https://doi.org/10.33472/AFJBS.6.6.2024.6946-6955

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

"Blockchain-Centric Approach for Clinical Trial Environment"

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Article Info

Volume 6, Issue 6, July 2024

Received: 23 May 2024

Accepted: 20 June 2024

Published: 09 July 2024

doi: 10.33472/AFJBS.6.6.2024.6946-6955

ABSTRACT:

Introduction: Clinical trials play a crucial role in generating research data that aids in obtaining approval for innovative drugs, instruments, and medical procedures for human use. Clinical data management (CDM) is an intricate and multidisciplinary process that plays a vital role in collecting high-quality and reliable data generated through clinical trials. However, the current workflow of clinical trials is characterized by independent, disconnected activities, leading to up to 10% of clinical research not being replicable due to high error rates caused by human error, fraud, or misbehavior. To address these challenges, blockchain technology has been advocated as a solution to introduce immutability, traceability, and potentially heightened reliability into clinical trial data.

Aim: To understand the role of blockchain technology in a clinical trial environment

Objectives:

1. To better understand the challenges present in the current clinical trial landscape and explore the potential of blockchain technology as a solution.
2. To evaluate the importance of focusing on the Indian clinical research context when considering implementing blockchain technology in clinical trial data management.
3. To assess the legal aspects of the blockchain's use in managing clinical trial data

Methods: This study conducted a systematic literature review to investigate the use of blockchain technology in clinical trial data management. The search was conducted in three databases, including PubMed, Scopus, and the Web of Science, using relevant keywords. Studies were screened for relevance, and the selected studies were subjected to data extraction and synthesis using a thematic approach. The study aimed to explore the current state of research on blockchain technology in clinical trials. The search was limited to studies published in English and conducted up to April 2023

Findings: The clinical trial environment involves planning, executing, and monitoring new treatments, drugs, or medical devices on human subjects, while also considering ethical and legal issues such as informed consent, privacy, confidentiality, and compliance with regulatory requirements. Clinical trials typically cost millions of dollars and require proper data management and security to protect public health and ensure confidence in marketed products. Blockchain technology can offer solutions for managing clinical trial data, but legal aspects such as GDPR, HIPAA, and DISHA must be considered to protect individuals' health data. Blockchain databases must adhere to HIPAA regulations on data processing and ensure the protection of PHI. Patients' enrollment in clinical trials, trial management, and ongoing monitoring can be handled through secure smart contracts.

Conclusion: Nationwide data protection regulations are crucial in clinical trials, as electronic health records serve as a national healthcare database. The collection, processing, and sharing of personal and medical information in clinical trials makes it essential to have a comprehensive data protection framework. This would encourage patient participation in clinical trials and innovative therapies, promoting trust and confidence in the healthcare sector. The implementation of blockchain technology, like Guardtime's Keyless Signature Infrastructure (KSI), can improve data protection and promote transparency in national healthcare databases, benefiting stakeholders in clinical trials. The successful implementation of blockchain technology in Estonia shows the importance of trust between private companies and government officials, who can collaborate to implement it in phases using consortium blockchains.

Keywords: Blockchain, Clinical Trials, HIPAA, GDPR, DISHA, Smart Contracts

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1. Introduction

The management of clinical trial data is a critical aspect of the drug development process, with data transparency, security, and integrity being of utmost importance. Blockchain technology is a promising solution for data management in clinical trials, as it provides secure, decentralized, and tamper-proof data storage. This literature review provides an overview of the literature on blockchain-centric approaches for clinical trial data management.

Hang et al. (2021) developed a permissioned blockchain-based clinical trial service platform to improve trial data transparency. The platform includes features like decentralized data storage, transparent data access, and immutability, ensuring data integrity and security.

Matkar and Gangawane (2017) provided an outline of data management in clinical research, emphasizing the importance of data quality and integrity. The authors highlighted the need for robust data management systems to ensure accurate and reliable data.

Hang et al. (2022) provided a taxonomy of blockchain applications in clinical trials, highlighting the potential benefits of blockchain technology for clinical trial data management. The authors identified several challenges and future directions for blockchain adoption in clinical trials.

Wong et al. (2019) developed a prototype for running clinical trials in an untrustworthy environment using blockchain technology. The authors highlighted the potential of blockchain technology to enhance data security, privacy, and transparency in clinical trials.

Benchoufifi et al. (2019) reviewed the potential of blockchain technology for improving transparency and trust in clinical trials. The authors discussed the potential applications of blockchain in clinical trial data management, highlighting the benefits of blockchain for data sharing, provenance, and auditability.

de-Melo-Diogo et al. (2021) reviewed the potential of blockchain technology for data security in clinical trials. The authors discussed the use of blockchain technology for ensuring data confidentiality, integrity, and availability in clinical trials.

