# Development of A Blockchain Framework for Virtual Clinical Trials

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**Abstract**

*Clinical trials are essential for discovering new treatments, but there are multiple challenges to patient recruitment, patient engagement, and cost containment. Virtual clinical trials (VCT) are an innovative approach that provides potential solutions by conducting home-based, rather than site-based, clinical trials. Virtual clinical trials are still the exception rather than general practice due to technical barriers. "Blockchain," a distributed ledger technology, is a perfect match for virtual clinical trials. Its peer-to-peer design, security settings, and data transparency meet the needs of many healthcare applications. The programmable "Smart Contract" feature makes blockchain more suitable and feasible for VCT by solving computational issues. Our previous work has shown the power of applying blockchain to clinical trial recruitment. This work develops a comprehensive blockchain framework, with simulations and case studies, including patient recruitment, patient engagement, and persistent monitoring modules.*

**Introduction**

Clinical trials are a cornerstone of treatment discovery because they provide comprehensive scientific evidence on the safety, efficacy, and optimal use of therapeutics[1, 2]. However, traditional clinical trials face multiple challenges related to patient recruitment[3], patient engagement[4], and cost[5], as listed in Table 1. Clinical trials can't begin without adequate subjects, which may cause the study timeline to double or even fail to start if recruitment requirements are not met on time[6, 7]. There are many possible causes for this: inefficient advertising models such as flyers or cold calls which do not reach enough potential subjects[8], concerns about non-legitimate trials[9], complex inclusion/exclusion criteria radically reducing subject selection[10], and distant clinical trial sites which deter potential subjects with frequent travels to the site during the trial[8]. Patient engagement can provide insights and experience from patients to allow efficient and patient-centered research[11], taking the patient's objectives, preferences, and values into consideration, but low patient engagement can result in low patient retention and possibly lead to termination of clinical trials[12]. Several barriers make the patient engagement challenging in clinical trials: time and financial cost to travel to the trial site[13], lack of knowledge of the clinical trial so that patients could not have meaningful input[14], and absence of the perception of being a key role in the clinical trials[11]. The increasing cost of clinical trials also becomes a barrier for sponsors to conduct clinical trials. Besides the cost of drug development in the lab, the costs involved with trial site management, administrative staff, site monitoring, and site retention are substantial and rising[15]. These challenges impede the success of clinical trials. 19% of registered clinical trials are either terminated or completed with incomprehensive results[16]. A new type of clinical trial is needed to address these challenges and develop novel treatments for patients.

Table 1 Traditional clinical trials challenges and causes

| Challenges | Patient recruitment | Patient engagement | Cost |
|---|---|---|---|
| Causes | 1. Lack of awareness | 1. Inaccessible clinical sites | 1. Staff and administrators |
| | 2. Distrust of the trials | 2. Lack of literacy on the clinical trial | 2. Site monitoring |
| | 3. Protocol limitation | 3. Passive role in clinical trials | 3. Site retention |
| | 4. Inaccessible clinical sites | | |

Virtual clinical trials (VCT) represent a relatively new approach to conduct clinical trials solely through digital health platforms to make participation transparent for subjects[17]. Compared to traditional clinical trials, VCTs have three major advantages: 1) improving recruitment by maximizing opportunities for patients to participate at their homes rather than traveling to the clinical trial sites, which is particularly important for patients with mobility issues or who

live far from trial sites[18], 2) keeping subjects engaged throughout the study and providing a patient-centered approach through real-time data collection[19], and 3) preserving cost-effectiveness by minimizing money and time patients spend traveling to clinical trial sites[20] and reducing the cost of managing clinical trial sites for sponsors although assistance in the registration and education of patients by clinical sites is still required[15]. Pfizer pioneered the VCT using web-based platforms to conduct randomized clinical trials[17]. The VCT has had limited success and has failed to recruit enough subjects[21], but has shown a degree of success on the feasibility of home-based VCTs by distributing drugs in a double-blind study and using digital health platforms for data capture. Despite numerous benefits, VCTs remain the exception rather than general practice due to several persistent challenges: 1) an immature recruitment model reaching insufficient numbers of patients[20], 2) patient privacy and data security concerns caused by sharing health information over the Internet[18], 3) technical challenges in developing a distributed patient engagement and monitoring platform[20], and 4) cultural barriers such as skepticism about the technology or lack of computer literacy[18]. Considering these challenges and features, blockchain technology could be a perfect match for VCT.

