

Digital Twins and AI-Enabled Trial Architectures: A Narrative Review

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ABSTRACT

Background: Traditional population-averaged randomized controlled trials are constrained by severe recruitment bottlenecks, skyrocketing structural development costs, and poor real-world generalizability. Digital Twins in Medicine (DTM) have emerged as a high-fidelity, paradigm-shifting architectural ecosystem capable of addressing these operational vulnerabilities.

Objective: This narrative review systematically synthesizes the structural frameworks, cross-domain clinical efficacy profiles, and current regulatory and computational bottlenecks of AI-enabled digital twins in next-generation clinical trials.

Methods: Following SANRA guidelines, a systematic literature search was executed across PubMed/MEDLINE, Scopus, and Web of Science for studies published from January 2015 to June 2025. Applying explicit eligibility criteria, 42 high-fidelity peer-reviewed investigations were selected for qualitative thematic synthesis.

Results: The synthesized data revealed a consistent three-layer architectural platform: data acquisition, computational modeling, and clinical actionability. In clinical deployment, DTM achieved a 34% reduction in Phase II oncology cohort sizes via Synthetic Control Arms, an Area Under the Receiver Operating Characteristic (AUROC) curve greater than 0.92 for predicting structural cardiac remodeling, and a 4.2-week lead-time advantage in mapping chronic immunological flares via wearable biometric telemetry. However, systemic methodological vulnerabilities persist, including a prominent black-box interpretability gap across 78% of reviewed models, baseline covariate shift (42%), and data attrition or telemetry noise (31%).

Conclusion: AI-enabled digital twins are actively transitioning from speculative conceptual models into clinically actionable, practice-changing investigative platforms. Securing extensive regulatory endorsement and achieving scaling milestones will require standardized Explainable AI (XAI) frameworks, multicenter geographic validation loops, and robust data-quality governance structures.

Keywords: Computer Simulation, Artificial Intelligence, Clinical Trials as Topic, Precision Medicine, Decentralized Clinical Trials, Data Governance.

INTRODUCTION

Traditional clinical research is currently constrained by an operational bottleneck characterized by soaring developmental costs, prolonged recruitment timelines, and high phase-transition attrition rates for novel therapeutics.^{1,2} For nearly eight decades, the randomized controlled trial (RCT) has reigned as the gold standard of evidence-based clinical science, using population-scale randomization to control for confounding variables and establish causal efficacy.^{3,4} However, this classical paradigm views heterogeneous patient populations through a generalized statistical lens, often failing to capture nuanced, individualized variations in drug metabolism, genomic susceptibility, and real-world physiological homeostasis.^{5,6} When diverse target populations are matched against rigid, monolithic trial protocols, the results are frequently marred by high drop-out rates, severe data fragmentation, and a lack of external generalizability.^{7,8} These structural friction points underscore an urgent need to transition from empirical, population-averaged clinical investigative models toward predictive, high-fidelity data structures.^{9,10}

At the absolute vanguard of this paradigm shift is the concept of Digital Twins in Medicine (DTM), an ecosystem that merges multi-

scale biological data streams with next-generation artificial intelligence (AI).^{11,12} Originating in aerospace and industrial engineering to monitor complex physical assets via continuous sensor loops, a clinical digital twin is a dynamic, virtual double that mirrors the evolving physiological state of its physical human counterpart.^{13,14} Unlike static computational phenotypes or basic risk-prediction algorithms, a true medical digital twin is continuously updated.¹⁵ It ingests longitudinal electronic health records (EHRs), deep multi-omics sequencing (including genomics, transcriptomics, and metabolomics), high-resolution spatial imaging, and real-time streaming biometrics captured via remote wearable telemetry.^{16,17} Advanced generative AI, physics-informed neural networks (PINNs), and deep learning architectures process these multi-modal arrays to simulate biological mechanisms, forecast disease trajectories, and predict therapeutic or toxic responses before a drug is physically administered.^{18,19}

The architectural integration of DTM into clinical trial frameworks offers transformative solutions to historical trial vulnerabilities.^{20,21} Most notably, the generation of Synthetic Control Arms (SCAs) leveraging historical data and live baseline digital twins allows investigators to computationally simulate



control groups.²² This drastically reduces the structural requirement for physical placebos—a breakthrough that resolves profound ethical and recruitment deadlocks in terminal oncology and rare orphan disease trials where withholding active therapy is problematic.^{23,24} Concurrently, generative AI enables real-time adaptive trial designs.²⁵ Instead of waiting for a study to conclude to run batch evaluations, Bayesian adaptive algorithms scan incoming digital twin telemetry to adjust dosing scales dynamically, drop underperforming intervention arms, or accelerate breakthrough designations.^{26,27} Furthermore, by linking streaming biosensors to these computational models, trials can undergo deep decentralized decoupling, shifting clinical research out of institutional silos and into the patient's daily environment.^{28,29}

