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Clinical Trials on Blockchain

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INTRODUCTION

The objective of this paper is to describe how blockchain technology can be used to optimize the clinical trial workflow. We will demonstrate how pharmaceutical companies and other clinical trial participants (such as CROs, regulatory agencies) can collect and store subject's data and analysis results in a secure, distributed manner and how "smart contracts" can be used to optimize and automate the clinical trial workflow. In addition, we will introduce a sample use case and technical architecture used for implementation of a blockchain based Clinical Trial Management Solution.

We will demonstrate this concept using Hyperledger Fabric, an open source enterprise blockchain hosted by The Linux Foundation.

CHALLENGES IN RUNNING CLINICAL TRIALS

Conducting clinical trials is a time consuming, expensive affair that involves close collaboration between multiple stakeholders, often geographically distributed, and one that needs high level of monitoring, regulation and precision. This process brings along its unique intrinsic challenges as described below:

DATA MANAGEMENT

- Dynamic access management of data - access rights are time based as determined by blinding/unblinding of data, database lock.
- Multiple versions of data created from variety of sources – external labs, CROs, other vendors. This issue gets compounded by increasing globalization of clinical trials. Data is stored in a wide variety of siloed systems which leads to duplication and difficulties in accessing the required data.
- Non-aggregation of Clinical Data – Data is not easy to access which makes answering even the simplest research question a big challenge. Time is spent in pulling data from a variety of sources and cobbling together reports.
- Data Entry – Database systems that facilitate manual data entry do not always automatically link subject data into a broader record. Often, the investigator does not have tools to analyze the data in real time because time is wasted to integrate data with a centralized repository.
- Regulatory authority compliant system such as 21 CFR Part 11.
- Necessary regulatory processes slowing research because timely approval not given for data use.
- Management of strategic partnerships and study sites. Involvement of several vendors in the studies.

DATA SHARING AND SECURITY

- Preventing leak, fraud, abuse of confidential information.
- Data Verification through multi party channels.
- Sharing of data in a controlled manner: It must be ensured that the data sharing is consistent with federal and local regulations.

SUBJECT ENROLLMENT

- Ability to recruit, enroll, and retain appropriate volunteers.
- Absence of adequate return of investment in the form of personal benefits for subjects, leading to increased burden for subjects in study participation.
- Assuring Subject Safety – Development of safety oversight that include Serious adverse event (SAE) and adverse event (AE) reporting, compliance with GCP, local regulations, and trial protocol, remote or onsite monitoring and setup of a safety review committee and an independent data safety monitoring board (DSMB).
- Inefficient Study Recruitment - difficulty in finding the right subjects.

SPIRALING COSTS

As an inevitable consequence of the above issues, the cost of conducting clinical trials is at an all-time high. Increasing complexity of clinical trials and tight delivery timelines is putting more pressure on the already stretched out resources. In the end, patients suffer because new discoveries are getting delayed and opportunities to participate in new forms of treatment get reduced.

Blockchain is the technology that can solve some of the problems described above. We will talk about Blockchain in the subsequent section and how it can be put in action.

INTRODUCTION TO BLOCKCHAIN

Blockchain is a distributed, decentralized database where each record provides reference to the next record and the database is kept in sync through cryptography. Data points are grouped together in a "block". Each new block contains a reference to the previous block. As new blocks are added, they are "chained" together through these references to the previous block – hence the name Blockchain.

The blockchain can be updated when different participants (or nodes) reach a consensus and add a new block. There are different algorithms/approaches to reach consensus. In bitcoin, the most famous blockchain, consensus is reached when 51% of the nodes agree and validate the new block.

Blockchain has the following key features that are relevant for clinical trials:

IMMUTABILITY

In a blockchain, data blocks are linked together using hash functions. If a data in any of the block is changed, it will update the hash function of future blocks and thus change the final state of the whole blockchain. During the consensus process the hash of the changed node will not match the hash of other unchanged nodes. The differing node will be excluded, and differing data point will not be added thereby ensuring immutability of the information in blockchain.

This property of Blockchain has immense use in Clinical trials as no valid clinical records can be omitted or altered.