Blockchain is an open-source distributed ledger technology, mostly known to the public because of its success as the backbone of the Bitcoin cryptocurrency[22]. The features of blockchain – security, immutability, decentralization, and anonymity – are a good fit for the needs of healthcare applications[23]. Previous studies have proven the feasibility, stability, and robustness of the blockchain model for healthcare applications[24, 25]. Our previous work utilized the features of blockchain for Health Information Exchange (HIE) and clinical trial recruitment to solve patient recruitment issues[26, 27]. This work provides an inclusive framework that contains the previous patient recruitment module to ensure the completeness of the VCT process but focuses more on new modules of patient engagement and a persistent monitoring module to achieve effective, secure, and patient-centered VCTs. Our previous approach to achieve HIE relies on the blockchain to manage only the records-retrieval permissions granted by patients to healthcare providers[28]. After permission is granted, multiple clinical sites provide secure portals off the blockchain to proceed with data exchange. In this work, the patient engagement module also contains the process of data exchange but purely relies on the blockchain to provide a patient-centered, secure, efficient, and anonymous data delivery from subjects to sponsors. The new persistent monitoring module detects anomalies over time to provide patients a better understanding of their health conditions. This increases engagement and can support real-time alerts for emergency situations. The persistent monitoring module can also provide the authority, the sponsor, and the subjects a comprehensive report generated directly from the data stored in the blockchain.

Blockchain is a peer-to-peer network based on the consent of all users, without the management of a third party. The blockchain built for Bitcoin is called a "public chain," which means any user can join the system without any permissions[26]. A "private chain" or "permissioned chain" requires permission from the initiator to join the system[26]. In the VCT scenario, if there is an authority such as the Food and Drug Administration (FDA) to start the system, participants such as clinical trial sponsors and clinical trial sites must prove their identities to the FDA before they can join the system. This ensures that all participants in the private chain are legitimate. All transactions that have occurred in blockchain are publicly auditable by any users in that blockchain. This feature can ensure that users in the private blockchain designed for VCTs receive all the recruiting information[29]. Blockchain is considered an "un-hackable" system with unique security features to protect data security[30]. Each blockchain generates a public key and a paired private key for users to represent their identities. This protects patients' privacy. All transactions must be signed with the user's private key. There is an auditing mechanism inside the blockchain for all users to automatically validate whether the sender's public key and private key have been matched, without revealing private keys. All the information can be tested for legitimacy to eliminate the possibility of dishonest clinical trials. The data inside the transactions are only accessible to the sender and the receiver to prevent data breaches. Blockchain has an immutable feature that ensures data consistency and prevents any later changes to the data.

Applying the original blockchain for the VCTs can protect the data security and patient privacy, ensure data consistency, and publicize the information to all the users. The Ethereum blockchain keeps all original blockchain features and adds a new function called a "smart contract" which makes blockchain more suitable for healthcare applications. A smart contract is a self-executing protocol running on blockchain to regulate transactions[31]. Smart contracts in Ethereum can be coded to solve any computational problems since they are coded using Solidity, a Turing-complete language[32]. For example, a data analytics tool can be coded inside the smart contract to do real-time anomaly detection during the VCT. Sponsors or the VCT authority (such as the FDA) can ensure timely medical assistance for patients.

This work demonstrates the feasibility and robustness of applying blockchain to VCT by implementing a functional blockchain system with multiple smart contracts. We have also conducted simulations of the VCT process, from patient recruitment to persistent monitoring of anomalous patient outcomes. To achieve efficient VCT using the

blockchain model, we need to make the following assumptions: (1) the clinical trial authority, each healthcare facility, and each sponsor provides at least one blockchain node, which can be any electronic device that can install the blockchain system; (2) patients opt-in to the system; (3) all participating parties have an administrator to operate the system; (4) patients and administrators input their data correctly.

**System Design**

We implemented a private Ethereum blockchain framework, shown in **Figure 1**, consisting of three different modules to simulate the VCT process: (1) *Patient Recruitment* module: a smart contract that automatically matches potential subjects, asks matched patients for consent to join the VCT, and generates a specific trial contract for each VCT that is only accessible to the participants. (2) *Patient Engagement* module: a smart contract to allow patients to input data and interact with clinical trial sponsors or principal investigators, and (3) *Persistent Monitoring* module: a smart contract to persistently monitor anomalies through the analytics tool, either installed on the sponsor's node or embedded inside the monitor contract.

