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Blockchain technology in management of clinical trials: A review of its applications, regulatory concerns and challenges

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ABSTRACT

The concept of Blockchain Technology was developed by Satoshi Nakamoto, in 2008. This technique involves the recording of information in such a way that it becomes very complicated and impossible to modify, hack, or deceive the system. A blockchain is fundamentally an electronic record of dealings that is copied and scattered athwart the complete association of computer systems. This technique consists of an arrangement that keeps the transactional archives, also called as the block, of the community in numerous datums also recognized as the "chain," in a network connected throughout peer-to-peer nodes. Characteristically, this storage space is also called as a digital ledger. This technology finds various applications in medical field including the clinical trials. There are many problems in the management of the data of clinical trials due to which the study these studies get delayed. Traditionally the data transfer was done manually which involved a high risk of errors. Due to the time constraints it becomes very essential to opt for an advanced technology which would help overcome these problems. Blockchain offers a remedy to these issues. The assessments can be programmed and made in parallel in harmony with the 'contract' decided amid parties and without the requirement for centralization and consequential batching. Such necessities should be considered while designing the blockchain-enabled submission for clinical trials, which completely confine their venture character, permit quick swap over of high eminence facts and information, and assist setting up and budgeting of assets. Thus, the current review aims to outline the applications of blockchain technology in clinical trials, its regulatory requirements and the challenges.

1. Introduction

1.1. Blockchain

The blockchain is a method of data management that prevents data manipulation. Each unique event is recorded in a new "block" of data. Each block is time stamped and contains the previous block's cryptographic information (a "hash"). These hashes protect the connections between blocks to form chains, rendering data modification impossible without affecting the entire chain. The blockchain is duplicated by all participants of a network. Since any change must be approved by all users, this decentralization of data allows for greater transparency and protection. Such assurance is lacking in today's centralized data management methods. Blockchain tools has a wide variety of features that are worth investigating because it not only improves existing technologies but also allows for the creation of new ones [1–3]. Fig. 1 shows how the blockchain works.

The blockchain is essentially a public ledger that stores all authenticated transactions as a sequence of blocks. As new transactions and blocks are added to the chain, it continues to expand. The core features of the blockchain network make it promising new machinery that brings down the reliance on conventional data processing systems. Blockchain can be used in applications that handle transfers and wealth management. A smart contract is a collection of regulations written in the form of documents that can be stored in a database and used to handle a transaction. As a smart programme agent, this automated contract is immediately carried out before a transaction commits [4]. Ethereum protocol was created to improve accessibility and permit for greater consistency in the programming of various forms of smart contracts on

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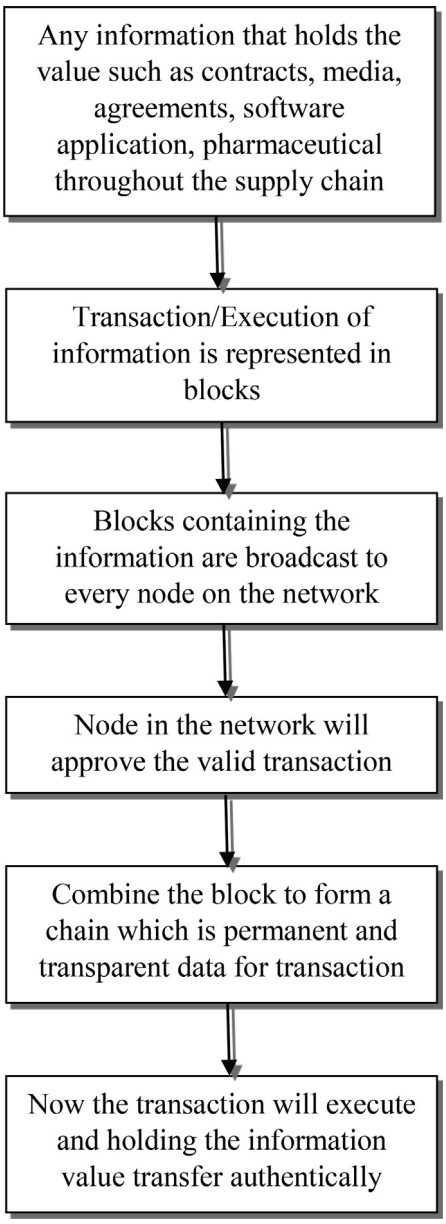

Fig. 1. Working Of Blockchain.

the Ethereum platform [5]. Decentralized storage processes are preferable for blockchain technique implementation because of storage cost. The freedom to hold files without the intervention of a third party is provided by decentralized storage systems. The InterPlanetary File System is an example of decentralized computing technology (IPFS) [6]. File stored on the IPFS network is given a specific cryptographic hash in this scheme, rendering the file's history permanent and traceable. Furthermore, since the files are spread across the network, the uploading speed is quicker under this scheme. Since IPFS uses timestamped blockchain technologies, it's a great place to keep notes because of these features. As a result, without storing the individual data on the database, the data hoard on the IPFS network is directly referenced by IPFS references stored on the blockchain. As a result, combining these 2 innovations is advantageous, as IPFS can be utilized in blockchain implementations that necessitate a public catalog that can be confirmed. FileCoin and Swam are the examples of decentralized storage technologies.

The block chain could be an opportunity platform to improve transparency & trust with customers being able to track pharmaceutical product throughout the supply chain. Followings are the points where blockchain meets the Pharma value chain:

- Drug discovery
- Drug development
- Drug manufacturing
- Supply chain management & distribution
- Sales & marketing

1.2. Clinical trials

A clinical trial is a laboratory project that examines whether a proposed experimental procedure or a novel application to a current medication is a safer way to avoid, diagnose, or treat illness [9]**.** Before a new medication will be used in a clinical trial, preclinical trials must be performed. Preclinical testing includes all in vitro (test-tube or laboratory) studies and animal species trials. To attain preliminary effectiveness, toxicity and pharmacokinetic details, animal subjects are given a number of dosages of the test drug or an in-vitro substrate [10]**.**

1.2.1. Pre-clinical studies

In preclinical tests, in vitro experiments and laboratory trials are used to estimate the initial safety and efficiency of the drug. This data aids pharmaceutical companies in determining whether additional testing is required [11].

1.2.2. Phase 0

According to FDA's 2006 guidelines, Phase zero is the new phase of clinical trials where the IND (Investigational New Drug) should be explored for its pharmacokinetics and pharmacodynamics by administering of single subtherapeutic dose of the investigational drug to a limited number of participants ranging from ten to fifteen [11,12].

