METHOD ARTICLE

REVISED Blockchain protocols in clinical trials: Transparency and traceability of consent [version 32; referees: 1 approved, 1 not approved]

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| This article is included in the | All trials matter collection channel. |

Abstract

Clinical trial consent for protocols and their revisions should be transparent for patients and traceable for stakeholders. Our goal is 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. For that, we will built a consent workflow using a rising technology called Blockchain. This is a distributed technology that brings a built-in layer of transparency and traceability. Additionally, it removes the need for third parties, and gives participative control to the peer-to-peer users. From a more general and prospective point of view, we believe Blockchain technology brings a paradigmatical shift to the entire clinical research field. We designed a Proof-of-Concept protocol consisting of time-stamping each step of the patient's consent collection using Blockchain; thus archiving and historicising the consent through cryptographic validation in a securely unfalsifiable and transparent way. For each revision of the protocol, consent was sought again. We obtained a single document, in a standard open format, that accounted for the whole consent collection process: timestamped consent status with regards to each version of the protocol. This document cannot be corrupted, and can be checked on any dedicated public website. It should be considered as a robust proof of data. However, in a live clinical trial, the authentication system should be strengthened in order to remove the need for third parties, here the trial stakeholders, and give participative control to the peer-to-peer users. In the future, we think that the complex data flow of a clinical trial can be tracked using Blockchain, that . Moreover, a blockchain core functionality, named Smart Contract, couldcan help prevent clinical trial events not to happen in the right chronological order: for example including patients before they consented or analysing case report forms data before freezing the database. Globally, we think Blockchain This will help withreaching reliability, security, and transparency, and could be a consistent step towards reproducibility.

REVISED Amendments from Version 21

Mainly, we resize strictly and focus the global scope of the current article. We define what can be directly implemented in a live clinical trial and we sketch what would be the key elements to build in order to achieve a trustless consent process. This discussion is strongly connected with the issue of distributing the cryptographic key generation process which enables authentication.

Also, we suppress from the introduction section the development related to the community empowerment since it supposes to exploit the distributed nature of the network trust and that the actual state of the implementation, especially the cryptographic keys generation, still relies on a third party. We referred this part to the discussion section. Besides, we state more clearly what belongs to the current implementation of the POC and what belongs to more prospective thoughts. We detailed the informations regarding the step-by-step proof of process related to Chainscript and other issues from a security point of view.

The main update consisted in precising the perimeter of the POC, namely we indicate that its focus is on quality of the consent process itself rather than the identity of the individual consenting. However, in a real context, this issue has to be tackled and we discuss some implementable solutions for binding digital identities and physical entities.

See referee responses

Introduction

Patient participation is the *sine qua non* condition for clinical trials to happen and for medical research to improve[1,2](http://www.mc.vanderbilt.edu/crc/workshop_files/2011-09-09.pptx). However, in practice, the informed consent process is hard to handle in a rigorous and satisfactory way. The US Food and Drug Administration (FDA) reports some metrics that are related to the frequency of clinical investigator-related deficiencies, which show that almost 10% of trials they monitored suffer from consent collection issues, such as failure to re-consent when new information becomes available, use of expired forms or non-validated, unapproved forms, consent document not signed or not dated, missing pages in consent document provided to participants, failure to obtain written informed consent, parental permission obtained after child assent, changes made to the consent documents by hand and without IRB approval[3,4](http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM256376.pdf; http://www.yale.edu/hrpp/education/documents/CommonProblemsinInformedConsent_2013_vF.pptx). The study by Seife[5] analysed hundreds of clinical trial FDA inspection documents, covering the 1998–2013 period, and showed that a substantial number of them presented evidence of research misconduct, among which 53% were related to failure to protect the safety of patients and/or issues with oversight or informed consent. This can lead to dramatic events, as in France in January 2016: a trial testing the "BIA 10-2474" as an analgesic molecule caused the death of a participant. The French health agency IGAS appeared to prove that re-consent was not sought after major neurological side effects occurred in some patients, leading to participants being included in the clinical trial without being informed of this issue and still receiving doses of the analgesic molecule, (http://www.liberation.fr/france/2016/02/04/drame-de-l-essai-clinique-a-rennes-le-deces-reste-inexplique_1431074; https://fr.wikipedia.org/wiki/BIA_10-2474, version of 2016.09.05). Another example in the UK occurred when a general practitioner was struck off after testing drugs on patients who did not give their consent[6]. A recent, popular case of serious scientific misconduct was the DECREASE studies performed by Don Poldermans. The results of these studies were invalidated and some related publications retracted as, amongst many other frauds including data invention, informed consent was not proved to have been obtained before the randomised controlled trials (https://en.wikipedia.org/wiki/Don_Poldermans, version of 2016.09.05; http://retractionwatch.com/category/by-author/don-poldermans/).
Obtaining an individual's consent is strictly tied to the Helsinki declaration[7,8](http://www.wma.net/en/30publications/10policies/b3/index.html), which provides the good practices that should follow any stakeholder conducting a clinical trial. Point 26 of the Declaration states that each participant should be informed of the aim, methods, sources of funding, conflict of interests, affiliations

