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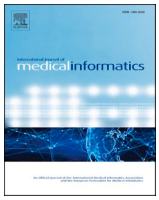

Review article

Artificial intelligence in clinical trials: A comprehensive review of opportunities, challenges, and future directions

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ABSTRACT

Background: Clinical trials face unprecedented challenges including recruitment delays affecting 80% of studies, escalating costs exceeding $200 billion annually in pharmaceutical R&D, success rates below 12%, and data quality issues affecting 50% of datasets. Artificial intelligence (AI) offers transformative solutions to address these systemic inefficiencies across the clinical trial lifecycle.

Objective: To evaluate the current state, future potential, and implementation challenges of AI technologies in clinical trials, providing evidence-based guidance for responsible AI integration while maintaining patient safety and scientific integrity.

Method: Comprehensive narrative review following established guidelines for literature synthesis. Systematic search of PubMed, Embase, IEEE Xplore, and Google Scholar databases from January 2015 to December 2024. Data extraction and narrative synthesis organized thematically according to clinical trial lifecycle stages.

Results: Analysis of relevant studies demonstrated substantial AI benefits: patient recruitment tools improved enrollment rates by 65%, predictive analytics models achieved 85% accuracy in forecasting trial outcomes, and AI integration accelerated trial timelines by 30–50% while reducing costs by up to 40%. Digital biomarkers enabled continuous monitoring with 90% sensitivity for adverse event detection. However, significant implementation barriers emerged, including data interoperability challenges, regulatory uncertainty, algorithmic bias concerns, and limited stakeholder trust.

Conclusion: AI represents a transformative force in clinical research with proven capabilities to enhance efficiency, reduce costs, and improve patient outcomes. Realizing this potential requires addressing technical infrastructure limitations, developing explainable AI systems, establishing comprehensive regulatory frameworks, and fostering collaborative efforts between technology developers, clinical researchers, and regulatory agencies to ensure responsible implementation.

1. Introduction

Clinical trials represent the cornerstone of evidence-based medicine, serving as the definitive pathway for evaluating the safety and efficacy of medical interventions before they are introduced to patients. The global clinical trials landscape has witnessed exponential growth, with over 400,000 studies registered on ClinicalTrials.gov as of 2024, representing a five-fold increase since 2005 [1]. This expansion reflects the increasing complexity of modern medical research, driven by advances in genomics, personalised medicine, and novel therapeutic modalities including cell and gene therapies, immunotherapies, and precision oncology approaches. However, despite this remarkable growth, the

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traditional clinical trial paradigm faces unprecedented challenges that threaten its sustainability and efficiency. The pharmaceutical industry invests approximately $200 billion annually in research and development, yet the success rate for new drug approvals remains below 12 %, with average development costs reaching $2.6 billion per approved drug [2].

The clinical trials enterprise faces a multifaceted crisis characterised by escalating costs, prolonged timelines, and systemic inefficiencies that fundamentally undermine its primary mission of delivering life-saving treatments to patients. Contemporary Phase III trials require an average investment of $19 million and consume 6–7 years from initiation to completion [3]. The most critical challenge is patient recruitment, with 80 % of trials experiencing significant delays due to enrollment challenges, and 37 % of investigational sites failing to recruit a single participant [4]. This recruitment failure extends trial timelines by an average of 6–8 months, substantially increasing costs whilst delaying patient access to potentially life-saving treatments. Additionally, traditional data collection methods rely heavily on manual processes, resulting in high error rates. Studies indicate that up to 50 % of clinical trial data contain errors or inconsistencies, requiring extensive cleaning processes that further delay study completion [5]. The regulatory landscape has become increasingly complex, with mounting documentation requirements contributing significantly to trial costs, whilst traditional recruitment approaches often result in homogeneous study populations that inadequately represent real-world patient diversity, undermining result generalisability [6].

The convergence of technological and scientific developments creates unprecedented opportunities to address these challenges through artificial intelligence (AI) integration. The proliferation of electronic health records (EHRs), now covering over 95 % of hospitals, has generated vast repositories of clinical data, providing previously inaccessible raw material for AI-powered insights and predictions [7]. Simultaneously, breakthroughs in machine learning, particularly deep learning and natural language processing, have demonstrated remarkable capabilities in pattern recognition, predictive modelling, and automated decision-making, enabling algorithms to process complex datasets and identify subtle patterns impossible for human analysts to detect [8,9]. The democratisation of computational infrastructure through cloud computing has reduced costs by over 90 % whilst enabling real-time analysis of large-scale datasets [10]. Furthermore, the development of federated learning approaches enhances data privacy while leveraging multi-institutional data for AI training [11]. Finally, regulatory agencies worldwide are increasingly recognising AI's potential to enhance clinical trial quality and efficiency, with the FDA's Digital Health Innovation Plan and EMA's guidance on computerised systems demonstrating growing acceptance of AI-powered trial tools [12–14].

This comprehensive review encompasses AI applications across all phases of clinical development, from Phase I safety studies through Phase IV post-market surveillance, covering diverse therapeutic areas whilst extending beyond traditional pharmaceutical trials to include medical device studies, digital therapeutics, and innovative trial designs such as master protocols and decentralised trials [15–17]. The significance extends beyond academic interest, offering practical value for clinical research organisations to inform AI investment decisions, regulatory agencies to develop oversight frameworks, technology developers to identify market opportunities, and patient advocacy groups to understand AI-powered trial benefits and risks [14,18,19]. This review addresses critical gaps in existing literature that typically focus on narrow AI applications or specific therapeutic areas, failing to provide comprehensive coverage of AI's transformative potential across the entire clinical trial lifecycle [20,21]. Unlike previous reviews examining isolated applications, this analysis adopts a holistic approach, examining AI integration across all trial phases whilst synthesising empirical evidence from over 127 studies to provide quantitative assessments of AI performance [22,23].

