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REVIEW

Blockchain for applications of clinical trials: Taxonomy, challenges, and future directions

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Abstract

Patient enrollment, data sharing, and data privacy are enormous medical challenges for clinical trial studies. In recent years, blockchain technology has drawn the attention of various researchers and institutes. As a new and innovative distributed ledger technology, blockchain can be critical to addressing these challenges, thus making clinical research transparent and building public trust fairly and openly. However, the existing literature lacks a comprehensive survey on the adoption of blockchain in clinical trials. To fill the research void, this paper presents a punctilious taxonomy of blockchain technology in clinical trials according to the literature. This taxonomy comprises decentralized scenarios, decentralized practices, blockchain types, deployment methods, and consensus algorithms. The results show that blockchain technology can cover all aspects of the clinical trial study in a decentralized, secure, transparent manner. Besides, some open research challenges of blockchain are categorized into three groups: technical challenges, security challenges, and organizational challenges. Moreover, some recent blockchain projects, micro applications in clinical trials, and several research areas or technologies for future research and development are discussed.

1 | INTRODUCTION

The clinical trial is an important part of drug development, and a means to ensure drug efficacy and safety [1]. During the trial, researchers collect data from the subject at preset intervals, including vital signs, changes in symptoms, and side effects caused by the study medicine. In general, the clinical trial requires collaboration among several parties, including regulatory agencies, pharmaceutical companies, clinical sites, and most importantly, the participants [2–4]. In addition, each participant in a clinical study contributes a unique set of capabilities to support the infrastructure of the clinical trial. As shown in Figure 1, the current workflow of clinical trials consists of different, independent activities [5]. In this paradigm, data is collected from disparate sources (smart devices, clinical trial sites), processed, and analyzed according to the preferences of each organization.

It is believed that around 10% of clinical research cannot be replicated [6]. The high mistake rate is most likely caused by human error, fraud, or misbehaviour. Typical errors in data collecting and transcription may directly impact the quality of the data collected in clinical studies [7]. Data inconsistency in clinical trials can lead to the imprecision medicine problem [8]. Due to these concerns, more supervision requirements are required, raising the regulatory burden of document inspection. Under the existing system for clinical trials, assessing data quality is not a simple task. It is not easy to find data exceptions in a timely manner, and business domain and data modelling expertise are required to maintain a reasonable degree of data quality [9]. Currently, domestic and international drug clinical trial supervision consists mainly of post-monitoring, and there is a time gap in the supervision of data quality management and operational planning requirements.

Blockchain is a decentralized, verifiable, and tamper-resistant electronic ledger suitable for application domains where collaboration between multiple participants and data transparency are equally important in the network. In 2008, Satoshi Nakamoto established blockchain as the public record for the digital currency Bitcoin [10]. From the introduction of cryptocurrencies

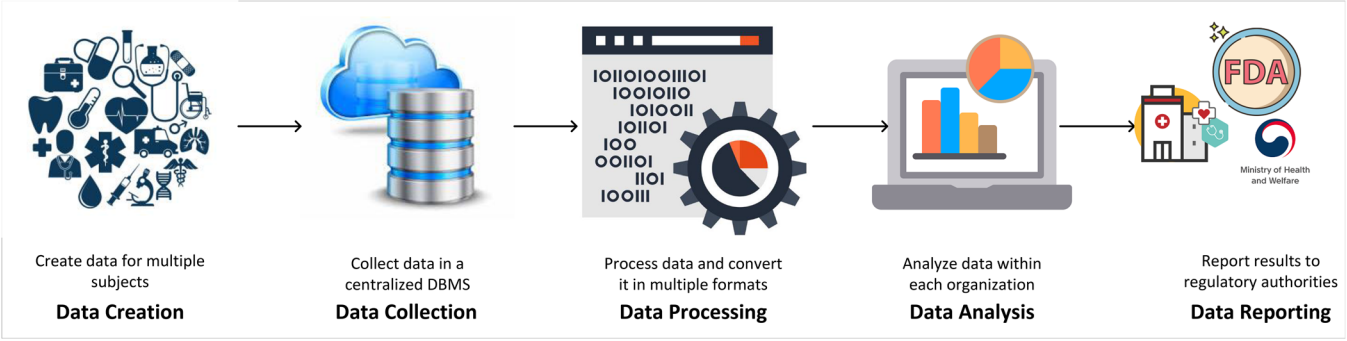

FIGURE 1 The current process for clinical trials

to distributed ledger systems and mobile apps, this technology is being embraced across all industries, and its use has become a significant plus for businesses. As the technology improves, different applications beyond financial and banking services have been investigated [11–14]; the healthcare business could benefit from its adoption [15–23]. For instance, blockchain-based models for electronic medical records have been suggested to enable individuals to exert more control over their medical data and improve data exchange across platforms [24–26]. Furthermore, blockchain technology has been used in forestalling pandemics [27] and remote patient monitoring [28]. The features of blockchain technology, such as data transparency and traceability, have accelerated the reformation of current healthcare institutions, including health data interchange and patient follow-up through transaction trace [29].

Utilizing blockchain technology to manage clinical trial databases shows great potential for enhancing research in pharmaceutical industries. Besides, blockchain can disrupt the clinical trial industry while diminishing the use of legacy data management platforms [30–32]. Blockchain technology could directly address the present issues with clinical trials and improve the management of clinical trials by regulatory bodies and research institutes. Besides, it could enhance the underlying technology of clinical trial research, ultimately boosting the credibility of clinical studies. In clinical trials, a Peer-to-Peer (P2P) network is created using blockchain technology to record data interactions throughout clinical trials, enable data exchange, and make trial data visible and immutable [33–35]. The smart contract [36], which functions as a decentralized program that lives on the blockchain, can automate these procedures. For example, it could fulfil numerous functions concurrently, such as automating the business logic of an application without involving third parties, assuring data provenance, producing immutable audit trails, and imposing duties on an action if specific rules are satisfied [37]. Tools using blockchain technology can automatically link and distribute healthcare data to other researchers and clinics. As a result of the immutability of blockchain records, auditing and data verification are facilitated. The integrity of immutable clinical trial data stored on a blockchain can inspire more faith, resulting in safer medications and increased public confidence in scientific research.

Figure 2 describes the process of a clinical trial based on blockchain technology. Unlike the current process of clinical trials shown in Figure 1, the data among different stakeholders is transparent and accessible. The blockchain preserves a complete, up-to-date history of all trial-related data, including the clinical protocol, visit history, subject info etc., which would track the enrolled subject during the clinical trial study. The data lake serves as an isolated data repository, known as off-chain storage. The blockchain network consists of trusted validating peers, and each peer holds a copy of the ledger for the network to maintain the consistence of the distributed ledger. The clinical director can access the trial-related data through any network peer where their information is preserved. This is realized by specifying the access control policy in the smart contract, which is deployed into the entire blockchain network to ensure data privacy and security. All the end users and blockchain interactions are encrypted with a digital signature to ensure the system's security.

Table 1 outlines and compares the proposed survey with recent, state-of-the-art reviews of using blockchain in the healthcare sector. The development of blockchain technology is still in its infancy, though previous studies have validated it in several use cases in the healthcare sector. The current literature lacks a comprehensive survey on the adoption of blockchain technology in clinical trials. To fill this gap, we review the state-of-the-art of blockchain technology in clinical trials and explain the key concepts that enable blockchain technology to enhance the process and management of clinical trials. Some recent blockchain projects and micro applications in clinical trials are discussed, as well as the open challenges and future research directions.

The key contributions of this paper are highlighted as follows:

- Providing a detailed review of the state-of-the-art blockchain technology in clinical trials fulfils the research gap in the current works.
- Overviewing the issues in current clinical trial research.
- Discussing many characteristics and premier advantages of blockchain solutions in clinical practice and the underlying concepts.

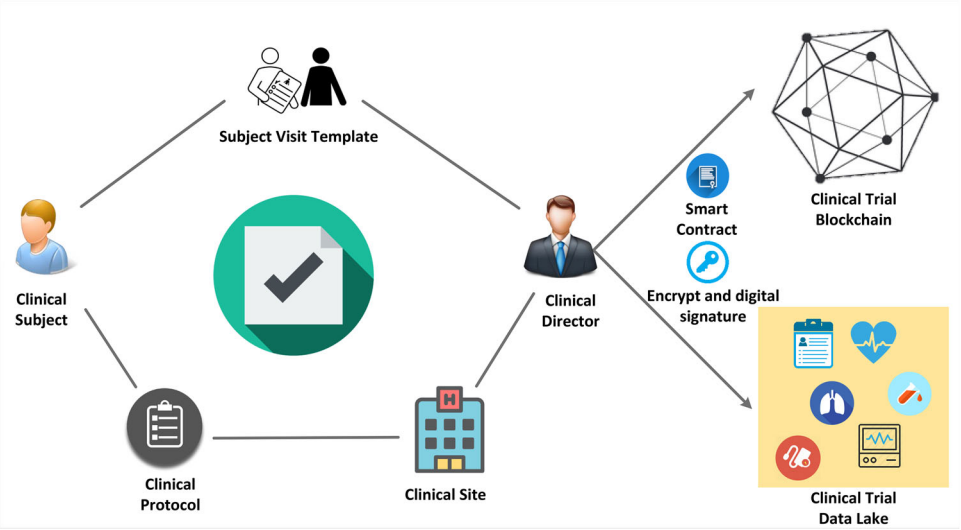

FIGURE 2 Blockchain-based process for clinical trials

- Presenting a thematic taxonomy to evaluate the role of blockchain in clinical trials regarding trial-related scenarios and practices, blockchain type, and consensus protocol.
- Highlighting ongoing efforts to use blockchain technology in clinical trials.
- Identifying, enumerating, and discussing several crucial challenges and future research directions toward using blockchain technology in clinical trials.

The remainder of this paper is structured as follows: Section 2 elaborates on phases of current clinical trials. Section 3 overviews the issues in current clinical trials. Section 4 describes the taxonomy of blockchain in clinical trials. The development trend of blockchain applications in clinical trials is discussed in Section 5. Some recent micro blockchain applications in clinical trials are reviewed in Section 6. Section 7 outlines some open research challenges using blockchain technology in clinical trials. Section 8 highlights future research directions, and finally, Section 9 concludes the survey.