1.2.3. Phase I

The primary level of clinical experimentation is known as phase I trials. A small group of twenty to eighty balanced human volunteers is generally selected. This phase targets to evaluate the safety profile of the drug along with its pharmacodynamics, pharmacokinetics and tolerability. These studies are often carried out in clinical sites having the inpatient division where the patient can always remain under supervision of the team of investigators. The patient taking the medication is normally held under observation for many half-lives of the drug. Dose-ranging, also known as dose elevation, experiments are often used in Phase I trials to determine the best dose for medicinal use. Safe subjects are often used in phase I experiments. True patients are used in some cases, such as where patients are near the close of their medication services and have no other options. Oncology (cancer) and HIV drug trials are the most common exceptions to the law. Volunteers are compensated for their hours spent in the volunteer centre. Depending on the duration of participation, pay varies from a modest fee for a brief time of residency to a greater amount costing up to £4000 [11,13].

1.2.4. Phase II

Phase II studies are conducted on bigger samples containing twenty to three hundred individuals and are intended to test how well the medication performs and also to continue with the efficacy evaluation of Phase I with a larger population of participants after the preliminary safety profile of the drug has been established in Phase I. Phase II experiments can be classified into two categories: Phase IIA concerned with estimating the amount

of drug to be administered and Phase IIB with the efficacy of the drug [11,14].

1.2.5. Phase III

Phase III experiments are "Randomized controlled multicenter trials" carried out with a large patient population usually ranging between 300 and 3,000 or even more that are designed to provide a decisive assessment of the drug's efficacy. The studies of this phase are very expensive, complicated and of longer duration. Though not always needed, minimum two satisfactory Phase III trials establishing the drug's safety and effectiveness are usually required in order to gain clearance from the relevant regulatory bodies such as FDA (USA), EMEA (European Union) and others. Once Phase III trials established the safety and efficacy of the drug, the data are normally compiled into a long paper that includes an exhaustive synopsis of the methods and effects of in vitro and *in vivo* testing (in animals and human beings), methods for processing and specifications of the product including the shelf life details. This material is compiled into a "regulatory request" that is sent to the appropriate regulatory agencies indifferent countries for approval [11,15].

1.2.6. Phase IV

The Post Marketing Surveillance Trial is another name for a Phase IV experiment. Phase IV trials are used to monitor a drug's safety (pharmacovigilance) and have continued technical assistance after it has been approved for sale. Regulatory agencies may mandate Phase IV tests or the sponsoring firm may conduct them for strategic (finding a potential demand for the medicine) or additional use (such as testing the drug interactions or studying the drug on some specific group of people like pregnant women who cannot be a part of clinical trial studies). The observation of safety profile is essential to detect any of the prevailing adverse effects. Phase IV trials may lead to a medication being withdrawn from the market or limited to certain uses such as troglitazone (brand name Rezulin), cerivastatin (Baycol and Lipobay) and rofecoxib (Vioxx) [11,16].

2. Applications of blockchain in clinical trials

2.1. Patient recruitment

Enrolling the patients for clinical trial studies is a very complicated part of the research involving drug development. A latest study has shown that around $2.6 billion total is used for the drug development processes [17] of which majority is spared for enrolling the patients and in searching a suitable methodology for retaining them throughout the clinical study. According to a study, around 80% of the clinical trials are not completed on time due to delay in the patient recruitment [18]. A number of challenging apprehensions are involved in these studies due to which the patients, sponsors and the principal investigators are unable to arrange for meetings at a single point of time. If the sufficient numbers of patient are not recruited for a study, it may result into ineffective results and impulsive termination of the trial. The Blockchain technique offers a special advantage for patient recruitment maintaining the confidentiality of the patient and safety of the data. Using the Blockchain disseminated ledgers leads to the reduction of patient recruitment time as the anonymously registered patients to different clinical trial sites can be connected. Consequently, the investigator can choose the required participants from a collection of patients as per the study protocol. Even the blockchain sculpt involving numerous contracts for clinical trial for engaging the patients and managing the studies have also been proposed [19].

An automatic and encrypted agreement known as Smart Contract given by Nick Szabo (1996) has the capability of regulating all the dealings of the dispersed ledger arrangement [16]. Hyperledger and Ethereum are the examples of smart contract agreement [20]. The Ethereum blockchain consists of integrated computationally universal set of computer's instructions for enrolling patients or for examining the legitimacy of a clinical study [21]. This creates an ABI (Application Binary Interface) consisting of smart agreement and smart contract address for clients. All the consumers should trail the regulations of smart contract for making the deals. The users can view the addresses and ABI but cannot execute the functions. This solely depends upon the privilege of the customer. For say, if the criteria of inclusion or exclusion is to be added into the setting of patient enrollment then it can only be done by the authorized in charge of the clinical study. The matching appeal can be send by the sponsor only after which the automated blockchain can match the possible individuals. This saves time and guarantees the completion of the protocol. After the identification of appropriate patients, a suitable location for carrying out the trial can be selected. The authenticity of the clinical study can also be ensured by smart contract by examining the NCT (National Clinical Trial) identifier number and the sponsor's identity representing that the study has the approval from the authority [22,23].

The assimilation of Internet of Things (IoT) and Blockchain technologies can enhance the required significant outputs. With the help of IoT, a huge amount of information can be uploaded on the websites of clinical trials which shall aid in selecting the applicable candidates according to the required criteria. It also helps in assuring that the sufficient number of suitable patients is available or not. Additionally, it also assures the patient regarding the maintenance of confidentiality [24].

2.2. Consent traceability

One of the very difficult aspects of clinical trial study is to attain the acceptance from the patients. Approximately 10% of such studies face problems associated with the consent from the patient such as unauthentic consent forms and non-submission of reconsent in cases where the study protocol has been redrafted [25]. The findings of research investigation for the proof-of-concept revealed that blockchain could map out and associate each recent proof-of-concept testing carried out by investigators. It also displayed that when cryptographic authentication was added to every operation, the blockchain had the capability of trailing and evaluating each time stamped patient approval to the accurate description of the rationalized clinical study protocol. The approval for a collection of confidential data is applied in particular manner by normal database fields that represent the status (e.g., unopened, displayed and signed) of individual (physical) records that are already part of the initiation step of the clinical trials [26].