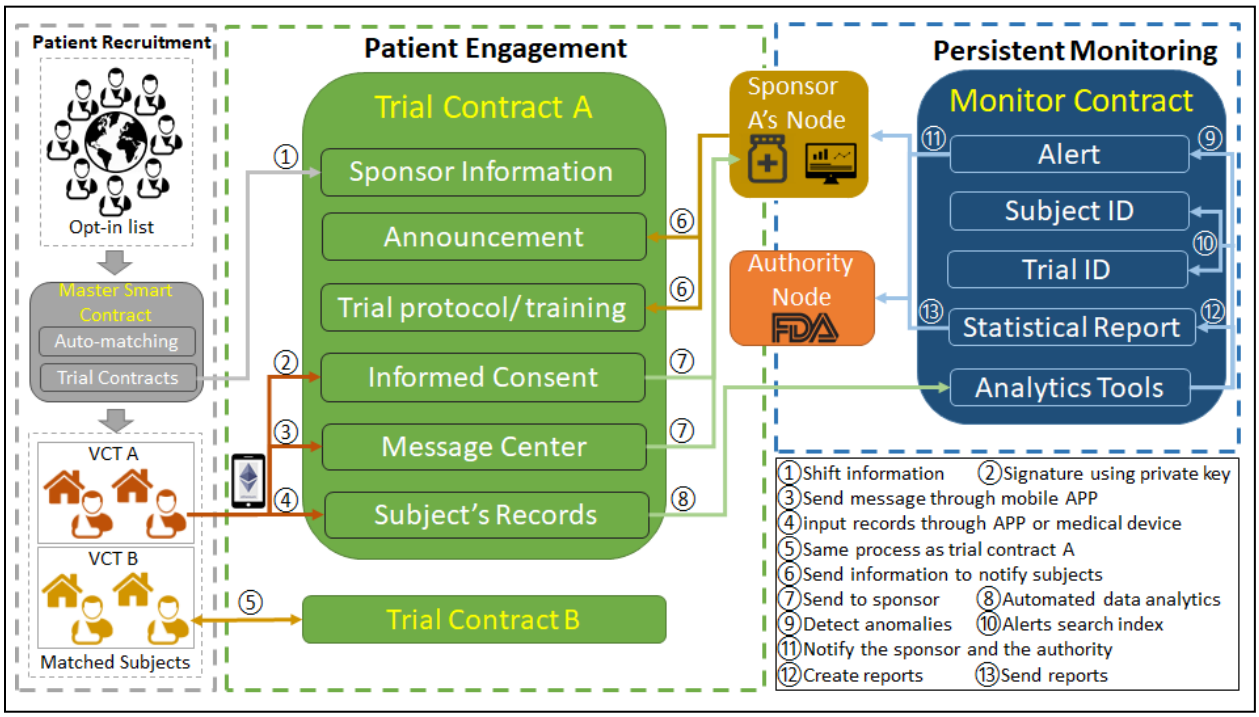


**Figure 1.** Blockchain framework with multiple smart contracts across three different modules: patient recruitment (based on prior work), patient engagement, and persistent monitoring

*Environment Setup*

Our blockchain system requires the authority, each VCT sponsor, and each clinical site to provide a blockchain node. We have packaged the setup process into an executable program for the authority node to initiate a unique private blockchain. All other parties receive permission through a JSON file that contains the information of the private blockchain from the authority, then deploys the file using the user's blockchain node. After the setup procedures, all the nodes are in the same blockchain network and can communicate with each other. When a blockchain node joins the blockchain, a blockchain account with a public/private key pair is automatically generated for the system administrator. Patients go to clinical sites to opt-in the system to prove their identities, and to get orientation on operating the system. The clinical site administrator creates a blockchain account for the patient and links their information to the blockchain account with their consent for future subject matching. Patients can add biometric information to their accounts for future authorizations.

Two smart contracts, a "master smart contract" which is mainly used for patient matching, patient recruitment, and trial contract generation, and a "monitor contract" which is used for persistent anomaly monitoring during the VCT, are automatically deployed after the authority builds the blockchain. Web-based graphical user interfaces (GUIs) are

implemented on each blockchain node for users to interact with the smart contracts. Patients can use GUIs through their smartphones or home computers to participate in VCTs.