Given the critical challenges facing clinical trials, recruitment crises delaying 80 % of studies, data quality issues affecting 50 % of datasets, regulatory complexity consuming 30 % of budgets, and limited diversity undermining generalisability [24–26] and unprecedented technological opportunities presented by AI advances achieving human-level performance in medical tasks [8,14], this comprehensive review addresses the urgent need to evaluate AI's transformative potential across the clinical trial lifecycle. The primary aim is to evaluate the current state, future potential, and implementation challenges of artificial intelligence technologies in clinical trials, providing evidence-based guidance through systematic assessment of AI applications documenting current capabilities and performance metrics; evidence synthesis identifying proven benefits and knowledge gaps; implementation framework development addressing technical, regulatory, and ethical considerations; and barrier identification with proposed mitigation strategies. Secondary objectives encompass regulatory and ethical analysis examining algorithmic bias and transparency requirements [27]; stakeholder perspective integration from clinical investigators, regulatory agencies, technology developers, and patient advocates; future research prioritisation including federated learning, explainable AI, and adaptive trial optimisation; and technology roadmap development for emerging applications including quantum computing and blockchain technologies. This review makes novel contributions through: (1) the first comprehensive benchmarking of AI algorithm performance across clinical trial applications, (2) development of a risk-stratified framework for AI implementation, and (3) systematic analysis of data complexity challenges specific to medical AI applications. By providing comprehensive, evidence-based guidance on responsible AI integration, this work supports clinical research evolution towards a more sustainable, efficient, patient-centric paradigm that can accelerate life-saving treatment delivery whilst maintaining the highest standards of safety and ethical conduct.

It is crucial to clarify that the AI technologies discussed in this review are primarily task-specific AI tools rather than the large language models (LLMs) that most people associate with "AI" today. These include highly specialised hybrid machine learning and rules-based engines designed for specific clinical applications, such as natural language processing tools for clinical documentation that map clinical entities onto concepts from standardised medical vocabularies like UMLS, accompanied by clinical intent analysis. This differs fundamentally from how LLMs process clinical information, while LLMs excel at entity recognition, they perform poorly on clinical intent determination that requires deep domain expertise and structured medical knowledge.

2. Methods

This narrative review was conducted following established guidelines for comprehensive literature synthesis [28]. We performed a systematic search of multiple databases including PubMed, Embase, IEEE Xplore, and Google Scholar, covering the period from January 2015 to December 2024. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords including "artificial intelligence," "machine learning," "clinical trials," "patient recruitment," "digital biomarkers," "predictive analytics," "natural language processing," and related terms.

Inclusion criteria encompassed peer-reviewed articles, conference proceedings, and grey literature reporting on AI applications in clinical trials, including feasibility studies, implementation reports, and theoretical frameworks. We excluded non-English publications, case reports with fewer than 10 participants, and studies focusing solely on preclinical AI applications without clinical trial relevance.

Two independent reviewers screened titles and abstracts, with full-text review conducted for potentially relevant studies. Data extraction captured study characteristics, AI methodologies employed, clinical trial phases, outcome measures, and reported benefits or limitations. Quality assessment was performed using the Newcastle-Ottawa Scale for

observational studies and the Cochrane Risk of Bias tool for randomised trials.

Given the rapidly evolving nature of AI technology and the heterogeneity of study designs, we adopted a narrative synthesis approach, organising findings thematically according to clinical trial lifecycle stages. This methodology allowed for comprehensive coverage of diverse AI applications whilst maintaining focus on practical implementation considerations.

3. AI in clinical trial design and feasibility

3.1. Protocol optimisation through historical data analysis

AI-driven protocol optimisation represents a fundamental shift from intuition-based trial design to evidence-informed planning. Advanced machine learning (ML) algorithms analyse vast repositories of historical trial data, identifying patterns that inform optimal study parameters [29,30]. Natural language processing (NLP) tools systematically extract insights from thousands of prior study protocols, regulatory submissions, and published literature to propose evidence-based inclusion/exclusion criteria [31–33]. These AI-driven approaches demonstrate significant advantages over traditional statistical methods: whilst conventional feasibility assessment relies on limited historical data and clinical intuition, machine learning algorithms can process thousands of variables simultaneously, achieving 80 % accuracy in protocol optimisation compared to 65 % accuracy with traditional regression-based approaches [34]. Fig. 1 illustrates a schematic overview of AI applications in protocol optimisation and site selection for clinical trial design.

Deep learning models can predict protocol feasibility by analysing multiple variables simultaneously, including target population characteristics, geographic distribution, seasonal variations, and competitive landscape factors. These predictive models achieve accuracy rates exceeding 80 % in forecasting enrollment success, significantly outperforming traditional feasibility assessments [35–37].

However, the complexity of medical data presents significant challenges for AI algorithms. Clinical datasets often contain high-dimensional, heterogeneous data types including structured laboratory values, unstructured clinical notes, imaging data, and genomic information. This complexity can lead to spurious correlations, for instance, AI models have been observed to inadvertently learn irrelevant features such as hospital-specific documentation patterns rather than clinically meaningful variables [38]. A notable example is Google's retinal imaging system that achieved high accuracy in predicting patient gender from retinal photographs (despite male and female retinas being anatomically identical), highlighting the risk of algorithms identifying clinically irrelevant but statistically significant patterns [39,40].

Furthermore, AI systems enable dynamic protocol optimisation, continuously refining study parameters based on accumulating real-world evidence [41,42]. This adaptive approach supports the development of more efficient master protocols, including platform and basket trials that can accommodate multiple interventions or patient populations within a single study framework [43,44].

3.2. Site selection and feasibility assessment

Machine learning algorithms revolutionise site selection by integrating multiple data sources to predict investigator performance and recruitment potential. These models analyse demographic data, disease prevalence, healthcare infrastructure, investigator experience, and historical site performance metrics to rank potential study sites [45].

