Political and Economic Implications of Blockchain Technology in Business and Healthcare

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Chapter 10
Data Security in Clinical Trials Using Blockchain Technology

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ABSTRACT

Blockchain technology in a clinical trial setting is a valuable asset due to decentralization, immutability, transparency, and traceability features. For this chapter, a literature review was conducted to map the current utilization of blockchain systems in clinical trials, particularly data security managing systems and their characteristics, such as applicability, interests of use, limitations, and issues. The advantages of data security are producing a more transparent and tamper-proof clinical trial by providing accurate, validated data, therefore producing a more reliable and credible clinical trial. On the other hand, data integrity is a critical issue since data obtained from trials are not instantly made public to all participants. Work needs to be done to establish the significant implications in security data when applying blockchain technology in a real-world clinical trial setting and generalized conditions of use to establish its security.

INTRODUCTION

Since its discovery, Blockchain is emerging as an innovative technology to provide data transactions and storage in an effective, secure, and timely manner system. This technology has been applied to many sectors of activity, potentializing its features and improving processes and business mindsets.

The health sector is no exception, and many uses of this technology have been reported. Blockchain's full applicability in healthcare is still underway, and many optimizations are needed to be made, not

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only from a technology development perspective but also concerns about ethical and data protection regulation are raised and need improvement.

It is considered essential to mention that the interest in the applicability of blockchain systems in the healthcare sector has been increasing since 2016. More specifically, the number of published articles related to Blockchain in the Pubmed bibliographic database has increased drastically in 2018 (only five studies were published in 2016 and only 16 in 2017), reflecting the potential and growing interest of these systems in the healthcare sector (Mackey et al., 2019). Only 4% of these studies were related to clinical trials, and 32% were related to healthcare data (Mackey et al., 2019).

Particularly in clinical trials, this technology is yet to reach its full potential. Nevertheless, considering the dimension and complexity of a clinical trial network and process interlined, blockchain technology might improve data sharing, management, and access to all key players. However, identifying the risks and threats of applying this technology in such an environment is still amiss, and work needs to be done to establish them in a realistic scenario setting.

Therefore, the purpose of this chapter is to map the current use of blockchain systems in clinical trials, particularly data security managing systems, and its characteristics, such as applicability, interests of use, limitations, and issues, as reported throughout the literature review.

BACKGROUND

Although variations of term have been used before, Blockchain came around in 2008 when this technology was created by Satoshi Nakamoto to support and securely record Bitcoin cryptocurrency transactions (Meunier, 2018; Monrat et al., 2019). Since then, the interest in this technology has increased and soon was applied into other areas of interested such as government, manufacturing, finance, healthcare and distribution (Monrat et al., 2019).

Blockchain is an advanced data structure, designed for storing and sharing information, composed by a growing chain of blocks organized by chronological order (Agbo et al., 2019)(S Chen, Hannah et al., 2019). Each block stores information with digital signatures in a decentralized and distributed network, it allows to record a transaction by binding different blocks connected with chains (S Chen, Hannah et al., 2019) (Abu-elezz et al., 2020) (Monrat et al., 2019). This transaction is validated by a consent algorithm, and therefore, needs no third-party validation to complete an action. The chain continues to grow as new transactions are built and blocks are added into it (Omar, Jayaraman, Salah, Yaqoob, et al., 2020).

Unlike traditional methods, blockchain enables peer-to-peer transfer of digital assets without any intermediaries. All the transactions occur in a decentralized manner that eliminates the requirement for any intermediaries to validate and verify the transactions. Every transaction is regulated by the participants who store and share the information throughout the private key: an unique and individual signature linked to each transaction recorded (S Chen, Hannah et al., 2019).

The digitalization era is reaching almost every industry and is expected that the Distribution Ledger Technology, where technologies such as blockchain, artificial intelligence and Internet of Things are inserted, to reach a market value of $60.7 billion by 2024 (Smetanin et al., 2020).

The features of blockchain, include (Hussien et al., 2019):

- Decentralization, access of information through third parties with multiple copies in multiple locations;

- Consent, the consensus algorithm created controls the access and distribution within a network;
- Immutability: once the information has entered a blockchain no longer can be changed or altered; a
- Auditability and transparency, every transaction information and signature can be traced; interoperability, different systems are connected and communicate in an autonomous manner.

The blockchain platform is distinguished by its key characteristics enabling it to be a promising disruptive technology that reduces the emphasis on traditional data management systems (Omar, Jayaraman, Salah, Yaqoob, et al., 2020). The blockchain is poised to innovate and transform a wide range of applications, including goods transfer (supply chain), digital media transfer (sale of art), remote services delivery (travel and tourism), platforms for example, moving computing to data sources and distributed credentialing.

Healthcare systems are complex and multi-dimensional organizations, involving multiple professionals whin different functions and degrees of access information, multiple organizations of different sectors of activities such as regulatory agencies, insurance companies, suppliers, technical supports and many others. Providing care to a patient involves many professionals and actions, therefore is important that health records are available and updated in time to provide the accurate and appropriate care to each patient at all times. On the other hand, it is also important that every patient owns is medical record and has fully knowledge of the parties that have been granted access to the very same.