Aside from the conventional difficulties associated with managing consent for real medical data, tying the consent to research data such as cumulative and post-analysis data generated by elaborating the medical data also necessitates additional research [27]. Furthermore, non-compliance with permission, the pitfalls of biassed reporting, prejudice and corruption, both of which can lead to more serious consequences, can impact clinical trial studies at any stage of their growth. Blind Controllled Trials are said to be capable of playing a critical role in clinical studies in this regard. Despite this, there are few practical implementations. BlockTrial involves the blind controlled trials deployment in its early stages [28]. It utilizes a web-based boundary permitting the clients to carry out the Smart Contracts associated with trials on an Ethereum network. This system allows the patients to give the access to the investigators permitting them to submit their queries

regarding the data of the study. Here, the patients and the investigators act like nodes of Block trial each having a unique Smart Contract. The concealed edition of Ethereum blockchain is utilized to implement the network in this mission. "Korean TIP" is also a trustworthy source used for sharing the participant's information, though it does not target the strategy for consent management [29].

Other prototypes, such as mobile-based data collection programme, investigated means of preserving data privacy by demonstrating what kinds of data a participant is able to share with researchers [30]. It is critical to comprehend the complexities of data exchange, which could involve the patients' relatives, casual nurses and others [31].

2.3. Maintaining the confidentiality of the patient's data

Almost 50% of the clinical trials do not succeed due to their failure to produce the desirable results. According to a survey conducted by "The Stat News" approximately 90% of the clinical studies enrolled in "ClinicalTrials.gov" are deficient of the study outcomes [32]. This gives rise to an apprehension regarding the patient's safety and generates an awareness gap for the prospective drug researchers. Therefore, blockchain offers a safe tracking method as it contains all the recent data thus permitting all the participants to be acquainted with the present condition of the clinical study. Moreover, it also helps to shield the patient's identity as each participant has an encoded address delineated to his/her individuality which allows for two way access of the information. Either the participant gives consent for providing his/her personal keys to the nominated study location or the allotted physician generates and retains the keys all through the clinical trial for monitoring the healing effects of the drug. A number of illustrations are there for smart contracts for various clinical study procedures [33]. The maximum prerogative is with FDA for registering the catalog of the sponsors of the clinical studies. Only FDA has the freedom of adding, deleting or changing the sponsors. Even in case of any alteration in the supporter's personnel, the FDA should be informed and accordingly the suitable modifications shall be done in the list. After the process of FDA registration is completed, FDA allocates a smart contract address to the sponsors who can then utilize the smart contract function for adding the participant's public keys. This leads to the creation of an exclusive patient identity for each individual utilizing the hashing algorithm. The registered patients are then able to obtain the Smart Contract Address. For logging in into the system, they require an exclusive patient identity. They are also required to input the name of their enrolled hospital. There is also an option for inputting the numerous hospitals. The subject identity will be mapped to their actual patient identities from every clinical spot. Nevertheless, simply the subject identity is observable by all the clients in the blockchain organization. The entire procedure is encoded. The private chain serves as the storehouse for all the public keys. Merely the FDA and sponsors can verify the list of addresses. The patients can only enquire regarding their own data via the Smart Contract [34].

2.4. Data integrity

It is anticipated that the clinical trial data should be authentic and accurate. A consensus algorithm is used to maintain the integrity of the data.It is possible to track back and locate the source of the issue, as well as the individual responsible for entering this information in the event of chain fault or error detection. Thus, one can very easily trust the data of clinical studies documented in the blockchain [35].

"Hyperledger Fabric" is a concealed blockchain structure designed by "The Linux Foundation". It provides a commutable design sustaining pluggable parts like consensus procedure, encoding, managing uniqueness and association assistance. Numerous nodes, smart contract/chain code and record with datum and chronicle of dealings comprise the components of the private network. The task of maintain the node can be performed by a single individual or even by many clients together. Depending upon their performance, nodes can be of following types: client node, peer node and orderer node. The Client node is responsible for invoking the dealings. It is linked to both the other nodes. It presents the deal acknowledgement to the endorser and the deal manifesto to the orderer. The responsibility of maintaining and updating the records lies with the peer node. The ordered node performs the task of supporting the communiqué and maintaining the order of dealings. An automated logic part of the Hyperledger Fabric is known as chain code or smart contract. It constitutes the contract or regulations governing the dealings in a blockchain system. The regulations are applied as functions in smart contract. The analogous smart code function is invoked whenever it is required to assess the ledger for data transactions. The planned deals need to be authenticated. On the proposal of the transaction by the user, the approval signatures are gathered and forwarded to the orderer who authenticates the message and send it as a fresh block to the peers. MSP (Membership Service Provider) recruits the patients in the system and allots a digital ID to all the units in the blockchain system, example clients, orderers and peers. It provides the reliable authority which MSP provides a variable digital identity to all entity in the blockchain network, such as peers, orderers, and clients. It serves as a trust authority which is involved in the procedure of authenticating the users and supplying the cryptographic certification [36,37].

The Hyperledger Fabric portrays the characteristics of confidentiality (permitting the formation of customized channels consisting of a part of a group of network subjects and allowing the access of the information to the members only), organization of cryptographic distinctiveness (managing the user identity and authenticating the subjects) and modular proposal (allowing the functioning of the diverse parts and supporting the modular layout) [38].

2.5. Transparency

Use of Blockchain technique in tracking the clinical trials althrough their duration not only imparts confidence in the results but also motivates other people to contribute towards the clinical research. During the investigation of novel drugs, transparency is a very significant factor as it can result into the decrement of the number of clinical locations involved in selective coverage of positive results. Thus involvement of Blockchain technology in clinical trial does not only impart data integrity and transparency but also encourages the enhance association among the sponsors and various clinical research sites. As reported by "Healthcare IT News" in 2017, the FDA (Food and Drug Administration) and CDC (Centers for Disease Control and Prevention) planned to partner with IBM Watson Health in operating pilot blockchain ventures to investigate its real-world settlement in information processing and information allocation [39].

A transparency should be maintained regarding the consent for clinical trials including any of the updation and this should be trackable by the sponsors. Thus, the procedure should permit for assortment of participants, conversant approval from participants which shall be subjected to revision, storing and tracing the consent in a safe manner allowing the data to be shared in real time. Thus Blockchain technology offers a consent workflow which is a dispersed technique bringing an integrated level of clarity and ver-

ifiability. For conducting live clinical trials, the verification mechanism should be improved to eliminate the requirement for third parties, such as trial partners, and to allow peer users participatory authority. The dynamic data flow of a clinical trial could be monitored in the future using Blockchain, whose central feature, known as Smart Contract, could help determine clinical trial activities from unfolding in the proper chronological order, such as involving patients until they consented or analysing case report type data before freezing the database. Blockchain may help with stability, protection and accountability on a global scale, as well as be a consistent move toward reproducibility [40].