*Patient Recruitment*

When patients opt-in to the system, their primary visiting histories are input to the smart contract by the clinical sites, including demographic information and primary diagnosis and treatments from each visit. These records are used for primary subject matching. The authority node automatically extracts the inclusion/exclusion criteria from the clinical trial database and inputs to the master smart contract after a VCT is approved. Patient matching is a two-step process: first, the master smart contract automatically matches potential subjects using their primary visiting histories; second, clinical sites help the sponsor find precise matches with consenting patients. The smart contract requires patients to provide consent to share their full records with the sponsor if they are primarily matched. If the patient is fully matched the smart contract sends a notification to the patient asking for consent to join the VCT and permitting them to access the trial contract. This recruitment module can save time for patients by only checking the potential matched clinical trials rather than browsing all recruiting trials. The VCT's information is input by the authority which eliminates the concern of scam trials and "spearphishing" for the patients. As shown in Figure 1, the potential subjects for each VCT can be matched from registered users all over the world through the master smart contract. Matched patients can engage in the VCT through the trial contract automatically generated by the master smart contract. More details of implementation and simulation results can be found in our previous work[27].

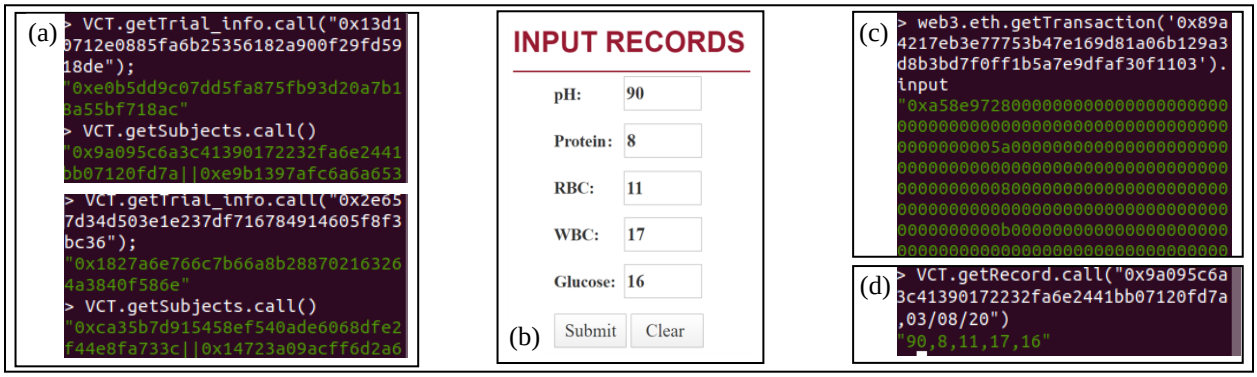


**Figure 2** (a) Trial contract information retrieved by the trial sponsor through the blockchain console, (b) GUI for patients to input data manually or from a connected medical device, (c) scrambled patient records retrieved by unauthorized users through the blockchain console, (d) the patient record retrieved by the sponsor through the trial contract function by inputting the patient's blockchain ID and the input date

*Patient Engagement*

The master smart contract automatically generates a random ID for the VCT and a pre-coded trial contract if the VCT is approved. The trial contract's information is stored in the master contract for management. Only the sponsor, the authority, and matched subjects are granted access to the trial contract. Other users will not see the contents of the trial contract. We supported two simultaneous ongoing VCTs in our simulation. Figure 2(a) shows the information included in two trial contracts and their access list within our simulation. The upper figure shows the trial contract address and subject list for VCT 89938. The lower figure shows the information for VCT 71115. Only the listed users have access to the trial contract. Other users are not able to execute any functions through the trial contract. These figures show the result of inputting commands through the blockchain console using the corresponding sponsor's blockchain account. The sponsor inputs the informed consent form to the smart contract for the subjects to sign digitally using their private keys. After signing the consent form, patients can have access to the other functions of the trial contract, such as getting the trial protocol and training, getting announcements from the sponsor, and sending messages to the sponsor or principal investigators, and inputting health information, as shown in Figure 1 ②-⑧. Patients input their measurement records to the blockchain through the web-based interface, mobile app, or even automatically from a connected medical device. Figure 2(b) shows the GUI for patients to input their measurement records. After the record is input through the GUI, it is automatically sent through a transaction in the blockchain. The patient's records are automatically encrypted by the sponsor's public key and can only be decrypted by the sponsor's private key. The sponsor can automatically view this decrypted record through the GUI for trial management. However, since all the transactions are publicly auditable, other users can still see the transaction through the blockchain console. Figure 2(c) shows the patient record as viewed by an unauthorized user; without the sponsor's private key the input data is

unreadable. Figure 2(d) shows the patient records retrieved by the sponsor from the blockchain backend console by inputting the patient's blockchain account and the input date. This process only shows the security setting for the data exchange platform. Users can always choose the user-friendly interface to operate the system.