Data security and ownership represent two of the most sensitive topics of today's generation. In fact, since the approval of General Data Protection Regulation in 2016 in European Union, when it comes to medical records these two topics became even more important and prominent. Besides this, managing patient data integrity is one of the major concerns for the healthcare industry, combining the need to access each patient characteristics and complete medical records at any time.

The introduction of blockchain systems in healthcare might be the solution to some of the concerns raised in data security and medical records accessibility and might the solution to gather and improve communications and data sharing between every player in the healthcare systems.

Concerning blockchain applications in healthcare, blockchain benefits are the following (Agbo et al., 2019)(Hasselgren et al., 2020):

- Decentralization: Healthcare access is spread to multiple players, such as doctors, hospitals, health insurance companies, pharmacies, etc. This feature of blockchain allows access to multiple stakeholders in a timely manner and provides information sharing in real time.
- Transparency: Given the security and transparency of transactions, information systems and storing systems are very reliable, and therefore provide a solid source of information for healthcare stakeholders. This feature is very important for example, when submitting information to regulatory agencies.
- Data verifiability: every transaction can be check for its integrity and validity. This information is important for healthcare records validation, insurance claim verification and in pharmaceutical supply chain to detect contrafact products.
- Transparency and trust: given the amount of information stored and that every transaction is record, blockchain provide for healthcare providers and stakeholders an ambient of trust and transparency since every information is available to consult.

- Robustness: The blockchain storage method guarantees that data is available and prevented from loss.
- Data ownership: given the levels of access and control of access of a blockchain, through this data storage system, patients are able to a more detailed control of the availability of their medical records to third parties.
- Data security and privacy: once an information has entered in a blockchain it is extremely difficult to alter through maleficent intentions. Additionally, every transaction is recorded in chronological order and is also traceable by its time stamp and user responsible for that action.

Concerning healthcare, blockchain systems can be applied in different areas such as (PwC, 2018) (Deloitte, 2020)(S Chen, Hannah et al., 2019)(Tan et al., 2020) (Smetanin et al., 2020) (Omar, Jayaraman, Salah, Yaqoob, et al., 2020)(Monrat et al., 2019):

- Supply chain: products status can be checked by the supplier at all times. This includes information regarding the transportation route, and more importantly, about controlled factors such as temperature and humidity throughout the transportation, contributing for a better monitorization and assuring the quality and safety of the products delivered. This contribution is especially important when it comes to products that need refrigeration, such as vaccines and biological products. Blockchain systems also improve security and authenticity of the products delivered, tacking the issue of distribution of falsified drugs.
- Precision medicine and medical records: the access of multiple players in healthcare to medical records of a patient in real time not only can improve the care provided, and can also potentiate the uses of precision medicine, since the patient medical records and genomic data can by easy shared between doctors and researchers.
- Data management: Gathering medical records, expenses and reports concerning a medical treatment could be time consuming and an extensive process. Blockchain can improve this field since data sharing would be available and updated by the multiple players making the communication between them more efficient, for example between a hospital and an insurance company.
- Electronic prescription: electronic prescription would be improved by blockchain systems, given the ability of the information can be spread throughout the different services such as hospital-doctor-patient-pharmacy. Patient electronic devices can be also updated with app to monitor the adhesion to therapy, giving precious information to the doctor and pharmacist about the success of the treatment in a timely manner.
- Regulatory compliance: given the security and data authenticity provided by blockchain systems, regulatory compliance and monitorization of records by the regulatory agencies can be improved and in case of no compliance, actions could be performed in a timely manner.
- Research and development: clinical research data throughout every step of a clinical trial could be actively monitored, the information shared between multiple stakeholders have a high classification of security and authenticity, logistical processes can also be improved, such as patient recruitment, payments, consent and authorization, etc.

It is clear that Blockchain technology can bring many improvements for the healthcare sector, in fact, by 2022 it is expected that the blockchain market in healthcare sector is valued in $500 million and those investment would be in the clinical trial management, improvement of sharing electronic records and fulfilling regulatory compliance (Hasselgren et al., 2020).

One of the essential uses of blockchain in the healthcare is, undoubtedly the clinical trials, the theme of this chapter. Specifically, the key features of blockchain technology, such as data provenance, transparency, decentralized transaction validation, and immutability, may contribute to overcome data management issues in clinical trials (Omar, Jayaraman, Salah, Yaqoob, et al., 2020). Areas of clinical trials where blockchain represents an improvement also include patient recruitment, medical data sharing and privacy, data integrity, consent traceability and transparency, as mentioned before (Omar, Jayaraman, Salah, Yaqoob, et al., 2020).

On the other hand, another important topic in authenticity in clinical trials is related to data management. Data could be altered or lost which could represent a major problem in a clinical trial setting creating an untrustworthy environment. In fact, 80% of the assays submitted to FDA are not reproductible due to the presence of various errors, such as fraud, data misrepresentation, and trial misconduct (Petre & Haï, 2018). This is one of the factors that contributes to data obtained from clinical trials not being immediately made public to key-players.