2.6. Persistent monitoring

Patients interact only with hospital centers where their symptoms are reported using a questionnaire or diary in conventional Clinical Trial programmes. Nonetheless, since blockchain technology is a distributed public database, the data is open to all network users, allowing the FDA and subsidizers to continuously track the collected data. The FDA has the authority to inspect any blockchain operation and to review records transmitted straightforwardly by doctors instead of waiting for them to arrive from supporters. Clinical centres, promoters, the FDA and the IRB will all be willing partners in a private blockchain that ensures continuous surveillance. The transactions are validated by miners in a network and they are disseminated in such a manner that 51 percent attacks are avoided. Every participant is able to view and inspect the ledger. So, in case of any fake entry it shall be observable by all the clients available in the network. This is advantageous because the FDA can view the raw information in real time without having to go through mediators. It also eliminates the possibility of data forgery and creates an eternal sequence of registered transactions [41].

3. Regulatory concerns

For clinical research methdology, the technology needs to conform the recent research laws, rules and regulations. In United States (U.S.), rules and guidelines applicable for medical study vary on the funding resource, even if the research includes a covered individual and secure fitness particulars or the investigate is financed by, or will be put forward to a particular governing organization. Although, the regulations, data, technology standards related to clinical research are unaware to blockchain developers and operators [42]. Also among stakeholders who are knowledgeable of regulatory standards, regulatory analysis interpretations applicable to blockchain are unclear [43].

3.1. An outline on U.S. Regulations for clinical research

3.1.1. Human research protection regulations

In the section of Health and Human Services (HHS) in U.S., the two major centralized agencies which have the responsibility to include dictatorial guidelines and implementation of security of human subjects are FDA (Food and Drug Administration) and OHRP (Office of Human Research Protections).

3.1.2. Food and drug Administration (FDA)

As per Food and Drug Amendments Act 2007, medical investigate of new medicines, natural materials and therapeutic appliances are regulated by FDA. Fortification of human beings and clinical trial integrity is under the 14 regulations of FDA [44,45] however the relevance of these set of laws depends on the character of new invention and/or skill. “Part 11” is simply referred to as is most relevant for employing blockchain in clinical investigations.

This regulation indicates the administrative, technical and procedural controls for electronic data that are produced, tailored, sustained, retrieved, cached or transferred to conform to rules of FDA. Electronic recordsand signaturesthat are presented to the FDA also implies under this part, even though these records may not be particularly found in FDA system [46].

3.1.3. Office for human research protections (OHRP)

“The Common Rule” is the other name for the regulation and protection of human subjects. Authoritarian principles for secure and appropriate management of human beings are research is given in this rule. This rule has been implemented by several federal agencies performing research on human participants. Protection of expectant women, kids and hostages also required to be included as additional subparts by OHRP, which are not implemented by all other federal agencies [47].

3.1.4. Health insurance portability and accountability Act (HIPAA) privacy and security rules

HIPAA focus on permissions and protections for health information whereas FDA and OHRP include protections to monitor the research conducted on human participant. This refers to a group of independently secluded wellbeing particulars created or stored by a covered individual. Covered individuals like people concerned with providing healthiness concern, clearing houses or wellbeing plans who convey information related to health electronically in lieu of claims or entitlement investigations. The administrative, physical, and technological protections required for the protection of data storage and transmission related to health is covered under the “security rule”. When an individual or agency creates, collects, processes, retains or conveys PHI infavor of a covered entity, they are acting as the covered entity’s “business associate.” A business associate needs to comply with all the principles, supplies and provision required by a covered entity as per the regulation of Health Information Technology for Economic and Clinical Health Act (HITECH Act) [48].

3.1.5. Institutional review boards

IRBs review the testing procedures and associated resources (e.g., well-versed assent forms and enlisting supplies) to safeguard the health and interests of human involved inresearch. Role of IRBs is to verify that all criterions set by directives for principled fortification are met by research or not.

3.2. Regulatory contemplation for blockchain in clinical research

3.2.1. Regulatory contemplations for generating a clinical investigate record

Generation of blockchain design which aims to collect details that might be utilized for medical investigate, authoritarian control vary on the design and storage character. The expressions such as “database”,“repository”,“data bank”,“data warehouse”,“registry” is not clearly described throughout regulations or in literature [50]. However, a fine variation among these terms is observed; hence, “database” is planned to include the entire comparable and associated expressions.

3.2.2. Anticipated rationale

The purpose of medical catalog for the disease management, healthcare operations or payment not only emphasize on protection to human participant or additional privacy regulations but can also be utilized for the research investigation [51]. For instance, companies regularly utilize medical datum to monitor disease succession, supervise ailment incidence in particular patient’s population, evaluate the effectiveness of program, implement the excellence upgrading ventures and trace the efficacy criterion [52].

However, datum intended to hoard, retain and disseminate information of human applicants for the purpose of further research might be desirable to track the protection regulations onhuman subject research and/or other HIPAA regulations. While scheming a research investigation datum built on blockchain, operators and developers are motivated to write firstly a "parent" protocol which mainly defines how the investigate datum will be generated and ruled, the type and sum of perceptible particulars and exclusions alongside liberating "code keys" that associated to contributor distinctiveness [53]. Study procedure in addition includes the procedure for requesting data from the database and generating contracts regarding data confidentiality with data receivers. This procedure assists to supervise the datum maneuver as well as support investigators and IRBs in establishing the suitable authoritarian control.

3.2.3. Regulatory oversight

This clause includes general dogmatic details which will be appropriate to creation of datum for blockchain, its circulation and use.

3.2.4. Creation of database

When a centralized bureau or section conduct or support blockchain research database, the datum architects and managers are aggravated to review OHRP judgement charts and assess whether the database contains individual objects and will be vulnerable to control [54]. Human subjects would be taken into consideration for research by OHRP if the records cover personal, independently identifying particulars that let the investigators to effortlessly recognize the persons in the dataset. On the contrary, confidential detail is not deemed as identifiable and human subjects will not be taken into consideration for clinical study, if the information cannot be connected with exact persons openly or using cryptogram keys/structure [55].

3.2.5. Sharing and handling: Study carried out or sustained by HHS

Policies are being developed by NIH for recipients of NIH funds and access to further data for analyses and encouraging reproducibility of science is the interest of investigators [56]. Additionally, NIH makes sure that information organization strategy should cover comprehensible procedure for data distribution in open sources in device comprehensible layout. Hence, for scheming an investigation based on blockchain databases which is reinforced by NIH, a procedure should be there to transfer facts in instrument understandable configure. Since 2017, for research funded by NIH, automatic issuing of certificates of confidentiality providing further privacy protections of names of the participant, details of research investigation, records or biological samples collected or used in the research are available [57,58]. While revealing recognizable and confidential information under an official document, the entity which is revealing data makes sure that receivers of data should need to be agree with the confined revelation of information even though the investigation is not supported by NIH straightforwardly [57,58].

