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Conference Paper · August 2021

DOI: 10.1007/978-3-030-85902-2_11

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Abstract. Efficiency and resilience of the clinical trials supply chain are of particular prevalence in the current global context. The unique characteristic of the reverse logistics flow in the supply chains for clinical trials is the foundation for the digital transformation framework presented in this paper. This paper proposes a novel framework that integrates internet of things (IoT) and blockchain technology for the reverse logistics supply chain for clinical trials. The framework is implemented in a Contract Research Organisation operating clinical trials in Europe and North Africa and results are discussed. The main contribution of the proposed novel framework is the integration and interaction of both IoT and blockchain in a reverse logistics process.

Keywords: IoT, Blockchain, Reverse Logistics, Clinical Trials.

1 Introduction

Efficient, effective, and secure logistics processes for clinical trials is essential for the advancement and development of improved medical treatments, pharmaceuticals, and vaccines. Clinical trials are organised and run by contract research organisations (CRO) and have a characteristic reverse logistics supply chain that requires a high level of confidentiality and security. The reverse logistics process of a clinical trials supply chain is a unique context for digital transformation. Reverse logistics using internet of things (IoT) devices and blockchain in the logistics process can generate new data, such as additional real-time tracking and traceability capabilities as well as temperature monitoring and the possibility to alert logistics providers of immediate issues. Putting this into a blockchain based system can create a full unchangeable record of the clinical trial supply chain transactions.

To date, blockchain and IoT devices have not been considered together in the reverse logistics process of CRO operating clinical trials. The current technological extent of blockchain in CRO is limited to document sharing ensuring the information security of the patient recruitment process and medical records. This highlights the importance of tracking and tracing the location of the incoming shipments, as well as the condition of its contents, to optimise the complementary processes in CRO such as the arrival logistics area, re-distribution, and scheduling laboratory testing to support the resilience of the reverse logistics process.

This paper proposes a framework of a reverse logistics clinical trials supply chain that integrates digital technology, in the form of blockchain and IoT, into the logistics process. The paper is structured in the following way: the next section reviews the literature of the use of IoT and blockchain in CRO; section 3 presents the proposed framework; section 4 presents the results of the framework implementation in a real CRO; and finally, section 5 concludes the paper including the limitations of the proposed solution and suggested future.

2 Literature Review

Reproducibility, data sharing, personal data privacy, traceability concerns and patient and investigators enrolment in clinical trials are big medical challenges for contemporary clinical research and have a direct impact on the supply chain [1]. Although technological integration is most prevalent in other industries, there have been several applications and research related to blockchain which is progressively edging toward the healthcare field [2–4].

IoT devices are already prevalent in the clinical trials industry. [5] highlighted the importance of IoT devices in both recruiting participants in clinical trials and patients' follow-up process. However, a previous study by [6] showed that smart wearables in many cases have limited capabilities for monitoring, signal processing, and communication due to operating in uncontrolled environments. Due to these constraints, applying standard security and privacy requirements is extremely challenging. [7] provide a proof-of-concept study of a digital health application enabling the recruitment process in clinical trials by using IoT data and blockchain. The results show that the combination of these technologies can be implemented to provide a robust digital clinical trials information system.

In terms of the use of blockchain in transportation systems, [8] study the use of blockchain in intelligent transportation systems (ITS) which and conclude that blockchain represents the future of autonomous transportation systems such as ride-sharing and taxi services [9], and [10] develop an approach to securely share information in the transportation of dangerous goods using Smart Contracts based on blockchain technology. Blockchain aids with the secure storage of transportation documents, and facilitates the custom documents which increases efficiency of inspections and consequently reduces overall lead-time [11]. [12] explore the digital transformation of logistics documentation by smart contracts and blockchain technology via analysis of the literature and use cases from industry. They find that logistics providers are digitalising the documentation in the logistics process to increase transparency, to reduce the associate time and cost related to preparing paper-based documentation, which is highly prone to counterfeit and human errors, and to facilitate trade documents with customs authorities for the transportation and tracking of shipments across borders.