Taking all of this into consideration, to further explore the benefits, disadvantages, threats and opportunities of blockchains in clinical trials in data management, a review as conducted to map this information.

Review Methods

Research Objective

There are several studies reporting the advantages and disadvantages and applicability of blockchains in clinical trials, however the knowledge of those characteristics when applied to data security in clinical trials is lacking.

The role of this review is to map the current utilization of blockchain systems in clinical trials, particularly the data security managing system and its characteristics, such as applicability, interests of use, limitations and issues, as reported in literature.

In this section we report the methodology applied to conduct this review including the selection process.

Research Protocol

To identify potentially relevant publications a search was conducted on November 8th, 2020 in the following online bibliographic databases: PubMed, Science Direct and Google Scholar.

Backward-reference list checking was conducted to identify other relevant references.

The search was conducted using several combination of search terms in order to establish first the amount of information available related to blockchain and to clinical trials or health care sector, and secondly directly related to data security provided by a blockchain in a clinical trial setting. Therefore, several search terms were used and ultimately the search words used to retrieve studies from databases has: “blockchain” AND “Healthcare” AND “Clinical trials” AND “data security”.

Data Base Selection Criteria

Search was conducted simultaneously in three data bases: PubMed, Science Direct and Google Scholar.

Pubmed database was considered, as it is one of the leading databases in healthcare content. Google Scholar database was chosen in order to bring different background and variability content sources. Science Direct database was chosen considering the high percentage of peer-review content.

Eligibility Criteria

In this review were included studies and review studies that reported the advantages and disadvantages of use of blockchain in clinical trials particularly in the data security optic. For the purpose of this study were excluded studies that merged blockchain and other technologies not related to the theme of this chapter and that targeted blockchain uses in healthcare other than clinical trials.

Information from magazines with peer-review, newspapers, conference abstracts and book chapters were excluded from this review. Were included studies from 2017 onwards since no relevant information before that year has found in the literature associated with blockchain and its uses in clinical trials.

Additionally, studies that were written in languages other than French and English were excluded. This criteria was established given the authors proficiency in the selected languages.

The study eligibility criteria are described in Table 1.

Table 1. Eligibility criteria of studies included in this work

Inclusion Criteria	Studies that address benefits and/or threats of blockchain in Clinical trials
	Studies from 2017 onwards
	Studies reported in English or French
Exclusion Criteria	Information from magazines, newspapers, conference abstracts and book chapters
	Studies that merged blockchain and other technologies not relevant to the theme of the chapter
	Studies that targeted other uses of blockchain in healthcare other than clinical trials

Study Selection Process

As mentioned above, studies were retrieved from multiple bibliographic databases resulting from a process divided into four phases: (i) screening phase, were multiple search words were used to establish the amount of studies related to the theme; (ii) identification phase, were the citations were retrieved from the several databases; (iii) screening phase, where titles and abstracts of citations were screened to select or exclude articles; (iv) duplicates screening phase, were the citations whom were considered as relevant during screening phase were checked for duplicates; (v) eligibility phase, where the full-texts of articles were read to assess their relevancy to this study.