DISTRIBUTED & DECENTRALIZED

Blockchain is not controlled by a single authority. Distributed nature ensures that different parties don't have to trust each other to participate in the network. Some of the benefits of such a network for clinical trials and pharmaceutical industry are:

- Data Replication - The blockchain data is replicated across different nodes and different organizations which ensures that each node has its own copy of the data.
- User Empowerment and ownership - Decentralized systems allows the participants to keep their own version of the data. This ensures that users have control over who access their data and how it is accessed.

PERMISSIONED BLOCKCHAIN

The most popular Blockchain – Bitcoin is an example of a public blockchain network. Public Blockchains are open and anyone can join, update, read and validate the transactions on the network. Any individual can run a node for the Bitcoin blockchain and download the entire ledger data as the data is public and start participating in the network.

Permissioned Blockchains on the other hand operate in a controlled environment. The nodes of the permissioned blockchains are not public and only pre-authorized or approved entities can join and participate in the network. A similar analogy would be that permissioned blockchains are to public blockchains what intranet is to internet.

Permissioned blockchains solve three fundamental problems of public blockchains that relate to healthcare and clinical trial data:

DATA PRIVACY

Unlike public blockchains, data is not stored on public nodes but only on organization nodes that are part of the network. Using permissioned blockchains we can ensure that only authorized organizations/entities with designated permissions as defined by a set protocol can join the network(s) and perform only certain activities on the network.

COMPLIANCE

Permissioned blockchains can achieve data privacy and security compliance such as HIPAA or PIPEDA as data is stored only on authorized "nodes".

COST AND SPEED

The maintenance of a public blockchain ledger requires heavy power consumption. This makes transacting on a public blockchain network both slow and expensive. With a private and permissioned blockchain, we can utilize computationally inexpensive protocols for verifying transactions. This can make transacting on permissioned blockchains much faster and significantly cheaper as compared to traditional public blockchains.

CURRENT IMPLEMENTATION OF CLINICAL TRIAL WORKFLOW

In the present times, the different steps of clinical trials are conducted independently of each other (Figure 1). This is partly because of legacy technology and legacy approach to conducting clinical trials and partly because of lack of a better alternative.

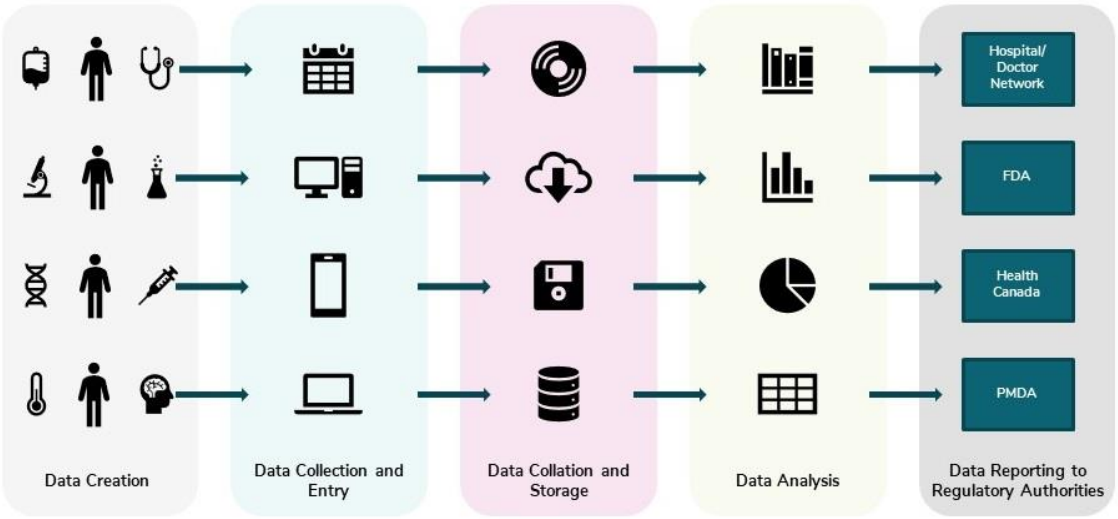

Figure 1 – Present Day Clinical Management Workflow

Data gets created for multiple subjects from multiple channels – hospitals, clinical trials, smart devices. Data is then collected and entered in a Centralized Database Management System (DBMS) separately for each organization. Different pharmaceutical companies, hospitals, CROs, Biotech, laboratories have their own decentralized databases. Different organizations then collate and store data in their own preferred way and own preferred format in their own IT environments. Data is then analyzed separately within each organization and results are presented to regulatory authorities.