Logistics in a supply chain can be supported using Smart Contracts based on blockchain technology [13]. Suppliers search for transportation partners which are in the blockchain and linked by Smart Contracts that outline the terms and conditions as well as fees, payment terms and shipping times. Smart Contracts which are stored in blockchains can decrease administration and service costs as they can be automatically trigger the logistics activities in a decentralised way as well as improve efficiency in payment of suppliers to transportation partners based on the pre-defined conditions in the contract [13]. [14] develop a system architecture and a software prototype tested on the Ethereum test network for the use of Smart Contracts based on blockchain for the fair exchange of goods between suppliers and customers, and [15] develop a framework for using blockchain and smart contracts in the pharmaceutical supply chain which covers logistics processes, supplier transactions, tracking and tracing of shipments, quality monitoring of shipments, among others. They test the use of Smart Contracts for the real time tracing by storing the sequence of timestamps during the logistics process and quality monitoring of shipments. [16] propose a Smart Logistics solution based on Smart Contracts with a focus on transportation of dangerous goods which includes supplier recommendation, contract negotiation, condition monitoring via IoT devices and payment to suppliers. Their Smart Contract is on a cloud-based system which deploys the agreed upon Smart Contract on an Ethereum Virtual Machine which executes and monitors the details in the Smart Contract. They develop a prototype and find that the proposed architecture allows for quicker payments to suppliers and updated supplier ratings based on the details in the Smart Contracts.

Traceability accounts as one of the top issues to track the error back to its original source and is currently lacking in the traditional clinical trials database systems [17]. Blockchain technologies can enforce a high level of transparency, traceability and control over the interconnected processes in clinical trials' supply chains [18], however, in this regard, very little research exists. [19] propose a 4 components blockchain platform architecture for clinical trial and precision medicine built on top of the traditional blockchain to achieve reliable and safe transaction. [20] propose a private, permissioned Ethereum blockchain network maintained by regulators, the pharmaceutical industry and CRO to be used in parallel with traditional clinical data management systems in order to increase trust in the data they hold and the credibility of trials findings. [21] explore the role of blockchain in clinical trials data management and develop a proof-of-concept of a patient-facing and researcher-facing system based on Smart Contracts. The system uses a web-based interface to allow users to run trials-related Smart Contracts on an Ethereum network allowing patients to grant researchers access to their data and allowing researchers to submit queries for off-chain data. [22] develops a proof-of-concept study aiming to implement a process allowing the collection of patients' informed consent, which is bound to protocol revisions, storing and tracking the consent in a secure, unfalsifiable and publicly verifiable way, and enabling the sharing of this information in real time. [23] design workflows for using smart contracts in healthcare and clinical trials which focus on cost and healthcare optimisation.

Although IoT and blockchain are used independently for patient follow-up in the clinical trials industry, there is an opportunity to extend these technologies to the reverse logistics supply chain to improve the overall resilience of material and information flows. It has been highlighted in the literature that both IoT and blockchain are not only beneficial in many situations, but also complementary of each other. The following section proposes a novel framework that addresses the integration of both technologies to handle material and information flows which show to improve the digital activities in the reverse logistics clinical trials supply chain.

3 Proposal for a New Framework

Currently, the existing logistics processes in clinical trial companies use physical logistics-related documentation transfer. In addition, the visibility provided by digital documentation based on blockchain allow CRO to prioritise shipments based on information collection at the source, track and trace shipments and the environmental conditions via the installed IoT devices. This, in turn, allows them to better schedule arrivals, laboratory testing, redistribution of packaging, and decreased supply chain costs due to improved planning and prioritisation.

The specific nature of a clinical trials supply chain that works in a reverse logistics flow, requiring a high level of security, creates a unique context for the proposed framework development.

The proposed framework, shown in Fig. 1. integrating IoT and blockchain in clinical trials consists of 1) tracking and tracing of location and environmental conditions via IoT devices and a communication infrastructure; and 2) secure digital logistics document sharing between supply chain stakeholders based on blockchain technology and infrastructure.