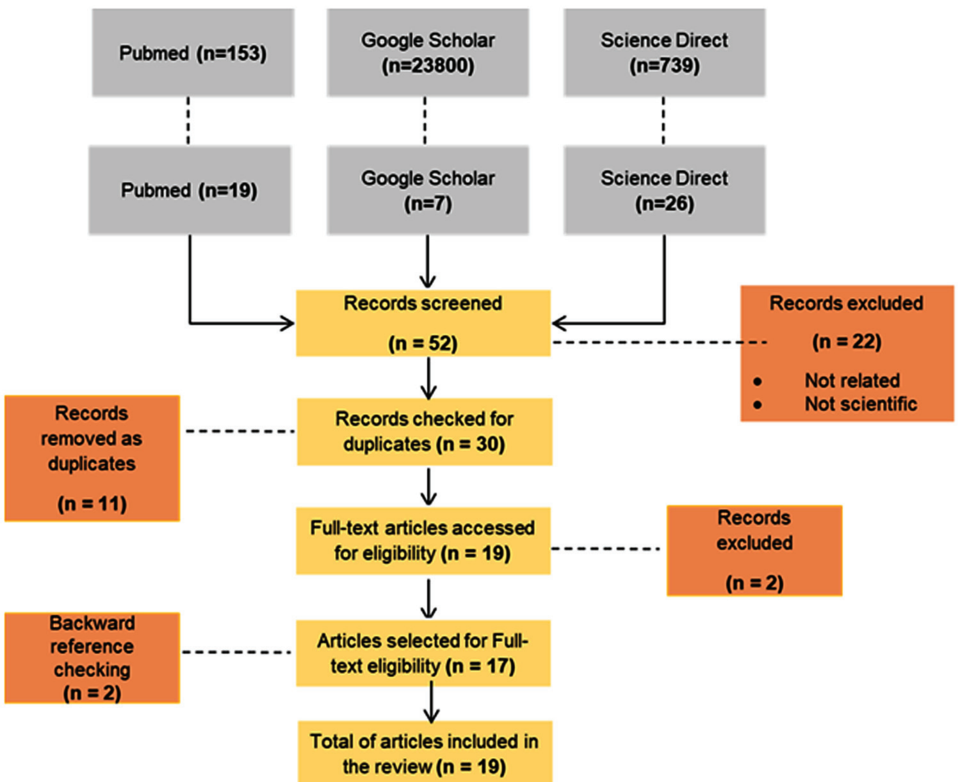
Data Extraction and Data Synthesis

A summary of the included studies related to the theme of this review were extracted from the selected citations and the articles were categorized by the type of publication. The year of publication was also extracted from the articles.

Search Findings

The number of articles retrieved and consequent process of studies search and selection is described in Figure 1.

Figure 1. Study selection and research process.



As a result from the initial search with search terms "blockchain" AND "healthcare", a total of 24692 results were obtained gathered from the three bibliographic databases used. After a combination of different search words, as described in Table 2, the search words used ("blockchain" AND "healthcare" AND "clinical trials" AND "data security") produced a total of 52 records to be screened considering the inclusion and exclusion criteria mentioned above. Therefore, these records were screened through their title and abstract and 22 were excluded considering the fact they were not related to the theme or not scientific content. Afterwards, the records were checked for duplicates and 11 records were deleted. A number of 19 records were gathered to check its full text for eligibility and 17 records were considered relevant.

Backward reference was partially conducted to gather additional studies relevant to the theme. Overall, 20 studies were included in this review.

Table 2. Results obtained using the several search terms across the three bibliographic databases (Pubmed, Science Direct and Google Scholar)

Search Terms	Number of Results (n)
"blockchain" AND "Healthcare"	24692
"blockchain" AND "Healthcare" AND "Clinical trials"	1534
"blockchain" AND "Healthcare" AND "Clinical trials" AND "security"	1130
"blockchain" AND "Healthcare" AND "Clinical trials" AND "data security"	52
"blockchain" AND "clinical trials"	19[1]

List of the Articles Reviewed

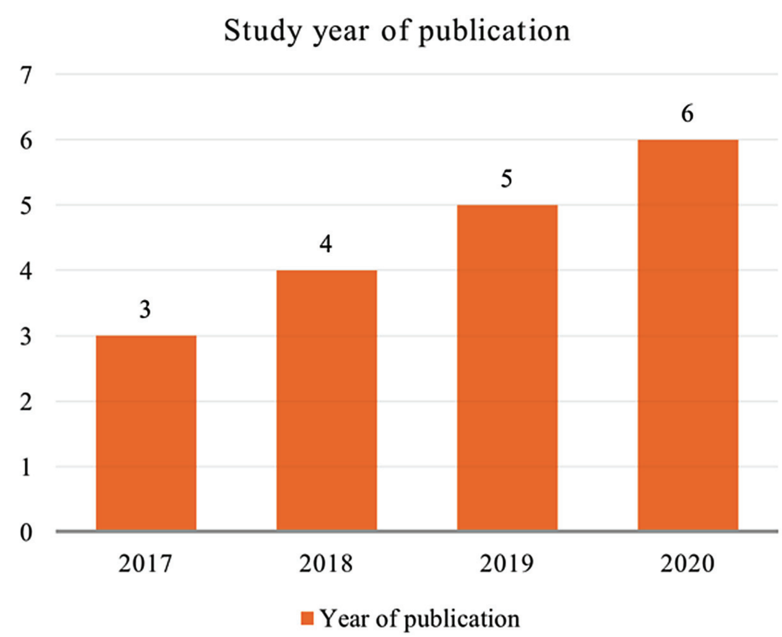
- Abu-elezz et al., (2020) - The benefits and threats of blockchain technology in healthcare: A scoping review
- Angeletti et al., 2017 - The role of blockchain and IoT in recruiting participants for digital clinical trials
- Benchoufi et al., 2017 - Blockchain protocols in clinical trials: Transparency and traceability of consent
- Benchoufi et al., 2019 - From Clinical Trials to Highly Trustable Clinical Trials: Blockchain in Clinical Trials, a Game Changer for Improving Transparency?
- Benchoufi & Ravaud, 2017. Blockchain technology for improving clinical research quality.
- Choudhury et al., 2019 - A Blockchain Framework for Managing and Monitoring Data in Multi-Site Clinical Trials
- Drosatos & Kaldoudi, (2019) - Blockchain Applications in the Biomedical Domain: A Scoping Review
- Hirano et al., 2020 - Data Validation and Verification Using Blockchain in a Clinical Trial for Breast Cancer: Regulatory Sandbox
- Kamel Boulos et al., 2018 - Geospatial blockchain: promises, challenges, and scenarios in health and healthcare
- Mackey et al., 2019 - 'Fit-for-purpose?' – challenges and opportunities for applications of blockchain technology in the future of healthcare
- Maslove et al., 2018 - Using Blockchain Technology to Manage Clinical Trials Data: A Proof-of-Concept Study
- Monrat et al., 2019 - A survey of blockchain from the perspectives of applications, challenges, and opportunities.
- Omar, Jayaraman, Salah, Simsekler, et al., 2020 - Ensuring protocol compliance and data transparency in clinical trials using Blockchain smart contracts
- Omar, Jayaraman, Salah, Yaqoob, et al., 2020 - Applications of Blockchain Technology in Clinical Trials: Reviewand Open Challenges
- Petre & Haï, 2018 - Opportunities and challenges of blockchain technology in the healthcare industry
- Radanovic et al., 2018 - Opportunities for Use of Blockchain Technology in Medicine