The OECD (2020) policy brief provided an overview of the opportunities and challenges of blockchain technology in healthcare. The brief highlighted the potential of blockchain technology for improving data security, transparency, and interoperability in healthcare.

Gupta (2013) discussed the challenges of fraud and misconduct in clinical research. The author highlighted the importance of data integrity and the need for robust data management systems to prevent fraud and misconduct.

McCurry (2014) reported on the arrest of a former Novartis employee over valsartan data, highlighting the importance of data integrity and the potential consequences of data manipulation.

Lehman and Loder (2012) discussed the issue of missing clinical trial data and its impact on the drug development process. The authors emphasized the need for improved data sharing and transparency in clinical trials.

Valkenhoef et al. (2012) reviewed existing systems and standards for the transfer and availability of clinical trials evidence. The authors highlighted the deficiencies of current systems

Zhao (2022) explored the application of the right to be forgotten in the context of machine learning and proposed a framework for ensuring GDPR compliance in machine learning using blockchain technology.

Finally, the Examination of Clinical Trial Costs and Barriers for Drug Development report (2018) by the Department of Health and Human Services highlighted the need to reduce the

costs of clinical trials and emphasized the potential benefits of using blockchain technology in clinical trial data management.

2. Research Methodology

In this study, a systematic literature review was conducted to explore the use of blockchain technology in clinical trial data management. The literature search was conducted in four databases, including PubMed, Scopus, Web of Science, and the WHO Global Health Library. Grey literature was also searched to ensure a comprehensive review. The search was conducted using the following keywords: blockchain, clinical trials, clinical trial data management, Acts for blockchain, HIPAA, GDPR AND DISHA. The search was limited to studies published in English and those conducted up to April 2023.
The search strategy involved the use of Boolean operators to combine the keywords, and both MeSH terms and free text words were used. The studies were screened for relevance based on predetermined inclusion and exclusion criteria. The selected studies were then subjected to data extraction and synthesis using a thematic approach.

Findings

5.1 Clinical Trial Environment: Challenges and Blockchain-driven Solutions:
The clinical trial environment is a complex and highly regulated setting that involves careful planning, execution, and monitoring to ensure the safety and effectiveness of new treatments, drugs, or medical devices on human subjects. The clinical trial environment also includes a number of ethical and legal considerations, such as informed consent, privacy, the confidentiality of the participants, and compliance with regulatory requirements. **Exhibit 1** provides the challenges and related issues in the clinical research landscape whereas **Exhibit 2** highlights the application of blockchain technology in the real-world clinical research setting

Exhibit 1:The challenges and related issues in the clinical research landscape

Challenges	Issues	References
Data Reliability	• Data fraud • Selective publication • Data missing • Tampering of data • Concealing of data • Inability to trace original data	• Gupta *et al.*, 2013 • McCurry et al., 2014
Irregular informed consent process	• Lack of clarity among some patients about the process and content of the clinical trial • Expanding the scope of information acquisition without permission • Modifying informed consent without permission	• Hang *et al.*,2021

Data traceability	• Data forgery and human input errors due to multiple centers, sponsors, and regulatory agencies delays in data inspection and verification by relevant government supervision institutions • eClinical systems are prohibitively expensive and accessible only to major pharmaceutical companies • Lack a safe and easy way to access real-time results or track historical data • Data exchange in drug trials is complex, posing a challenge to monitoring and regulation	• Lehman & Loder 2012 • Valkenhoef *et al.*,2012 • Hume *et al.*, 2017
Data accessibility	• Use of own software systems, data formats, procedures, and organizations. • Fragmented patient data makes recruitment for clinical studies difficult • Inadequate consideration of medical conditions of patients can lead to flawed research	• DiMasi *et al.*, 2016

Exhibit 2: Applications of Blockchain technology in the real-world clinical research setting

Real-world clinical trial setting	**Blockchain application**	**References**
Patient recruitment	• Efficient patient recruitment by broadcasting information to specific physicians • Blockchain smart contracts match patient profiles with trial criteria and ensure the legitimacy of sponsors and clinical studies, informing patients of new trials	• Zhuang *et al.*, 2018 • Zhuang et al., 2019

Consent traceability	• Create a timestamped document in an open format that records the consent collection process for each protocol version	• Benchoufi *et al.*,2017
Persistent monitoring	• A permissioned blockchain enables continuous monitoring and traceability of data, and Application Program Interface (API) can facilitate patient data sharing through smart devices. • Smart contracts can validate participants' identities and query health data, enabling the FDA to check raw data and analytics reports, while patients can communicate with the FDA directly	• Zhuang *et al.*, 2018
Data management	• Safe data monitoring • Safe data sharing • User privacy • Archival solution eg: Vechain Thor blockchain	• Hang *et al.*,2021 • Vechain
Data analytics	• Real-time data analytics through storing all transactions • Smart contracts can automate data analysis and detect data falsification with no intervention from clinical sites or sponsors • Support Vector Machine (SVM) training helps smart contracts get tamper-proof results during the learning phase.	• Hang *et al.*,2021 • Shen *et al.*, 2019