3.3. Regulatory concern for the construction and transmission of electronic storage

In a block chain-based system, while designing the backend programming, standards are imposed by some regulations for distribution of information, digital storage setting and digital broadcast including a investigation datum. Standardizing compliance of authoritarian information and creating customary erratic criteria for saving, retrieving and sharing data inside and beyond the database operating system are becoming increasingly important. Consequently, blockchain plan characteristics are becoming crucial gradually. The following parameters are for the research carried out or assisted by HSS.

3.3.1. Standardization of records

In a meeting conducted on sharing of information, the Institute of Medicine (IOM) (2013) encouraged for data sharing with main emphasis on standardization of data and it is observed by IOM that, customary data essentials enable data sharing with associates and helps improved dataintegration with other data sets. Since then, use of common data elements (CDEs) for disease registries and human beings research funded by NIH are being advised by NIH. CDEs illustrate the type of data for collection and givestandardized language or input values. The goal of NIH is to encourage standardization of data by collecting data from various resources together with digital fitness report. In NIH CDEonline portal, NIH funded CDEs, sources for developing datafields and CDEs utilization protocols can be find out by database operators and investigators. Hence, it is recommended to review NIH CDEs to expand the worth of accumulated facts while scheming the fields of record and definitions to be used in blockchain databases [59].

3.3.2. Electronic protections

Protecting the integrity of electronic data or data systems is not particularly specified by OHRP, while it is specified that cautious awareness is required to shelter the secrecy of patient's information [60]. Methods to protect confidentiality should be specified in data management plan. Such methods can contain process for creating cryptogram, parting of exclusive particulars and protections to avoid improper delivery of data [55]. Training and guidance of persons approved to access the database is recommended for any confidentiality plan.

3.3.3. Clinical studies controlled by the FDA

The criteria under which the FDA considers electronic documents and electronic signatures to be consistent and comparable with paper records are set out in 21 CFR Sect 11 (2018) of the Regulations. This directive extends to electronic records production, updation, distribution, retrieval or deposition in digital form pursuant to any FDA regulation, as well as digital proceedings presented to the FDA including records not explicitly specified in FDA convention.

3.3.4. Data standards

For depositing information for FDA compliance while designing database, the information must be proposed in compatible layout for FDA to review and process further. FDA standards catalog for data contains the eminent or perfect records [60] and standards for pharmaceutical studies are being continuously established by FDA. In data standardization plan, the guarantor must define the selected standard, document and submission plan while designing the data management system. Since the FDA applies this strategy to find out the issues early in the process, the proposal should also be used in the investigation strategy for the investigation of new drug trials [61].

3.3.5. Digital security

Sponsor's data management plan should clearly indicate the usage of electronic system during the FDA regulated clinical investigation. Description includes an illustration of movement of digital information and safety procedures to guard the digital proceedings. Consideration of data protections and reliability should also be assessed. Both system designers and system-based organizations must enforce technological controls, administrative controls and formal controls. For instance, there are strict criterion for digital security together with assessment controls, admittance controls, information backing, eminence controls and confirming

admittance to dictatorial establishments. FDA permits digital thumbprints or other adjuncts based on biometrics for access of traditional logon codes, keys, or passwords. There should be a control mechanism so that the only the particular user can achieve admittance to those testimonials [61].

3.4. Regulations to obtain well-versed consent from participants

3.4.1. Research subject to FDA regulations

Conversant consent contains the basic information similar to those requisites by OHRP and needs to be recorded in a black and white agreement form (or in digital form). Consent form signed by participant will get a replica of the same and a digital facsimile should also fulfill this prerequisite. However, FDA convention does not include that consent form signed by individual will receive a copy of the same. FDA advises to provide a signed version of copy [62]. An increasing access to clinical investigations is becoming feasible by an online and inaccessible contribution in FDA-controlled trials and legally effective informed consent is main the responsibility of investigator. The information should also be accessible in black and white if using digital mode to present the data exclusive for an investigation [63]. If research team does not witness the consent process, then a method should be available to verify that consent has been provided by the participant. Verification process may involve analysis ID cards provided by the government, biometric procedures, conferencing through video call and using the individual queries or security questions. Researchers have no right to assign this accountability to the digital scheme [64].

3.4.2. Child research participants who reach the age of majority

During research including participation in databases, if a child participant attainsadult age, then the informed consent of that child must be collected by investigator prior to perform any further research relating to that participant. The IRB may pay no attention to this condition for study if there is minimal risk [63].

4. Confronts with usage of blockchain technology in clinical trials

4.1. Privacy leakage

Since users create addresses rather than using their actual identities to make transactions, blockchain networks must be safe. Nevertheless, there is no assurance of transactional anonymity in networks based on blockchain because each public key's balances and transactions are available to all network users [5]. According to a recent research, user's data may be correlated to their purchases. Even when users are behind firewalls, pains have been taken to connect their IP address to their pseudonyms, which can then be used to trace the origins of a specific transaction. In the medical field, this issue is important because securing patients' personal details is critical. Additionally, more analysis is needed to ensure that blockchain complies with GDPR, FDA and other regulatory agencies in order to protect patients' privacy. According to a study, the resources work to raise reader understanding of cryptography and privacy issues, as well as address the complexities of using blockchain for cybersecurity in healthcare [65].

4.2. Scalability

Owing to the rising amount of transactions that exist everyday in some clinical trial contexts, the blockchain becomes strong, resulting in scalability problems. For illustration, around 288,000 m communications take place each day in a Bitcoin PoW model. Owing to the block size restriction and the duration needed to generate a fresh chunk, the highest hypothetical figure of dealings for Bitcoin is seven dealings/second. When developing synchronized blockchain-based systems for medical purpose, this becomes a problem because they would be unable to perform the processing of millions of medical information in actual instant. Furthermore, since the block capability is at present limited, insignificant dealings can be delayed because miners tend to validate dealings with lofty transaction rewards, whereas large blocks stagnate the speed of transaction. As a consequence, scalability is a challenge in the present blockchain implementations, chiefly clinical studies, since they involve a large number of participants, perhaps around ten hundred, will generate a large number of transactions per second [5,66].

4.3. Storage of big data and low cost allowance

Blockchain allows for shared data access for Clinical studies. While decentralized storage frameworks increase CT storage capacity, they present a number of challenges in terms of large volumes, diversity and rapidity of records also recognized as Big Data. It's very complicated to control such a large number of CT files effectively. In the other hand, the price of utilizing blockchain systems for clinical trials has restricted their widespread adoption. Using blockchain technologies in clinical trials necessitates the development of innovative apps, which is very expensive. Software development is expected to cost anywhere from ten thousand dollars for simple apps to eight lakh dollars or more for advanced software. Because of the sky-scraping expenditure, it is improbable to be used in clinical studies. As a result, considerable consideration must be given for resolution of the problem of increased price [67].