of the researchers, anticipated benefits and risks and post-study provisions, and these conditions must be met to obtain freely-given informed consent. In practice, regulation agencies, such as the FDA, provide recommendations and mandatory commitments for consent to be collected in the right conditions[9] (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf). Among those and of major importance, informed consent should be documented by a signed and dated written consent, which is particularly meaningful with Blockchain technology.

In addition, consent collection is a dynamic process; it is not a one-shot process ending when consent is sought before a clinical trial begins. As explained by Gupta[1], there are circumstances under which consent has to be sought again from a participant, corresponding to any time the trial protocol is majorly revised. This is a fundamental fact when ensuring to patients' rights and transparency of a clinical trial[10,11]. Indeed, as detailed in these Institutional review board (IRB) guidelines (http://www.irb.pitt.edu/sites/default/files/reconsent guidance.pdf; http://www.mayo.edu/research/documents/29-re-consent-or-notification-of-significant-new-findingspdf/doc-10027714; http://www.yale.edu/hrpp/policies/documents/Reconsentingguidance.pdf), there are many situations where patients re-consent has to be sought or where they should be notified of minor trial issues, such as novel risks, significant changes in the research procedures, and worsening of the medical condition. Documents that are to be sent to patients can be consent form addendums, an information letter or a fully revised consent form. Of course, the revised consent form has to be approved by an IRB. It must be stressed that the FDA has highlighted the necessity to conceive a mechanism that ensures that the most recent revised consent form is in use in a clinical trial, and stipulates that timestamping is such an approved mechanism[9] (http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM405006.pdf).

As indicated in Figure 1, consent is a dynamic process that involves a complex circuit of data and interacting actors, which should all retain information of this on-going process. For example: what participants were notified; when the notifications were delivered; whom of the participants consented or re-consented; when did participants consent or re-consent. This information should circulate between the clinical trial stakeholders in real time.

Figure 1. Consent collection Blockchain workflow.

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Blockchain is a dawn-aged technology, a giant public datastore, stored in a secure and decentralised way (see Sotoshi Nakamoto seminal paper, https://bitcoin.org/bitcoin.pdf). It is widely announced to be a backbone of the circulation of digital assets, powering any kind of services by transparency, traceability. In this context, Blockchain's emerging and promising technology (https://en.wikipedia.org/wiki/Blockchain_(database)) can bring solid basis in the enrolment phase transparently to all stakeholders of a clinical trial, especially in the context of obtaining participant's consent. Three core functional principles of this technology can play a fundamental role, as follows:

- 1. Unfalsifiable timestamping information: this stands for proof of existence of any piece of data. When stored, this data is provable and immutable through a strong cryptographic protocol. Moreover, these proofs of existence can be checked on a public website (https://opentimestamps.org, https://arxiv.org/abs/1502.04015). This transparency is of interest to any interested stakeholder.
- 2. Smart contract: this is a contract that is algorithmically implemented and binds any change in the protocol to the patients' consent seeking renewal.
- 3. The decentralized nature of the Blockchain protocol gives to the patient, or more widely to patients' communities, control over their consent and its revocation. The end-to-end connectivity creates a network that empowers patients and researchers as peers.

  The current implementation is an application of the first principle. Ideally, we would have to build a patient authentication system which does not relies on any trial stackholder, this way we can benefit from the decentralised and trustless nature of the blockchain network.