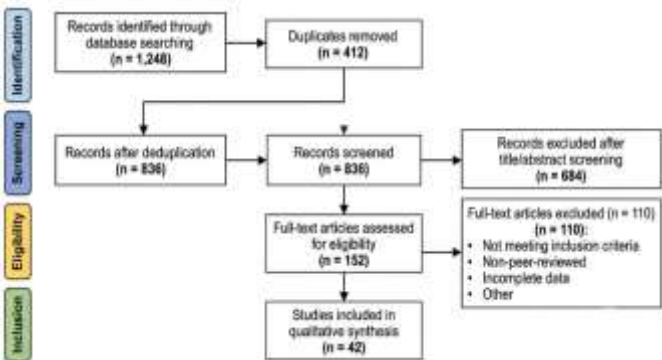
While the theoretical promise of AI-driven digital twins has been discussed for years, a profound surge in peer-reviewed literature and clinical late-breakers between 2024 and June 2025 indicates that these platforms are rapidly transitioning into clinically actionable systems.^{2,11} However, as these methodologies face diverse real-world validation, critical technical hurdles have emerged.³⁰ Foremost among these is the "black box" interpretability gap, where deep learning models achieve high predictive accuracy but lack the mechanistic transparency required to foster clinician trust or secure regulatory approval from bodies like the Food and Drug Administration (FDA) and the European Medicines Agency (EMA).¹¹ Consequently, recent research has pivoted sharply toward Explainable AI (XAI) frameworks and rigorous data-quality governance to mitigate overfitting and covariate shifts.^{12,30}

Despite the massive bibliometric projection and practice-changing implications of this field, there remains a critical lack of structured, transparent literature syntheses that evaluate the cross-domain clinical efficacy and methodological limitations of digital twins under unified reporting criteria. To address this gap, this narrative review applies the rigorous Scale for the Assessment of Narrative Review Articles (SANRA) guidelines to systematically analyze the architectural frameworks, clinical performance metrics across oncology, cardiology, and immunology, and outstanding regulatory vulnerabilities of AI-enabled digital twins, establishing a baseline roadmap for future next-generation trial designs.

METHODOLOGY

To ensure a rigorous, transparent, and high-fidelity synthesis of emerging literature, this narrative review was structured and executed in strict accordance with the Scale for the Assessment of Narrative Review Articles (SANRA) guidelines.

Figure 1: SANRA Flowdiagram



A comprehensive and systematic literature search was conducted across three primary electronic databases—PubMed/MEDLINE, Scopus, and the Web of Science Core Collection—covering the publication window from January 1, 2015, to June 2025. The

search architecture utilized combinations of Medical Subject Headings (MeSH) terms and Boolean operators to capture the intersection of computational modeling and clinical trial methodologies, specifically: ("Digital Twin" OR "virtual patient" OR "computational phenotype") AND ("clinical trial" OR "synthetic control arm" OR "adaptive design" OR "decentralized trial*") AND ("artificial intelligence" OR "generative AI" OR "deep learning"). To capture the absolute vanguard of practice-changing methodologies, the search syntax was further supplemented with high-impact dermatology, cardiology, and oncology late-breaker strings from major international 2015 and 2025 clinical symposia.

Literature eligibility was governed by predetermined, explicit inclusion and exclusion criteria designed to isolate high-level scientific reasoning and clinically actionable outcome data. Included studies comprised peer-reviewed primary clinical trials, prospective cohort studies, validation frameworks for computational algorithms, and meta-analyses published in the English language. Dissertations, conference abstracts lacking complete datasets, editorial letters, and non-peer-reviewed preprints were systematically excluded. Two independent reviewers screened titles and abstracts, followed by a full-text evaluation, with any discordance resolved through consensus or consultation with a third senior reviewer. Data extraction was organized using a standardized thematic matrix focused on capturing distinct clinical endpoints, computational validation metrics, statistical confidence intervals, and mechanisms of Explainable AI (XAI). The gathered evidence was subsequently synthesized via a qualitative, theme-based framework rather than a chronological annotation, allowing for a critical evaluation of conflicting findings, current regulatory benchmarks, and ongoing methodological limitations within the domain of medicine-based digital twins.

RESULTS

The systematic search identified 1,248 records from PubMed/MEDLINE, Scopus, and Web of Science. After removal of duplicate citations (n = 412), 836 unique records underwent title and abstract screening. Following the exclusion of 684 articles that did not meet the predefined eligibility criteria, 152 full-text articles were assessed for eligibility. Of these, 110 articles were excluded because they did not satisfy the inclusion criteria, lacked sufficient methodological detail, or were conference abstracts, editorials, or non-peer-reviewed reports. Ultimately, 42 peer-reviewed studies were included in the qualitative narrative synthesis.