4.4. Selfish mining

Blockchains are susceptible to assault for around 51% of the time [44]. This happens when the number of malevolent blocks in a network exceeds the number of truthful blocks. As a consequence, there's a chance that a fresh chunk will be added to the malevolent sequence. Selfish miners use this tactic so they maintain the secrecy of their blocks and merely reveal them without any restrictions when their personal series is longer than the existing communal series, allowing it to be approved by every miner in the system. This approach is known as "selfish mining" since selfish miners maintain the privacy of their blocks and disclose them to the civic merely when the personal series is longer than the present communal chain, and consequently, it may be acknowledged by every miner in the network. Though decent miners are squandering money on a pointless division, greedy miners are forging their own path in the deficiency of opponents. As a result, greedy miners benefit more. As a consequence, nodes with more than 51% of the processing capacity in a blockchain will reverse transactions. As a result, it poses a significant security risk to CT applications [66].

4.5. Cultural shift and data disclosure willingness

Despite the fact that digitization is contributing to greater insights and patient outcomes in clinical trials, many such studies yet depend on paper for some procedures. Instantaneous implementation of clinical studies based on blockchain will not be a simple job, since shifting behavior of individuals and changing their habit roles are extremely difficult for every trade; thus, strong employee confrontation is anticipated. Thus, CT businesses need to work out how to persuade their workers in the context of a cultural transition. Any new reward strategies need to be proposed in this sense. Adequate instruction must also be given to staff for the

implementation of blockchain technologies. Contrarily, the majority of the health care centers do not want to share their precise details of their estimate with insurance providers and they normally bill each patient accordingly. In such scenarios, where different parties are not able to exchange accurate details, integrating blockchain technologies will be a critical challenge [67].

5. Conclusion

The article summarizes the role of blockchain technology in clinical trials mainly emphasizing on the basics of blockchain technology and clinical trials including its different phases, applicability of blockchain in clinical studies, the regulatory concerns and the challenges of these applications.

This technology is very beneficial in numerous aspects of Pharmaceutical Industry especially in the tedious, exhaustive and time taking process of drug discovery and drug development. Talking specifically about clinical trials, the blockchain technology eases the procedure of enrollment of participants for clinical study which otherwise is the most complicated and challenging aspect of clinical research. It also helps in tracing the consent of the patients, in maintaining the confidentiality of the patient's data, in preserving the data integrity and transparency. Additionally, it also aids in persistent monitoring of the entire process of the clinical research.

The current review also summarizes the regulatory requirements for using blockchain technology in the clinical trials. The US regulations for clinical research have been very briefly described. FDA (Food and Drug Administration) and OHRP (Office of Human Research Protection) are the two agencies which design and implement the regulations pertaining to human research. Moreover, the regulatory requirements for generating the clinical investigate record, construction & transmission of electronic storage and to obtain well versed consent from participants have also been outlined.

The utility of the recent technologies also face some of challenges. Thus, the review elaborates the challenges that are met by the usage of Blockchain Technology in clinical trials. These have been visualized as privacy leakage, scalability, big data storage, low cost adoption, selfish mining, cultural shift and data disclosure willingness. Thus, more elaborative research is required to overcome these challenges and bridge all the existing gaps between the concepts and applicability.

Declaration of Competing Interest

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

References

[1] H. Hasan, K. Salah, Blockchain-based solution for proof of delivery of physical assets, Springer LNCS, Seattle, USA, 2018. https://doi.org 10.1007/978-3-319-94478-4_10

[2] J. Garay, A. Kiayias, N. Leonardos, The Bitcoin Backbone Protocol: Analysis and Applications, Springer, Berlin, 2015, https://link.springer.com/chapter/10.1007/978-3-662-46803-6_10.

[3] K. Salah, N. Nizamuddin, R. Jayaraman, M. Omar, Blockchain based Soybean traceability in agricultural supply chain, IEEE Access 7 (2019) 73295–73305, https://doi.org/10.1109/ACCESS.2019.2918000.

[4] A. Kosba, A. Miller, E. Shi, Z. Wen, C. Papamanthou, Hawk: the blockchain model of cryptography and privacy-preserving smart contracts, in: In: IEEE Symposium on Security and Privacy (SP'16), 2016, pp. 839–858, https://doi.org/10.1109/SP.2016.55.

[5] H. Watanabe, S. Fujimura, A. Nakadaira, Y. Miyazaki, A. Akutsu, J. Kishigami, Blockchain contract: Securing a blockchain applied to smart contracts. In: IEEE International Conference on Consumer Electronics (ICCE'16), 2016. https://doi.org/10.5121/csit.2017.71011

[6] J. Benet, IPFS-Content Addressed, Versioned, P2P File System. https://arxiv.org/pdf/1407.3561.pdf. (Accessed 25 Feb 2021)

[9] Information about clinical trial. Available from: URL http://www.temple.edu/pascope/about_trials.html (Accessed 25 Feb 2021)

[10] Clinical trial wikipedia, the free encyclopedia. Available from: URL http://en.wikipedia.org/wiki/clinical_trial (Accessed 25 Feb 2021)

[11] S.B. Thorat, S.K. Banarjee, D.D. Gaikwad, S.L. Jadhav, R.M. Thorat, Clinical trial: a review, International Journal of Pharmaceutical Sciences Review and Research. (2010) 101–106.

[12] A. Sajita, Phase 0 Clinical Trial – an overview. International Journal of Students' Research, North America, 1 (2011). http://www.ijsronline.com/index.php/IJSR/article/view/120/255.

[13] K.E. Peace, D.-G. Chen, Clinical Trial Methodology, CRC Press, Chapman & Hall/CRC Biostatistics Series, 2010.

[14] US Food and Drug Administration, Draft Guidance for Industry-Adaptive Design Clinical Trials for Drugs and Biologics. US Food Drug Admin, Rockville, 2010. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-design-clinical-trials-drugs-and-biologics-guidance-industry

[15] A. Elsaber, J. Regnstrom, T. Vetter, F. Koenig, R.J. Hemmings, M. Greco, M. Papaluca-Amati, M. Posch, Adaptive clinical trial designs for European marketing authorization: asurvey of scientific advice letters from the European Medicines Agency, Trials. 15 (2014) 383, https://doi.org/10.1186/1745-6215-15-383.