- Tandon et al., 2020 - Blockchain in healthcare: A systematic literature review, synthesizing framework and future research agenda
- Wong et al., 2019 - Prototype of running clinical trials in an untrustworthy environment using blockchain
- Yan Zhuang et al., 2019 - Applying Blockchain Technology to Enhance Clinical Trial Recruitment
- Yu Zhuang et al., 2018 - Applying Blockchain Technology for Health Information Exchange and Persistent Monitoring for Clinical Trials

Characteristics of the Selected Studies

As presented in Figure 2, more than 50% of the studies selected for this article were published afterwards the year of 2019 (5 published in 2019 and 6 published in 2020, therefore 11 of 19 studies selected). Additionally, 4 of the selected studies were published in 2018 and only 3 studies were published in 2017.

Figure 2. Distribution of included studies by year of publication.



As presented in Figure 3 the selected studies for this article have a heterogenous distribution if the type of publication is considered. In fact, 3 of the studies were classified as articles, 4 as research articles, 4 as reviews, 1 as a paper, 2 as editorials, 1 as method article, 4 as research articles and 3 as proof of concept work.

Figure 3. Study type of publication

Summary of the Included Studies

Several citations enumerate the major benefits and threats of blockchain technology application in a healthcare system, including in a clinical trial setting (Abu-elezz et al., 2020) (Drosatos & Kaldoudi, 2019) (Petre & Haï, 2018) (Tandon et al., 2020) (Choudhury et al., 2019) (Omar, Jayaraman, Salah, Yaqoob, et al., 2020) (Angeletti et al., 2017) (Kamel Boulos et al., 2018)(Mackey et al., 2019) (Tandon et al., 2020)(Benchoufi et al., 2017; Yan Zhuang et al., 2019) (Yu Zhuang et al., 2018). They reflect that this technology adds significant value through improved efficiency, access control, technological advancement, privacy protection, and security of data management processes. However, in general, there are also some disadvantages mentioned related to high implementations costs, need for robust systems and specialized human resources, difficulty of scalability and data security and protection issues.

Several studies develop and implement blockchain systems in hypothetical real-life clinical trials. Omar, Jayaraman, Salah, Simsekler, et al (2020) propose a blockchain-based framework for clinical trial data management, using Ethereum smart contracts, concluding that the use of these systems assures data integrity, transparency, and traceability of the process in a clinical trial. Wong et al (2019) proposes a blockchain-based system to make data collected in the clinical trial process immutable, traceable, and potentially more trustworthy, and its resilience to data tampering. Maslove et al. (2018) explores the role of blockchain in supporting clinical trials data management and develop a proof-of-concept implementation of a patient-facing and researcher-facing system. Hirano et al (2020) validate a system that enables the security of medical data in a clinical trial using blockchain technology.

Tandon et al (2020) addresses the concerns for the improvement of regulatory compliance and security. Several important aspects are highlighted, particularly that further work needs to be done to address blockchain systems vulnerabilities and robustness, data privacy and authentication in shared storages.

BLOCKCHAIN IN CLINICAL TRIALS

As mentioned before, the interest of the applicability of blockchain systems in the healthcare sector has been increasing since 2016. In fact, this growing interest was also palpable through the research made for this chapter in Pubmed database, using the search words "blockchain" AND "healthcare" 153 results were obtained. This represents an increase of about 139% of the number of citations published in this database since 2018. Additionally, using the search words "blockchain" and "clinical trials" in Pubmed database 19 citations were obtained, which also represents an increasing number of citations since 2018 related to clinical trials and blockchain systems.

Blockchain Advantages and Disadvantages in Clinical Trials

Clinical trials require data and information to be well organized and categorized for the submission of the findings to the regulatory agency for the approval of the drug in test. Such compliance can be time consuming and resource consuming considering the amount of data, number of individuals and entities involved, and therefore it is a process particularly prone to human and system errors.

Blockchain can be the solution for the majority of errors that happen in clinical trials. Therefore, this technology can solve human errors such as: inconsistent data entry (transcription and transposition errors) and missing signatures/authorizations and system errors such as loss of data. Having a blockchain system that allows, in real time, the users in the network to verify, identify and solve the errors, can be a major improvement in clinical trials.