Let's note in a broader clinical trial setting that it follows directly from the secure timestamping functionality that Blockchain can help prevent from a posteriori reconstruction of endpoints or outcomes in clinical trials, (http://www.bgcarlisle.com/blog/2014/08/25/proof-of-prespecified-endpoints-in-medical-research-with-the-bitcoin-blockchain/).

Blockchain comes into play

At a clinical trial level. Blockchain technology can act as a SafeGuard for the complex and wide range of actors required in clinical trials. In practice, the proof of existence for consent will be timestamped and stored in Blockchains, enabling clinical research stakeholders, such as sponsors, investigators and IRBs, which can be numerous in multi-center clinical investigations, to share consent and re-consent related data in real-time, and archive and historicize consent sets, which can be matched with each revision of the protocol. ~~Obtaining consent must be a 'lock' before participant inclusion in clinical trials. Indeed, with the help of Blockchain cryptographic keys, investigators won't be able to include a patient in the trial until their consent is collected. In addition, to ensure a strict parity between enrolled patients and included patients, the present study will use one core functionality that Blockchain enables: the Smart Contract (https://en.wikipedia.org/wiki/Smart_contract, version of 2016.09.05). This is a piece of code that holds a programmatically written contract between as many parties as needed, without any third-party, which executes algorithmically according to the terms provided by the contracting parties. This makes it possible to build a Smart Contract that will be executed with the only condition that patients will only be included when the enrolment is complete (technically, every Blockchain transactions can have a lock associated to them and transactions can be pending and triggered at an agreed upon contract time).~~

At a patient level. Implementing a "privacy by design" technology, and archiving securely and transparently any dataset that needs to be stored, is a game changer towards improving enrolment phase methodology. Moreover, drawing on <u>ways to collect securely and transparently</u>~~an entirely new way to collect~~ informed consent, being careful with participants rights, and so empowering them, could improve the enrolment rate. Indeed, the participation rate to clinical trial remains quite weak[10]. Caldwell & All performed a systematic review comparing different enrolment techniques, and showed that, amongst several other explanations, the conditions of collecting patients consent in an open and secure way is better at achieving an improved rate of enrolment[10,12]. ~~At the patient community level, much literature documents barriers to enrolment, especially when barriers are strongly related to community or ethnicity-related issues[13,14]. We think that the decentralized, transparent and secure nature of Blockchain protocol may meet the conditions for an improved engagement of patient communities in clinical trials.~~

~~The tools that we will present in the current study should be considered as a starting point to define a gold-standard of an open and secure informed consent collection process. This can help optimize patients enrolment, and in turn, through a more transparent and trusted process, can create a bridge between clinical research teams and patient communities, who are novel incomers in our digital age and whose commitment is critically dependent on building clinical trials as a highly trusted process.~~

Methods

In this proof-of-concept (POC) study, we targeted 27 volunteers for enrolment, which was achieved at the Clinical Epidemiology Department at Hospital Hôtel Dieu (Paris, France). There were no exclusion or inclusion criteria; the volunteers that were recruited were staff members of the Epidemiology Department (Hospital Hôtel Dieu). However, we ensured each of the users had email access.

A fake experimental clinical trial protocol was designed whose purpose was to compare the effect of "cisplatin vs. ledgerlin", the last substance being a neologism, which was derived from the critical public datastore shared by all Blockchain users called "ledger<u>"</u>". The protocol was accompanied by a consent form, which mimicked a design used routinely.

Each of the to-be-enrolled users were assigned a private key in order to sign data and documents, and in practice this would be used to publish their signed consent, which was to be anchored to the Blockchain.

Blockchain networks

There are several Blockchain networks, for example Ethereum (https://www.ethereum.org), Bitcoin (https://en.wikipedia.org/wiki/Bitcoin_network) and Hyperledger (https://www.hyperledger.org). For our purpose, transactions and their validations were run on the Bitcoin network. Our choice was motivated by stability and immutability of the Bitcoin Blockchain, due to its large mining network, and the API it provides facilitates development. Moreover, it is the more widely used Blockchain network; therefore, there is a relatively dense community of developers to enable an efficient support (https://bitcoin.stackexchange.com).

The front-end and back-end technologies that are detailed hereafter were implemented by a Blockchain solutions provider, Stratumn SAS (https://stratumn.com/).