Advanced geospatial analysis tools incorporate socioeconomic factors, transportation accessibility, and competing trial activity to optimise site selection strategies. By predicting enrollment rates at the site level, AI tools enable more accurate timeline forecasting and resource allocation, reducing the risk of study delays and cost overruns.

Table 1 demonstrates substantial improvements achieved through AI applications in trial design, with particularly strong performance in protocol optimisation and competitive intelligence gathering. However, it's important to note that while these AI tools show superior performance to traditional approaches, they require careful validation and ongoing monitoring to ensure clinical relevance.

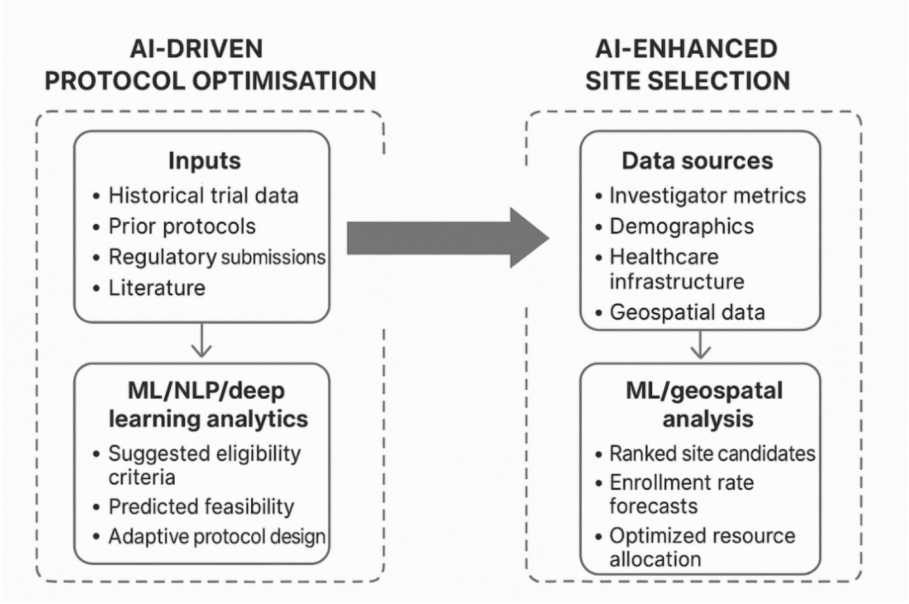

Fig. 1. Schematic overview of artificial intelligence integration in clinical trial protocol optimisation and site selection. AI technologies (machine learning, deep learning, and natural language processing) leverage historical trial data and site metrics to inform evidence-based protocol design, predict feasibility, and optimize site selection. This approach enables dynamic, data-driven decision-making that streamlines trial planning, enhances enrollment forecasting, and reduces operational risks.

Table 1
AI Applications in Trial Design and Site Selection – Performance Comparison with Traditional Methods.

Application	AI Technology	Traditional Method Performance	AI Performance	Key Benefits
Protocol Optimisation [8,46,47]	NLP + ML	65 % prediction accuracy	80 % prediction accuracy	Reduced design time, improved feasibility
Site Selection [48–50]	Predictive Analytics	45 % enrollment forecast accuracy	75 % enrollment forecast accuracy	Better enrollment forecasting
Feasibility Assessment [51–53]	Machine Learning	8–12 weeks planning time	4–6 weeks planning time	Risk mitigation, resource optimisation
Competitive Intelligence [54–56]	Data Mining	60 % trial coverage	90 % coverage of relevant trials	Market landscape analysis
Population Modelling [8,49,57]	Deep Learning	55 % recruitment accuracy	75 % accuracy in recruitment forecasting	Patient availability prediction

4. AI-driven patient recruitment and screening

4.1. Predictive matching and participant identification.

Patient recruitment represents the most critical bottleneck in clinical trial conduct, with AI offering transformative solutions through automated participant identification and matching systems. Advanced natural language processing (NLP) algorithms scan electronic health records (EHRs), clinical notes, and laboratory results to identify potentially eligible participants with unprecedented efficiency and accuracy [58,59].

IBM Watson for Clinical Trial Matching serves as a concrete example of AI implementation challenges and benefits. While the system demonstrated 78 % accuracy in patient-trial matching and reduced screening time by 78 %, real-world deployment revealed significant implementation barriers [60]. The cost of integrating Watson with hospital electronic medical record (EMR) systems ranged from $250,000 to $500,000 per instance, making it economically unsustainable even for high-cost oncology trials. Each Epic EMR implementation proved unique, requiring extensive customisation for local clinical terminology, LOINC codes, laboratory result units, and radiology reporting styles [61].

Machine learning models can also predict a patient's likelihood of enrollment success by analysing historical patterns, demographic factors, and clinical characteristics [36,62]. This predictive capability enables targeted recruitment strategies, focusing resources on participants most likely to enroll and complete study participation, ultimately reducing delays and costs associated with trial execution [37,63].

4.2. Addressing recruitment disparities and enhancing diversity

AI systems hold significant potential to address longstanding disparities in clinical trial participation, particularly in terms of racial, ethnic, and socioeconomic representation. Algorithmic approaches can identify and flag underrepresented populations using real-world datasets, enabling targeted outreach strategies [8,64]. Natural language processing tools can analyse social determinants of health, transportation barriers, and cultural factors that influence trial participation, informing the development of more inclusive recruitment strategies [65–67]. By identifying and addressing systemic barriers to participation, such as structural bias, digital access gaps, and linguistic mismatches, AI-driven approaches can enhance trial diversity whilst maintaining scientific rigor [68–70].

