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FEATURE

ESSAY

Blockchain's potential to improve clinical trials—an essay by Leeza Osipenko

There's more to this tamperproof technology than bitcoin. It could be used to improve the administration of clinical trials, ensuring transparency and yielding better quality data, writes **Leeza Osipenko**

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Blockchain is the digital technology that underpins cryptocurrencies such as bitcoin (box 1). In essence it uses cryptography to guarantee that multiple sets of the same data, held by separate users, are identical.

Box 1: What are blockchains and smart contracts?

Blockchain is a way of managing data that prevents their manipulation.[1] A new "block" of data records each specific event. Each block is time stamped and includes cryptographic information (a "hash") from the previous block. These hashes link blocks securely to form chains, making data modification impossible without changing the entire chain.

All users in a network have their own copy of the blockchain. This decentralisation of data enables transparency and further security, because any modification has to be sanctioned by all users.[1] Current, centralised ways of managing data lack such assurance.

Blockchain cannot protect from errors when data are entered, but it can ensure the provenance of data and improve transparency. Erasing blockchain data is impossible, so data can be updated or modified only by adding new blocks, and any obsolete blocks will remain.

Smart contracts are versatile computer algorithms mandating that all users follow prespecified rules for a given task,[1] without the need for centralised supervision or inspection. For example, smart contracts could replace many activities in auditing clinical trials. Currently, auditors ensure that specific documents are in order before an investigator can begin a trial. A smart contract could be coded to mandate that patient enrolment cannot begin before all documents are uploaded.

Blockchain's underlying technical features make no difference to users, who interact with a conventional web based interface for entering and retrieving data.

Blockchain's applications in finance have given it a questionable reputation because many hyped cryptocurrency projects have failed. But blockchain has some features that could, if applied well, improve the quality of clinical research.

Data from clinical trials belong to a sponsor, an academic, or a charity. Even data from publicly funded research are not public property, and accountability for transparency and impartiality can be lacking. Most patients and their carers never find out how trial participation informs clinical practice or further research.

Clinical trials are prone to research misconduct, data falsification, or simply unintended errors.[2-4] Trials often deviate from prespecified protocol or may record inaccurate case histories.[5] The extent of these problems is difficult to quantify,[3] but—along with inappropriate trial design and data analysis, under-reporting of results, and publication bias—it leads to significant waste in clinical research.[6 7] Legislative, cultural, and practical solutions are needed.

Blockchain offers a technical solution that could eradicate data manipulation, improving the transparency, security, quality, and efficiency of clinical trials as well as the auditing of data and processes.

Running trials using blockchain

Today's centralised data processing and storage systems cannot ensure data security and integrity. Servers can be hacked, and data can be corrupted. Users with access to databases can tamper with data, and it may not be possible to find out who changed records and when. Blockchain could solve these problems.

Blockchains can be public or private. Because clinical trials concern sensitive information they would use a private blockchain network including all parties who are conducting, auditing, analysing, and assessing the trial. Data would be visible only to participating regulators, academics, independent assessors, sponsors, and funders.

The smart contracts that blockchain facilitates could also improve quality control and trial efficiency (box 1). These algorithms could replace some functions of third parties such as auditors and contract research organisations by verifying data or confirming that particular actions have occurred.

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Smart contracts can be configured to streamline complicated processes. For example, they could mandate that users enter data on the blockchain according to a prespecified sequence of events. This could reduce missing data and improve trial quality. A smart contract could dictate, for example, that an investigator must log a record of a patient's outcome, or a patient's absence, on day 28. If this does not happen the system could alert all users in the network and require data entry before the next step (say, the entry of outcome measures on day 56).

Could it work?

Blockchain is already used successfully in supply chain logistics, entertainment, insurance, and other applications[8]—but not in clinical trials. The drug and medical device industry may lack interest because blockchain is unlikely to translate into profits. And public sector organisations are notoriously slow to adopt new technology, even though regulators and funders mandate integrity and transparency of trial data. As a result, blockchain's potential in clinical trials remains theoretical, but proofs of concept exist.

Wong and colleagues developed a blockchain prototype for a completed trial of omalizumab. They showed how the technology could have been used in trial governance and data management.[9] A simulated corruption of a trial record showed how easily data on blockchain can be checked for tampering without having to inspect each file. The work showed how cryptographic labels attached to transaction records can ensure security of data.

In a similar approach, Nugent and colleagues used modelled data representing trials of oseltamivir to show how blockchain can eliminate data manipulation and provide an immutable record of a trial's history.[10] They also showed how the state of the data can be queried to show the number of trials under way, the number of participants recruited to each trial, and the user making each transaction, resolvable to a specific contract research organisation. Current systems, even those that allow such detailed inquiries, cannot guarantee the provenance of data.