2 | PHASES OF CLINICAL TRIALS

Human participants are used in clinical trials to determine if a drug is useful and what negative effects it may produce. The trials collect information on a treatment whose efficacy in treating a particular ailment has not yet been established. A drug being evaluated in a clinical study is an experimental drug [38]. Before a novel treatment can be utilized in a clinical trial, it must undergo preclinical testing. All in vitro (test-tube or laboratory) research and animal experiments include preclinical testing. To determine preliminary efficacy, toxicity, and pharmacokinetics, several doses of the test medication or an in-vitro substrate are administered to animals [39–40].

In different rounds of clinical trials, new drugs and therapies are evaluated for their ability to combat freshly discovered or existing pathologies. These clinical trial stages are the measures scientists take to test the effectiveness of novel drugs or therapies on a limited sample of patients. As represented in Figure 3, a new treatment goes through several phases. Each phase has a different purpose: phase 1 trials test if a new treatment is safe and look for the best way to give the treatment. Phase 1 trials usually include less than 100 patients divided into small groups. Doctors also look for signs that the disease responds to the new treatment; Phase 2 trials test if one type of disease responds to the new treatment, 100–300 patients usually join a phase 2 trial. If the new treatment works, doctors may go on to study in a phase 3 trial; Phase 3 trials test if a new treatment is better than a standard treatment. Phase 3 trials may include 300–3000 patients worldwide; Phase 4 trials find more information about long-term benefits and side effects.

Table 2 details the roles and responsibilities of stakeholders in clinical trials. US Food and Drug Administration (FDA), Institutional Review Board (IRB), Sponsor, Contract Research Organization (CRO), Principal Investigator (PI), Clinical Research Coordinator (CRC), and the subject are the parties participating in a clinical trial system. The current approach for clinical trials is centred on the sponsor, and the CRO monitors and controls the process.

3 | ISSUES IN CURRENT CLINICAL TRIALS

A continual and effective flow of medical advances is essential for meeting society's rising medical demands. Ongoing study indicates that drug development costs increase by 9% annually [43]. There are issues with all facets of drug clinical trials, including preparation before clinical trials, protecting subjects' rights and interests, and implementing, recording, and managing clinical trial samples. This section discusses several issues in current clinical trial research.

TABLE 1 Summary of related surveys in the healthcare sector

Ref	Problem Statements	Blockchain Services	Open Challenges	Research Directions	Theme of Work
[15]	Inaccurate information, speculations, and uncertainties about the potential utility of blockchain in the healthcare industry	1. Electronic Medical Record (EMR) 2. Pharmaceutical supply chain 3. Biomedical research and education 4. Remote patient monitoring (RPM) 5. Health insurance claims 6. Health data analytics	1. Interoperability 2. Security and privacy 3. Scalability 4. Speed 5. Patient engagement	1. More prototypes 2. Open standards	Use cases for the application of blockchain in healthcare, limitations, and areas for future research
[16]	Unrealistic proposals and ideas and current literature provide a little overview of applications	EMR	N/A	1. More technical details 2. Compliance of blockchain systems with current health data laws and standards	Examples of utilizing blockchain to improve processes and services in healthcare, health sciences, and health education
[17]	N/A	1. Healthcare data sharing systems 2. Blockchain platform for clinical trials and precision medicine 3. Healthcare data gateway	1. Scalability 2. Interoperability and security	1. Conduct with real-world datasets 2. Realm of Identity verification	Blockchain applications in healthcare, research challenges, research opportunities
[18]	It is crucial to identify those issues and challenges of the Internet of Things (IoT)s and blockchain technology in the healthcare sector	1. Drug traceability 2. RPM 3. EMR	1. Interoperability 2. Security 3. Scalability and Storage Requirement Handling 4. Lack of Standardization 5. Hesitation and lack of trust 6. Data ownership and accountability	N/A	The applicability and challenges of IoT and Blockchain in the medical sector
[19]	Previous surveys focus on the adoption of blockchain in healthcare applications and lack discussion of other important aspects of blockchain	1. Drug traceability 2. EMR 3. Clinical trials and precision medicine 4. Consistent permissions 5. Telehealth systems 6. Health insurance claims 7. Medical billing systems	1. Scalability 2. Navigate regulation uncertainty 3. Interoperability 4. Irreversibility and quantum computing 5. Tokenization 6. Data accuracy 7. Culture adoption and blockchain developers	1. Moving toward the IoT-based healthcare systems 2. Interoperability with legacy systems 3. Blockchain policies 4. Secure smart contracts 5. Performance bottlenecks	Blockchain features, advantages, opportunities, recent case studies, open challenges in healthcare data management
[20]	Current literature provides a little overview of blockchain applications that have been developed, tested, and deployed	1. EMR 2. Data sharing 3. Data security and identity management 4. Financial and records 5. Pharmaceuticals 6. Public health 7. Organ transplant	1. Technical challenges 2. Organizational challenges 3. Drivers for adoption 4. Government regulations	More research in real-case applications	A literature review to find out the pivotal roles blockchain technology play in solving some of the most critical and challenging issues facing the healthcare industry
[21]	Lack of bibliometric studies of blockchain technology in the industry of healthcare	1. Telecare medical information system (TMIS) 2. E-health system	1. Scalability 2. Blockchain size 3. Interoperability and standardization 4. Organization skill	1. User authentication 2. Authorization and access control 3. Secure search	Address the gap between the healthcare industry and blockchain technologies by evaluating previous activities
[22]	N/A	EMR access	1. User and attribute revocation 2. Data privacy 3. Scalability 4. Blockchain latency	N/A	An extensive survey on blockchain-based access control methods in the healthcare domain

(Continues)

TABLE 1 (Continued)

Ref	Problem Statements	Blockchain Services	Open Challenges	Research Directions	Theme of Work
[23]	N/A	1. EMR 2. Clinical trials 3. Medical supply chains 4. Medical product integrity	Lack of expertise	N/A	A brief overview of blockchain technology applications in healthcare
This Survey	Current literature lacks a comprehensive survey on the adoption of blockchain in clinical trials	1. Patient recruitment 2. Consent traceability 3. Persistent monitoring 4. Data management 5. Data analytics	1. Technical challenges 2. Security challenges 3. Organizational challenges	1. Combination with Artificial Intelligence (AI) and big data 2. Promotion of unified data standards 3. Integration of regulators and industry associations	A comprehensive survey of the blockchain technology for clinical trials, blockchain services, taxonomy, projects, challenges, and future research directions

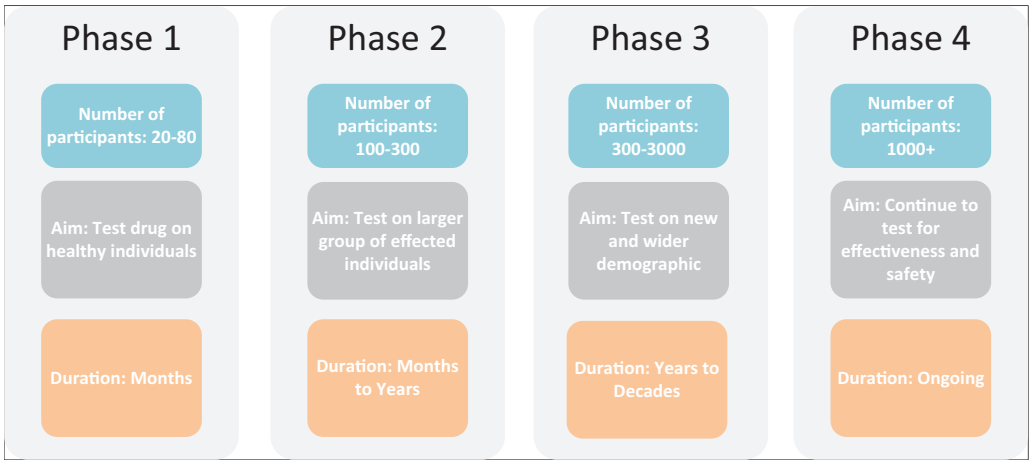

FIGURE 3 Current phases of the clinical trial [41]

3.1 | Data reliability

In recent years, there have been some cases of clinical trial fraud at home and abroad, mainly involving data fraud and selective publication, which have caused public bias against clinical trials. In a survey of researchers in clinical drug trials, about 17% reported being aware of data tampering or falsification [44]. For instance, in July 2014, Science reported that Japanese researchers falsified data in the antihypertensive drug Diovan clinical trial. Data integrity, standardization, and authenticity are essential requirements for clinical trials. The problems of integrity and standardization are mainly due to data missing, which is insufficient to judge the validity and safety. The authenticity problems involve fraud, including the fabrication, tampering, concealing of data, and the inability to trace the original data.

3.2 | Irregular informed consent process

Clinical trials cannot be separated from the participation of patients. However, the informed consent process in previous clinical trials was not rigorous, and some patients participating in clinical trials were not clear about the process and content of the trial. The FDA pointed out in the research report that nearly 10% of the trials had defects in implementing informed consent, such as expanding the scope of information acquisition and modifying informed consent without permission. Article 25 to 32 of the Declaration of Helsinki [45] stipulates that subjects in clinical trials must obtain consent from the subjects. Researchers must inform the clinical trial objectives, methods, risks, and other contents. In practice, the number of tested patients is large, and the number of phase 4 clinical trial subjects is more than 2000. It is a significant workload to obtain informed consent, and informed consent is not a one-time but a repeated cycle process. Therefore, it is urgent to adopt a new method to improve the efficiency of informed consent in clinical trials.