Blockchain in the patient engagement module provides the function of an electronic data capture system that is designed for the collection of clinical data during clinical trials[33]. Patients can input their data through the GUI in the format defined by the sponsor. All records are securely stored in the blockchain and can only be retrieved by sponsors. This blockchain framework can serve as a general platform used for all VCTs through the unique trial contract without third party management. Sponsors can develop their VCT applications to improve patient engagement through quality evaluation for the application design, such as the COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN)[34]. Our blockchain framework is expected to enhance patient engagement in the following three aspects: 1) Informing patients[35]: VCT application deployed on the blockchain through trial contracts is accessible for participants. In addition, trial updates will be delivered to patients timely through the blockchain; 2) Engaging patients[36]: patients can access their trial records anytime through the trial contracts, which act as a patient portal to provide the functions for patients to interact with principal investigators and sponsors; and 3) Empowering patients[37]: in this platform, patients are not only data points but also involved in the trial by interacting with the principal investigators and sponsors to express their feelings about the trial through anonymous secure messages using the trial contract.

*Persistent Monitoring*

This module contains two parts to persistently monitor the subjects' physical conditions and the VCT status. The first part is alert creation when anomalies are detected and the second part is statistical report generation after the clinical trial is finished, as shown in Figure 1 ⑨-⑬. Subject records can be retrieved by the sponsor with a log file stored in the blockchain. The monitor smart contract will automatically use the analytics function to analyze the patients' records inside the blockchain when a new record is input to the system and generate a periodic report of all patients which is viewable by the authority. As all the transactions are publicly auditable, the analytics process is also under the authority's surveillance, which eradicates the concern of tampering with data in the sponsor's final report.

When an anomaly occurs in a patient's record, such as lab test results outside pre-defined threshold values, as shown in **Figure 3**(a), or an abrupt change of previous records, or a severe vital sign measurement values, the smart contract automatically sends an alert to the sponsor for immediate action. This action may include sending a notification through blockchain to the patient to ask whether the change is caused by human error, having a clinician communicate with the patient to provide medical help, or even calling an emergency telephone number after locating the patient through the registered clinical site. **Figure 3**(b) shows the alert received by the sponsors and **Figure 3**(c) shows the patient's GUI when they received the alert. This protects patients' safety while obtaining their acknowledgment of their physical condition during the VCT.