5.2 As reported by Aylin Sertkaya et al Clinical trials across various therapeutic areas typically cost an average of $4 million for phase 1, $13 million for phase 2, and $20 million for phase 3. Pivotal phase 3 studies, which are essential for the Food and Drug Administration's (FDA) approval of new drugs, have a median cost of $41,117 per patient (Aylin Sertkaya et al.,2014). Therefore, India is becoming a popular choice for multinational pharmaceutical companies for clinical trials of new products due to its large and diverse population, which provides easy access to therapy-naïve patients with a vast gene pool, and the lower cost of technical services, which results in a lower per patient trial cost. However, proper data management and security are crucial to achieving the ultimate goal of clinical data management: protecting public health and ensuring confidence in marketed therapeutics or devices. A BMJ medical journal report cited a study which analyzed 526 trials submitted to the journal Anesthesia between February 2017 and March 2020 revealing that over a three-year period, a staggering 54% of clinical trials published by Indian researchers were found to contain fraudulent data(BMJ).

5.3 Legal Aspects for Implementing Blockchain Technology in the Management of Clinical Trial Data:

HIPAA, GDPR, and DISHA are regulations that govern the collection, processing, storage, and sharing of personal health information in the US, Europe and India respectively. Each of these regulations has its own set of rules and requirements, and they all aim to protect the privacy and security of individuals' health data.

GDPR: GDPR includes provisions for healthcare services that expose information such as biometric data, genetic data, and data related to sex life and sexual orientation and protects information about a person's past, present, and future physical or mental health. (Article. 4(15)). Unless certain requirements are completed, the GDPR bans the transfer of personal data outside of the EU (Arora et al., 2022). Organizations must make sure they are applying the proper technical and organizational procedures to secure personal data while developing a blockchain-based system and that they are including data protection principles in the system's design (Article 25) (Haque et al., 2021). It's crucial to make sure that all data transfers adhere to GDPR rules if Blockchain technology is utilized to hold clinical trial data. Blockchain database secures consent, allowing participants to control data and withdraw it. According to Article 6(1)(a) of the GDPR, personal data can only be processed with the data subject's consent where it is required for the completion of a contract, to uphold a legal obligation, or when it is necessary for the vital interests of the data subject or any other natural person. Data processing is only permitted for legitimate purposes, however, some types of personal data, such as genetic and biometric information (Article 9), require explicit consent and should be carried out in the public interest (Arora et al., 2022). Article 18 underlines the circumstances where data should be restrictively processed instead of erased and thus offers an alternative way to address RTBF issues. What Article 18 stipulates could also be considered as an alternative to the erasure if the data subject repudiates the deletion of personal data used for illegal processing according to Article 17(1) (d), but expects to keep the data archived for the sake of their interests (Zhao et al., 2022). This right guarantees that the data subject has the autonomy to request the removal and erasure of their personal data in situations when the data storage is unnecessary, unequivocal permission has been withdrawn, etc. The EU Court of Justice's 2014 ruling adequately highlights the significance of such a right for the data subject and ensures that the EU legislation adequately summarizes it (Arora et al., 2022).

HIPAA: Health information permissions and protections are covered by the HIPAA Act (45 CFR Section. 164 Subpart E, 2013). Blockchain databases that are designed to store, retain, and distribute personally identifiable information about users for future usage should adhere to HIPAA and privacy regulations. The Privacy Rule treats the creation or upkeep of research databases containing Protected Health Information (PHI) by a covered entity or business partner as a research activity. According to the safe harbor technique (45 CFR Section. 164.514(b) (2)) and expert decision method (45 CFR Section. 164.514(b)), 18 different types of identifiers should be deleted while building a blockchain database. The type of variables that will be gathered must therefore be specified in order to evaluate whether HIPAA laws apply (Charles et al.. 2019). The use of blockchain technology in clinical trial data must adhere to HIPAA regulations on data processing, as outlined in the 45 CFR Section. 164 Subpart E, to ensure the protection of Protected Health Information (PHI). Patients' enrollment in clinical trials, trial management, and ongoing persistent monitoring are all handled via smart contracts. It enables secure users to link medical records to Blockchain (Bhara et al., 2019). All health information is regarded as PHI when personal identification numbers are present. PHI is a subset of individually identifiable health information that is subject to the HIPAA Privacy Regulation (PHI). According to HIPAA, the 2013 revision of the Privacy Rule, 45 CFR Sect. 164.512(i)(1)(ii), states that covered entities may use or disclose PHI for "preparatory to research" activities (Charles et al., 2019).