3.3 | Data traceability

The FDA only collects clinical trial data management reports from clinical trial sponsors but cannot participate in clinical

TABLE 2 Responsibilities of clinical trial stakeholders [42]

Stakeholder	Responsibilities
FDA	1. To develop a regulatory structure that all clinical trials must follow 2. To assure the availability of medications that meet national standards for safety, quality, and effectiveness. 3. To terminate an ongoing trial if there are serious Good Clinical Practice (GCP) violations
IRB	1. Approve the clinical trial protocols, which explain the participants eligible for the clinical trial, the schedule of tests and procedures, the drugs and doses to be tested, the duration of the research, the study's goals, and other information. 2. Ensure that the study is ethical, that participants have provided informed permission, that they are aware of the risks, and that researchers take the necessary precautions to safeguard patients from damage.
Sponsor	1. Companies, research institutes, and other groups responsible for a drug's development 2. Show the FDA the findings of preclinical animal testing and what they intend to undertake for human testing
CRO	1. To examine administration and management 2. To qualify, select, and initiate of a site 3. To manage the database
PI	1. To create the trial's conceptual framework 2. To compose and submit the clinical trial protocol for IRB clearance. 3. Patient recruitment and management of the informed consent procedure
CRC	1. To provide care under the clinical trial protocol 2. To analyze and interpret, among other things, laboratory data, Electrocardiographs (ECGs), and adverse occurrences 3. Maintain a record of how each patient reacts to therapy and note any adverse effects
Subject	1. To provide the permission form 2. To comprehend the function of the IRB in safeguarding patient health

trial data inspection in real-time to detect potential data quality management problems [46]. Data forgery and human input errors may occur between multiple drug clinical trial centres and sponsors or between sponsors and government-related regulatory agencies. In the current drug clinical trial system, the inspection and verification of data by the relevant government supervision institutions are delayed significantly. The efficiency of reviewing different drug clinical trial data needs to be further improved. Several eClinical technologies have arisen in the last decade to streamline trial operations and data administration. Existing fully-integrated and comprehensive eClinical systems are only available to major pharmaceutical companies since they are prohibitively costly. For authorities that have difficulty monitoring research data, there is no easy and safe way to see the complex network of data exchange, no real-time access to results once they are made, and no simple way to track historical data [47–48]. Thus, the FDA recognized a lack of traceability as one of the clinical research's most serious data problems [49].

3.4 | Data accessibility

Accessibility of patient data is another significant issue in the current clinical trials business since it includes several specialty parties and spans organizational and national lines. Participants in clinical trials operate in relative isolation, using their software systems, data formats, procedures, and organizations. Patient data are often spread across many private systems with no connection or collaboration, making it incredibly difficult to recruit participants for clinical studies [50]. Even worse, when scientists recruit enough patients to launch a clinical trial, patients' medical conditions for that particular therapy may continue to be a problem, resulting in flawed research with false positives and hazardous mistakes.

4 | TAXONOMY OF BLOCKCHAIN TECHNOLOGY IN CLINICAL TRIALS

This section overviews some essential characteristics that enable blockchain technology to transform conventional clinical trials. As shown in Figure 4, these characteristics are summarized and categorized into a tree-based structure according to existing literature. The taxonomy of blockchain technology in clinical trials comprises decentralized scenarios, decentralized practices, blockchain types, deployment methods, and consensus algorithms. The relevant literature in clinical trials analyzed in this section is summarized in Table 3. The conceptual diagram of the blockchain-based clinical trial platform is briefly presented in Figure 5. The physical layer consists of a variety of devices for gathering vital signals from patients. These devices allow for objectively measuring intervention effects in clinical and distant settings. The service layer's modular architecture makes the blockchain network easier to maintain and expand. This layer incorporates many properties of blockchain technology as separate modules, including P2P protocol, certificate authority, event hub, and consensus. The distributed ledger is a decentralized storage system for replicating and sharing data throughout the network. The smart contract specifies the business logic for all clinical trial-related processes, such as subject management. Various APIs encapsulate the functions defined in the smart contract. By contacting these APIs, other smart devices and apps could interface with the network. The application layer explains how the end user is presented with the blockchain's services. The user group consists of users with various responsibilities, such as the CRA, who may conduct audit inquiries on clinical trial data. The blockchain network is accessible through responsive web apps or native applications on mobile devices such as smartphones and tablets. The following sections explain each category in detail.

4.1 | Decentralized scenarios

Blockchain technology can promote the transformation of clinical trials with its decentralization, security sharing,

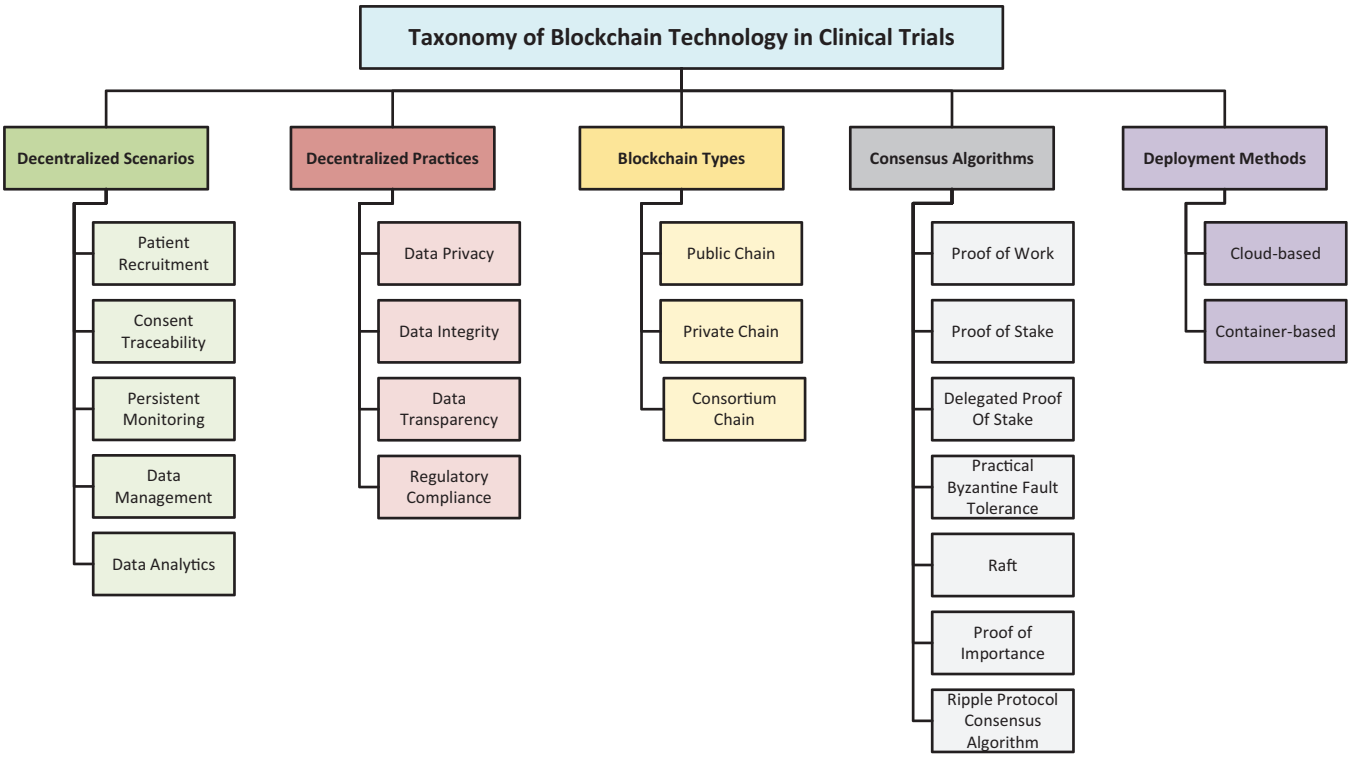

FIGURE 4 Taxonomy of blockchain technology in clinical trials

non-tampering, and high privacy characteristics. This subsection explains how blockchain technology helps to enhance various scenarios in conventional clinical trials.

4.1.1 | Patient recruitment

It is highly esteemed and turned out to be the common concept that enrolling patients for clinical trial studies are very complicated during drug development. It is claimed that a considerable portion of the expenditures associated with developing a novel drug is allocated to recruiting eligible patients and identifying adequate retention strategies throughout the clinical trial process [51]. Furthermore, it has been stated that most clinical studies are postponed or even forced to cancel due to recruitment issues [52]. The conventional patient recruitment process can benefit from the characteristics of blockchain technology, maintaining the patients' confidentiality and the safety of trial data.

Blockchain technology can handle two major clinical trial recruitment tasks. First, it can help sponsors recruit patients efficiently [53] to reach out to the right population of patients in a timely fashion. The clinical trial general information can be broadcasted to specific recruiting physicians through the blockchain network. Second, it can inform patients of new trials by automatically matching their profile with the trial's inclusion and exclusion criteria. This is accomplished via smart contracts [54], which can automatically authenticate transactions inside the blockchain to assure the legitimacy of sponsors, clinical studies, and patient eligibility. All participating trial sites could receive recruitment information from the sponsors without going through the conventional digital medial channels.

Another study explores the potential of merging the IoT and blockchain technology in the digital health sector [55]. The IoT devices can continuously collect the personal data preserved in clinical sites to prescreen the potential participants in terms of specified inclusion and exclusion criteria. Before an agreement is made, the patient can keep the data secret, and the Clinical Research Institute can be satisfied that the data is useful and legitimate. Thus, the convergence of IoT and blockchain can safeguard the interests of the patients and the Clinical Research Institute. The authors in [56] propose using mobile computing with blockchain technology to implement a patient-centred model in participant recruitment and data sharing. However, this study only presents a conceptual architecture and lacks proof-of-concept.

4.1.2 | Consent traceability

Patient participation is a prerequisite for better clinical trials and medical research [57]. However, informed consent is challenging to manage rigorously and successfully. According to research published by the FDA [58], about 10% of clinical studies have various concerns with consent gathering. Some regulation agencies, including the FDA, have provided recommendations and commitments to promote consent collection under suitable conditions [59]. According to the recommendation