In this model, collaboration is not only difficult between different organizations, but collaboration is also difficult within organizations. And often the proverbial wheel is reinvented for each trial.

OUR SOLUTION

Our solution is a permissioned blockchain product in which:

- Various Stakeholders (such as Pharma companies, CROs, Regulators, Subjects) participate in a network such that,
- Data sharing, and the clinical trial execution take place in a distributed manner with programmable Smart Contracts based on the Clinical Trial Protocol,
- All Stakeholders run their own version of Smart Contract that updates their own local version of the ledger (i.e. Blockchain Database), and
- The organization nodes remain in sync through consensus algorithm.

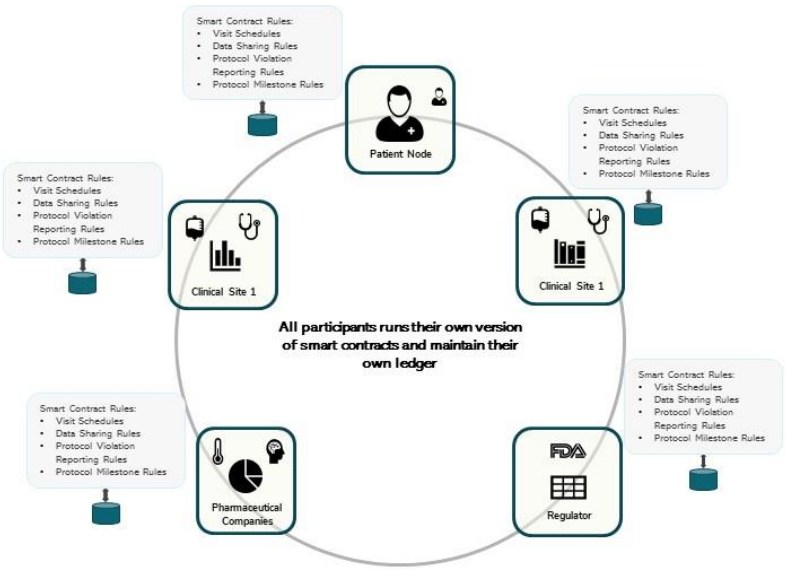

Figure 2 – Entities running Smart Contracts on Permissioned Blockchain

KEY COMPONENTS OF OUR SOLUTION

ORGANIZATION NODES

Organization refers to a business entity (such as Pharmaceutical company, Regulator, Hospital) that participates in the network. For instance, each Pharmaceutical company is an organization. Similarly, each hospital is an organization, and each regulator (such as FDA, PMDA) is an organization.

CHANNELS

Channels represent Private Blockchain Networks that organizations can create amongst themselves. Each channel can have multiple organizations, different identities, and data visibility rules. Each channel is a Private Network such that data is shared only within a channel between the channel participants.

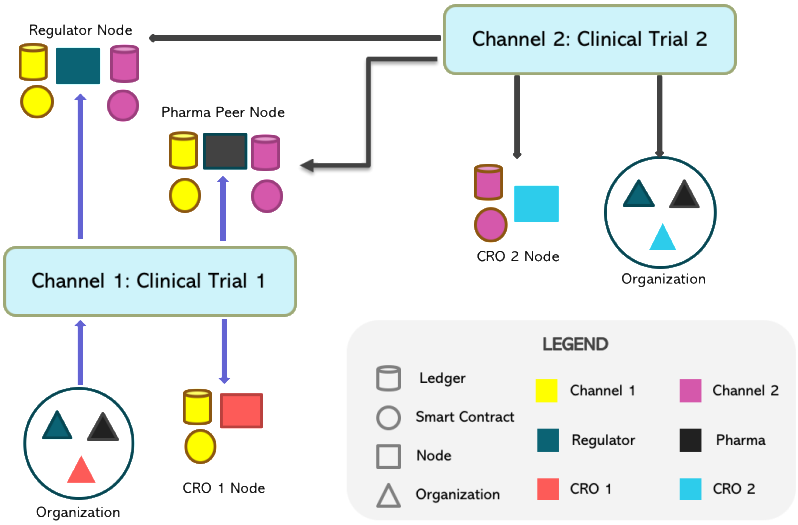

Figure 3 – Sample Blockchain Network with 2 Channels – One channel for each clinical trial