DISHA: In India, electronic records of health-related information about the person derived from tests or relating to the clinical establishment accessible, are governed by DISHA. In a similar vein to HIPAA's privacy rule, DISHA governs related personally identifiable information (PII) (Section 3(1) (k)). A list of PII (unique identity of an individual) is included in Schedule 1 of the Bill and includes name, address, financial information, medical records, and details on one's physical, physiological, and mental health, among other things. (Arora et al., 2022). Although there is no explicit law governing the creation of Blockchain-based clinical trial systems, companies must make sure they are following Section 4 of the standards for electronic health records when employing standardised terminology and formats to guarantee system compatibility.

Exhibit 3: Outlines the Articles, Sections and Schedules in consideration for the usage of Blockchain technology in clinical trials.

Laws	**Article /sections**	**Description**	**Usage**	**Reference**
GDPR	Article 25	Provides technical and organizational procedures, incorporates data protection principles in system design, and ensures all data transfers meet GDPR requirements.	Blockchain-based database design	*Haque et al., 2021*
	Article 9	Permits you to process special categories of data such as genetic data, biometric data, health data or health concerning a person's sex life or sexual orientation.	Explicit consent for processing participant data	Arora et al., 2022
	Article 6(1)(a)	This article specifies processing personal data is only permitted for legitimate purposes, and requires the data subject's consent, unless it's necessary for a contract or legal obligation, or vital interests of the data subject or any other person.	Consent for processing data for legitimate purpose	Arora et al., 2022
	Article 17(1)(d)	Erasure of personal data upon request	Right to be forgotten	Zhao et al., 2022
	Article 18	As per this article, an individual can limit the way that an organization uses their data. This is an alternative to requesting the erasure of their data.	Right to restrict the processing of their personal data	Zhao et al., 2022
HIPAA	45 CFR Section. 164 Subpart E, 2013	This act covers health information permissions and protections in the context of Blockchain.	Data storage	Charles *et al.*, 2019
	45 CFR Section. 164.514(b)(2)	The Privacy Rule considers the creation or maintenance of research databases with PHI as a research activity	Database creation and maintenance	

	45 CFR Section. 164 Subpart E	Data processing, as outlined in Section. 164 Subpart E, to ensure the protection of Protected Health Information (PHI).	Data processing	
DISHA	Schedule 1 (Section 3(1)(k))	Contains list of personally identifiable information (PII) in EHR	Regulation of personally identifiable information (PII).	Arora *et al.*, 2022

3. Discussion & Recommendations

To overcome the limited adoption of blockchain technology in the clinical research landscape, the focus must be on factors such as the lack of technical expertise, high implementation costs, and regulatory barriers. Therefore, to fully leverage the benefits of Blockchain technology in clinical trials, the following strategies can be implemented.. Healthcare professionals involved in clinical trials should receive technical training on Blockchain architecture, smart contracts, cryptography, and data security. This will guarantee they have the essential skills and knowledge to deploy Blockchain in clinical trials effectively and securely.Collaboration with the government: The Indian government should play a crucial role in promoting the use of Blockchain technology in healthcare by supporting the implementation of the Digital Information Security in Healthcare Act (DISHA). The Indian government may explore the possibility of introducing specific regulations in the DISHA Act to govern smart contracts run on blockchain in clinical trials.To ensure seamless data exchange and interoperability among different healthcare systems, Blockchain-based clinical trials must adopt standardized protocols, data formats, and APIs. This will improve data quality and foster cooperation among stakeholders, leading to better patient outcomes. Healthcare organizations should collaborate with technology providers and Blockchain experts to develop new use cases and solutions for Blockchain in healthcare. This will accelerate the adoption of Blockchain technology and enhance the overall efficiency and security of healthcare data. The successful implementation of Guardtime's Keyless Signature Infrastructure (KSI) based blockchain technology at a national scale in Estonia is a testament to the importance of trust between private companies and government officials

4. Conclusion

The implementation of singular nationwide data protection regulations is crucial in clinical trials, as electronic health records (EHRs) are used as a national healthcare database. Data protection measures are necessary to protect sensitive patient data. Clinical trials collect, process, and share personal and medical information, making it essential to have a comprehensive data protection framework for the healthcare ecosystem. This would promote trust and confidence in the healthcare sector, encouraging patient participation in clinical trials and innovative therapies. Therefore, the government needs to introduce robust data protection regulations to ensure that patient data is handled with care while advancing medical research.

While the use of blockchain technology for securing information exchange requires high computing power, both government and private players can collaborate to implement it in phases, using consortium blockchains. Overall, the implementation of blockchain technology can improve data protection and promote transparency in national healthcare databases, benefiting the stakeholders in clinical trials.

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