In fact, the most pressing challenges in clinical trials include access and management of clinical trial data; data integrity and provenance for clinical trial processes for regulatory purposes; updating and maintaining patient consent; and patient recruitment and enrolment, reproducibility of results, protocol compliance and data sharing (Mackey et al., 2019) (Omar, Jayaraman, Salah, Simsekler, et al., 2020).

Blockchain systems have the ability of transforming this process by revolutionizing the way data is stored, transmitted and managed throughout the network of participants, investigators and entities engaged in a clinical trial. Therefore, blockchain can lead to the structuration of a global community gathering all the key player involved in a clinical trial setting, such as researchers and patient communities, social networks and Internet of Things data flows with features of individual granularity, decentralization and security and with transparent interactions to ensure easier and more transparent analysis (Benchoufi & Ravaud, 2017). An additional asset is the possibility of a closer monitorization of patient health data tracking and health status (Abu-elezz et al., 2020).

Disadvantages of blockchain system in clinical trials are related to organizational difficulties, such as installations and transactions costs, operability issues and the need of specialized technical resources to manage these systems scalability issues, authorization and security issues, high energy consumption, and slow processing speeds. It is important to emphasize that the interoperability is also one of the major challenges for the blockchain adoption due to the lack of trust between healthcare organizations and lesser number of IT (Information Technology) professionals available to implement the technology. Lack of sufficient technical skills while implementing blockchain technologies may lead to disastrous consequences (Abu-elezz et al., 2020).

The principal advantages and disadvantages of the utilization of blockchain technology in clinical trials is summarized in Table 3.

Table 3. Advantages and disadvantages of blockchain technology used in clinical trials

Advantages	Monitorization
	Transparency
	Immutability
	Decentralization
	Real-time consent
	Real time access to all key players involved
Disadvantages	General access to all key players (need to constrain access depending on its user)
	Implementation system difficulties
	Need of specialized technical resources
	High levels of protection needed
	Implementation costs
	Scalabilities difficulties
	Appropriate software and hardware

Advantages of Blockchain Applied to Data Security in Clinical Trials

Considering the four main assets of blockchain systems in a clinical trial setting monitorization, transparency, immutability, and decentralization, blockchain technology might also prove to be useful in supporting or even supplanting the traditional data infrastructure used in clinical trials. Blockchain enables to establish a permanent record agreed upon by all participating parties, therefore has a tremendous potential to mitigate some of the threats related to data validity.

Taking all of this into consideration, in a real-world setting blockchain technology might have the following characteristics in terms of data security:

- Establish a more difficult precedent to falsifications or adulterations of data, since every transaction is monitored, time-stamped, transparent and in real time;
- Enables permanent recordings, a very desirable asset for clinical trial auditing;
- More compatibility between the results presented to the regulatory agency and later published in scientific publications;
- More efficient volunteer recruitment and protocol attribution;
- More accurate access and recording of data;
- Overall, less time consuming and more, efficient process of data recording, processing and storage.

Ultimately, blockchain systems in terms of data security, specifically, address the questions of data validity, integrity and reproducibility and therefore stands to achieve more confidence and veracity in the results obtained in a clinical trial (Maslove et al., 2018).

Types of Blockchain and Their Applicability in Clinical Trials

Blockchain can be applied in the healthcare sector due to its many characteristics such as immutability, decentralization, traceability and transparency (Abu-elezz et al., 2020). This technology has a potential in protecting sensitive information such as patient related information (medical records and personal information). Therefore, these characteristics have the most relevant interest in the clinical trials setting.

The potential of the Blockchain applicability to clinical trials relies on the type of Blockchain technology used. As described by Abu-elezz et al., (2020) there are three different design types considering their access permissions: public (permissionless), private (permissioned) and hybrid blockchains. Public blockchains allow anyone to participate and allow a complete transparent view to anyone participating in it, and there is no control by any single user on identity. On the other hand, private blockchains are only open for those who are invited to join the network, but nevertheless, the process remains transparent for everyone included in the network. Finally, it is important to characterize the third different type of blockchain. Hybrid Blockchains are a type of blockchains that are flexible because they allow the users to choose the data they want to be made available for the public and the data they want to be kept private for them (Abu-elezz et al., 2020) . To be easily understood, they can be seen as a public blockchain where a private network is hosted, where all of the users only have access to the data that is available for them. Taking all of this into consideration, hybrid blockchains associated with smart contracts could represent a solid method to use in a clinical trial setting since it has the possibility to select a specific amount of data to be available or kept private to the public, as previously mentioned (Kamel Boulos et al., 2018). This platform is more flexible compared to other types of blockchain because it enables the consensus mechanisms to be controlled by selected users in a decentralized manner, which in other hand, makes its structure more vulnerable to information (Omar, Jayaraman, Salah, Yaqoob, et al., 2020).

Smart Contracts

Another major contribution of blockchain technology in a clinical trial setting is the ability to provide in real time consent by the patient to protocol alterations by the sponsor (Petre & Haï, 2018). This process is followed through smart contracts.