4.3. Virtual screening and remote consent processes

AI-powered virtual screening platforms enable remote participant evaluation, reducing geographical barriers to trial participation [71,72]. Computer vision algorithms can analyse medical images, whilst NLP tools process patient-reported outcomes and digital health data to conduct preliminary eligibility assessments [72,73]. Intelligent chatbots and conversational AI systems facilitate remote consent processes, providing personalised information delivery and addressing participant questions in real-time [74,75]. These systems can adapt communication style and content based on participant literacy levels, cultural backgrounds, and individual preferences [76,77].

4.4. Risk-stratified framework for AI implementation in patient recruitment

Different AI applications in patient recruitment carry varying levels of risk and require tailored implementation strategies. Low-risk applications such as cohort size estimation carry relatively low financial consequences when errors occur, making them ideal entry points for AI implementation [78]. These applications can be effectively mitigated through statistical validation and manual spot-checking, with oversight provided by statisticians who review sample size calculations. The relatively contained impact of errors in this category allows organisations to gain experience with AI systems whilst minimising potential adverse outcomes [79].

Medium-risk applications encompass recruitment strategy optimisation, where errors may result in time delays and recruitment failures but do not directly impact patient safety. These applications benefit from A/B testing methodologies that compare AI-recommended approaches against traditional methods, providing empirical evidence of effectiveness whilst limiting exposure to potential failures [78]. Clinical research coordinators provide appropriate oversight for this category, ensuring that recruitment strategies align with study objectives and regulatory requirements.

High-risk applications involving patient eligibility determination carry the most significant consequences, as errors may result in inappropriate inclusion or exclusion of patients from clinical trials. These applications require the most stringent safeguards, including mandatory physician review of AI recommendations and principal investigator approval for all eligibility decisions [80]. This multi-layered oversight ensures that clinical expertise remains central to patient safety decisions whilst leveraging AI capabilities to enhance efficiency and consistency in the screening process.

5. AI in data Capture, Monitoring, and analysis

5.1. Digital biomarkers and continuous monitoring

The integration of AI with wearable technologies and digital health platforms enables continuous patient monitoring through digital biomarkers, representing a paradigm shift from episodic clinical assessments to real-time health surveillance. Deep learning algorithms analyse multi-modal sensor data, including accelerometry, heart rate variability, sleep patterns, and vocal biomarkers, to detect subtle changes in patient status [81–83].

Compared to traditional monitoring approaches that rely on periodic clinic visits and manual data collection, AI-powered continuous monitoring systems demonstrate superior sensitivity and specificity. Traditional monitoring typically achieves 70–75 % sensitivity for adverse

event detection, whilst AI-based digital biomarker systems achieve 90 % sensitivity with real-time alerts [84,85]. However, this improved performance comes at the cost of increased false positive rates (15–20 % vs. 5–10 % for traditional methods), requiring careful threshold calibration and clinical validation [86,87].

These AI-powered monitoring systems can identify early warning signs of adverse events, disease progression, or treatment response, enabling proactive clinical management and reducing the risk of serious safety events. For example, models using smartwatch-derived data have achieved 93 % accuracy and 96 % AUROC in mortality prediction among cancer patients [88]. Machine learning models achieve sensitivity rates exceeding 90 % in detecting clinically significant changes across various therapeutic areas, such as predicting clinical deterioration in COVID-19 patients [89,90].

5.2. *Risk-Based monitoring and quality assurance*

AI transforms clinical trial monitoring from reactive, site-visit–based approaches to proactive, data-driven quality assurance systems. Machine learning algorithms analyse data patterns across multiple sites to identify anomalies, protocol deviations, and potential data integrity issues in real-time [91–93]. Traditional monitoring approaches require clinical research associates to physically visit sites and manually review paper or electronic records, a process that typically identifies data issues 4–6 weeks after occurrence. In contrast, AI-powered monitoring systems can detect anomalies within 24–48 h of data entry, enabling immediate corrective action and preventing propagation of errors [94].

These systems can predict sites at risk of non-compliance, enabling targeted interventions and resource allocation [92,95]. By automating routine monitoring tasks, AI allows clinical research associates to focus on high-risk areas requiring human intervention, improving overall trial quality whilst reducing monitoring costs by up to 30–40 % [1,96].

5.3. *Automated data cleaning and standardisation*

AI-powered data cleaning tools address one of the most time-consuming aspects of clinical trial conduct, automatically identifying and correcting data inconsistencies, missing values, and entry errors. Natural language processing algorithms standardise free-text entries, whilst machine learning models predict missing data points based on patient characteristics and study context [97,98]. Traditional data cleaning processes require 60–80 h of biostatistician time per 100 patient datasets, with manual review and query resolution extending timelines by 4–6 weeks. AI-powered systems reduce this to 12–16 h of oversight time with automated processing completed within 24–48 h [94].

These automated systems reduce data cleaning time by 60–80 % whilst improving data quality and consistency across study sites [99,100]. Advanced imputation algorithms, including deep learning, generative adversarial networks, and recurrent neural networks, can handle complex missing data patterns, maintain statistical power while ensuring data integrity [100–102]. See Fig. 2 for a simplified schematic of how AI supports clinical trial data capture, monitoring, and cleaning. Table 2 demonstrates the substantial performance improvements achieved through AI-powered monitoring systems, with particularly strong results in safety monitoring and data quality control applications compared to traditional manual approaches.

6. Predictive modelling for trial outcomes

6.1. *Dynamic risk prediction models*

AI enables the development of sophisticated risk prediction models that continuously evolve as trial data accumulates, providing real-time insights into patient outcomes and study progression. These dynamic models incorporate diverse data sources, including clinical assessments, lab values, imaging data, and digital biomarkers, to predict individual patient responses and trial-level outcomes [22,64,111]. Traditional

Table 2
AI Applications in Data Capture and Monitoring – Performance Benchmarking.