3.1 IoT Integration

The implementation of real-time sensors can eliminate many manual tasks and allow rapid reaction in case of a problem. A sensor could quickly detect a problem during the journey, sending an alert to the logistician. After looking at the data transmitted by the sensor, the logistician could instruct the carrier to continue the delivery or to proceed with an intervention on the shipment. The delivery process can then be interrupted to investigate the problem and restart the delivery process if necessary. This eliminates the need to wait for the package to arrive and be examined after delivery to determine if the sample is usable.

The IoT devices are physically attached to the packages to monitor geo-localization and temperature and connected to relay communication nodes that connect to a base station which send the information to the clinical trials company which is monitoring the shipment.

3.2 Blockchain Implementation in Digital Documentation

The logistics documentation is accompanied by a digital version based on blockchain which is a transaction protocol that executes, controls, and documents each event in the reverse logistics flow of the clinical trials supply chain based on the terms of the Smart Contract with the transporters. The information is stored and shared on various servers globally based on the blockchain process. This information is then accessible by the clinical trials company logistics management team.

Blockchain implementation to track and trace logistics and transportation documents, which will allow those with the right to obtain the information about the various actions taken on the transportation documents, for example, who was the last person to view the document or the time when the document was opened. The documents concern the sending and receiving of the clinical trials products. An open-source project

“HyperLedger”, used as a framework for the private blockchain which allows the use of Smart Contracts, has consensus algorithms to validate transactions and maintains confidentiality due to access restrictions. However, the storage capacity is limited and the blockchain does not store the documents themselves, therefore a secure cloud storage is used which is compatible with the blockchain system.

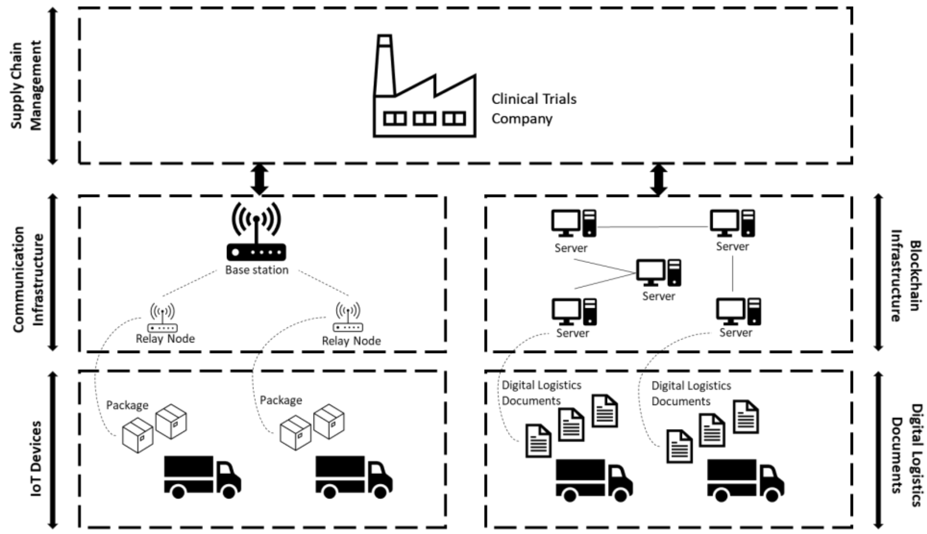

Fig. 1. Framework integrating IoT and blockchain in clinical trials.

The structure of the “HyperLedger” blockchain consists of several nodes (participants) which perform different roles: *Peers*: members of the organization participating in the blockchain network; *Endorser peer*: This type of node performs two important functions within the blockchain. These are the validation of transactions, thus verifying the certifications of the participant who sends a transaction request and the execution of the smart contract. Once the two previous tasks are completed, the endorser peer can approve or reject a transaction; *Ordered peer or ordering node*: this is the node that will receive the block and add it to the blockchain. In addition, this node will forward the approved blocks to the network participants. We define the components using the “HyperLedger” Business Network Definition model: 1) Network Participants: Carriers, Clients, CRO; 2) Assets: Transportation documents for goods; 3) Transactions: Transmission of transport documents when goods are sent and received as well as Smart Contracts. These documents digitally accompany the goods throughout the transport and are exchanged between the network participants.