Smart contracts are a type of code that is stored, executed, and verified on a blockchain, and also has the ability to act on clinical data sharing, either through storing the data itself or instructions on who can access that data (Maslove et al., 2018)(Kamel Boulos et al., 2018). Smart contracts can play several roles, including encoding the business logic for an application, ensuring that preconditions for action are met before itis executed, and enforcing permissions for an action. As described by Maslove et al. (2018), smart contracts run on a blockchain, they have unique characteristics compared with other types of software. First, the program itself is recorded on the blockchain, which imparts the blockchain's characteristic permanence and resistance to censorship. Second, the program can control blockchain assets. Third, the program is executed by the blockchain, meaning it will always execute as written and no one can interfere with its operation.

Since Smart Contracts all transactions follow rigorous protocols under secure conditions, their use has the possibility to ensure data provenance and create immutable audit trails, and potentially add more integrity and confidence to a clinical trial, by reducing, prevent and detect fraudulent activities and errors (Yu Zhuang et al., 2018).

Benchoufi & Ravaud (2017), described a Smart Contract example applied to a clinical trial setting. In their example, each of the clinical trial steps (trial protocol setup, patient enrollment, data collection, trial monitoring, data management, data analysis, study report, diffusion of results) as described in Figure 4, can be chained together in a preceding order, consolidating a transparent trial and preventing *a posteriori* reconstruction or beautification of data by granting several levels of access. This example represents a piece of code that holds a programmatically written contract between as many parties as needed, without any trusted third party, and that executes algorithmically according to the terms provided by the contracting parties, making the process more automatic, transparent and less prone to falsifications (Benchoufi & Ravaud, 2017).

Blockchain Systems Protection Against Liabilities

Blockchain technology allows the users to track more closely and in real time, the series of events occurring in clinical trials. This is crucial when we are talking about security and protection. By tracing and controlling the processes of clinical trials, Blockchain can prevent frauds or at least discourage them, because they become traceable and averted. But this technology cannot protect against every threat, such as data invention or data falsification since it only protects the information with time stamps and traceability once the information has entered the system (Benchoufi et al., 2019).

Other threats to the validity of clinical trials data stand to undermine the veracity of a clinical trial. These threats could be defined as internal, when they occur within the users of a blockchain, or external, when they came from outside the network of blockchain users, for example in a cyber-attack.

Maslove et al (2018) identified some of these threats. Data can be altered or lost, either accidentally or by nefarious intent; there is a risk that the published analysis is not a true representation of the analysis that was initially planned due for example to lack of monitorization resulting in a bias of the information presented to the regulatory agencies and later published in scientific publications; and lastly, data may be fabricated, manipulated, or duplicated by researchers committing outright fraud.

Some of the functionalities of the Blockchain technology like timestamping, time-ordering and the smart contracts can define a roadmap, that helps tracking errors and frauds. Clinical trials can benefit a lot from using these roadmaps (Benchoufi et al., 2019).

Omar, Jayaraman, Salah, Simsekler, et al., (2020) developed a blockchain-based solution and simulated several data mistakes or internal malicious attempts. These were stopped since the recorded data is validated using consensus algorithms resulting in a tamper-proof system.

As described by Omar, Jayaraman, Salah, Simsekler, et al., (2020) one of the biggest threats to the blockchain technology are the selfish mining external attacks. Blockchains are vulnerable to 51% of these attacks. This generally occurs when malicious blocks are higher than honest blocks in a network. As a result, one of the possibilities is that a new block gets attached to the malicious chain. This strategy is called selfish mining because selfish miners keep their blocks private and reveal them to the public only when the private chain is longer than the current public chain, and thus, it may be accepted by all miners in the network (Omar, Jayaraman, Salah, Simsekler, et al., 2020).

SOLUTIONS AND RECOMMENDATIONS

Clinical trials require data and information to be well organized and categorized for the submission of the findings to the regulatory agency for the approval of the drug in test. Such compliance can be time and resource consuming considering the amount of data, number of individuals and entities involved, and therefore it is a process particularly prone to human and system errors.

In fact, the most pressing challenges in clinical trials include access and management of clinical trial data; data integrity and provenance for clinical trial processes for regulatory purposes; updating and maintaining patient consent; patient recruitment and enrolment, reproducibility of results, protocol compliance and data sharing.

From the review conducted it is possible to point out that the operational benefits of implementing a blockchain technology to conduct a clinical trial are hardly contestable. Indeed, this technology solves many logistical constrains in terms of data sharing, communication between each involved parties and data storage and traceability.

Blockchain certainly represent a technology capable of managing and improving the information system in the healthcare sector and, particularly, in the clinical trial area, by allowing a more transparent, real time and authentic process when submitting a new drug for regulatory approval. Blockchain allows several levels of optimization regarding the organization aspects of a clinical trial (number of participants, number of departments and their areas of action) and in an individual level (the patient has more control and monitorization of his own progression), also.

Reproducibility and data integrity are crucial factors in a clinical trial setting. Regulatory agencies not only shall be able to trace back and identify the players responsible for any information in a clinical trial environment, but also be able to trust the validity of that content. In fact, 80% of the assays submitted to FDA are not reproductible (Petre & Haï, 2018). Blockchain improves the traceability of data and therefore stands to tackle this issue.