TABLE 3 Summary of recent blockchain research in clinical trials

Ref	Description	Benefits	Research Challenges
[51]	-Use a generic model for the digitization of clinical trials	-Assure data integrity and traceability -Preserve user's privacy	N/A
[53]	-Public blockchain setting for clinical trial recruitment	-Broadcast recruitment to all participating clinical sites and specific patients -Data visible to all users in the chain	N/A
[54]	-Multiple smart contracts to regulate trial-related operations	-Optimize the recruitment process	N/A
[55]	-Combine blockchain with IoT technologies	-Safeguard both the patients' and the Clinical Research Institute's interests	N/A
[56]	-Explore the use of mobile computing and blockchain technology in participant recruitment and data sharing	-Facilitate a patient-centred data stewardship model	N/A
[60]	-Time step each stage throughout the patient's consent collection	-Help with reliability, security, transparency, and reproducibility	-Cannot address the question of consent collected in singular situations
[61]	-Introduce an e-consent model based on the access control scheme	-Provide a fine-grained way of handling access requests for consent data	N/A
[62]	-Build blockchain-based smart contracts using the Ethereum platform	-Increase the trust in data collection during clinical research	-Cannot guarantee absolute data integrity -Vulnerability of data entry
[63]	-Use blockchain technology for sharing information about national R&D projects	-Ease the process of viewing and using project-related information	-Do not target consent traceability
[64]	-User-centric solution for personal data accessing	-Ensure the integrity of personal data processing consent	-Data privacy ontologies and intelligent components need to be improved
[65]	-Integrate blockchain technology with an active assisted living-based data collection scheme	-Can be applied in different domains that deal with sensor data	-Lack of actual implementation and production environment deployment
[53]	-Private blockchain for persistent monitoring	-Reduce data integrity threats -Interact with legacy systems	N/A
[66]	-A generalized 3-layered blockchain architecture that provides data coordination functions	-Ease the application development	-Additional setup requirements for each clinical trial site
[67]	-Customized smart contract settings to monitor clinical trials across different census regions	-Advanced data analytics using AI methods	-Lack of data analytics tools with smart contracts -Lack of integration with patient-generated IoT data
[68]	-Enhanced blockchain architecture with IoT	-Enhance IoT challenges in terms of security and availability	-Require transaction cost optimization
[71]	-Conceptual blockchain platform architecture for clinical trial and precision medicine	-Helpful in building a medical data sharing ecosystem by combining big data technology with blockchain technology	-Lack of actual implementation
[72]	-A permissioned blockchain platform to ensure clinical data transparency	-Ease the human-computer interaction with a web user interface -Automate trial-related operations without third-party involvement	-Lack of testing in the production environment
[86]	-A blockchain-based framework for clinical trial data management	-Advantages to all stakeholders -Ensure data transparency, data integrity, and protocol compliance	-Scalability issues and system running cost
[87]	-A blockchain platform that can be used to validate data integrity from extensive biomedical research studies	-Provide a data governance solution and cryptographic assurance of data authenticity	N/A
[89]	-Utilize smart contracts to address data manipulation issues for clinical trials	-Improve the transparency of data management in clinical trials	N/A
[90]	-A blockchain-based system to make data collected in the clinical trial process immutable, traceable, and trustworthy	-Offer an improvement in clinical trial data management -Bolster trust in the clinical trial research process	-Do not solve the complex issues of public data sharing

(Continues)

TABLE 3 (Continued)

Ref	Description	Benefits	Research Challenges
[93]	-Test the blockchain-based approach in a clinical trial protocol	-Low-cost, verifiable method to audit	N/A
[94]	-A permissioned blockchain-based data management framework for managing and monitoring data in multi-site clinical trials	-Ensure enforcement of IRB-related regulatory requirements across multiple sites and stakeholders	-Incentive mechanisms required -Burden of maintaining a node for each clinical trial
[95]	-A blockchain-based framework using Ethereum smart contract	-Ensure transparency by triggering events whenever a particular activity is completed -Simplify the patient enrollment process	N/A

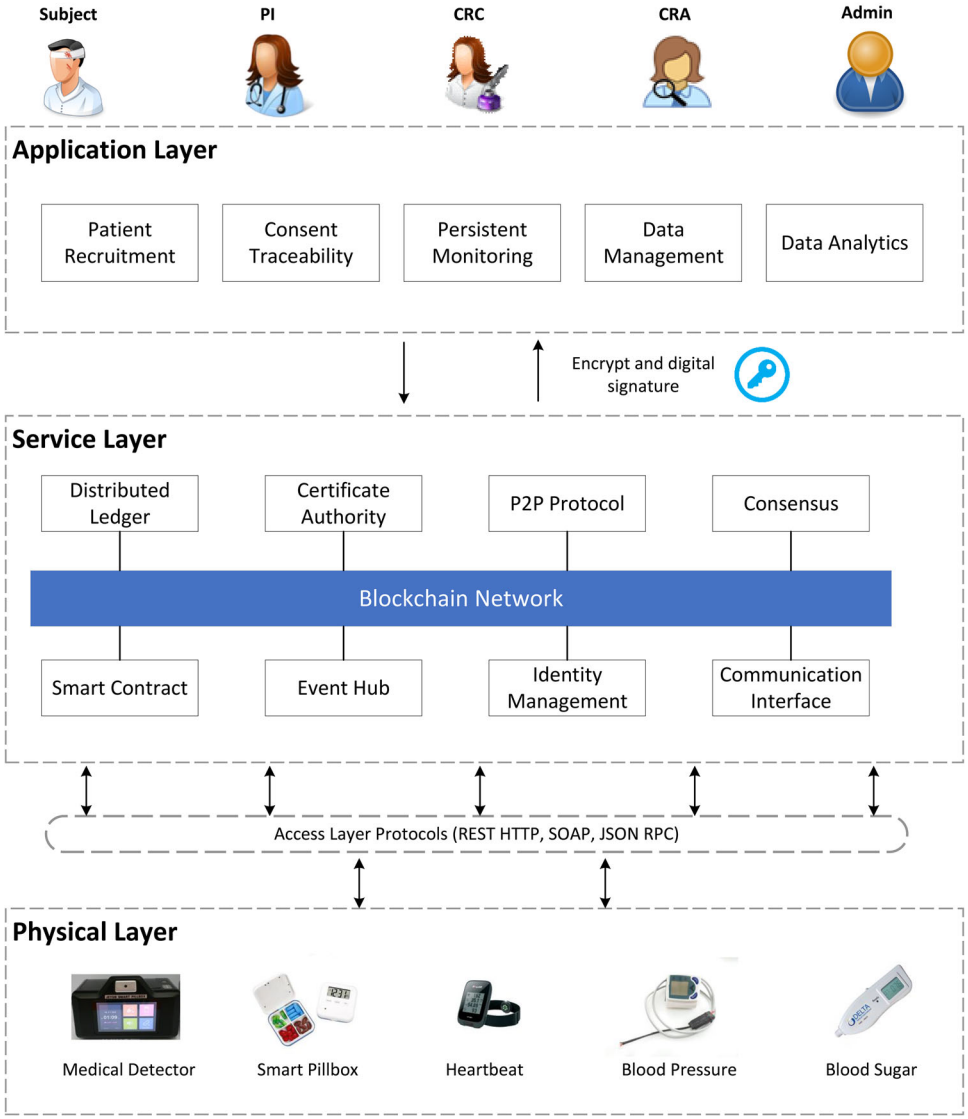

FIGURE 5 Layer-based decentralized scenarios in clinical trials

report, blockchain technology can provide a secure and straightforward way to sign and date the written consent form. In this context, the blockchain can bring a solid basis for transparency in gathering patients' consent. The authors in [60] design a blockchain-based proof-of-concept protocol to time step each stage throughout the patient's consent collection. A single document is obtained to depict the whole consent collection process, where a time-stamped consent status is attached once the

protocol version is updated. This document is thus secure, solid evidence of existence that can be confirmed on any public website devoted to the purpose. The e-consent model employs an access control technique developed on the Hyperledger Fabric blockchain architecture [61]. It maintains all information associated with patient records, consents, and data access that may be transferred across participating organizations. BlockTrial [62] is an additional mechanism that enables patients to authorize researchers to access their data and submit queries for blockchain-stored data. It provides a web-based interface allowing the end-users to invoke the trial-related services exposed in the smart contract.

The Trusted Information Project Platform (TIP-Platform) [63] is a trustworthy study that enables participants to view and use project-related information such as research results and duplication reviews. However, it does not target consent traceability. Other prototypes allow data subjects to control consent regarding access to their data in the IoT ecosystem. ADvoCATE is a user-centric solution that ensures the integrity of personal data processing consent [64]. Another similar project utilizes an Active Assisted Living (AAL) technology-based data collection scheme to integrate with the blockchain to improve transparency in the consent management process [65].

4.1.3 | Persistent monitoring

In conventional clinical trial programs, patients' symptoms and physical conditions are reported using a questionnaire or a diary to the clinical site. Data accuracy and integrity are hard to maintain since the FDA only receives combined reports from sponsors. It is difficult for the current system to feature real-time collection and analysis of the data as the process is complex. Furthermore, the FDA lacks the workforce to perform regular inspections of all clinical trial data reported from each clinical site. Blockchain can allow the FDA and sponsors to trace the monitored data incessantly, open to all participants within the same network as a distributed ledger technology. In this context, permissioned blockchain is more suitable than permissionless blockchain since it outperforms transaction processing capability. The FDA, clinical sites, sponsors, and patients can participate in a permissioned blockchain that establishes an incredible trust. Moreover, an Application Program Interface (API) can be used in permissioned blockchain to allow all patients to send their questionnaires or diaries to other network participants through smart devices.

Authors in [53] present a permissioned blockchain-based reference model for persistent monitoring. This model covers different phases of the clinical trial program. The smart contract validates the participants' identity and can query the health data within the permissioned blockchain. Unlike the conventional system, the proposed model allows the FDA to check the raw data and other analytics reports; meanwhile, patients can communicate with the FDA directly. Another study presents a layered blockchain system for most healthcare sectors involving data coordination across multiple facilities [66]. It provides some standard functions to ease the application development without concerning the infrastructure of the blockchain. The authors in [67] also present a permissioned blockchain model to tackle issues in current clinical trials. A proof-of-concept work is implemented to simulate scenarios in clinical trials. It can connect multiple Healthy Eating Research (HER) databases from clinical sites. A suite of smart contracts is also utilized to set the levels of data access privileges and emulate the workflow protocols for each stakeholder in clinical trials. The authors in [68] propose an IoT-based blockchain architecture comprising five layers. The blockchain infrastructure is built on the Ethereum platform, and the smart contract is programmed in Solidity language.

4.1.4 | Data management

The type and quality of clinical data are essential in determining clinical trial research results. A clinical data management system must handle the information collected during clinical trials. It is widely acknowledged that the clinical trial sector is crucial in enhancing human health. The reliability of trial data is essential to contemporary medical theory and practice but cannot be guaranteed for the reasons outlined in the preceding section. Blockchain is regarded as a basis for enhancing clinical research techniques and a step toward achieving more openness to increase confidence among research organizations, clinical locations, and patient populations. The adoption of blockchain technology in healthcare offers several advantages, including safe data monitoring and sharing, data availability, and user privacy. The authors in [69] outline the scope, needs, system architecture, and problems unique to clinical trials and precision medicine for blockchain technology. Several organizations and institutions, including International Business Machines (IBM) Watson Health, and the FDA, are initiating a project describing how blockchain might be used for healthcare data from various sources, including clinical trials, wearables, and electronic health records [70].