[16] P.B. Fontanarosa, D. Rennie, C.D. De Angelis, Postmarketing surveillance-lack of vigilance, lack of trust, JAMA 292 (2004) 2647–2650, https://doi.org/10.1001/jama.292.21.2647.

[17] J.A. DiMasi, H.G. Grabowski, R.W. Hansen, Innovation in the pharmaceutical industry: newestimates of R&D costs, J. Health Econ. 47 (2016) 20–33, https://doi.org/10.1016/j.jhealeco.2016.01.012.

[18] F. Angeletti, I. Chatzigiannakis, A. Vitaletti, Privacy preserving data management in recruiting participants for digital clinical trials, HumanSys'17. (2017) 7–12, https://doi.org/10.1145/3144730.3144733.

[19] Y. Zhuang, L.R. Sheets, Z. Shae, Y.-W. Chen, J.J.P. Tsai, C.-R. Shyu, Applying blockchain technology to enhance clinical trial recruitment, AMIA Annu Symp Proc. 2019 (2019) 1276–1285. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7153067/.

[20] "Ethereum: Blockchain App Platform," https://www.ethereum.org/.

[21] "IoT-LAB: a very large scale open testbed," https://www.iot-lab.info/.

[22] M. Lichman, UCI machine learning repository, 2013. http://archive.ics.uci.edu/ml.

[23] F. Pedregosa, G. Varoquaux, A. Gramfort, V. Michel, B. Thirion, O. Grisel, M. Blondel, P. Prettenhofer, R. Weiss, V. Dubourg, J. Vanderplas, A. Passos, D. Cournapeau, M. Brucher, M. Perrot, E. Duchesnay, Scikit-learn: Machine learning in Python, J. Mach. Learn. Res. 12 (2011) 2825–2830. https://www.jmlr.org/papers/volume12/pedregosa11a/pedregosa11a.pdf.

[24] F. Angeletti, I. Chatzigiannakis, A. Vitaletti, The role of blockchain and IoT in recruiting participants for digital clinical trials, 25th International Conference on Software, Telecommunications and Computer Networks (SoftCOM), 2017.

[25] P. Schueler, B. Buckley, Re-Engineering Clinical Trials-Best Practices for Streamlining the Development Process, Academic Press, New York, 2014, https://www.elsevier.com/books/re-engineering-clinical-trials/schueler/978-0-12-420246-7.

[26] S. Jadhav, Blockchain: the next big disruptor in clinical trials? Pharm. Eng. 38 (2018)25. https://ispe.org/pharmaceutical-engineering/july-august-2018/blockchain-next-big-distruptor-clinical-trials

[27] H. Jahankhani, S. Kendzierskyj, Digital transformation of healthcare. Blockchain and Clinical Trial, Advanced Sciences and Technologies for Security Applications. (2019) 31-52. https://doi.org/10.1007/978-3-030-11289 -9_2

[28] D.M. Maslove, J. Klein, K. Brohman, P. Martin, Using blockchain technology to manage clinical trials data: a proof-of-concept study, JMIR Med Inform. 6 (2018), https://doi.org/10.2196/11949 e11949.

[29] E. Lee, Y. Yoon, Trusted information project platform based on blockchain for sharing strategy, J Ambient Intell Hum Comput. (2019), https://doi.org/10.1007/s12652-019-01421-z.

[30] F. Beierle, V.T. Tran, M. Allemand, P. Neff, W. Schlee, T. Probst, J. Zimmermann, R. Pryss, What data are smartphone users willing to share with researchers?, J Ambient Intell Human Comput 11 (2019) 2277–2289, https://doi.org/10.1007/s1265 2-019-01355-6.

[31] C. Jaschinski, S.B. Allouch, Listening to the ones who care: exploring the perceptions of informal caregivers towards ambient assisted living applications, J Ambient IntellHumanizComput. 10 (2019) 761–778, https://doi.org/10.1007/s12652-018-0856-6.

[32] C. Cai, New rule on clinical trial reporting doesn't go far enough, STAT, 2017. https://www.statnews.com/2017/01/17/clinicaltrial-reporting-new-rule/

[33] G. Wood, Ethereum: A secure decentralisedgeneralised transaction ledger, Ethereum project yellow paper. 151 (2014) 1–32. https://gavwood.com/paper.pdf.

[34] L. Luu, D.-H. Chu, H. Olickel, P. Saxena, A. Hobor, Making smart contracts smarter, CCs'16: Proceedings of the 2016 ACM SIGSAC Conference on Computer and Communications Security. (2016) 254–269.https://doi.org/10.1145/2976749.2978309.

[35] D. Wong, S. Bhattacharya, A. Butte, Prototype of running clinical trials in an untrustworthy environment using blockchain, Nat. Commun. 10 (2019) 9555, https://doi.org/10.1038/s41467-019-08874-y.

[36] R. M. Parizi, A. Dehghantanha, Smart Contract Programming Languages on Blockchains: An Empirical Evaluation of Usability and Security, vol. 10974.