The process begins by the clinical trials company connecting to the platform using the login information and obtain their certificate that they can use the blockchain. The system creates certificates for all new users. Then the user uploads the document to the platform which is automatically saved in the external cloud storage. A request will then be sent to the *endorser peer* or approved node, to check whether the user uploading the document to the network is certified and has the authorisation to perform this action. Once the transaction is validated, the approved node will call the *ordered peer* to add the new block to the blockchain and then distribute it to all the nodes in the network. After completion of the verification and validation steps, the document is indefinitely saved on the external cloud storage.

The framework integrating IoT and blockchain in a reverse logistics clinical trials supply chain is implemented in a real case and the results are presented and discussed in the next section.

4 Results of implementation

The framework is applied to a CRO with headquarters in Switzerland that specializes in clinical trials and plans to integrate IoT devices onto the shipments and digital logistics documentation based on blockchain in their reverse logistics supply chain. Fig. 2. illustrates the business processes related to the outgoing and incoming logistics of the reverse logistics supply chain for clinical trials implemented in the CRO. Contrary to the typical forward material and information flow of a supply chain, Fig. 2. starts with the outgoing logistics process first in which the CRO requests the medical samples for the clinical trials to be sent to the clients / investigators. They first request the shipment to be picked up from their depots by the transporter. Upon the reception of the order request, the transporter creates and shares a contract proposal to the clinical trials company, which accepts or rejects it. Each step of the digital contract process is based in the HyperLedger blockchain to record each action of the *peers*. If the contract is accepted, the shipment is picked up and delivered to the clients.

The incoming logistics process begins with the clients requesting the pickup of the clinical samples to the transporter. The packaging wears an IoT device monitoring the real-time temperature of the samples and their geo-localisation and sends an alert to the transporter in the occurrence of a problem, which then relays the information to the CRO. The CRO then makes a logistics decision based on the alert information and the geo-localisation, which can include reducing the transportation priority or changing the rest of the transportation journey to express and communicates this to the transporter which makes the necessary changes to the delivery as per the pre-agreements made in the Smart Contract.

The implementation of the new framework that integrates both IoT and blockchain in the reverse logistics process for clinical trials, impacts the entire CRO supply chain, from the outgoing logistics to the incoming logistics processes. The additional steps in the process shown in Fig. 2. are related to the agreement, or not, of the smart contract between the CRO and the transporter that not only outlines the conditions of transportation as in any contract but also covers and controls the relevant logistics activities related to the temperature control and geo-localisation from using IoT devices, as well as the management of the IoT devices themselves. Another notable impact is the decision-making opportunity in the incoming logistics process coming from the information from the IoT devices regarding the real-time temperature of the samples. This allows the CRO to reschedule the planned treatment and reception of the sample if it is considered expired, or to organise express shipment if the data indicates more rapid treatment is necessary. The terms of the Smart Contract also dictate and control the responsibilities and actions required by the parties in these instances. Additionally, all documentation and communication within the logistics process is recorded in the “HyperLedger” blockchain to ensure not only the security of the information but the validity of the data in case of any issues that occur during the transportation and logistics.