For instance, the authors in [71] present a conceptual blockchain platform architecture for clinical trials and precision medicine in the current studies. However, this study only clarifies the potential of blockchain technology in clinical trial data management and lacks real implementation. The authors in [72] provide a blockchain-based service platform with permissions to assure clinical data transparency and provide clinical trial-related smart contract solutions. A proof-of-concept is implemented using Hyperledger Fabric, and the system performance is tested in different metrics.

Moreover, some start-up companies also investigate blockchain technology in clinical data management. Examples of such projects include Gem Health Network [73], GuardTime [74], Chronicled [75], and Patientory [76]. Furthermore, the Mediterranean Hospital in Cyprus has adopted the E-HCert application [77], which provides an archival solution based on the Vechain Thor blockchain [78]. Vechain states that it would now be helpful for hospital patients to conduct COVID-19 tests and store their results on the Vechain blockchain.

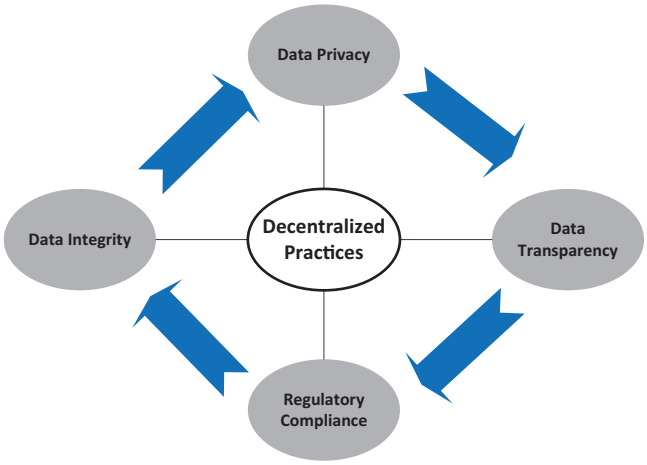

FIGURE 6 The decentralized practice of blockchain in clinical trials

4.1.5 | Data analytics

The current clinical data management systems still require the clinical sites to upload the data manually. Since the blockchain stores all transactions, real-time data analytics is achievable. The data analysis process can be automated using the smart contract to collect or detect data falsification. With the help of machine learning, blockchain technology can perform data analytics in the healthcare sector [79]. It is worth noting that some researchers have tried to apply machine learning algorithms in the smart contract to adjust the transaction traffic of blockchain in real-time [80]. Another project [81] utilizes the Support Vector Machine (SVM) training method to partition the dataset from various data providers vertically. The smart contract can obtain decisions and analytics results that cannot be tampered with for the learning phase. Although not related to clinical trials, these attempts show that the data analysis process can be carried out automatically in the smart contract without any intervention from clinical sites or sponsors. Therefore, integrating blockchain with machine learning can provide an immutable, decentralized and secure environment for learning sensitive data, providing substantial development in various domains, including the healthcare sector, as discussed in [82].

4.2 | Decentralized practices

Blockchain technology can establish a new trial process standard of guaranteeing data privacy and maintaining data integrity and transparency while assuring regulatory compliance. Four decentralized practices of blockchain in clinical trials are demonstrated in Figure 6. The subsection describes how blockchain technology can facilitate the decentralization of these practices in clinical trials.

4.2.1 | Data privacy

Because of the fast development of information technology, hospital information systems have also become a hot research topic. However, these medical data stored or shared on public networks and the cloud are threatened by security attacks, tampering, and leakage during data transmission [83]. Data privacy is one of the characteristics of blockchain that best fits for solving this issue. Blockchain-based systems utilize cryptographic algorithms to enhance data privacy and security. For instance, the Secure Hash Algorithm (SHA) is one of the cryptographic hash algorithms used extensively in blockchain systems. The Bitcoin network employs the SHA-256 algorithm, which provides a 256-bit fixed-size hash that is almost unique. It is a one-way encryption function that cannot be reversed. Thus, it is appropriate for transaction validation, antitamper, and digital signatures [84]. Elliptic Curve Digital Signature Algorithm (ECDSA) is another popular cryptographic algorithm used in existing blockchain systems to ensure the effective and secure control of ownership of funds [85]. ECDSA utilizes asymmetric cryptography, consisting of a mathematically linked key pair, namely public and private keys. The public key encrypts data, while the private key decrypts data.

4.2.2 | Data integrity

Within clinical trials, the data integrity of trial-related reports and documentation are critical keys to determine the success or failure of the whole clinical trial process. In most instances, clinicians, medical labs, and even sponsors are accountable for data fabrication due to data entry mistakes. Therefore, ensuring data accuracy remains challenging for the FDA since they only get aggregated reports from sponsors after each trial; thus, the clearance process is lengthy because it is challenging to make timely changes to missing or incorrect data under the present clinical trial system. In addition, the FDA lacks the staffing needed to undertake periodic audits of all registered clinical trial applications. Blockchain technology can utilize consensus algorithms to prevent mistakes or malicious attempts [86]. Besides, hashing-based algorithms can make the trial data tamper-proof since all the blocks are logically linked to each other. All transaction logs are preserved on the network, making the FDA easy and quick to identify and locate the source of problems such as human input error. As discussed in [87], permissioned blockchain has many advantages that support clinical trials strongly. Permissioned blockchain is more appropriate for clinical trials as it provides an isolated environment to record more sensitive data.

4.2.3 | Data transparency

Data from clinical trials are routinely withheld from different stakeholders, leading to a lack of trust in the trial process [88]. Lack of data transparency can hinder patients from getting a fuller and clearer picture of treatment conditions. The blockchain is a distributed ledger technology allocated among all trial-related stakeholders to minimize the probability of clinical sites burying negative results. Clinical sites and stakeholders can keep a copy of the distributed ledger and get the

notification in real-time once transactions are attached to the ledger. The method for using blockchain to provide data transparency in clinical trial protocols is first reported in [89]. The authors propose an Ethereum-based platform with conventional clinical data management systems parallelly. This system composes a regulator contract and a trial contract responsible for different trial-related processes. The authors in [90] perform a simulation onto a proof-of-concept web portal service with raw data collected from a completed clinical trial. The results indicate that the proposed service can improve trial data transparency to strengthen trust among stakeholders in the clinical research process. The advantages of applying blockchain technology in clinical trials, such as improving the development of trusted processes, gathering data, and reinforcing transparency, are discussed in [91].

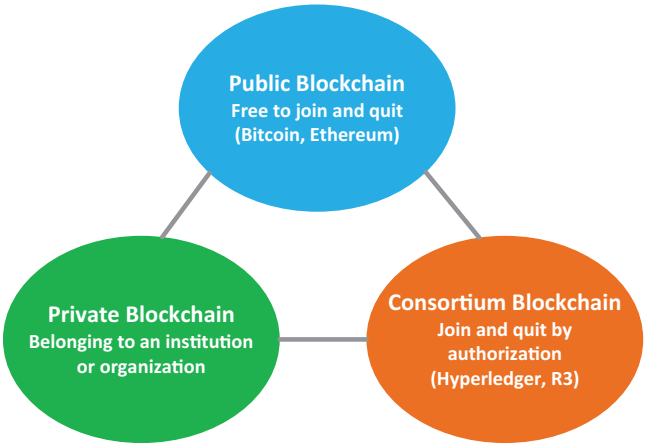

FIGURE 7 Overview of three types of blockchain

4.2.4 | Regulatory compliance

It is essential to follow guidelines set by regulatory authorities to protect the wellbeing of the patients involved in the clinical trial. The FDA is generally responsible for conducting random visits to the clinical sites. Once a study protocol is approved, it is not easy to track the activities of participating sites and ensure that they comply with the required guidelines [92]. The smart contract on the blockchain is a decentralized application that can capture these guidelines as a set of rules. It can ensure that all participants in the clinical trial follow a particular procedure in which no one is granted permission without the approval of related authorities. The first attempt to empirically test the blockchain-based approach using a publicly available clinical trial protocol is presented in [93]. The text of the study protocol is first transferred into SHA256 digest and then converted into a bitcoin private key and public key. As a result, the document's existence can be proved with the bitcoin address. The authors in [94] present a permissioned blockchain-based data management framework in a multi-site study. The smart contract is utilized to enforce the rules of IRB-related regulatory requirements across multiple sites and stakeholders. A similar approach is proposed in [95] to tackle regulatory compliance challenges in clinical trials. Ethereum-based smart contracts capture three stages of a trial process, including new drug application, clinical trial initiation, and patient enrollment.

4.3 | Blockchain types

Blockchain is now being used by companies in different industries with different systems and processes. Different types of blockchain networks have different technical specifications. An essential task for business managers is to know which blockchain site is suitable for their business. As described in Figure 7, the blockchain can be divided into public, private, and consortium chains according to the access condition. The former is permissionless blockchain, and the latter two are permissioned blockchain. A public chain refers to a blockchain that any participating node can access. The transaction can be effectively confirmed, and anyone can participate in its consensus process. Public chains usually apply to virtual currency, e-commerce for the public, Internet finance, and other Business to Consumer (B2C), Consumer to Consumer (C2C), or Consumer to Business (C2B) application scenarios. Due to its open nature, public chains must be protected with inherent cryptography to incentivize extravagant mining or fuel transaction processing to compensate for the lack of privacy. A negative association exists between the usage of native digital currencies and the transaction cost and speed as a whole [96].

In addition, it complicates communication with other decentralized systems since the tokens used on each platform must be the same. Bitcoin, a well-known public blockchain system, is limited to 7 transactions per second, making it incapable of handling high-frequency trading [97]. A private chain is an organization or institution that controls a blockchain whose writing rights and participating nodes' eligibility are strictly limited. The application scenarios of the private chain are generally internal applications of enterprises, such as database management and auditing. There are also applications in government industries, such as government budgeting and execution or government industry statistics, which are generally registered by the government but monitored by the public. The value of a private chain is mainly to provide a safe, traceable, non-tamper, automatic operation platform that simultaneously prevents internal and external security attacks on data. A consortium chain is a blockchain managed by several institutions, each of which runs one or more nodes. Data only allows different institutions within the system to read, write, send transactions, and record transaction data together. The confirmation time and the number of transactions per second of a consortium chain are pretty different from that of a public chain, and the requirements for security and performance are higher than that of a public chain. Compared with the public chain, the consortium chain can be regarded as partially decentralized, and at the same time, because of the reduced number of nodes, it can have faster transaction speed and lower costs.