Springer International Publishing, 2018, pp. 75–91.: http://link.springer.com/10.1007/978-3-319- 94478-4.
[37] J.C. Kvedar, A.L. Fogel, mHealth advances clinical research, bit by bit, Nat Biotech. 35 (2017) 337–1334, https://doi.org/10.1038/nbt.3851.
[38] T.-T. Kuo, H.-E. Kim, L. Ohno-Machado, Blockchain distributed ledger technologies for biomedical and health care applications, J. Am. Med. Inform. Assoc. 24 (2017) 1211–1220, https://doi.org/10.1093/jamia/ocx068.
[39] T. Nugent, D. Upton, M.Cimpoesu,Improving data transparency in clinical trials using blockchainsmart contracts, F1000Res.5 (2016) 2541. https://doi.org/10.12688/f1000research.9756.1.
[40] M. Benchoufi, R.Porcher, P.Ravaud, Blockchain protocols in clinical trials: Transparency andtraceability of consent, F1000Res.6 (2017) 66. https://doi.org/10.12688/f1000research.10531.5.
[41] A. Ekblaw, A. Azaria,MedRec: Medical Data Management on the Blockchain, Viral Communications.(2016) 1-10. https://www.media.mit.edu/publications/medrec/.
[42] H. Kakavand, N. Kost De Sevres, B. Chilton, The blockchain revolution: an analysis of regulation and technology related to distributed ledger technologies, SSRN. 2017. https://doi.org/10.2139/ssrn.2849251
[43] P. Filippi, S. Hassan, Blockchain technology as a regulatory technology: from code is law to law is code, First Monday. 21 (2016), https://doi.org/10.5210/fm.v21i12.7113.
[44] Food and Drug Administration, Impact of Certain Provisions of the Revised Common Rule on FDA-Regulated Clinical Investigations: Guidance for Sponsors, Investigators, and Institutional Review Boards, Silver Spring, MD, 2018. https://www.regulations.gov/contentStreamer?documentId=FDA-2018-D-3551-0001&attachmentNumber=1&contentType=pdf (Accessed 2 March 2021).
[45] Food and Drug Administration, Regulations: Good Clinical Practice and Clinical Trials, 2018. https://www.fda.gov/science-research/clinical-trials-and-human-subject-protection/regulations-good-clinicalpractice-and-clinical-trials (Accessed 2 March 2021)
[46] Food and Drug Administration, Use of Electronic Records and Electronic Signatures in Clinical Investigations Under 21 CFR Part 11 - Questions and Answers: Guidance for Industry (draft), Silver Spring, MD, 2017. https://www.fda.gov/media/105557/download (Accessed 2 March 2021)
[47] AAHRPP, Tip Sheet 2: Determining Whether an Activity Is Research Involving Human Participants, Washington, DC: Association for the Accreditation of Human Research Protection Programs, Inc, 2017. https://admin.aahrpp.org/Website%20Documents/Tip_Sheet_2_Determining_Whether_an%20_Activity_is_Research_Involving_Human_Participants.PDF (Accessed 2 March 2021).
[48] Office for Civil Rights, Is a Software Vendor a Business Associate of a Covered Entity? Washington, DC, 2002. https://www.hhs.gov/hipaa/for-professionals/faq/256/is-software-vendor-business-associate/index.html (Accessed 2 March 2021).
[50] S.M.C. Gibbons, J. Kaye, A. Smart, C. Heeney, M. Parker, Governing genetic databases: challenges facing research regulation and practice, J.L. Soc. 34 (2007) 163–189, https://doi.org/10.1111/j.1467-6478.2007.00387.x.
[51] R.S. Dokholyan, L.H. Muhlbaier, J.M. Falletta, J.P. Jacobs, D. Shahian, C.K. Haan, E.D. Peterson, Regulatory and ethical considerations for linking clinical and administrative databases, Am. Heart J. 157 (2009) 971–982, https://doi.org/10.1016/j.ahj.2009.03.023.
[52] J. Pollak, HIPAA Questions and Answers Relating to Research Databases, Baltimore, MD: Johns Hopkins Medicine, 2006. : https://www.hopkinsmedicine.org/institutional_review_board/hipaa_research/faq_databases.html (Accessed 5 March 2021)
[53] Office for Civil Rights, Research, Washington, DC: Department of Health and Human Services, 2017. Available online at: https://www.hhs.gov/hipaa/forprofessionals/special-topics/research/index.html (Accessed 5 March 2021)
[54] Office for Human Research Protections, Human Subject RegulationDecision Charts, Rockville, MD, 2016. https://www.hhs.gov/ohrp/regulations-and-policy/decision-charts/index.html (Accessed 5 March 2021).
[55] Office for Human Research Protections, Coded Private Information or Specimens Use in Research, Guidance, Rockville, MD, 2008. Available online at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/researchinvolving-coded-privateinformation/index.html (Accessed 5 March 2021).
[56] M. Benchoufi, P. Ravaud, Blockchain technology for improving clinical research quality, Trials 18 (2017) 335, https://doi.org/10.1186/s13063-017-2035-z.
[57] National Institutes of Health, Notice of Changes to NIH Policy for Issuing Certificates of Confidentiality. Bethesda, MD, 2017. https://grants.nih.gov/grants/guide/notice-files/NOT-OD-17-109.html (Accessed 5 March 2021).
[58] Office for Civil Rights, How Do HIPAA Authorizations Apply to an Electronic Health Information Exchange Environment? Washington, DC, 2008. https://www.hhs.gov/hipaa/for-professionals/faq/554/how-do-hipaa-authorizations-apply-to-electronic-health-information/index.html (Accessed 5 March 2021).
[59] National Institutes of Health, Common Data Element (CDE) Resource Portal, Bethesda, National Library of Medicine, MD, 2019, https://www.nlm.nih.gov/cde/ (Accessed 5 March 2021).
[60] Food and Drug Administration, Providing Regulatory Submissions in Electronic Format-Standardized Study Data: Guidance for Industry, Silver Spring, MD, 2014, https://www.fda.gov/media/82716/download (Accessed 7 March 2021).
[61] Food and Drug Administration, Electronic Source Data in Clinical Investigations, Silver Spring, MD, 2013, https://www.fda.gov/media/85183/download (Accessed 7 March 2021).
[62] Food and Drug Administration, Informed Consent: Guidance for IRBs, Clinical Investigators, and Sponsors, Silver Spring, MD, 2014b. Available online at: https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/informed-consent-children (Accessed 7 March 2021).
[63] Food and Drug Administration, IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More Than Minimal Risk to Human Subjects: Guidance for Sponsors, Investigators, and Institutional Review Boards, Silver Spring, MD, 2017, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/irb-waiveror-alteration-informed-consent-clinical-investigations-involving-no-moreminimal-risk (Accessed 7 March 2021).
[64] Department of Health and Human Services, Use of Electronic Informed Consent in Clinical Investigations - Questions and Answers: Guidance for Institutional Review Boards, Investigators, and Sponsors, 2016. https://www.fda.gov/media/105557/download (Accessed 7 March 2021)
[65] A.M. Tang, M. Jian, Deep Learning Applications for Cyber Security, Springer, Berlin, 2019.
[66] Y. Zhuang, L. Sheets, Z. Shae, J.J.P. Tsai, C.-R. Shyu, Applying blockchain technology for health information exchange and persistent monitoring for clinical trials, In: AMIA Annual Symposium Proceedings Archive, 2018. https://pubmed.ncbi.nlm.nih.gov/30815159/.
[67] I.A. Omar, R. Jayaraman, K. Salah, I. Yaqoob, S. Ellahham, Applications of Blockchain Technology in Clinical Trials: Review and Open Challenges, Arabian Journal for Science and Engineering 46 (2020) 3001–3015, https://doi.org/10.1007/s13369-020-04989-3.

Further reading

[7] P. Labs, Filecoin: a decentralized storage network. https://filecoin.io/filecoin.pdf. (Accessed 25 Feb 2021).
[8] J.H. Hartman, I. Murdock, T. Spalink, The Swarm scalable storage system, In: 19th IEEE International Conference on Distributed Computing Systems, 1999.
[49] Office for Human Research Protections Companion, Q&As About the Revised Common Rule, 2018. https://www.hhs.gov/ohrp/sites/default/files/Revised-Common-Rule-Q%26As-08-20-2018.pdf (Accessed 2 March 2021)