For instance, consider a scenario in which a Pharmaceutical Company is running 2 clinical trials - Clinical Trial 1 and Clinical Trial 2. In this scenario –

- Each trial will have its own channel – Channel 1 for Clinical Trial 1 and Channel 2 for Clinical Trial 2 respectively.
- If a CRO 1 is a participant in Clinical Trial 1 then CRO 1 will be part of Channel 1 and if CRO 2 is participant in Clinical Trial 2 then CRO 2 will be part of Channel 2.
- Let's also assume that Regulator (such as FDA) is part of both the channels – Channel 1 and Channel 2.

In such a scenario, Data for Clinical Trial 1 will be only shared across all participants of Channel 1 - CRO 1, Regulator and Pharmaceutical Company and Data for Clinical Trial 2 will only be shared across all participants of Channel 2 i.e. CRO 2, Regulator and Pharmaceutical Company.

- All the data associated with a Channel is stored in the Ledger.
- Each Channel maps to one Ledger.
- Each Organization that is part of the Channel maintains its own copy of shared ledger for the channel.

Two Data types are stored in the ledger:

Transaction History

Transaction History is historical log of all the transactions on the network. Since the Ledger is append only, all the transactions can be replayed to arrive at the current state. Each participant stores their own version of the Ledger. Transaction History is available to view for all allowed participants in the network in real time.

World State

World State stores the current state of ledger. Each time a new transaction is agreed upon and added, the World State will update to reflect the latest transaction.

For instance, consider a scenario wherein data for a particular visit is updated afterwards. World State will store the last entry for the visit whereas historical ledger will store all changes performed for the particular visit.

SMART CONTRACTS

Smart Contract define any arbitrary piece of code that executes within a Channel. Smart Contracts can change the state of the ledger of the channel. Each channel is linked to a Smart Contract. Smart Contracts define the logic of clinical trials. Smart Contracts are Turing complete i.e. any business logic can be embedded into Smart Contracts.

For example, one of the clinical trial rules that can be embedded into the Smart Contract is that subjects can only be administered a drug if they have provided an Informed Consent. Another rule that can be embedded into a Smart Contract is to automatically record and report any deviation from study protocol.

PROPOSAL

A proposal is created when a node requests data to be added to the ledger.

PRIVATE DATA OPTIONS

Data within the channel (or the network) is private. However, data can further be encapsulated into different sub private networks.

For instance, In the sample scenario in Figure 4, a private sub network can be created between the Clinical Site 1, Pharmaceutical Company and the Regulator while another sub network can be created between Clinical Site 2, Pharmaceutical Company and the Regulator. This ensures that Clinical Site 2 does not get any access to data from the Clinical Site 1 and vice versa. However, as Regulator and the pharmaceutical company are part of both the networks, they get access to data from both the networks.