Table 4 compares and analyzes the differences between three types of blockchain systems. Private and consortium chains

TABLE 4 Differences between public, private, and consortium chains

Property	Public chain	Private chain	Consortium chain
Ownership	Public ownership	Centre node	The selected set of nodes
Privacy	Public	Private	Could be public or restricted
Transaction Rate	Slow	Fast	Fast
Identity Management	Do not have identity management capabilities	Have identity management tools	Modular architecture that enables identity management tools
Regulations	Take longer to make compliance changes	Rules can be changed and updated at any time to be compliant with existing data policies	Similar to a private chain
Cost	Not cost-effective	Cost-effective	Cost-effective
Consensus Process	Proof of Work (PoW), Proof of Stake (PoS), Delegated Proof Of Stake (DPoS), Proof of Importance (PoI)	Practical Byzantine Fault Tolerance (PBFT), Raft, Paxos	PBFT, Raft, Ripple Protocol Consensus Algorithm (RPCA)

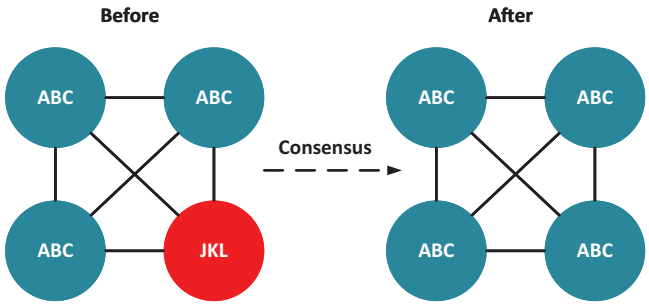

FIGURE 8 Concept of the consensus algorithm

are faster, more energy-efficient, and less complicated to construct than public blockchains. However, research examining and enhancing the performance of blockchains is less in-depth and comprehensive. According to findings in [98], the performance of blockchains may begin to rival that of traditional databases for small systems. Nevertheless, consistent models and setup changes may significantly impact the final product's performance.

4.4 | Consensus algorithms

Unlike conventional transactions, which require a trusted third party to act as an intermediary, blockchain technology can decentralize transactions while ensuring data consistency across the network, making peer-to-peer transactions possible. This requires the design of the transaction confirmation rule, which is the consensus algorithm. As shown in Figure 8, blockchain systems are decentralized in design, with nodes scattered and independent of each other. The system made up of different nodes must rely on a system to maintain data consistency. As the core of blockchain technology, the consensus algorithm plays a decisive role in the security and efficiency of the blockchain. This subsection overviews some popular blockchain consensus algorithms and makes comparisons of these algorithms, as described in Table 5.

4.4.1 | PoW

The PoW is the first widely used consensus algorithm used in Bitcoin networks. Its core is that nodes compete for accounting rights and Bitcoin rewards through computing power. In PoW, different nodes compete to solve a mathematical problem based on specific information. This mathematical problem is challenging to solve, but it is easy to verify the results. The node that solves this mathematical problem can create the next block and get a certain amount of currency reward. Satoshi Nakamoto adopted the mathematical problem of HashCash [99] mechanism design in Bitcoin. PoW is based on computing power as the basis of competing accounting rights, the workload as the guarantee of security, and all miners follow the most extended chain principle. However, one of the limitations of PoW is its high requirement for computing power to validate transactions, thus leading to inefficiency. Besides, it is also reported that PoW is vulnerable to 51% attacks [100].

4.4.2 | PoS

As more and more people participate in Bitcoin mining, many problems of PoW gradually emerge. For example, with the rapid increase of competition for computing power, the energy consumed to obtain replacement coins increases significantly. The accounting rights are gradually concentrated in the "mining pool" with a large amount of computing power [101–102]. To this end, researchers try to adopt a new mechanism to replace the proof of workload. The concept of Proof of Stake (PoS) was mentioned in the earliest Bitcoin projects but was not used for reasons such as robustness. PoS puts forward the concept of coin age, which is the sum of the product of the token held and the holding time. Using coin age competition instead of computing power competition, the proof of blockchain is no longer only dependent on workload, which effectively solves the problem of PoW resource waste. The key advantages of PoS are higher transaction processing capability and lower energy consumption compared to PoW. However, despite many apparent

TABLE 5 Comparison of blockchain consensus algorithms

Consensus algorithm	Strength	Weakness	Use case
Proof of Work	Build trust among fully anonymous nodes	Low efficiency and high requirement for computing power	Bitcoin, Ethereum
Proof of Stake	Lower requirement for computing power	Nothing-at-Stake problem	Peercoin, Terndermint
Delegated Proof of Stake	Relatively high performance and low energy consumption	Partially decentralized	CryptoCoinPay, Lamden
PBFT	High performance and low energy consumption	Complexed communication and low scalability	WutongChain
Raft	High consistency, performance, and reliability	Security vulnerability	Hyperledger Fabric
PoI	Low energy consumption, performance, and fair	Lack of community consensus and account importance does not equal device contribution	NEM
RPCA	High performance and high fault tolerance	Partially decentralized and security vulnerability	Ripple

advantages, PoS is vulnerable to the Nothing-at-Stake problem [103].

4.4.3 | DPoS

In the blockchain, using the DPoS algorithm, each node can vote to select representatives according to its share rights and interests [104]. In the whole network, the nodes that participate in the election get the most votes to get the right to account, produce blocks in a predetermined order, and get certain rewards. The successful delegate node must pay a certain amount of deposit and be online for a certain period. If the node that should generate the block does not perform its duties at some point, it will be disqualified from the delegate, and the system will continue to vote for a new delegate to replace it. All nodes in DPoS can choose the voting objects independently, and the elected representatives keep accounts in order, saving computing resources compared with PoW and PoS [105]. Moreover, there are only a few consensus nodes, and the efficiency is also improved. In addition, each participating node has the right to vote. Despite these advantages, DPOS is widely suspected of being partially decentralized, and there is artificial operation space to control the election process of agent nodes.

4.4.4 | PBFT

In the PBFT algorithm, all nodes run in the same configuration, with a primary node, and other nodes serve as backup nodes [106]. The primary node is responsible for sorting client requests and sending them to the backup node in the sequence. The main advantages of PBFT are that it has lower energy demand than PoW, and its transactions do not require multiple confirmations. PBFT is a promising solution only when a small group of nodes is involved. However, it becomes inefficient in the case of large networks. PBFT algorithm is first adopted by a permissioned blockchain, namely Hyperledger Fabric. The functions of authorization and endorsement are integrated into consensus nodes. Such a design results in the overloading of nodes, which significantly impacts transaction processing capability and scalability. Some efforts have been made to improve the performance of PBFT; for instance, the Tendermint algorithm [107] used in the Cosmos project combined PBFT and PoS algorithm and selected part of consensus nodes for BFT consensus by the token mortgage, which weakened the asynchronous assumption and integrated the concept of lock based on PBFT. Consensus nodes could reach consensus through two-stage communication in the partially synchronous network. Based on Tendermint, Hotstuff [108] integrates the blockchain structure with each stage of Byzantine fault tolerance (BFT), confirms the signature of the previous block, and constructs the new block simultaneously between nodes in each stage, making the algorithm simpler to implement.

4.4.5 | Raft

The most commonly used consensus algorithm in traditional distributed systems is based on Paxos [109]. This kind of algorithm can quickly complete data synchronization of a distributed system under the condition of a limited number of nodes and relative trust and tolerate Crash Fault. In other words, in the traditional distributed system, there is no need to consider participating in malicious data tampering and other behaviours of nodes, but only need to tolerate the failure of some nodes. However, the Paxos algorithm is too theoretical and difficult to understand and implement. Raft algorithm was proposed in 2013[110], it has the same effect as Paxos and is more convenient for engineering implementation. The leader is dominant in Raft, and the server nodes must be secure. Many permissioned chains use Raft algorithms to improve consensus efficiency without considering BFT. However, despite many apparent advantages, the transaction volume of Raft is limited by the maximum throughput of the node. Besides, the leader can cause significant damage if a malicious node takes over.

4.4.6 | PoI

When the PoI algorithm runs, nodes need to provide their importance to get the right to generate a new block [111]. Equity

held by nodes is no longer the main factor of importance but the volume of transactions at nodes and the relationship between the two parties. The node's importance is evaluated according to the wallet's transaction times and monetary assets. However, the agreement may encourage the nodes to collude in trading volume, and the frequent trading of large asset nodes may also cause the problem of centralization of importance.

4.4.7 | RPCA

There are currently several feasible solutions to the Byzantine general problem, such as the POW algorithm used by Bitcoin and Ethereum and the PBFT algorithm used by Hyperledger. However, consensus efficiency is relatively low in this distributed payment system due to the synchronous communication between nodes. In order to reduce the cost of such synchronous communication, a scheme of mutual trust within the sub-network is adopted in the RPCA algorithm [112]. These internal trusted sub-networks form an extensive network. The trust cost of the sub-network is meager and can be further reduced to the atomic selection of network nodes for other nodes in the sub-network. In addition, to maintain the data consistency of nodes on the whole network, the connection degree between sub-networks must not be less than a threshold. RPCA can be a high Byzantine fault tolerance algorithm with high performance through these solutions. The RPCA algorithm has been applied to the Ripple consensus protocol.

4.5 | Deployment methods

Blockchain is an underlying technology architecture system that overturns the existing pattern. The deployment of a blockchain system involves establishing hardware, software, and other tools and technical environments. This subsection describes the current methods to deploy a blockchain system.

