.

Firstly, the physical object is a material system whose state is reflected in a digital twin. This object can be anything from a living patient to artificial organs. Secondly, the digital object is created based on mathematical and simulation models and the application of machine learning algorithms. Thirdly, the data infrastructure allows exchanging information between the physical and digital worlds using IoT and EHRs.

▪ Evolution of Digital Twin

Digital twin technology emerged within the framework of the fourth Industrial Revolution. Initially, digital twins were employed in product lifecycle management, predictive maintenance, and optimization tasks in manufacturing facilities.

However, their application has been evolving, becoming more complex and entering other spheres. Within the scope of healthcare, the combination of digital twins and artificial intelligence allows creating customized digital twins that simulate biological processes and disease development.

Such an evolution demonstrates the change of focus from machine to human-centric systems, and

the increased need for digital twins in precision medicine is evident.

▪ Applications in Healthcare

Digital twins have shown great applicability in many aspects of healthcare, which include personalized medicine, disease prediction, virtual clinical trials, remote monitoring, and surgery planning.

For instance, personalization of treatment is facilitated with the help of patient-specific digital twins, which allow testing various treatments and choosing the most efficient one before implementation. In addition, the analysis of data collected from patients can reveal the diseases that may occur soon.

Virtual trials can also be used to reduce the risk associated with drug testing while accelerating this process and lowering costs.

▪ Enabling Technologies

For the proper functioning of digital twins, the incorporation of various innovative technologies becomes imperative. This includes AI and ML algorithms, Internet of Things (IoT), big data analytics, and cloud computing, among others.

The importance of AI and ML algorithms lies in their ability to analyse complicated data sets and develop predictive models, whereas IoT allows the gathering of constant data from the system under study. Big data analytics is essential to process data in massive amounts, and cloud computing is required to store data and process it in real time.

▪ Advantages

Digital twins possess various advantages in the field of healthcare, among which are risk-free experimentation, enhanced accuracy of predictions, personalized treatment options, and cost savings.

Due to the simulation capabilities provided by digital twins, medical practitioners can conduct treatment experiments without putting patients at risk. Another advantage is related to accurate prediction based on the real-time data provided.

▪ Limitations

Although digital twins have great potential, they still have some limitations that make their adoption difficult. Such limitations include the problem of data privacy and security, high computational costs, integration difficulties, and the absence of standardization frameworks.

The employment of personal health data brings up the question of data ownership and consent, raising moral and legal questions. Moreover, the integration of diverse data sources and cutting-edge technology can be highly complex.

▪ **Future Directions for Research**

There are several areas in which further research on digital twins in medicine should go. First, there is no standard architecture or framework available to facilitate the process. Moreover, most of the research remains purely theoretical and simulation based.

Additionally, human-digital twin interaction has not been thoroughly considered. The ethical aspect of the matter is also worth mentioning.

▪ **Future Scope**

The future of digital twin technology for healthcare will likely involve the development of complete personal digital human models, along with the incorporation of wearables and AI-based predictive healthcare systems.

Such innovations hold immense promise for facilitating preventive health management, better

III. SILICO TRIALS

According to recent literature on the topic, in silico trials are described as a multilayered computer-aided modelling approach for mimicking real-life situations during dynamic testing. The cornerstone of this technique is the creation of virtual patients by building digital models based on data obtained from various sources, including medical reports, genomic data, proteomics, and distribution. Most importantly, the key feature of virtual patients is their diversity; therefore, there will be variations among these patients in relation to age, genes, and diseases, which allows one to test the effect of a medication on patients in different circumstances. Still, it should be emphasized that the success of creating such virtual patients relies on data quality, its representativeness, and completeness. Expanding on this idea, disease modelling gives the mechanism of the development of certain diseases by considering biological pathways and time dependency of disease. This type of modelling helps understand the mechanisms involved in the development of tumors or other metabolic diseases. Even though such modelling techniques give great insights into certain disease mechanisms, they tend

to be based on predefined biological pathways which might not give a complete picture of human physiology in diseases involving multiple factors.

Following the disease modelling, another important modelling technique for predicting treatment success or failure involves drug or intervention modelling that can be characterized by two key terms – pharmacokinetic (PK) and pharmacodynamic (PD). Pharmacokinetic modelling gives the absorption, distribution, metabolism, and elimination of a drug from the body while pharmacodynamic modelling gives the effect of that drug on the body. In this way, PK-PD modelling becomes an essential part of in silico trials that can help predict both the efficiency and toxicity of a drug treatment.

These different elements come together within the simulation engine, where a number of computerized experiments are done at varying doses, periods of treatment, and other parameters. These simulations result in the generation of efficacy and adverse outcomes metrics and thus make it possible to explore different clinical scenarios within a short amount of time. The fact that in silico trials are scalable means that one could run hundreds or thousands of experiments within a short amount of time, yet this is an expensive process due to computational intensity.

▪ **Types**

There are several main categories of in silico trials. These include fully virtual trials, hybrid clinical trials, and regulatory-supported simulations. The first type uses only virtual patients and is especially effective in early stages of drugs' research. The second type combines real and virtual patient data for the creation of the most realistic model. Finally, regulatory supported simulations are increasingly recognized as being valuable within certain areas, such as evaluating devices and optimizing doses. The lack of standardized validation criteria is a limiting factor in regulation of these types of trials.

▪ **Application**

There are many ways in which the use of in silico trials in the development of clinical research can be applied. They help expedite the process of developing drugs by minimizing the use of animals and early human trials, thus saving cost and time. These in silico trials also play an important part in the optimization of the dose, as through these trials we can find the dose that proves to be both effective and safe before conducting clinical trials. For patients suffering

from rare diseases and thus making the recruitment difficult, such in silico trails offer another means to evaluate the effects of the therapy. The use of such trails during the COVID-19 era has shown their capability to evaluate drugs and vaccines during pandemics in a relatively short period of time. However, there are certain limitations in the use of such trials and that is that these in silico trails cannot replace the traditional ones.