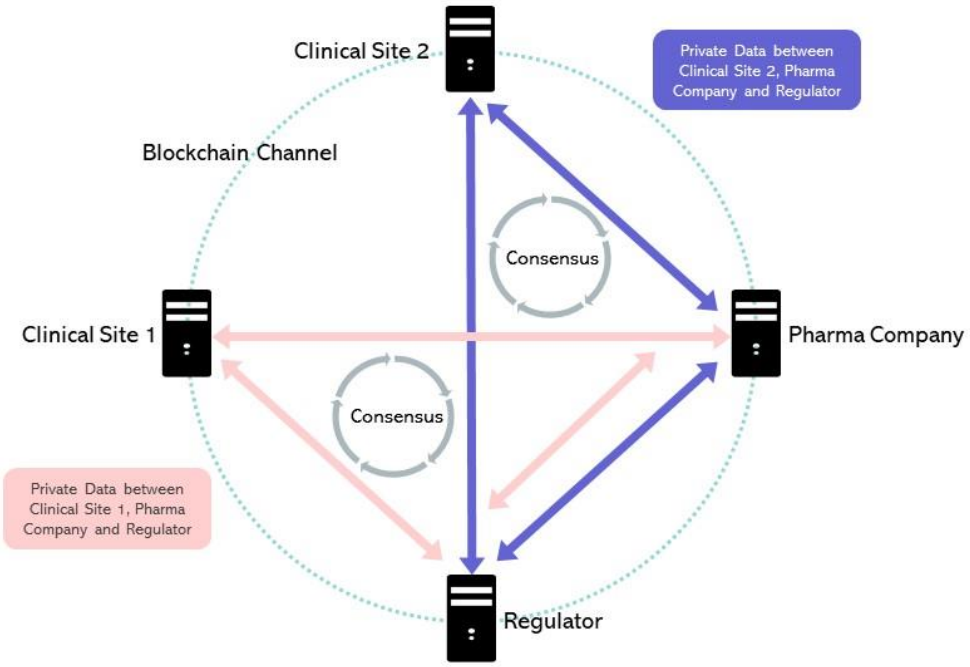

Figure 4 – A blockchain clinical trial network with 2 clinical sites (Clinical Site 1, Clinical Site 2), one pharmaceutical company (Pharma Company), and one regulator (Regulator). Configuration for private data is set such that Clinical Site 1, Pharma Company and Regulator form one private sub network, while Clinical Site 2, Pharma Company, and Regulator form another private sub network

CUSTOM IMPLEMENTATION OF OUR SOLUTION

Consider sample clinical trial channel with following participants -

1. Pharmaceutical Company
2. Regulator
3. Clinical Site 1
4. Clinical Site 2
5. Subject 1001 – registered at Clinical Site 1
6. Subject 1002 – registered at Clinical Site 2

Now consider, the following sequence of events happen -

Step 1: Subject 1001 visits Clinical Site 1 and Subject 1002 visits Clinical Site 2.
Step 2: Clinical Sites collect data for the subjects for the particular visit.
Step 3: Both the sites create separate proposal to add data to the respective ledgers for respective Subjects (Site 1 for Subject 1001, Site 2 for Subject 1002).

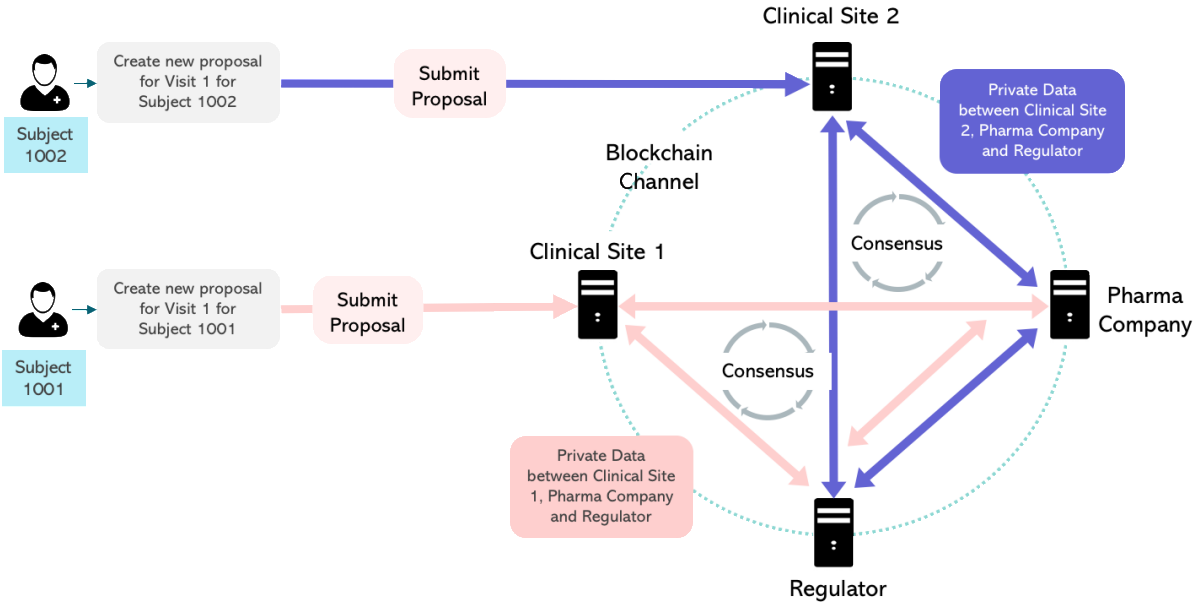

Figure 5 – Proposal creation stage – For each new data entry request, a proposal is created which is validated and confirmed by participating nodes of the sub network (Clinical Site 2, Regulator and Pharma Company for Subject 1002) (Clinical Site 1, Regulator and Pharma Company for Subject 1001)