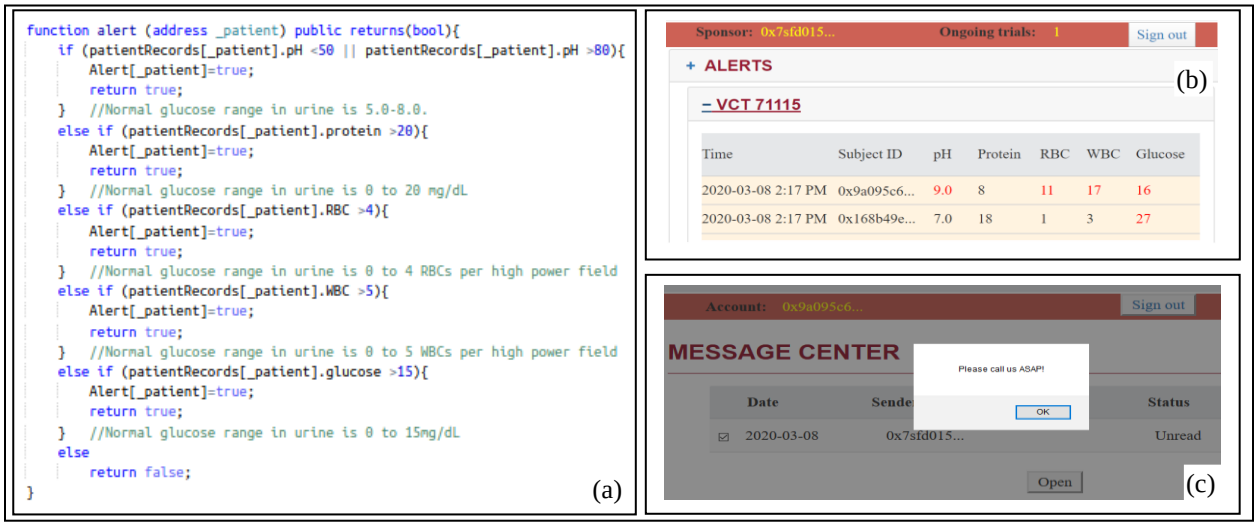


**Figure 3** (a) an alert system defined in the smart contract to detect abnormal values, (b) the GUI for sponsors to receive alerts during the clinical trial. Abnormal values are marked as red font automatically, (3) the GUI for patients to receive messages from sponsors.

The monitor contract can also trigger an analytics tool installed on the sponsor's node and keeps a log of data use in the blockchain. The tool can be a basic comparison model as shown in **Figure 3**(a), a simple statistical model to summarize the effectiveness of the new treatment, or even a sophisticated machine-learning model with AI components to detect comorbidities and predict outcomes depending on the needs of the sponsor.

**Simulation and case study**

We have simulated the patient engagement process using our system to test the feasibility, security, and efficiency of this system. We deployed six physical nodes using Intel NUC machines representing one authority node to initiate the private blockchain environment, two sponsor nodes to start two different VCTs simultaneously, and three different clinical site nodes for patient registration. We set up 1,000 synthesized patient accounts on each clinical site's node and randomly chose 3,000 patient records from the MIMIC-III (Medical Information Mart for Intensive Care) Clinical Database for our simulated patients[38]. We used MIMIC-III for this simulation because it contains lab test data for each patient visit. The commonly encountered lab values selected for this simulation were urine tests for pH, protein, red blood cells, white blood cells, and glucose. For the purpose of this simulation, we assumed that the subjects were performing the tests at home with a medical device that automatically inputs the data to the blockchain. Each simulated VCT randomly enrolled 1,500 patients distributed over three clinical sites. We created a script to send records from each patient's account to the smart contract for the corresponding trial contract. The script recurrently sends 10 patient test results to the smart contract every second for 24 hours, which simulates 288 days of VCT with 864,000 transactions in total. The average time for the sponsor to receive the data is 8.31 seconds.

We have created pre-defined thresholds for each test item in the smart contract as shown in Figure 3(a). The case study tests the alert system provided by the persistent monitoring module; after each record is input by the patient, the monitor contract automatically detects abnormal values and sent an alert to the simulated sponsor. There were 95,934 alerts in total, at an average of 1.17 seconds after the data was sent to the smart contract. By the end of the simulation, the monitor contract had generated statistical reports for two VCTs for the sponsor and the authority to review. Statistical reports can also be generated for individual subjects to have a better understanding and engagement of the VCT. Subjects can check the statistical reports based on different test items throughout the VCT so that they can acknowledge the long-term trend of their physical condition, as shown in **Figure 4**(a). Comparing to the overall statistical report, as shown in **Figure 4**(b), subjects can have a better understanding of the VCT outcomes such as efficacy and safety of the treatment. These graphs were generated by passing the values from the blockchain to the Google chart application programming interface from the monitor contract.

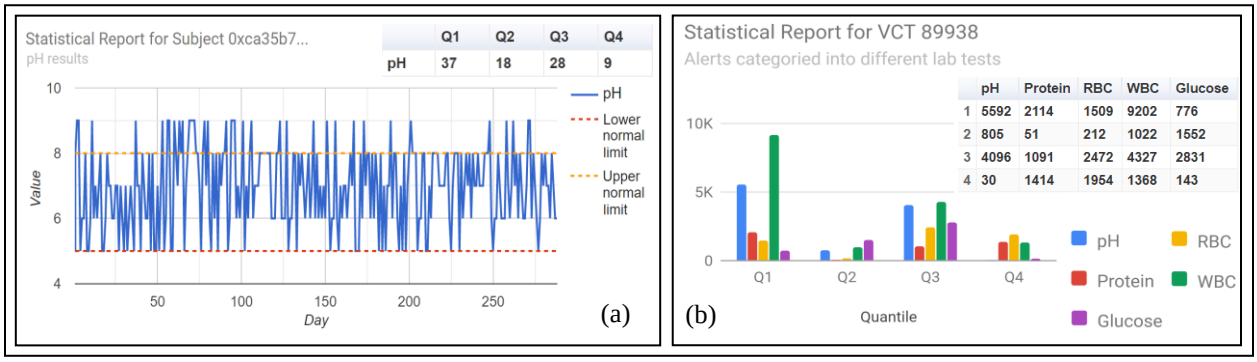


**Figure 4 (a)** Statistical report of pH test of an individual subject with normal limit labeled. Subjects can acknowledge the long-term trend based on occurring anomalies and the comparison of the VCT report, **(b)** the statistical reports on the total alerts received on abnormal values in VCT 89938. The alerts have been divided into four quantiles of the studying period to show change over time.