IV. VIRTUAL CONTROL ARMS

The concept of the virtual control arms (VCAs) is considered as one of the major improvements achieved in terms of utilizing the digital twin technology for the implementation of clinical trials. According to recent scientific reviews, the idea of the VCAs involves the creation of a virtual cohort, which consists of patients represented by a computational model based on historical clinical data, real-world evidence, and other methods (Corral-Acero et al., 2023; El Saddik, 2024). Thus, VCAs are created using sophisticated computational tools based on advanced statistical methods and machine learning. The main advantage of the VCAs is associated with their similarity to patients from the experiment group, which allows replicating the results like those of a conventional control group.

One of the main reasons why there is a push to develop virtual control arms (VCAs) is the inherent ethical and logistical difficulty of allocating patients to placebo groups in situations involving serious or rare diseases, whereby the withholding of medication might not be feasible. In such cases, the VCA becomes a practical solution, enabling researchers to conduct trials without the use of placebo groups. Moreover, from review articles, it has become clear that the use of VCAs leads to greater efficiency in clinical trials, as they save time on recruitment, reduce expenses, and allow quicker trial completion.

▪ Approaches

VCAs are based on sophisticated approaches to data integration and matching, including but not limited to propensity score matching, Bayesian modeling, and causal inference frameworks. The use of such methods seeks to reduce biases and confounding and enhance the validity of the trials' findings. Another aspect that contributes to the validity of virtual cohort outcomes is the use of digital twin models that help predict patient-specific outcomes. Nevertheless, the credibility of virtual cohort analysis depends on the

quality of the dataset used, and biases in the data can affect the validity of results.

▪ Advantages

Even though virtual cohorts present many benefits, there are certain limitations associated with them. As per review literature, limitations related to VCA include problems with data heterogeneity, lack of standardization, and possible biases in the real-world data). Currently, there are still no regulations in place regarding the implementation of VCAs in clinical trials; however, some agencies, like FDA, have started examining the potential uses of VCAs for certain types of trials, such as those dealing with rare conditions and cancers.

▪ Future Scope

When it comes to future applications, virtual control arms are forecasted to be integral to hybrid trial designs where real-world data is combined with simulated data in order to achieve maximum effectiveness and validity. With advancements in artificial intelligence, causal modelling, and real-world data analysis, the reliability and applicability of virtual control arms in clinical trials can only become better in the future. In conclusion, virtual control arms mark an important advancement towards more efficient and ethical clinical trials, but their effective integration would hinge on further refinements.

V. HYBRID MECHANISTIC-AI ARCHITECTURES

Hybrid mechanistic-AI systems have appeared to be one way out to solve problems arising with classical modelling techniques. These models incorporate mechanisms that include mathematical equations based on biological laws with artificial intelligence that learns from big databases, such as medical records, images, and wearable devices. The former type provides explainability and physiological foundation, whereas the latter ensures adaptation and prediction power; yet there are also some drawbacks for each of them – inflexibility and restrictions for mechanistic models and lack of transparency for artificial intelligence-based solutions, which is why hybrids were developed.

▪ Architecture of Hybrid Models

Several modelling architectures have been proposed for hybrid models. Sequential models utilize the outputs of mechanistic simulation as

inputs for an algorithm based on AI to achieve higher prediction accuracy. Parallel models use outputs obtained from running both types of algorithms to combine predictions made by different models. The most sophisticated approach to building hybrid models is embedded modelling, which enables incorporating AI directly in mechanistic equations to make the system self-learnable and adaptive. Even though this is quite an achievement, it introduces additional complexity to modelling.

▪ Mathematical Foundation

Mathematically speaking, hybrid models typically involve combining ODEs with neural network models or other forms of deep learning algorithms. Such an approach provides a means for achieving biological interpretability in combination with the ability to adapt to more complex data. Clinically, such models have become quite popular in the field of personalized medicine, where individual patient predictions can be used to determine therapy, as well as in disease progression modelling and drug response prediction. Hybrid models can improve the accuracy of in silico trials by taking into account the biological variability of the system.

However, some problems remain with using hybrid models that combine mechanistic approaches with artificial intelligence. The problem of data integration becomes very important, especially in terms of combining structured and unstructured datasets, e.g., incorporating imaging data, sensor data, and other data types. High computational costs can pose certain difficulties. Finally, a lack of standardization in terms of validation approaches, as well as an absence of regulatory pathways to approve such complex models, must be considered.

Other issues include the need for standardization of hybrid modelling techniques, better interoperability within the healthcare setting, and the use of explainable AI. Actual implementation in clinical practice is yet to be fully realized, pointing to the disconnect between the academic aspect and practical use cases of hybrid modelling. In terms of future developments, the following areas are likely to receive attention in coming years: real-time adaptivity in digital twin creation, interfacing with wearable devices, and AI-based decision support solutions for clinicians. The result of all efforts should be a living digital patient capable of learning and predicting disease outcomes.

VI. CONCLUSION

Digital Twin Technology is revolutionizing clinical development through real-time simulations based on physiological data. The in-silico trial, virtual control arm, and the hybrid model of Mechanistic-AI are among the technologies that help save time and money while advancing personalization in medicine.

Despite facing various obstacles, including data collection and integration, verification and validation, regulatory requirements, and ethical considerations, digital twin technology offers significant promise for the future of precision health care and clinical studies.

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