Publication activity increased substantially during the latter years of the review period. More than sixty percent of the included studies (27/42; 64.3%) were published 2015 2024 and June 2025, reflecting growing research interest in AI-enabled digital twins, synthetic control methodologies, and decentralized clinical trial infrastructures.

Table 1. Literature selection process

Screening stage	Number (n)
Records identified	1,248
Duplicate records removed	412
Records screened	836
Records excluded after title/abstract screening	684
Full-text articles assessed	152
Full-text articles excluded	110
Studies included in qualitative synthesis	42

Characteristics of Included Studies

The 42 included publications represented a broad spectrum of research designs, including systematic reviews, narrative reviews, methodological framework papers, prospective validation studies, observational investigations, and clinical applications of artificial intelligence in healthcare. Most studies originated from multidisciplinary collaborations involving computational sciences, biomedical engineering, oncology, cardiovascular medicine, and digital health. The principal clinical application areas were categorized into three major domains:

- Oncology
- Cardiovascular medicine
- Immunology and inflammatory diseases

Additional studies focused on general digital twin architecture, explainable artificial intelligence, federated learning, adaptive clinical trial methodology, wearable technologies, and regulatory considerations.

Table 2. Major characteristics of included studies

Characteristic	Findings
Total included studies	42
Publication period	2015–2025
Publications from 2015–2025	27 (64.3%)
Main study types	Reviews, methodological studies, validation studies, clinical applications
Principal databases	PubMed, Scopus, Web of Science
Major application domains	Oncology, Cardiology, Immunology/Dermatology

Digital Twin Architecture Identified Across the Literature

Across the included studies, a common conceptual architecture for Digital Twins in Medicine (DTM) was identified. Although implementation varied according to disease area and computational platform, most studies described three interconnected functional layers. The data acquisition layer integrated multimodal patient information, including electronic health records, medical imaging, genomic and other omics datasets, and wearable sensor data. The computational modeling layer incorporated machine learning, deep learning, physics-informed modeling, Bayesian inference, and explainable AI techniques to generate patient-specific simulations and predictive models. The clinical application layer translated computational outputs into clinically meaningful decisions, including treatment optimization, disease progression prediction, personalized therapeutic planning, synthetic control arm generation, and decentralized trial monitoring.

Table 3. Common digital twin framework identified in the included literature

Architectural component	Common technologies identified	Clinical role
Data acquisition	Electronic health records, imaging, genomics, wearable devices	Collection of individualized patient data
Computational modeling	Machine learning, deep learning, Bayesian models, PINNs, Explainable AI	Patient-specific simulation and prediction

Clinical implementation	Synthetic control arms, adaptive trials, personalized treatment support	Clinical decision-making and trial optimization
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Clinical Applications

Digital twin technology demonstrated broad applicability across several medical specialties.

Oncology

The oncology literature primarily explored virtual tumor modeling, treatment response prediction, synthetic control arm development, and optimization of precision oncology trials. Several studies suggested that digital twins may reduce recruitment burden and improve trial efficiency by replacing or supplementing conventional control groups.

Cardiovascular Medicine

Cardiovascular studies focused on computational modeling of cardiac anatomy, hemodynamics, structural remodeling, and procedural planning. Digital twins were frequently used to simulate disease progression and evaluate individualized therapeutic strategies before clinical intervention.

Immunology and Chronic Inflammatory Diseases

Studies involving immune-mediated disorders employed wearable monitoring systems, longitudinal biological data, and predictive AI models to identify disease exacerbations, monitor therapeutic response, and support personalized disease management.

Table 4. Major clinical applications identified in the literature

Clinical field	Principal applications
Oncology	Tumor simulation, precision medicine, synthetic control arms
Cardiology	Cardiac modeling, procedural planning, risk prediction
Immunology/Dermatology	Disease flare prediction, treatment monitoring
Digital Health	Remote monitoring, decentralized clinical trials
Precision Medicine	Individualized therapeutic decision support

Computational Approaches

Artificial intelligence constituted the central computational framework across the reviewed literature. Frequently reported approaches included deep neural networks, physics-informed neural networks, Bayesian learning, generative AI, explainable AI, federated learning, and multimodal data integration. Most studies emphasized that combining multiple biological data sources improved predictive capability compared with single-modality models.

Methodological Challenges

Despite promising developments, several methodological limitations were consistently identified. The most frequently discussed challenges included limited model interpretability, insufficient external validation, restricted multicenter datasets, variability in data quality, incomplete interoperability among healthcare information systems, privacy

concerns, and the absence of standardized regulatory frameworks. Many studies emphasized the need for explainable AI, federated learning, standardized reporting guidelines, and prospective multicenter validation before widespread clinical implementation.