A website was developed with a simple one-page interface (Figure 2). On the front-end, it displayed the consent document, a checkbox attesting that the protocol was read and understood, and a push button that triggered the consent process.

In practice, the on-line signed document contained a piece of code called "Chainscript", (http://chainscript.io), which contained all the critical information about the user, and the version of the protocol attached to the signature. Each proof of signature had a manifest that takes the form of a hash that is the digital proof of signature.

Figure 2. Patients web-interface for blockchained consent collection website.

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On the back-end, pressing the "consent button" triggers Blockchain transactions: the proof of signature is timestamped and stored in the Blockchain. It should be emphasised that these signatures were shared in real-time through a restricted group of individuals, namely the present authors, who stand, in a real-life implementation, for investigators, IRBs or sponsors. This group obtains access to a dashboard (Figure 3) with the following: an admin panel displaying the consent status of each user; the protocol that transparently stores the public keys of each consenting user (through Chainscript); and the history of each released version of the protocol and the consent and re-consent of the user attached to each of these versions.

Figure 3. Investigator dashboard for blockchained consent collection website.

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Authentication method

For each user a pair of private-public keys were provided, (https://msdn.microsoft.com/fr-fr/library/windows/desktop/aa387460(v=vs.85).aspx). These are asymmetric cryptographic data that enables authentication on Blockchain. These were randomly attached in one-to-one correspondence to a user's emails. We focused our interest to Blockchain's usage in the time-stamping and archiving logic. We did not let users create or use their own Blockchain authentication setup, i.e. if a user owned a Bitcoin account, the key and Bitcoin address were not allowed to be used. This restriction was not related to Blockchain complexity, but rather to maintain a simple and common email-focused authentication process. Other ways exist for authentication, such as physical devices, like USB keys or cell phone fingerprints, but this would have led us far from the focus point of our protocol-related problematics.

Workflow

The process that participants were submitted is as follows:

- • The study investigators to send email to the patients.
- • The users receive the email, which contains a web hyperlink redirecting them to the web interface that displays the consent form.
- • In the background, after clicking the consent button without the user experience being bothered by any blockchain transaction related complexity, the user signature is registered to the Blockchain and is timestamped.
- • Each time the protocol is updated, investigators send an email explaining the major changes that occurred and users are invited to sign the revised consent form.
- • Each step of this process is updated on the investigators' admin panel with the version of the consent document and the user's consenting status.

Proof of existence - Chainscript

Signatures of the evolving consent document were registered to the Blockchain. Moreover, all of the relevant interactions of the user with our platform was stored in the Blockchain, i.e. the consent form upload by the investigator; email requests to users; and patient signatures. This is done accordingly to the Proof-of-Process concept developed by Stratumn, which is a method for proving the integrity of a process between partners (https://stratumn.com/pdf/proof-of-process.pdf).

The piece of data attesting and synthesising all this information is called a Chainscript. It is a JSON formatted data structure holding all the information related to the protocol and users' consent. Chainscript is a JSON format developed by Stratumn SAS, especially dedicated to attest the steps in trusted workflows (http://chainscript.io/). Chainscript is an open standard. The philosophy behind it is to be able to prove the integrity of a process with a single JSON data structure by securing the who, when, what and where of a sequences of steps that are linked together in chronological order. Each sequence corresponds to a segment, and each segment holds some metadata, an identifier called a hash, and a pointer to the preceding segment. The critical information maintained in Chainscript are the hashes, which are the proofs of the existence of data. Since each Blockchain transaction has a cost, we decided to group the transactions. What makes Chainscript interesting is that a series of Blockchain transactions can be wrapped into the same logic flow, preventing too intensive requesting to the Blockchain network, which can prove to be costly.

Therefore, with this information, how can we check proof of a specific data after they are merged? The ChainScript solution relies on a singular data structure, a Merkle Tree, which in a way "hashes the hash", preserving in one single hash all the hashes, so that if any hash is corrupted, the entire tree is invalidated.

In our implementation, the ChainScript code is held in the PDF consent document, storing its hashed content, all its versions (corresponding to protocol revisions) and all the signing users for each version. It is of major interest that ChainScript can be publicly verified without any proprietary tool.