4.5.1 | Cloud-based

While blockchain technology expands beyond Bitcoin, cloud computing undergoes a paradigm change to satisfy the requirements of the fourth industrial revolution [113]. As seen in Figure 9, Blockchain-as-a-Service (BaaS) refers to the cloud-based development, management, hosting, and use of blockchain technologies such as apps, nodes, smart contracts, and distributed ledger. This kind of cloud-based solution supports blockchain installation, platform, security, and other characteristics. Thus, BaaS presents the blockchain service platform, which supports basic features based on cloud computing infrastructure and a unified development environment for both developers and users. Microsoft Azure, IBM Cloud, Amazon Web Services (AWS), Oracle Cloud, and HP Helion are currently popular cloud platforms that support the infrastructure and software to deploy a complete blockchain application, as discussed in [114]. However, such blockchain system is generally

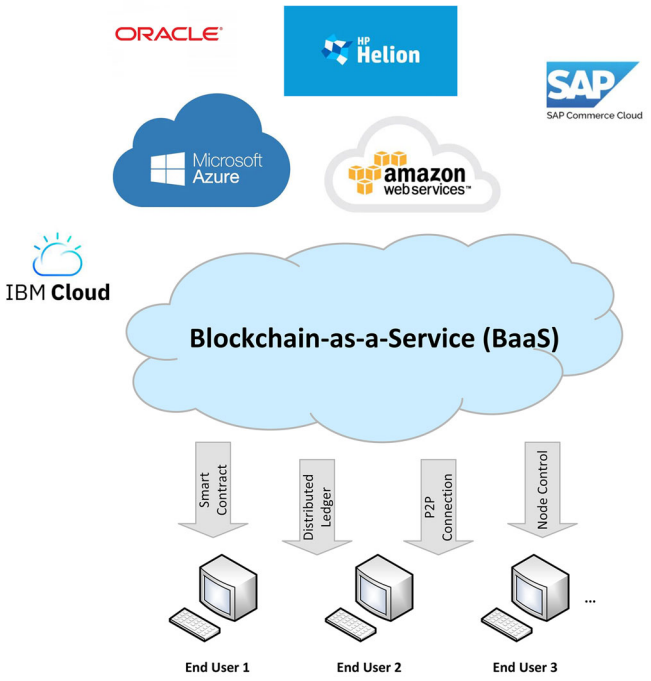

FIGURE 9 Architecture overview of BaaS-based blockchain deployment

controlled by large companies or institutions, which has a high risk of user data and user data being stolen. Moreover, the reliability requirement of the cloud platform is lower than that of the blockchain. The reliability of the blockchain system running on the cloud platform is insufficient.

4.5.2 | Container-based

The cloud computing paradigm is based on virtualization, enabling numerous virtual machines to coexist on a single physical device to enable scaling up and down of applications via elastic provisioning on demand [115]. Recent containers, such as Docker, have allowed a lighter mechanism than hypervisors and established themselves as a viable alternative to virtualization based on shared operating systems. Figure 10 illustrates the high-level architecture of Docker-based blockchain deployment. Most blockchain software is a high-level application requiring complex configuration, which would not have been friendly for ordinary users. On this basis, put the blockchain software into the container, and make the system send container rather than send data. Thus, the container that includes the blockchain software is sent to the client to form the blockchain system. If the blockchain container is delivered, the software in it is taken out of the blockchain container and deployed on a local server. This container technology is only a communication technology and does not have the function of protecting software and data in the container. In addition, in such a deployment model, the local blockchain software may be modified, and cannot be controlled, leading to a risk of tampering. Many types of research have been investigated using container technology to deploy blockchain systems, but most keep the blockchain code

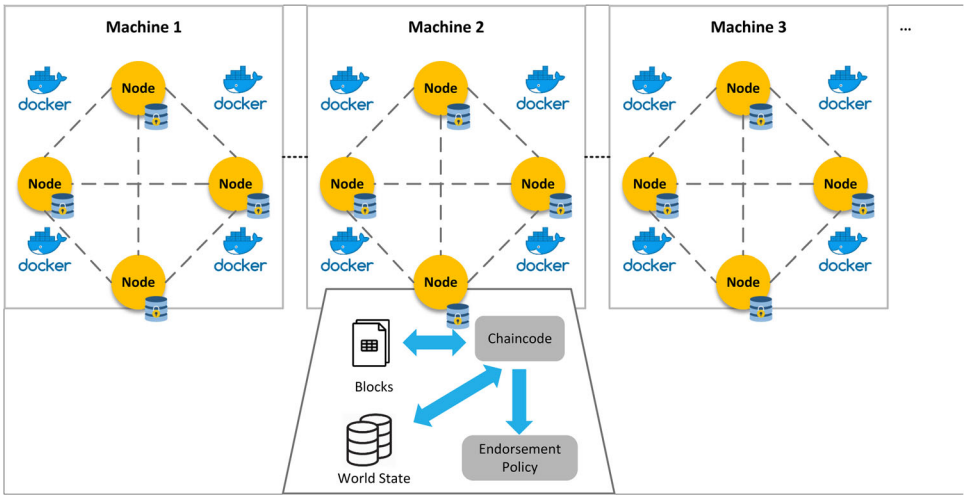

FIGURE 10 Architecture overview of Docker-based blockchain deployment

stored in the container [116]. The blockchain is executed in the container, but there may be issues in the transmission process, such as code changes.

5 | DEVELOPMENT TRENDS OF BLOCKCHAIN APPLICATIONS IN CLINICAL TRIALS

Deploying blockchain in the context of clinical trials could ease the development of transparent and highly dependable trials, improve patient recruitment, achieve complete decentralization, assisting regulatory compliance, and promote integration. It is a unique technology that offers robust governance and real-time choices regardless of geographic distance. The blockchain-based system could increase the data exchange process's integrity and trustworthiness while decreasing transaction costs. As a result, different companies are using it to build secure data and service management systems in intelligent healthcare. For example, IBM Watson Health has signed a joint-development agreement with the FDA to explore blockchain technology to exchange patient data, including EMRs, genomic data, and clinical trials [117]. Besides, DeepMind has announced it will utilize a decentralized ledger to build a real-time data audit platform for personal health records [118]. This section outlines and discusses the recent development trend of blockchain applications in clinical trials.

5.1 | Clinical trials intelligence

The Clinical Trials Intelligence founded by ClinTex, is a distributed technology platform that incorporates predictive data analytics, machine learning, and the innovative use of smart contracts to drive significant quality and operational improvements in clinical trials [119]. This platform is the first blockchain-based clinical trial ecosystem targeted to address the critical pain points of clinical trials, including operational excellence, predictive data analytics, site investigators, patient recruitment, vendor management, risk monitoring, and clinical data visualization. Clinical Trials Intelligence utilizes Ethereum-based smart contracts to facilitate access control, compensation payments, and clinical data hash storage. ChainLink is a decentralized oracle provider that allows smart contracts to access data from various resources. In Clinical Trials Intelligence, Storj is the decentralized storage provider for encrypted clinical data. Besides, it releases its native token, CTi, for the cost of data access and as payment for investigators and third parties. ClinTex has already partnered with Intellimed to deploy the Clinical Trials Intelligence in academic clinical research settings. Further demand will derive from ClinTex's publicizing its partnerships with some of the biggest names in the pharmaceutical industry.

5.2 | TriNetX

TriNetX is a global health research network that aims to make clinical research easy and efficient by sharing real-world data among pharmaceutical companies to various trial-related participants, such as study sites and investigators to patients. In 2017, TriNetX cooperated with the West Virginia Clinical and Translational Science Institute (WVCTSI) to increase investigators' access to trial opportunities and broaden research capabilities [120]. The TriNetX platform is built on blockchain, enabling WVCTSI researchers to access real-world data from more than 40 health organizations. The healthcare organizations part of the TriNetX platform provides their data through a live, federated model so that new observations, results, and medication orders are available monthly. These healthcare organizations represent renowned academic medical centres and public or private hospitals, representing all four U.S. census regions and patients of all demographics. Besides, this platform provides power logic to support a full range query on medical codes and advanced analytics tools to quantify the impact of

each criterion on patients and deliver statistical comparisons of outcomes.

5.3 | Innoplexus

Innoplexus specializes in life science research and offers methods for combining blockchain with AI [121]. In addition, Innoplexus employs 250 individuals who provide pharmaceutical and clinical trial solutions. Innoplexus can conduct multi-stage research designs for customers. This platform applies proprietary AI technologies and our life sciences ontology to provide a one-stop solution to optimize work potential, real-time intelligence, and discovery of new patterns across all phases of drug development. Blockchain is designed for customers who rely on distributed but private communication. In addition, blockchain is data-sensitive and ensures secure communication between selected participants through compliance with General Data Protection Regulation (GDPR).

5.4 | Triall

The clinical trial software market is growing due to the digitization and globalization of clinical research. Industry stakeholders are currently switching from general-purpose solutions to advanced, dedicated applications. Triall is building the world's first blockchain-enabled clinical research ecosystem, providing services and connections to all people involved in clinical trials [122]. Triall aims to leverage blockchain technology's benefits to enhance value truly, thereby promoting trust, research data integrity, auditability, and system interoperability. This is all part of an effort to address these persistent problems that make medical innovation too complex, tedious, and resource-inefficient. Triall envisions the world's first online environment available to all clinical research professionals, regardless of function, type of organization, or level of resource. The adoption of blockchain technology renders clinical trial data tamper-proof. Triall strives to protect clinical trial data by increasing all stakeholders' quality, efficiency, compliance, and confidence.

5.5 | Embleema

Embleema is another service that aids healthcare practitioners in constructing clinical trials, including patient recruiting and study design [123]. Embleema has created a virtual research suite for intuitive and traceable design. This platform gathers, analyzes, and organizes clinical and real-time global data with total user control, from patient recruiting through regulatory submission. Embleema restores accuracy and transparency to the healthcare and clinical trial industry by allowing patients to merge with healthcare stakeholders, which own and directly share their data, and be compensated with cryptocurrency tokens. The project proposes using wearable devices to attach data on the blockchain to ensure that real data is collected from real patients and give patients complete control over their medical data.

6 | CURRENT MICRO APPLICATIONS IN CLINICAL TRIALS

Blockchain is regarded as a basis for enhancing clinical research techniques and a step toward achieving more openness to increase confidence among research organizations, clinical sites, and patient populations. The adoption of blockchain technology in healthcare offers several advantages, including safe data monitoring and sharing, data availability, and user privacy. This section overviews some recent efforts on blockchain-based micro applications in the fields of clinical trials.

6.1 | Virtual clinical trials

Virtual clinical trials (VCT) are a relatively new method for conducting clinical studies primarily through digital health platforms to make subject involvement transparent [124]. Blockchain is a peer-to-peer network that does not need the administration of a third party and relies on the consensus of all users. Before entering the system under the VCT scenario, stakeholders such as clinical trial sponsors and sites must verify their identities with the FDA. This protects the legitimacy of all stakeholders in the private chain. All blockchain transactions are publicly auditable by all blockchain users. This functionality may guarantee that users of the private blockchain developed for VCTs get all recruitment-related data [125].

The use of the original blockchain to VCTs may preserve data security and patient privacy, assure data consistency, and make information accessible to all users. The Ethereum blockchain retains all the characteristics of the original blockchain and adds smart contracts, making it more appropriate for healthcare applications. A smart contract is a mechanism that automatically executes on the blockchain to control transactions. Since Solidity is used to create Ethereum smart contracts, any computational challenge may be solved. For instance, a data analytics tool may be included in the smart contract to identify abnormalities in real-time throughout the VCT. Sponsors or the VCT authority (such as the FDA) can guarantee that patients get prompt medical care.