Step 4: For each sub network, organization nodes within their network reach a consensus over the current state of the ledger as well as the validity of the proposal. Once the consensus is reached, they update the ledger state with the data defined in the proposal. The data is only synced with the organization nodes of the sub network. Therefore, the Data of Subject 1001 is synced with Pharma Ledger, Regulator Ledger, and the Clinical Site 1 Ledger, whereas the Data of Subject 1002 is synced with Pharma Ledger, Regulator Ledger, and Clinical Site 2 Ledger.

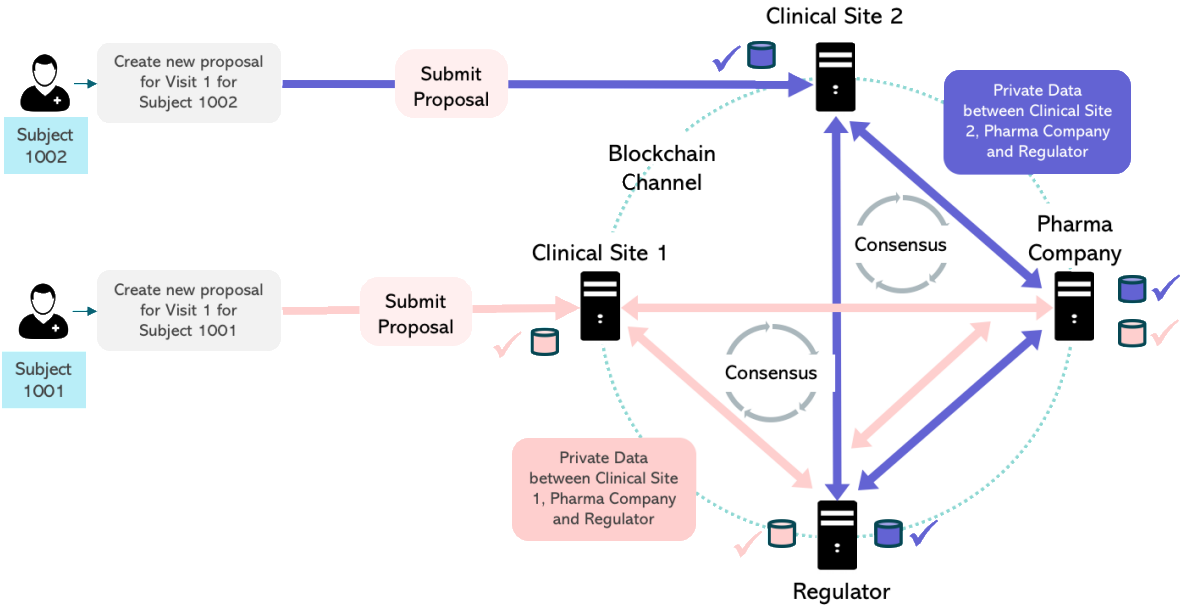

Figure 6 – Consensus State: Once confirmed, data is synced across respective nodes for the sub networks (Subject 1001 is synced across Clinical Site 1, Pharma Company and Regulator) (Subject 1002 is synced across Clinical Site 2, Pharma Company and Regulator)

The above steps repeat for all data entries. The blockchain network ensure that the respective ledgers are always in sync. At any time, any participant can view their copy of the ledger (transaction history and world state).

HOW DOES OUR SOLUTION SOLVE THE PROBLEMS?

IMPROVED PROTOCOL ADHERENCE AND VIOLATION REPORTING

Our approach digitizes the protocol through smart contracts that improves compliance, better management of protocol deviations and faster audits.
For instance, a smart contract can be created to ensure that unless subjects grant consent (through digital signatures), no data can be entered for the subjects. If subsequently subjects withdraw consent, no updates to subject data can be made unless reauthorized by the subjects.