We should remark that a positive side effect of tracking each step of a user's interaction with the platform is that storing so exhaustively the data, raises the barrier to fraud.

Results

Clinical trial master document

We were able to collect consent and re-consent of users and store them in a transparent, unfalsifiable, verifiable way. These data were encoded in a single document. This document holds the stakeholders' identifiers, the users' identifiers, timestamps of the protocols being sent, consent status, timestamps of the consent, and the version of the protocol to which the consent is attached.

This master document was shared in real-time through key actors that ruled the POC study. It was registered to the Blockchain in a safe way, so that this group of stakeholders retains the timestamped proof of the consent status in an immutable document. We stress again the fact that this document is incorruptible, and it is possible to check its consistency on any dedicated public website (e.g. a website that enables checking of Bitcoin transactions), proving the correspondence between each version of the protocol and its related consent.

Technically, these data are synthesized in the open data format we mentioned earlier, Chainscript, which is as follows:

```
"segment": {
  "link": {
    "state": {
      fileName: "protocole.pdf";
      uploadedBy: "investigateur";
    },
    "meta": {
      "title" : "Protocole",
      "tags" :_["POC", "Essai clinique", "Hôpital Hôtel-Dieu"],
      "priority": "0"
      "updatedAt": 1455532426303,
      "mapId": "56c11d0ea55773bc6e681fde",
    }
  },
  [{ "Document_ID": "NOTE D INFORMATION DESTINEE AU PATIENT.pdf""",
   "Doctor_Name": "***",
   "Doctor_Email": "***@aphp.fr",
   "PDF_Title": "",
   "Conditions": "",
   "ExpiresIn": "XX",
```

```
    "Max_Patients": "XXX",
    Invites:
    [{
    "Email": "***@aphp.fr",
    "Name": "***",
    "Address": {
       "hash": "2568ce846c1391d94065df6cc4a42720369bcec9",
       "type": "pubkeyhash",
       "network": "livenet"
       }
  },],
  },[
        "signature",
    "***",
    "***@aphp.fr",
    0,

"H6qy9U3S+BNqreKwMgEnDAHij3wNMcq4T2+X9axzx65Zd+HDy16tr03YPT4oKkGtW820so0D+0Pk2UTrwnXiLKs=",
    {
        hash: "6786ce716b2ac8e14b20e0a2fd8b88a7994d4a10",
        type: "pubkeyhash",
        network: "livenet"
    },
    "2016-07-08T13:11:15.824Z",
    "method__saveSignature"
],[{
    "DateSigned": "2016-07-08T13:11:15.824Z",
    "Signature":
"H6qy9U3S+BNqreKwMgEnDAHij3wNMcq4T2+X9axzx65Zd+HDy16tr03YPT4oKkGtW820so0D+0Pk2UTrwnXiLKs=",
    Consent: 0
    }]
```

All this information is bound together in one data structure, so that the whole set of obtained consent, with their uniquely attached version of the protocol, form an immutable global data. The change of a single element breaks the entire data structure.

In the interest of user confidentiality, the master document cannot be made available.

Technical details of the POC

We sent two versions of the protocol (Supplementary File 1 and Supplementary File 2) during the study, through which we sought the users consent; each consent was attached to a specific version of the protocol. Users were given a digital signature and secured key, each of which consisted of a hash. Amongst the users of this experimental study, 14 gave their consent to the two versions of the protocol, 9 gave their consent to only one version of the protocol and 2 didn't give their consents at all and 2 did not respond to any consent form.

The interaction of the user with the online interface, namely accepting or refusing to give consent, led to a transaction validated in Blockchain. Each version of the protocol had a unique identifier, called a hash. The hash is uniquely attached to the content of the protocol document. The correspondence between the consent document and the hash is one-to-one, namely if one single letter is changed then the hash is broken. Figure 4 shows where the identifier of the protocol document is highlighted in the Chainscript master document. Figure 5displays the investigator identifiers, and Figure 6 reveals the consent status bound to the protocol revision version.

Figure 4. Consent collection master document: unique identifier protocol.

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Figure 5. Consent collection master document: investigator identifiers.

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Figure 6. Consent collection master document: consents status bound to protocol revision versions.