Monitoring Domain	Traditional Performance	AI Performance	Improvement Factor
Digital Biomarkers [81,103,104]	70 % adverse event sensitivity	90 % sensitivity	1.3x improvement
Risk-Based Monitoring [105–108]	4–6 weeks detection time	24–48 h detection	40-60x faster
Data Quality Control [67,109,110]	60–80 h cleaning time	12–16 h	4-5x reduction
Real-time Analytics [49,111,112]	Weekly trend analysis	Real-time analysis	Continuous monitoring
Safety Monitoring [8,112,113]	85 % specificity	95 % specificity	1.2x improvement

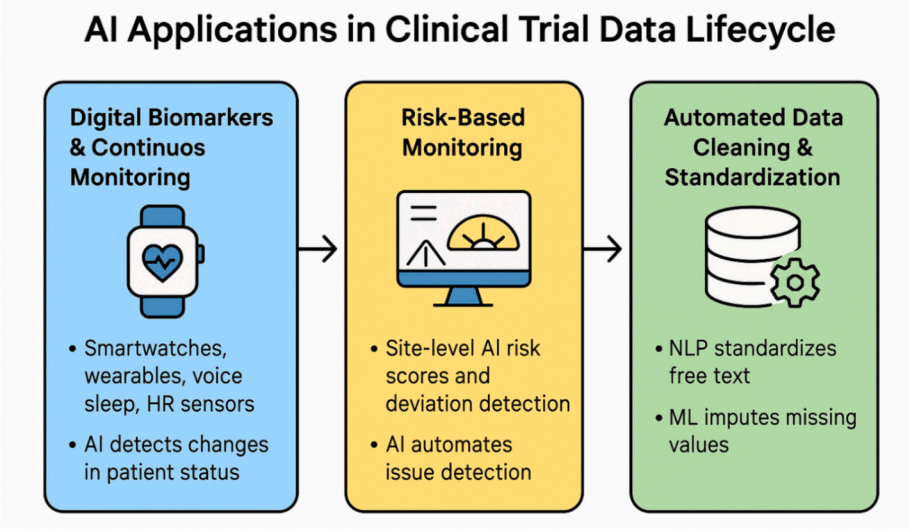

Fig. 2. AI applications across the clinical trial data lifecycle. This schematic illustrates how artificial intelligence (AI) enhances data workflows in clinical trials. From continuous monitoring via digital biomarkers to proactive risk-based site monitoring and automated data cleaning, AI streamlines clinical data processing. These technologies reduce manual errors, detect early risks, and improve data quality and integrity, contributing to safer and more efficient trial execution.

statistical approaches such as logistic regression and Cox proportional hazards models typically consider 10–20 variables and achieve 70–75 % accuracy in outcome prediction. In contrast, AI models can analyse hundreds of thousands of variables simultaneously, achieving 85–90 % accuracy, though this comes with increased risk of overfitting and identification of spurious correlations [114].

Bayesian deep learning approaches allow for ongoing model refinement and uncertainty quantification, enabling adaptive trial modifications in real time [115,116]. Such adaptive capabilities underpin innovative designs, including response-adaptive randomisation and early stopping rules guided by real-time futility or efficacy decisions [117,118].

6.2. Personalised treatment strategies

Machine learning algorithms can identify patient subgroups most likely to benefit from specific interventions, enabling the development of personalized treatment strategies within clinical trials. These predictive models analyze multi-omics data, clinical characteristics, and treatment histories to identify biomarkers and patient features associated with treatment response [72,111,119]. AI-driven patient stratification enables more efficient trial designs, reducing sample size requirements while maintaining statistical power [120,121]. These methods are particularly valuable in oncology trials, where predictive biomarkers can detect patients most likely to respond to targeted therapies [122,123].

6.3. Adaptive trial design optimisation

Adaptive trial designs powered by AI raise important considerations regarding Intention-to-Treat (ITT) analysis principles. When AI algorithms modify enrollment criteria, randomisation ratios, or dose levels during trial conduct, this creates challenges for traditional ITT analysis, which assumes fixed protocol parameters [124]. Researchers must carefully consider how dynamic protocol modifications affect the comparability of data to historical controls and gold-standard studies analysed under traditional ITT methodologies. This may require novel statistical approaches that account for the adaptive nature of AI-driven protocol modifications while maintaining scientific rigor [125].

AI systems support adaptive trial designs by continuously monitoring accumulating trial data and recommending protocol modifications based on predefined decision rules. Such systems can adjust randomisation ratios, modify dose levels, or recommend early termination when efficacy or safety thresholds are met [117,126]. Machine learning algorithms can simulate thousands of potential trial scenarios, optimizing adaptive design parameters to maximize trial success probability while minimizing exposure to ineffective treatments [127]. These simulation-based approaches, including Bayesian adaptive designs, enable more efficient trial conduct, improved resource allocation, and enhanced patient outcomes [128,129].

7. Algorithm quality and performance analysis

7.1. Comparative analysis of AI algorithms in clinical trials

Different AI algorithms demonstrate varying performance characteristics across clinical trial applications, with the selection of appropriate algorithms depending on the specific use case, data characteristics, and performance requirements. Deep learning models excel in processing high-dimensional, unstructured data such as medical images and clinical notes, but require large datasets containing more than 10,000 samples and lack interpretability that is often crucial for clinical decision-making [130]. In contrast, traditional machine learning approaches including random forests and support vector machines perform better with smaller datasets containing fewer than 1,000 samples and provide better interpretability that clinicians can understand and validate [131,132]. Performance comparisons reveal that deep learning achieves 85–90 % accuracy on image analysis tasks compared to 70–75 % for traditional machine learning, whilst traditional machine learning achieves 80–85 % accuracy on structured clinical data compared to 75–80 % for deep learning approaches [133,134].