**Discussion**

Our simulation shows the feasibility, stability, security, and robustness of applying blockchain technology to achieve better patient engagement and persistent monitoring during VCTs. Compared to traditional clinical trials, our simulation proves blockchain-based VCTs have a more efficient and secure patient recruitment process, a more patient-centered engagement platform that uses patient involvement to move the clinical trial forward by distributively collect health information, a better automated data analytics tool embedded in the system that can detect anomalies in patients' records in real-time, and better security to minimize the risk of tampering with records to manipulate

statistical reports at the end of the clinical trial for subjects, sponsors and the authority to have a better understanding of the VCT outcomes. The alerting system shown in the simulation empirically proves the practicability of real-time detection of anomalies. In the real VCT cases, subjects with different medical histories may have different reactions to the treatment so that subjects under the normal physical condition may have some test values exceeding the normal limits. To be specific, the normal limit of the glucose value in urine is 0-0.8mmol/L. However, there is a high possibility for a newly diagnosed type II diabetes patient to have glycosuria in the short term under the current treatment as taking metformin or insulins. Therefore, the sponsors or PIs can personalize the alerting mechanism by adjusting the trigger limits through the smart contract depend on the treatment effect on different populations. Since blockchain is a distributed ledger technology, subjects can participate from any place at their convenience, removing the burden of traveling to clinical sites.

Multiple smart contract settings optimize the clinical trial process and management. The master smart contract registers all patients who opt-in to the system, generates trial contracts for VCT management, and automates patient matching and recruitment. Patients are added to different trial contracts to conduct future VCTs after being matched. Trial contracts are accessible only to the participants in order to protect data privacy. Patients can use a patient-centered interface to engage with clinical trial sponsors through trial contracts. Rather than only being a data point in the system, patients contribute their conditions and insights to sponsors and the trial authority. The monitor contract persistently monitors the physical condition of each patient and the effects of the treatment. Subjects receive timely medical assistance if they report anomalous measurements or a health emergency during the VCT. Using the monitor contract to general the final report eliminates the concern of tampering with trial results.

The simulation mainly simulates the data input process, which is the core process in the VCT. To test stability and efficiency, we synthesized multiple patient records with test values in each record. This meant that each transaction contained lab test results so the final report was not statistically interpretable. In real-world scenarios, the monitor contract can generate contingency tables to test treatment effectiveness by using the chi-square test. Machine learning tools can also be installed on sponsor nodes and can be triggered by the monitor contract to provide more powerful real-time analysis, such as adverse-effects detection and prediction of possible outcomes.

The main limitation of this work is the patient recruiting process which still relies on clinical sites to prove patients' identities, perform precise matching using patients' records, and educate patients about VCTs and how to use the applications on the blockchain. The system needs a reward mechanism to offer incentives for clinical sites to participate. A business model must be developed with the cooperation of sponsors, clinical sites, and the authority. Another limitation of this work is the adherence of participants. A reminding system can be built on the blockchain to notify the patients who have not submitted the test results on time. However, it is beyond what blockchain is capable of achieving to provide a solution to enforce patients' compliance with the protocol.

**Conclusion and Future work**

Compared to traditional clinical trials, VCTs have shown multiple benefits in removing burdens from patient recruitment and patient engagement, as well as in reducing the cost. Blockchain, an emerging technology with unique features such as security, transparency, immutability, decentralization, and anonymous, provides potential solutions for VCTs' challenges. This study has developed a comprehensive framework that provides generic smart contract functions for VCT applications. The framework is flexible for application development for different VCTs. Sponsors can develop customized VCT applications using the blockchain framework and evaluate usability through the trial contracts. Our simulation demonstrated the feasibility and stability of using the proposed blockchain framework with the blockchain security property which is well-recognized. Our future work will continue to evaluate blockchain protocols to improve performance and will deploy blockchain frameworks for different healthcare applications.

**Acknowledgments**

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