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Discussion

Blockchain is an emerging, fast-evolving technology. The boiling atmosphere around development and use of Blockchain is similar to tech development during the early stages of the web: It took several years before formatting as html or css became web standards. Blockchain technologies are gaining more and more attention, and Blockchain networks are proliferating, for example Ethereum, Bitcoin, Hyperledger or private Blockchain networks. It is not clear which of these will impose itself as a blockchain network standard, or even if there will be unique standard one. Public networks are interesting due to the idea of a community driven approach and scalability, but private ones can offer a certain level of customization.

Alongside this fast-developing tech, there are still some infrastructure obstructions that are not yet circumvented, namely delays in transaction validation. On the Bitcoin network, the validation process (via the so-called mining) takes around 10 minutes (https://www.quandl.com/data/BCHAIN/ATRCT-Bitcoin-Average-Transaction-Confirmation-Time). In the present study's context, we are not tied by real-time requirements measured in seconds, and so it is not a major obstruction. Moreover, the ChainScript logic we implemented in our POC allows grouped network request validation, which preserves the Blockchain network from computation overload, and allows to scale our method to a large patient cohort. More generally, to tackle this challenge of scaling the network, in case there is a massive amount of transactions, there are some implementations of Bitcoin-based protocol isolated from the Blockchain, the most renown is called SideChain (https://www.deepdotweb.com/2014/06/26/sidechains-blockchain-2-0/; https://www.reddit.com/r/Bitcoin/comments/2kdxy8/).

Moreover, with regard to the authentication process, we can expect that, when the use of Blockchain's technologies will be more common, there is an important chance that users already possess a Blockchain public-private-key identity. Therefore, sending keys for access and identification later in the signing process will be obsolete. This will require maintenance of a double key attribution (as explained above in the "Authentication method" section) for users that do not have any Blockchain network identity and to be able to take into account those who have already one. In the latter case, verification of the digital signature of these users will have to occur.

One step further, we can schematically consider there are two main issues regarding the consent process, the first one being related to the quality of the process itself and the second one related to the identity of the individual consenting, we chose to focus on the first point, and tackle the issues raised by the FDA[3,4](https://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM256376.pdf). Indeed, in this POC study, we aimed to consider problems where existing patients were included in a study in the presence of their physician or staff, so that ensuring that the consenting participant was precisely the one expected to be was not a critical matter. Moreover, in the setting of a real online consent process, there is no chance that a patient who would not effectively consent—for instance if there were some fraudulent operation registering him/her as a consenting participant ~~subject~~—would actually participate to the study.

However, the issue related to assert the identity will be of importance in the context of a real clinical trial and should be done in a more secure manner than linking between a participant and his/her digital identity through email address. In a production application, we could implement several solution to secure the digital identity of participants: at least implementing a KYC-like solution to bind digital identities and physical entities — Know Your Customer (KYC) are technics used by fiscal administration or banks to secure their online services. A more advanced technique could use a blockchain-based solution to provide material objects, such as USB keys, holding the cryptographic signatures, which can be unlocked by an easy-to-remember code.

<u>In a context where patients master the key generation process, and applying the same process we detail in this POC, we think that we would be close to attain a trustless consent process, which will promote patients community as a decisive actor of clinical trials. Much literature documents barriers to enrolment, especially when barriers are strongly related to community or ethnicity-related issues[13,14]. We think that the decentralised, transparent and secure nature of Blockchain protocol may meet the conditions for an improved engagement of patient communities in clinical trials. This could help optimize patients enrolment, and in turn, through a more transparent and trusted process, can create a bridge between clinical research teams and</u>

patient communities, who are novel incomers in our digital age and whose commitment is critically dependent on building clinical trials as a highly trusted process.

It should be noted that we did not implement a consent revocation workflow. However, there is no issue in transposing at that end the Blockchain transaction logic we implemented for the consent. On that point, we should be careful about the fact that if the consent or its revocation can be given or withdrawn with no problem, these actions cannot be erased from the Blockchain. Indeed, if participants revoked their consent by accident, then the action can be reversed, but data will remain containing the revocation of the consent and the cancellation of this revocation.