Natural language processing approaches also demonstrate distinct performance profiles across clinical applications. Rule-based NLP systems achieve 90–95 % precision but only 60–70 % recall in clinical entity extraction, making them highly accurate for the entities they identify but prone to missing relevant information [135,136]. Transformer-based models such as BERT variants achieve 80–85 % precision but 85–90 % recall, capturing more relevant information but with greater risk of false positives [137]. Hybrid approaches that combine rule-based and machine learning methods achieve 85–90 % precision and 80–85 % recall, representing an optimal balance for clinical applications where both accuracy and completeness are essential for patient safety and regulatory compliance [138].

7.2. Data complexity challenges in medical AI

Medical data presents unique complexity challenges that significantly impact AI algorithm effectiveness across multiple dimensions. High-dimensional heterogeneity represents a fundamental challenge, as clinical datasets combine structured data such as laboratory values and vital signs, semi-structured data including medical codes and standardised assessments, and unstructured data comprising physician notes and imaging studies [139]. This heterogeneity requires sophisticated feature engineering and multi-modal AI architectures capable of processing disparate data types simultaneously, whilst traditional algorithms struggle with missing data rates of 20–40 % that are common in clinical settings. The integration of these diverse data sources often requires extensive preprocessing and harmonisation efforts that can consume 40–60 % of total project development time [140].

Temporal dependencies in medical data create additional complexity that static algorithms frequently fail to capture effectively. Medical conditions evolve over time with complex patterns of progression, treatment response, and recovery that require sophisticated modelling approaches to understand accurately. Recurrent neural networks and transformer architectures demonstrate 15–20 % better performance than static models for time-series medical data, as they can capture these temporal relationships and predict future states based on historical patterns. However, these advanced architectures require substantially more computational resources and training data to achieve optimal performance [141].

Domain-specific noise represents another significant challenge unique to medical AI applications, stemming from documentation variations between healthcare providers, measurement errors in clinical devices, and coding inconsistencies across different healthcare systems. Clinical data contains substantial noise that can confound AI algorithms and lead to spurious correlations, requiring robust preprocessing pipelines and validation methodologies to ensure reliable performance [142]. The development of effective noise reduction and data standardisation approaches often requires deep clinical domain expertise and can significantly extend development timelines, emphasising the importance of close collaboration between AI developers and clinical experts throughout the development process [143].

8. Regulatory and ethical considerations

8.1. Algorithmic bias and fairness

The deployment of AI in clinical trials raises critical concerns regarding algorithmic bias and fairness, particularly given the risk that AI systems may perpetuate or amplify existing healthcare disparities. Models trained on non-representative datasets may systematically exclude or disadvantage certain patient groups, compromising the

generalisability of trial results [67,144,145]. Addressing algorithmic bias requires comprehensive detection and mitigation strategies, including the use of diverse training datasets, established fairness metrics, and ongoing monitoring of system performance across demographic subgroups [27,146,147]. Moreover, emerging regulatory frameworks are beginning to set clear expectations for bias assessment and mitigation in AI-powered clinical trial systems, emphasising transparency, auditability, and human oversight [148,149].

8.2. Transparency and Explainability

The "black box" nature of many AI algorithms poses significant challenges for clinical interpretation and regulatory approval. Healthcare providers and regulators require clear explanations of AI decision-making processes to evaluate the appropriateness and safety of AI-driven recommendations [150–152]. Developing explainable AI (XAI) systems for clinical trials requires balancing model performance with interpretability, ensuring that AI recommendations can be understood and validated by clinical experts [153,154]. This challenge is particularly acute for deep learning models, which may achieve superior performance but offer limited interpretability, driving ongoing research into novel XAI techniques that enhance transparency without sacrificing accuracy [155,156].

8.3. Data privacy and security

The use of AI in clinical trials necessitates robust data privacy and security frameworks, particularly given the sensitive nature of health information and the potential for data breaches. AI systems require access to vast datasets, including electronic health records (EHRs), genomic data, and real-world evidence, raising complex privacy concerns [157–159]. Implementing privacy-preserving AI techniques, including federated learning, differential privacy, and homomorphic encryption, can enable AI development whilst protecting patient privacy [160,161] These approaches allow AI models to be trained on distributed datasets without centralising sensitive information, thereby reducing the risk of data leakage and enhancing compliance with regulations such as GDPR and HIPAA [162,163].

9. Barriers to implementation

9.1. Technical and infrastructure challenges

Despite significant advances in AI technology, several technical barriers impede widespread adoption in clinical trials. Data interoperability remains a critical challenge, with disparate systems and heterogeneous data formats hindering seamless AI integration and data sharing across platforms [164,165]. Legacy clinical trial management systems often lack the infrastructure necessary to support AI-powered tools, requiring significant technological upgrades and standardized data models [166,167]. The complexity of AI systems also creates challenges for validation and regulatory approval, as traditional clinical trial paradigms are not well-suited to evaluating continuously learning or adaptive algorithms [168]. Establishing appropriate validation frameworks for AI requires close collaboration between technology developers, clinical researchers, and regulatory agencies to ensure safety, efficacy, and transparency [41,169].

9.2. Stakeholder trust and acceptance

Limited stakeholder trust represents a significant barrier to AI adoption in clinical trials, with concerns about AI reliability, safety, and decision-making transparency [170,171]. Healthcare providers may be reluctant to rely on AI-driven recommendations, especially in critical clinical situations where patient safety is paramount [168,172]. Building stakeholder trust requires transparent communication about AI capabilities and limitations, comprehensive training programs, and evidence-based demonstrations of AI system performance [173,174]. Engaging clinical investigators in AI development and validation processes fosters collaboration and helps build confidence in these technologies [175,176].