Pseudo Code (Subject setting Informed Consent):

```
Within Consumer App/Portal: Smart Contract execution:
informedConsent = true //or false
authenticatewithBlockchainNetwork(self)
setInformedConsent(informedConsent, self.auth) // This function is only
accessible if subject is authenticated
….
…
Within Channel: Smart Contract execution:
func setInformedConsent(informedConsent,subjectAuth)
{
subject = getSubjectData(subjectAuth) //Get subject data based on authentication
info provided
subject.informedConsent = informedConsent
 }
```

Similarly, other smart contracts can be created such that any protocol deviation (for instance multiple visits missed or visit performed outside permissible visit window) will automatically be added in the deviation log.

IMPROVED DATA SHARING AND REGULATOR COLLABORATION

Regulators can act as a node and have real time access and visibility into the entire clinical trial generation and sharing process. As Regulators maintain their own version of Distributed Ledger, they do not have to rely on Pharmaceutical Companies or the Healthcare provider for data - which improves flexibility and can reduce the compliance requirements for pharmaceutical companies.

PATIENT CENTRICITY

Since Permissioned Blockchains enable secure transfer of data, set of contracts can be created to improve patient access and centricity. For instance, smart contract rules can be created such that patients will receive immediate ownership of their data at the termination of Clinical Trial.

WHAT PROBLEM(S) DOES BLOCKCHAIN SOLVE FOR CLINICAL TRIALS:

DATA MANAGEMENT

- Dynamic access management of data - access rights are time based as determined by blinding/unblinding of data, database lock.
- External Labs, CROs, other vendors can exist simultaneously on the same platform as pharmaceuticals and hospitals. Data redundancy can be become thing of the past.
- Regulatory Authorities can exist on the same network - This will give them easy access to monitor and audit collected data.
- Data can be verification through multi party channels.

DATA SHARING

- Data can be shared in a controlled manner by the permissioned blockchain. Access rights and duration can be implemented through smart contracts.
- Utilization of time and resources efficiently with research data facilitated by the ease of sharing of data.

SUBJECT ENROLLMENT

- Medical history, Subject Characteristics, vital parameters and relevant demographic information of subjects can be stored on blockchain. This can make it easy for Research companies to identify and target subjects that already meet specified Inclusion/Exclusion criteria for a trial.
- Subject Enrolment in the trial can be incentivized. Subjects can pre-load their data onto the blockchain and if/when they fulfil the inclusion/exclusion criteria for a trial, they can be compensated by the platform.
- Baseline information can be pre-filled for the selected group of subjects thus onboarding subjects to the trial faster.

FUNDING

- Each transaction on the network can be incentivized by incorporating a value transfer public blockchain layer. This makes it possible to add a buy/sell price to different transactions in the clinical trial

ecosystem such as sharing of data between two researchers, sharing of data between subject and researchers, continued subject participation in clinical trials.

CHALLENGES IN IMPLEMENTING CLINICAL TRIALS IN BLOCKCHAIN

Despite blockchain being seemingly perfect for conducting clinical trials, there are a lot of challenges with traditional blockchain implementations. These are some of the challenges that we might face in implementing clinical trials on Blockchain.

- Integration barriers - Integration with legacy systems and existing IT ecosystem
- Difficult to find experienced and knowledgeable blockchain consultants, programmers and architects.
- Lack of Regulatory Framework - uncertainty related to the way current regulatory frameworks would apply to Blockchain.
- Lack of clarity regarding the definition of smart contracts and their implementation in Blockchain. No clear legal enforceability of smart contracts.
- Connected-only mode – Difficulty in offline use cases such as data collection without internet.
- High costs of initial implementation.
- Negative Perception - Bitcoin and other cryptocurrencies used as ransom money
- Nascent technology and industry inertia.
- Emergence of multiple non-interoperable blockchain implementations can lead to a fragmented ecosystem and limit widespread adoption.

It will require great deal of effort and consensus from all stakeholders to overcome general distrust of new technology and an inertia to change.

SUMMARY

Blockchain has the potential to transform the clinical data collection, data sharing, and operations. Clinical Trials based on blockchain technology can streamline data transfer, ensure real time data access across clinical trial participants, reduce data entry errors, and simplify the clinical trial audit and compliance process.

Beyond clinical trials, blockchain opens new areas of collaboration and data sharing across the health care system. Blockchain and distributed ledgers can provide patients ownership of their data, as well as create economic and healthcare incentives for data sharing.

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