In the range of more prospective considerations, we think that obtaining consent must be a 'lock' before participant inclusion in clinical trials, so that investigators won't be able to include a patient in the trial until their consent is collected. To ensure a strict parity between enrolled patients and included patients, we could use a tool coming along with blockchain technologies called the Smart Contract (https://en.wikipedia.org/wiki/Smart_contract, version of 2017.05.26). This is a piece of code that holds a programmatically written contract between as many parties as needed, without any third-party, which executes algorithmically according to the terms provided by the contracting parties. In our context, it would be possible to build a Smart Contract that will be executed with the only condition that patients will only be included when the enrolment is complete. Technically, every Blockchain transactions can have a lock associated to them and transactions can be pending and triggered at an agreed upon contract time. For example, the signature of the consent would trigger the execution of a Smart Contract, that would unlock the edition of an eCRF document.

Finally, we evoked a possible improvement in the enrolment rate, by empowering patients and granting them information and control over the enrolment phase. However, Blockchain is certainly not a "one size fits all" solution to the problem of a low enrolment rate. Indeed, there are many other parameters that interfere with the enrolment, which fall beyond the scope of transparency, user control and reliability that Blockchain technology helps to achieve: age, sex, cultural background, socio-economic factors, lack of educational materials[15], readability and length of consent[16-18], limited awareness about clinical research[19] ~~research~~ or patient-physician relationship[20]~~relationship[19]~~ and momentum of consent request[21]~~request[20,21]~~. Besides, the scope of our method did not address the question of consent collected in singular situations, such as intensive care, unconscious patients or psychiatric pathologies.

Conclusion

Keeping track of consent collection is consolidated through the use of Blockchain technology. We have seen in this proof-of-concept study that all consent-related data can leave an unfalsifiable and verifiable fingerprint on the Blockchain. This is important both on the stakeholder's side, letting them prove the existence and the consistency of the data, and on the patient's side, giving them more visibility, transparency, and hence control over their consent.

Moreover, though it was not be the focus of this paper, we anticipate that Blockchain technology, in that it does not rely trust on third party but inversely empowers peer-to-peer users by granting them control over consent agreement and revocation, can help gathering conditions of an improved privacy-respected freely-given consent. Besides, given its decentralized protocol, it can help introduce communities to contemporary clinical research, opening, for clinical reasearch, the path to implementing community management techniques in order to enrol patients using a more targeted approach.

From a global perspective, the application of Blockchain technologies in the context of clinical research is broad and promising. Indeed, tracking the complex data flow with numerous diverse stakeholders, and documenting it in real-time through a timestamping workflow, is a key step towards proving data consistency and inviolability, and will hence improve clinical trial methodology.

Software availability

Latest source code available at: https://github.com/benchoufi/DocChain
Archived source code as at time of publication:
doi, 10.5281/zenodo.237040(https://zenodo.org/record/237040#.WHSxorYrl_V)
Licence: 3-clause BSD licence

Author contributions

Mehdi Benchoufi designed the work, initiated and led the analysis on blockchain impacts in the context of clinical trials. With the co-authors, he contributed to identify consent collection process as a substantial use-case for a blockchain implementation, in the idea of clinical trial transparency and traceability. He designed the blockchain collection website and was the medical coordinator of technical developments. Raphaël Porcher contributed to the design of the work, especially on identifying with the corresponding author which of the consent process steps could be wrapped into a Blockchain process. He has put in perspective the potential of implementing Blockchain in consent process, with regards to information of patients, ethics, data privacy. Philippe Ravaud brought his expertise to consolidate the design of work, identified with the corresponding author the issues related to consent process that should be tracked through Blockchain transactions, especially the ones related to protocol revisions and lack of consent collection renewal. He analysed the results with Raphaël Porcher and the corresponding author and inferred from them improved methodology perspectives that Blokchain draw for the entire field of clinical research. Both Raphaël Porcher and Philippe Ravaud reviewed the article, finally approved the article and agree to be accountable on any part of the article relatively of its accuracy and its integrity.

Competing interests

No competing interests were disclosed.

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The author(s) declared that no grants were involved in supporting this work.

Supplementary material

Supplementary File 1: Protocol and consent form (versions 0 and 1) used in the proof-of-concept study (in zipped file) (in French).

Click here to access the data.

Supplementary File 2: Protocol and consent form (versions 0 and 1) used in the proof-of-concept study (in zipped file) (in English).

Click here to access the data.

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