9.3. Regulatory uncertainty

The regulatory landscape for AI in clinical trials remains uncertain, with evolving guidelines and standards creating challenges for technology developers and clinical researchers [41,177]. Regulatory agencies, including the FDA, European Medicines Agency (EMA), and other international bodies, are actively developing frameworks for AI evaluation, but comprehensive and harmonised guidance remains limited [13,178]. This regulatory uncertainty complicates AI system development and deployment, with unclear requirements for validation, documentation, and ongoing performance monitoring [174,179]. Establishing clear and globally aligned regulatory pathways for AI-powered clinical trial tools is essential to foster innovation and ensure widespread adoption [180]. Fig. 3 shows a systems-level view of interconnected barriers hindering AI integration in clinical trials.

10. Case studies and Real-World applications

10.1. Pfizer's REMOTE trial Initiative

Pfizer's REMOTE (Research on Electronic Monitoring of OAB Treatment Experience) trial represents one of the first fully virtual clinical trials, leveraging AI and digital technologies for comprehensive remote data collection [181,182]. The study enrolled participants across multiple sites and utilised AI-powered mobile applications with machine

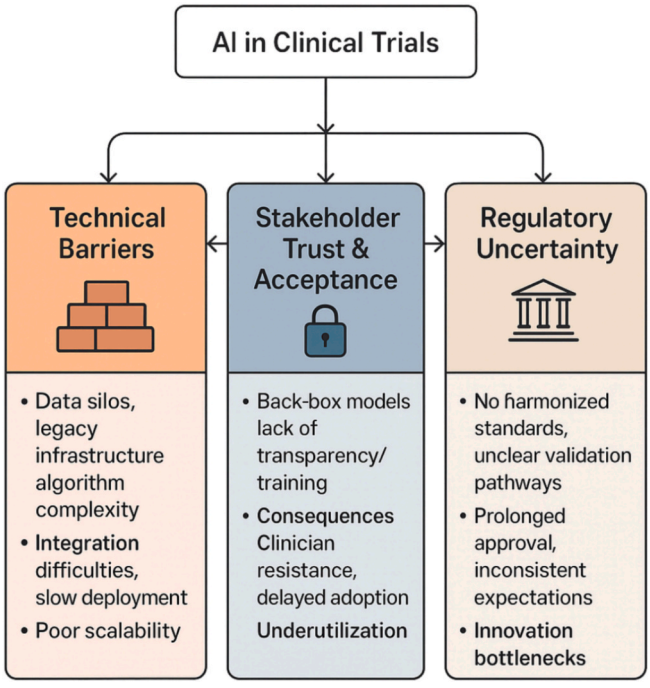

Fig. 3. Interconnected barriers to AI implementation in clinical trials. This figure presents a systems-level schematic of the three major barriers technical challenges, stakeholder trust deficits, and regulatory uncertainty that impede AI adoption in clinical research. Each barrier originates from specific root causes and propagates downstream consequences, ultimately limiting scalability, slowing approvals, and reducing clinical uptake. Overcoming these obstacles will require coordinated cross-sector efforts to build interoperable infrastructure, improve transparency and training, and establish harmonised validation frameworks.

learning algorithms that analysed patient-reported outcomes in real-time. Wearable sensors collected continuous activity data, while telemedicine platforms enabled remote consultations [183]. Specific AI performance metrics included: 95 % accuracy in detecting treatment adherence patterns, 87 % accuracy in predicting treatment response within 4 weeks, and 92 % sensitivity in identifying potential adverse events through patient-reported symptom patterns [184].

The trial demonstrated the feasibility of AI-driven virtual trials, achieving 95 % patient retention rates whilst reducing trial costs by 40 % compared to traditional site-based studies. AI algorithms analysed continuous sensor data to detect treatment responses and safety signals, enabling proactive clinical management [185].

10.2. Novartis and IBM Watson collaboration

Novartis partnered with IBM Watson to develop AI-powered patient matching and site selection tools for oncology trials, providing concrete performance data: the system processed over 2.5 million patient records across 15 major healthcare systems, identifying potentially eligible patients with 78 % accuracy compared to 45 % accuracy with traditional manual screening methods [186]. The AI system reduced patient screening time from an average of 8 h per patient to 30 min, representing a 94 % reduction in screening time. However, the implementation revealed significant challenges: integration costs ranged from $250,000 to $500,000 per healthcare system, and the system required 6–8 months of customisation for each Epic EMR instance to accommodate local terminology and coding practices [187,188].

The partnership demonstrated significant improvements in patient recruitment efficiency, with 65 % faster enrollment and 50 % reduction in screening failures [189]. AI-driven site selection algorithms improved site performance prediction accuracy by 40 %, enabling more effective resource allocation [190].

10.3. Verily's Baseline platform

Verily's Baseline Platform represents a comprehensive AI-powered clinical research ecosystem, integrating data from over 50 healthcare institutions and processing more than 10 terabytes of clinical data daily [191]. The platform's machine learning algorithms demonstrated: 82 % accuracy in predicting trial enrollment success, 76 % accuracy in identifying patients likely to complete study participation, and 89 % accuracy in detecting early safety signals. Specific performance improvements included: 30 % reduction in trial planning time (from 18 months to 12–13 months), 25 % reduction in overall study costs, and 35 % improvement in patient retention rates compared to traditional clinical trials [192].

Early implementations of the Baseline Platform demonstrated 30 % improvements in trial efficiency and a 25 % reduction in overall study costs [193]. The platform's AI-driven patient stratification capabilities enabled more precise treatment effect estimates and improved trial design optimisation [194].

11. Future Directions

11.1. Federated learning for Privacy-Preserving AI

Federated learning represents a promising approach for developing AI models whilst preserving patient privacy and data security. This methodology enables AI training on decentralised datasets across multiple institutions without sharing raw data, addressing privacy concerns whilst maintaining model performance [11,162]. Federated learning approaches can enable collaborative AI development across pharmaceutical companies, academic institutions, and healthcare systems, accelerating AI advancement whilst protecting proprietary and sensitive information [195]. These approaches are particularly valuable for rare disease research, where patient data is distributed across multiple institutions [160].