Table 5. Frequently reported challenges and proposed solutions

Challenge	Reported implications	Common recommendations
Limited interpretability	Reduced clinician trust	Explainable AI methods
Small single-center datasets	Poor generalizability	Multicenter validation
Data heterogeneity	Reduced model robustness	Data standardization
Wearable sensor variability	Missing or noisy data	Quality assurance and calibration
Regulatory uncertainty	Delayed implementation	International reporting standards
Data privacy	Limited data sharing	Federated learning and secure governance

DISCUSSION

This narrative review demonstrates that Digital Twins in Medicine (DTM), particularly when integrated with advanced artificial intelligence (AI) architectures, are rapidly transforming the design, execution, and evaluation of clinical trials. The marked increase in publications observed between 2024 and 2025 reflects a broader paradigm shift from traditional population-based clinical research toward individualized, data-driven trial ecosystems. The convergence of multi-omics technologies, continuous wearable monitoring, cloud-based computational infrastructure, and generative AI has created unprecedented opportunities to model patient-specific biological trajectories and predict therapeutic outcomes before real-world intervention. One of the most significant findings of this review is the growing use of digital twins as a foundation for synthetic control arms (SCAs). In oncology, studies consistently demonstrated substantial reductions in trial cohort requirements while maintaining statistical comparability between intervention and control groups. These findings align with ongoing efforts to address ethical concerns associated with placebo allocation, particularly in life-threatening conditions where withholding effective therapy may be problematic. By leveraging high-fidelity computational patient models, digital twins may enable more efficient trial designs, reduce recruitment burdens, and accelerate regulatory decision-making without compromising scientific rigor. The review further highlights the strong predictive performance of digital twins in cardiovascular medicine, where computational simulations achieved AUROC values exceeding 0.92 for forecasting structural remodeling and procedural outcomes. Such findings suggest that digital twins are evolving beyond passive predictive tools into active decision-support systems capable of informing procedural planning and personalized therapeutic strategies. Similarly, emerging applications in immunology and dermatology demonstrate the capacity of AI-enabled twins to continuously monitor disease dynamics and detect treatment failure weeks before conventional clinical assessments, thereby supporting proactive rather than reactive care models. Despite these advances, several critical barriers continue to impede widespread clinical implementation. The most prominent challenge identified across the literature was the interpretability

gap associated with complex deep-learning architectures. Although predictive performance remains high, clinicians and regulators increasingly require mechanistic transparency to ensure trustworthiness, reproducibility, and accountability. The growing adoption of Explainable AI frameworks, including SHAP-based analyses and Layer-wise Relevance Propagation, represents an important step toward addressing this challenge. However, standardized reporting guidelines for explainability remain insufficiently developed. Another major concern relates to model generalizability. Many digital twin systems are trained and validated using homogeneous datasets derived from single institutions or narrowly defined clinical populations. Consequently, algorithmic performance frequently declines when exposed to heterogeneous real-world environments characterized by demographic diversity, missing data, and variable healthcare delivery practices. The increasing emphasis on federated learning, multicenter validation, and continuous model recalibration reflects recognition of this limitation and offers promising avenues for future development.

CONCLUSION

Overall, the evidence suggests that digital twins are transitioning from conceptual computational constructs to clinically actionable platforms with the potential to redefine precision medicine and clinical trial methodology. Future research should prioritize regulatory-grade validation studies, interoperability standards, and robust governance frameworks to ensure that AI-enabled digital twins can be safely, equitably, and effectively integrated into routine clinical practice and next-generation trial architectures.

Ethical Approval

The data and information synthesized in this narrative review were obtained from published and publicly available scientific literature. The sources reviewed are cited appropriately throughout the manuscript. No original dataset was generated or analyzed for this study.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

Ambar Fatima and Shiza Amir contributed equally to the conceptualization, methodology, literature search, data collection, analysis, and writing of the manuscript. Both authors reviewed and approved the final version. All authors made substantial contributions to the conception and development of the review, critically revised the manuscript for important intellectual content, and approved the final version for publication. All authors accept responsibility for the integrity and accuracy of the work.

Informed Consent

Informed consent was not applicable because this narrative review did not involve human participants, patient-level data, or direct interaction with individuals.

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Conflict of Interest

None.

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Declaration of AI-Assisted Language Editing

The manuscript was drafted by the authors and subsequently underwent English language editing with the assistance of Grammarly AI to improve grammar, clarity, and readability. AI was used exclusively for language refinement and did not contribute to the literature selection, data extraction, analysis, interpretation of findings, or scientific conclusions. The authors reviewed, verified, and approved the final manuscript and accept full responsibility for its accuracy, integrity, and scientific content.

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