Blockchain offers a valuable contribution in addressing this problem since every transaction is validated using consensus algorithms and identity signatures with identification and date stamps.

Notwithstanding, blockchain cannot address a problem that still could affect the integrity and veracity of a clinical trial. In fact, if the information itself introduced in a software is wrong or misleading, this technology cannot address this issue. Blockchain, only, can track this wrong data and timestamp it. There is yet a need to find a solution within the design and operational side of a clinical trial to tackle this question.

Considering the four main assets of blockchain systems in a clinical trial setting, monitorization, transparency, immutability, and decentralization, blockchain technology might also prove useful in supporting or even supplanting the traditional data infrastructure used in clinical trials. Blockchain enables to establish a permanent record agreed upon by all participating parties, therefore has a tremendous potential to mitigate some of the threats related to data validity.

Disadvantages of blockchain system in clinical trials are related to organizational difficulties, such as installations and transactions costs, operability issues and the need of specialized technical resources to manage these systems scalability issues, authorization, security issues, high energy consumption, and slow processing speeds.

Overall, this technology has the ability of producing a clinical trial more transparent and tamper proofing by providing authentic validated data, and therefore, producing a more reliable and credible clinical trial. Nevertheless, there are some technical issues that need to be overcome, such as scalability, implementation costs, the need of technical resources and processing difficulties of implementation and operation. Solving all these issues, we can expect blockchain technology to be fully adopted in clinical trials, with substantial improvements.

FUTURE RESEARCH DIRECTIONS

Work needs to be done to establish the major implications in security data when applying blockchain technology in a real-word clinical trial setting and in generalized conditions of use, since as we move forward through the several phases of a clinical trial more data, more participants and more complexity of results are expected and thereby there is a need of a robust and reliable system to maintain the necessary trust levels to present the findings of a clinical trial to support the process of drug approval to a regulatory agency.

On a regulatory level, it is also important that key regulatory agencies such as FDA and EMA, provide guidelines to construct a blockchain managing system in clinical trials, in order to establish uniformity between the several systems used by different companies and guarantee the overall compliance with ethical, regulatory and safety requirements of a clinical trial.

Covid-19 pandemic lockdown revolutionized the use of technology and overall ability to distance and virtual communication in healthcare. Because of the pandemic, in one year, technology evolved exponentially, in a way never seen before. Given this opportunity, the bases of a digital revolution in healthcare are in order. However, it is important to take into consideration the technology literacy of healthcare professionals and volunteers in clinical trials. In fact, in a survey conducted by HSCB to Bitcoin users about Blockchain, 80% of the percentage of consumers that are familiarized with the term didn’t know or fully understand the concept (Radanović & Likić, 2018). Therefore, digital education and technological formation of each player in clinical trials should be a priority to the implementation of blockchain systems. This is essential for the correct adoption of the technology in the clinical trials and if it doesn´t happen, the errors that will occur, can be disastrous.

On the other hand, considering the high level of investment and the need of technological specialized work force to design and run a blockchain system, investments and grants should be also created to incentivize not only the adoption of these systems, but also to educate specialized work force. There aren´t many specialized professionals that know how to work with this technology and that fully understand it, so, this digital formation must be given to the healthcare professionals, in order to have the best results possible. Of course, this formation involves a large investment, so this must be taken into consideration.

Lastly, considering the importance and impact of the data stored in a clinical trial not only on a regulatory level but also on a personal level considering the number of volunteers involved, additional work shall also be made to establish the security of a blockchain system applied in a clinical trial setting to external hazards such as cyber-attacks.

CONCLUSION

Ultimately, blockchain systems represent a technology capable of managing and improving the information organization system in the healthcare sector, specifically in the clinical trial area, by allowing a more transparent, real-time, and exact process when submitting a new drug for regulatory approval.

Blockchain allows several optimization levels regarding the organizational aspects of a clinical trial (number of participants, number of departments, and their areas of action) and individual level (the patient has more control and monitorization of his progression). These advantages also reflect data security optic since this technology can produce a more transparent and tamper-proofing clinical trial by providing accurate, validated data, producing more reliable and credible outcomes from the research conducted in a clinical trial. Nevertheless, some technical issues need to be overcome, such as scalability, implementation costs, the need for technical resources, and processing difficulties of implementation and operation of blockchain technology.

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KEY TERMS AND DEFINITIONS

Blockchain: A decentralized, distributed ledger technology that records the provenance of a digital asset.

Clinical Trial: A research study performed in people that are aimed at evaluating a medical, surgical, or behavioral intervention.

Data Security: The process of protecting data from unauthorized access and data corruption throughout all lifecycle.

Decentralization: The transfer of control of an activity or organization to several local offices or authorities rather than one single one.

Immutability: The state of not changing or being unable to be changed.

Traceability: The quality of having an origin or course of development that may be found or followed throughout all lifecycle.

Transparency: The quality of operating in such a way that it is easy for others to see what actions or changes are performed.