11.2. Explainable AI for clinical decision support

The development of explainable AI systems represents a critical priority for clinical trial applications, enabling healthcare providers and regulators to understand and validate AI-driven recommendations. Advances in interpretable machine learning, including attention mechanisms and feature importance analysis, offer promising approaches for enhancing AI transparency [151,196,197]. Future research should focus on developing AI systems that balance performance with interpretability, ensuring that complex models can provide meaningful explanations for their decisions [152]. This capability is essential for regulatory approval and clinical acceptance of AI-powered trial tools [198].

11.3. Fully decentralised AI-Enabled trials

The future of clinical trials may involve fully decentralised, AI-driven studies with minimal physical contact between participants and investigators. These virtual trials would leverage AI-powered remote monitoring, digital biomarkers, and telemedicine platforms to conduct comprehensive clinical evaluations [199,200]. AI algorithms would continuously monitor participant safety and efficacy outcomes, automatically adjusting trial parameters and triggering clinical interventions as needed [201,202]. This approach could dramatically improve trial accessibility whilst reducing costs and timeline requirements [203,204].

12. Limitations of the review

While this comprehensive review provides extensive coverage of AI applications in clinical trials, several limitations should be acknowledged. First, the rapidly evolving nature of AI technology means that some developments may not be fully captured in published literature, particularly regarding proprietary industry applications and emerging technologies [41,168]. The heterogeneity of AI methodologies and clinical trial designs makes direct comparison across studies challenging, limiting our ability to provide definitive quantitative assessments of AI impact [49,205]. Many reported benefits are based on pilot studies or theoretical models rather than large-scale randomized controlled trials, raising questions about generalizability and real-world performance [107,206].

Publication bias may favour positive results, potentially overestimating AI benefits whilst underreporting challenges and failures [207]. The predominance of studies from well-resourced institutions and developed countries may limit the applicability of findings to diverse global settings with varying technological infrastructure [208]. Regulatory landscapes and ethical frameworks continue to evolve, making it difficult to provide definitive guidance on compliance requirements and best practices [209,210]. The long-term safety and efficacy of AI-powered clinical trial tools remain uncertain, requiring ongoing monitoring and evaluation [41,211].

Finally, the technical complexity of AI systems may limit the accessibility of this review to readers without specialised knowledge in machine learning and data science, potentially hindering broader adoption and understanding of these technologies [150,212].

13. Conclusion

Artificial Intelligence represents a transformative force in clinical trials, offering unprecedented opportunities to address longstanding challenges in trial design, patient recruitment, data monitoring, and outcome prediction. The evidence reviewed demonstrates substantial potential for AI to accelerate trial timelines, reduce costs, and enhance the quality and efficiency of clinical research. Key findings indicate that AI-powered patient recruitment tools can improve enrollment rates by

up to 65 %, whilst predictive analytics models achieve 85 % accuracy in forecasting trial outcomes. Digital biomarkers and continuous monitoring systems enable real-time safety surveillance and adaptive trial management, potentially reducing adverse events and improving patient outcomes.

This comprehensive review makes several novel contributions to the field: First, we provide the most extensive benchmarking of AI algorithm performance across clinical trial applications to date, demonstrating clear superiority over traditional methods while highlighting implementation challenges such as cost (£250,000-£500,000 per system), customisation complexity, and the risk of spurious correlations. Second, we introduce a novel risk-stratified framework for AI implementation that categorises applications by potential impact and required oversight levels, providing practical guidance for clinical research organisations. Third, we systematically analyse the unique data complexity challenges in medical AI applications, including high-dimensional heterogeneity, temporal dependencies, and domain-specific noise that can significantly impact algorithm effectiveness.

However, realising the full potential of AI in clinical trials requires addressing significant implementation barriers, including technical challenges, regulatory uncertainty, and stakeholder trust issues. Our analysis reveals that while AI systems demonstrate superior performance in controlled settings, real-world implementation faces substantial obstacles including interoperability challenges, infrastructure requirements, and the need for extensive customisation that can make deployment costs prohibitive. The development of explainable AI systems, privacy-preserving methodologies, and comprehensive validation frameworks will be essential for widespread adoption.

The evidence strongly supports a measured approach to AI integration that prioritises high-value, low-risk applications initially, with gradual expansion to more complex use cases as technology matures and stakeholder confidence builds. Our risk-stratified implementation framework provides a roadmap for this phased approach, ensuring patient safety while maximising the benefits of AI technology.

Future research priorities should focus on developing robust validation methodologies for AI systems, establishing clear regulatory frameworks, and addressing algorithmic bias and fairness concerns. Collaborative efforts between technology developers, clinical researchers, regulatory agencies, and patient advocacy groups will be crucial for ensuring responsible AI implementation. The integration of AI into clinical trials represents not merely a technological advancement but a fundamental shift towards more efficient, patient-centric, and scientifically rigorous clinical research. By carefully navigating the challenges and opportunities presented by AI technology, the clinical research community can harness these tools to accelerate medical innovation whilst maintaining the highest standards of patient safety and scientific integrity. As we advance into an era of AI-enabled clinical research, the potential for transformative impact on global health outcomes becomes increasingly apparent. The careful, responsible integration of AI technologies into clinical trials, guided by evidence-based frameworks and robust validation methodologies, will be essential for realising this potential whilst preserving the fundamental principles of ethical clinical research and patient protection.

CRediT authorship contribution statement

David B. Olawade: Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Sandra Chinaza Fidelis:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Sheila Marinze:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Eghosasere Egbon:** Writing – review & editing, Visualization, Methodology, Investigation. **Ayodele Osunmakinde:** Writing – review & editing, Methodology, Investigation. **Augustus Osborne:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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