6.2 | Dynamic consent management

In contrast to the present literature, there are very few real clinical studies using blockchain for the dynamic consent process. In addition, dynamic consent problems have been highlighted, including data readability and accessibility [126]. The authors of [127] constructed a blockchain-based architecture for dynamic consent and tested its real-world viability by using virtual drugs in a decentralized, multicentre clinical trial. Throughout the research, two major and three minor protocol adjustments were planned to imitate real-world study conditions. The platform

included a web and application-based user interface for consenting subjects. To optimize the simplicity of the permission procedure, we built a distinct user interface for subjects and researchers. After authentication, each subject browsed the website or application and created a user account. The platform was then granted access to the confirmed user. Hyperledger Fabric, an enterprise-grade private blockchain architecture, was used to create the blockchain component. This was the first investigation to examine study adherence in a decentralized clinical trial using virtual drugs. As most decentralized clinical trials include home-based drug administration and remote monitoring, it is crucial to monitor medication behaviour accurately. The virtual drugs offered drug adherence monitoring with little expense and danger. This methodology may be extended to future investigations, such as remote drug administration.

6.3 | Data validation and verification in a breast cancer clinical trial

Due to the prevalence of misbehaviour in clinical trials and the significant amount of revenue and time used by existing source data verification processes, blockchain is a suitable technology application for the data management of clinical trials. The authors of [128] presented a blockchain-based solution for securing clinical trial medical data. The technology was used in a clinical study conducted at the National Cancer Center of Japan to examine the effects of home-based high-intensity interval training on breast cancer survivors. Under the regulatory sandbox of the Japanese Cabinet Office, the project was designed to showcase clinical data management utilizing blockchain technology. This sandbox enables enterprises to demonstrate and evaluate emerging technologies, such as blockchain and the Internet of Things, without being subject to current restrictions. It simultaneously enables future deregulatory actions. On August 23, 2019, they noticed an interruption of AWS cloud servers in the Tokyo area during the experiment. During a dangerous server shutdown scenario, they observed that the blockchain network and health checkup feature enabled system survivability with minimal downtime and safe clinical data registration.

7 | OPEN RESEARCH CHALLENGES

7.1 | Technical challenges

Although all walks of life have optimistic expectations for blockchain applications, the real implementation still faces many technical challenges. The paradox of the ternary of blockchain, namely, efficiency, decentralization, and security, is the focus of many technical studies [129]. No project can simultaneously achieve the highest efficiency, decentralization, and security. It has always been the research direction of blockchain technology to explore the balance of the three and even explore the limits of Pareto improvement. This problem is the key to implement blockchain in all walks of life and is also universal to the medical industry.

Blockchain is a decentralized structure where each node is independent of ledgers. The whole transaction can only be confirmed after each node of the whole network has been completed and reached a consensus, resulting in low transaction processing performance. Furthermore, a noticeable barrel effect is presented as the system's overall performance depends on the block in the chain network node with the worst performance. The transaction throughput and latency have become critical bottlenecks hindering the implementation of blockchain application scenarios [80, 130]. For example, the Bitcoin network can only process 7 transactions per second due to the block size limitation and the time needed to create a new block, rendering it unsuitable for trading with a high rate of change [131]. Ethereum takes about 15 seconds to complete a transaction, but the average time increases exponentially as network conditions change [132]. Scalability is a severe issue when creating blockchain systems in clinical trials as they cannot fulfil the requirement of processing a large volume of patient data in a real-time manner, which would result in generating a large number of transactions per second [86].

Most blockchains have incredibly high storage costs because they need to be stored on every node in the network and require a lot of computing power. For example, the use of PoW wastes computing resources. It has poor transaction performance, increasing the additional operation and maintenance costs and creating a massive obstacle to implement practical applications [133]. All clinical sites are required to offer specific computational resources for data mining. A security concern may occur if one party owns more than 50% of computer resources. According to various clinical trial protocols, clinical sites may not disclose minor adverse events. In addition, with the increase in data volume, the information in the blockchain will show exponential growth, which puts forward higher requirements for storage space, download speed, and so on.

7.2 | Security challenges

Patient privacy data security is essential to information management for the medical industry. An essential feature of blockchain technology is that multiple nodes jointly maintain a set of data ledgers. All data in the ledger must be verified and stored by multiple nodes, exposing the issue of blockchain privacy protection. Therefore, blockchain information security and privacy protection is a research hotspot in this field [134]. Channel technology, zero-knowledge proof, homomorphic encryption technology, and other algorithms are constantly integrated with applications. Many technical solutions are in the continuous optimization and exploration stage.

The smart contract is visible to all participating users in the blockchain network. This can cause various vulnerabilities, including security holes visible to users, and may not be quickly fixed. For instance, there was a massive loss in June 2016 due to the Decentralized Autonomous Organization (DAO) Ether

vulnerability [135]. Moreover, with the system's business logic complexity, actions and results such as results audits and evaluations must be subject to subjective review. Without human intervention, assessing such activities through pre-written smart contracts is difficult.

7.3 | Organizational challenges

If the clinical trial blockchain system is widely promoted in clinical sites, all patients' medical data will be integrated into the blockchain ledger. In this case, the immutable nature of blockchain technology is a double-edged sword. Once the data is attached to the chain, it cannot be modified, making it impossible to modify health records even if there is a valid reason, such as a misentry due to human error. In complex data systems, data updates and modifications are inevitable, and no one can be sure that the original data uploaded to the blockchain is correct.

The efficient and universal cross-chain technology is the key to realize all-chain interconnection. The ecological island phenomenon of blockchain is serious, which has become a difficulty affecting the overall expansion of blockchain. For example, the underlying architecture between platforms cannot communicate, the design difference is profound, the cross-chain data cannot be verified, the interface protocol cannot be interconnected, the security mechanism cannot trust each other, and the business layer cannot exchange visits. Establishing an interoperable blockchain platform is challenging due to various issues, including differences in consensus algorithms, token transfers, and programming languages [136].

8 | FUTURE RESEARCH DIRECTIONS

In order to benefit more from blockchain technology in clinical trials. A number of research areas or technologies can be explored for future research and development. This section discusses several future research directions as follows:

8.1 | Combination with AI and big data

To a certain extent, blockchain technology solves the dilemma that medical information data is not flowing smoothly and all parties are mutually isolated data, avoiding the invariability caused by legal sensitivity of medical information in the past. Valid data recorded on the blockchain are accumulated into a massive database of higher quality. In recent years, the data-based AI medicine research, and development paradigm has emerged with the development of big data and AI technology. It is essentially autonomous learning through machine data and data mining and sums up the drug development rule of expert experience and optimization of drug development. Through processing a large amount of high-quality medical big data, recurrent deep learning and algorithm optimization are carried out to promote the development of AI in different areas, such as cases, images, and genes, and establish verifiable and repeatable medical standards. While advancing the development of medical science, AI also enables patients to consume standardized medical services no matter in and outside of the hospital.

In recent years, AI has also made many significant achievements in medicine. For example, Insilico Medicine released the first candidate drug system using the Generative Adversarial Network (GAN) to develop in vivo activity and found a candidate drug in 46 days [137]. The results, published in Nature Biotechnology, have been cited as one of the milestones in the rise of AI pharmaceuticals, significantly reducing the time to drug development compared to traditional methods. AI has also been used to screen patients for clinical trials, such as Mendel Recruit, which uses natural language to scan documents and clinical records to screen eligible subjects 24–50% more efficiently than conventional methods.

8.2 | Promotion of unified data standards

Interoperability and varying data standards are significant challenges that have vexed stakeholders for many years. As the current medical information data standards are not unified, sharing a large volume of medical information is difficult. The critical step to promoting medical information construction is unifying data standards. Along with advancing the national health insurance unit for health care reform, the current messy medical information data will gradually realize standardization and unification and be accepted by the parties. After that, the effect of information circulation realized by blockchain for the medical industry will be significantly improved. The industry's efficiency will be further sublimated, and the construction and development of the medical system will be promoted.

8.3 | Integration of regulators and industry associations

After the multi-party medical alliance chain is gradually established, further integration is bound to be carried out to achieve greater synergy. However, due to the different architecture and interest demands of all parties, there will be many difficulties in the integration process. Industry regulatory agencies or associations may become the best role in promoting integration. Taking the hospital system as an example, the significant medical associations have difficulties in cooperation and alliance. The information between medical institutions can only be transferred within each medical association. Suppose the hospital associated with the right to speak in the industry initiates the alliance integration, proposes a unified standard, takes the initiative to cooperate, and builds a trans-regional and trans-system large-scale alliance chain. In that case, it can achieve a broader range of medical data sharing. After that, it can connect with insurance institutions, pharmaceutical manufacturers, and other institutions to promote the data circulation of the whole industrial chain and eventually create a complete blockchain ecosystem.

9 | CONCLUSION

As a new technology, blockchain provides a new perspective for breaking through the bottleneck of the development of clinical trial informatization with its decentralization, security sharing, non-tampering, and high privacy characteristics. This study provides a taxonomy that identifies the aspects of clinical trials that blockchain technology can benefit from. The taxonomy is separated into decentralized scenarios and practices, blockchain types, deployment methods, and consensus algorithms. The blockchain application can cover all aspects of the clinical trial study, such as patient recruitment, consent traceability, persistent monitoring, data management, and data analysis, providing practical technical support for the reconstruction of the clinical trial informatization foundation and the process of reshaping clinical trial data management. Moreover, we outline recent development trends of blockchain projects and micro applications in clinical trials.

Furthermore, the threats of blockchain technology utilization within clinical trials, including privacy leakage, scalability issues, security, and interoperability, are discussed in this paper. These technical difficulties are also relevant to implementing blockchain in the clinical trial study. Only by overcoming the core technical difficulties can the advantages and potential of blockchain technology be genuinely brought into play in clinical trials.

Future clinical trials and decision support can be improved by integrating AI and big data technology. In addition, the promotion of unified data standards can facilitate the communication among different blockchain platforms, and the addition of integration of regulators and industry associations can promote the data circulation of the whole industrial chain and eventually create a complete blockchain ecosystem, which is conducive to the accurate completion of clinical trials.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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