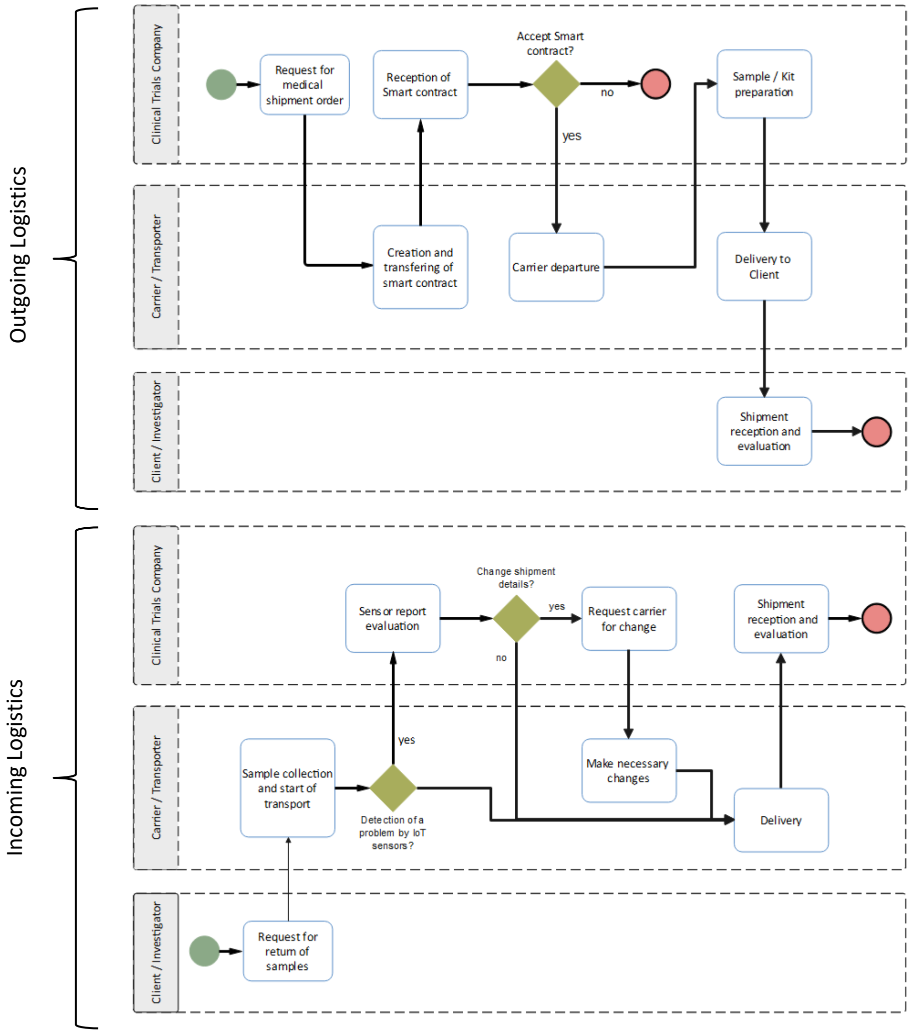

Fig. 2. Business Process Map of Reverse Logistics process for Clinical Trials integrating IoT Devices and Blockchain

5 Conclusion

This paper proposes a new framework that integrates IoT and blockchain technology in the reverse logistics supply chain for clinical trials. The novelty lies in the combination of both IoT and blockchain in this unique context of contract research organisations (CRO) specialising in organising and running clinical trials. The framework is implemented in a CRO in Switzerland and the resulting dynamic processes are presented and discussed.

The most remarkable impacts on the CRO supply chain include the decision-making opportunity based on the data originating from the IoT devices in the incoming reverse logistics flow, as well as the integration of Smart Contracts which automatically execute the code in the blockchain ledger when the conditions regarding IoT data is triggered in the contract. The digitalisation of the information flow derived from the combination of the IoT with the blockchain allows CRO to more efficiently manage the material flows and internal processes pertaining to clinical trials.

On the other hand, clinical trials require a high level of confidentiality which is the reason for using a private blockchain, HyperLedger, however it generates high usage costs as each transaction is invoiced. The costly nature of using a private blockchain may deter other CRO to consider such a framework. Consequently, a direction for future research may be to design an alternative process that reduces the number of transactions and cost. Another direction for future research is to appropriate the framework in the pharmaceutical and medical devices industries which have comparable logistics requirements to CRO.

6 Acknowledgements

This work was supported by the Swiss National Science Foundation under project n° [176349].

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