Another proof of concept study used a blockchain system to collect participants' consent for inclusion in a trial. Benchoufi and colleagues piloted smart contracts to mandate a pre-programmed order for trial events: for example, patients had to be enrolled before they gave consent, and case report forms had to be analysed before freezing the database on completion of the study.[11]

Events and outcomes

Blockchain could also improve other aspects of clinical trials, including adverse event reporting and endpoint adjudication. Regulators require drug trial sponsors to report any serious adverse events. But inefficient processes involve several steps, and many problems are cited by academia, industry, and contract research organisations,[2] including the bureaucratic burden and poor quality reporting. Blockchain with smart contracts could ensure that only reports meeting set criteria are submitted (such as specified by US federal regulations). This could decrease the number of uninformative reports and improve detection of valid safety signals. Using blockchain, reports could go directly to the regulator, without a contract research organisation intermediary.[9]

Incorrect classification of trial outcomes can reduce power and lead to biased estimates of a treatment effect.[12] Endpoint adjudication should be performed throughout trials. Once an investigator uploads a scan, an endoscopic video, or a clinical summary, a smart contract could ensure that it is sent to prespecified independent experts in the blockchain network to obtain their conclusions. For complex endpoints a review of many data sources (such as investigator reports, safety summaries, local and central laboratory data, hospital attendance records, and case reports) may be required to establish that the event has occurred.[13] The smart contract could include quality assurance to require that the investigator and independent assessors follow the same steps to detect the event or to determine that an endpoint has been reached.

A blockchain network could mandate many features of universal good clinical practice in processes and forms without third party audit. Smart contracts could allow auditing of each step in a trial according to protocol or other requirements. Regulators could be automatically alerted about non-compliance. Such advances could increase quality control, improving reliability, transparency, and reproducibility.[11] Eventually, observational studies, registries, genomic studies, and so on could also be managed using blockchain.

Embracing integrity in clinical research

Blockchain would be unable to improve many of the weaknesses in clinical trials (box 2), but its impact would be maximised if implemented with other reforms. Regulators, funders, and policy makers must challenge the status quo in clinical research. All trial protocols, including detailed plans for data analysis, should be pre-registered, peer or regulator reviewed, and published online before the trial starts. Deviations from protocol should be documented and explained in full. Data should be analysed in parallel by the sponsor and by independent groups, using clearly reported and replicable methods and according to prespecified hypotheses. Results should be factually reported, to minimise publication and interpretation bias.

Box 2: Blockchain's potential for clinical trials

Blockchain could:

- Improve data quality and completeness
- Prevent data tampering
- Ensure proper per protocol trial execution and governance
- Prevent endpoint switching
- Enable efficient information sharing (such as adverse event reporting, patient consent, or conflicts of interest)
- Improve integrity of outcomes data evaluation (endpoint adjudication), and
- Deliver the complete dataset to each stakeholder for parallel analysis.

Blockchain cannot:

- Advance the quality, rigour, and rationality of trial design
- Alleviate poor use of methods for data analysis
- Avoid hypothesising after the results are known
- Resolve methodological issues in endpoint adjudication
- Prevent data entry errors
- Ensure timely reporting of results, or
- Change stakeholder incentives.

Unfortunately, substantial incentives not to increase transparency and data integrity in medical research persist. Industry believes in data ownership and confidentiality because its proprietary analyses and strategic releases of data regulate share prices. Many academics receiving public funds feel entitled to own and analyse the data from their research. But overwhelming evidence of bias exists when commercial or academic investigators analyse and report their own findings.[3 4 6]

Today, data provenance and integrity cannot be assured even by allocating analysis to third parties. Blockchain could deliver

assured datasets to independent parties for analysis. This would separate the merit of doing a trial from its results and would allow researchers to focus on ideas and methods. In analyses that include more than a single trial or contain data from other sources, blockchain could make data compilation simpler.[9] In these collaborative initiatives the anonymised raw data could be shared, and blockchain would provide reassurance that records had not been tampered with.

Control of implementation

"Blockchain" has become a buzzword. Some entrepreneurs and researchers evangelise its promise of innovation, but others are turned off by the hype surrounding the technology. Blockchain sceptics warn about high costs. Indeed, when used with cryptocurrencies, blockchain deliberately uses resource intensive calculations to mint new currency. But blockchain solutions for clinical trials[9] do not need these slow and costly "mining functions."[10]

Blockchain solutions are evolving rapidly, becoming cheaper and more versatile. Any new technology can be slow to yield benefit. Whatever destiny awaits blockchain in clinical research, its implementation will be subject to technical, financial, and market driven risks; however, the major impediment is likely to be sociopolitical.

Policy change is notoriously difficult. In the past 20 years we have made much progress in increasing the bureaucracy and complexity of clinical research[14] but little in improving its quality, efficiency, and accountability.[6 7] Even when we succeed in introducing new policies their enforcement has often been interpreted as optional. Regulators are not collecting fines for trial non-reporting, for example, and pre-registration of protocols is still lacking.[7 15]

Patients taking part in clinical trials deserve every record to be counted, appropriately handled, and independently assessed. Increased transparency and data integrity would help to accomplish this. The remit of regulators and the funders of non-commercial research is to protect and advance public health—and therefore they, rather than industry or academia, should lead blockchain's implementation in managing clinical trials.

Biography

Leeza Osipenko has a background in systems engineering and health technology assessment. She was a head of scientific advice at the National Institute for Health and Care Excellence in 2014-18. She is currently a senior lecturer in practice in the department of health policy at the London School of Economics.

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