



METHOD ARTICLE

REVISED Blockchain protocols in clinical trials: Transparency and traceability of consent [version 2; referees: 1 approved, 1 not approved]

Mehdi Benchoufi ¹, Raphael Porcher¹, Philippe Ravaud^{1,2}

¹Département d'Epidémiologie Clinique, APHP, Paris, France

²Centre de recherche Inserm Epidémiologie et Statistique Paris Sorbonne Cité (U1153), Université Paris Descartes, Paris, France

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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 paradigmatic 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. In the future, we think that the complex data flow of a clinical trial can be tracked using Blockchain. Moreover, a blockchain core functionality, named Smart Contract, can help prevent clinical trial events not to happen in the right chronological order: including patients before they consented or analysing case report forms data before freezing the database. This will help reaching reliability, security, and transparency, and could be a consistent step towards reproducibility.



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report

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- 1 **Mike Clarke**, Queen's University Belfast
Ireland
- 2 **Daniel S. Himmelstein**, University of
Pennsylvania USA

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Corresponding author: Mehdi Benchoufi (mehdi.benchoufi@aphp.fr)

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REVISED Amendments from Version 1

The main update consisted in precisising 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 reports

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 Seife⁵ 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 consent⁶. 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 conditions⁹ (<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 Gupta¹, 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 mechanism⁹ (<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.

Blockchain is a dawn-aged technology, a giant public datastore, stored in a secure and decentralised way (see Satoshi 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

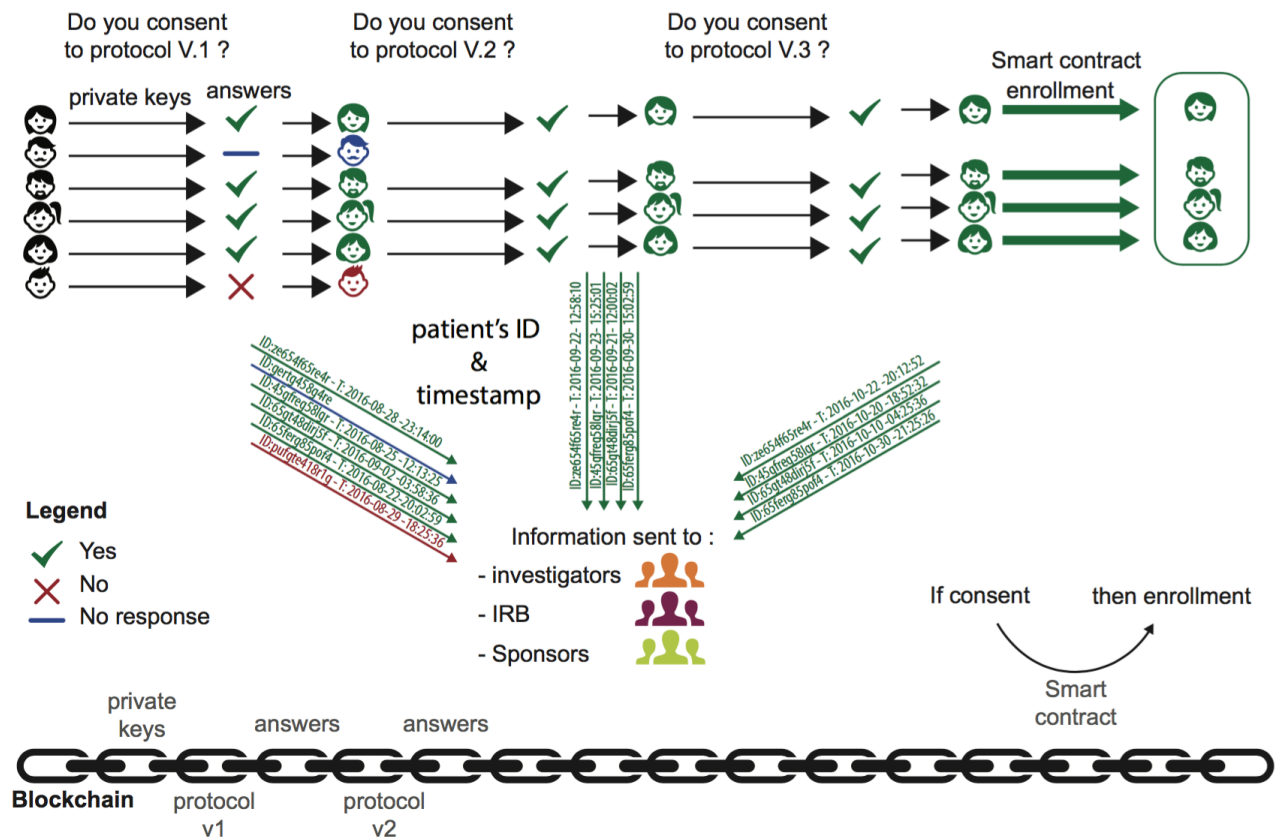


Figure 1. Consent collection Blockchain workflow.

([https://en.wikipedia.org/wiki/Blockchain_\(database\)](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.

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.bgcarnisle.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 Safe-Guard 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 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 weak¹⁰. 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”. 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, Stratum 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.

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.


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](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 hyper-link redirecting them to the web interface that displays the consent form.


 Nous vous proposons de participer à l'étude de recherche clinique "Efficacité et la tolérance de la Ledgerline versus Cisplatine"

Mes Informations de Sécurité ?

Votre signature

H10srm8NCsyM2V8DBKkzelqSrCwg4SvBI0crRIYaJa3tJgB6/wP.


Votre clé sécurisée


b7b55a9d2866be2ff431c80f15f150842caf101ac21d9bb5ce3a1.


Version encodée du formulaire de consentement


dabd7091e308902efb5b4847b75abda7994222346c8de08470e4

① Comparaison de l'efficacité et la tolérance de la Ledgerline versus Cisplatine


 Nom du Investigateur
mehdi benchoufi


 Email du Investigateur
mehdi.benchoufi@aphp.fr


 Votre Nom


 Votre Statut
J'ai accepté

NOTE D'INFORMATION DESTINE AU PATIENT PARTICIPANT A LA RECHERCHE

Titre de la recherche biomédicale : Essai de phase III, randomisé, en double aveugle, visant à comparer l'efficacité et la tolérance de la Ledgerline versus Cisplatine, dans le cancer gastrique après résection complète.

Investigateur coordonnateur :

Dr Mehdi Benchoufi

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


 Nom de l'investigateur
Mehdi Benchoufi


 Email de l'investigateur
mehdi.benchoufi@aphp.fr

① Comparaison de l'efficacité et la tolérance de la Ledgerline versus Cisplatine


 Statut
Pending


 Jours restants pour signer
150

Versions du protocole


 18 Jul 2016 14:23


 18 Jul 2016 09:29

Teste qui apparaîtra sur l'email envoyé aux participants

Nous vous proposons de participer à l'étude de recherche clinique "Efficacité et la tolérance de la Ledgerline versus Cisplatine"

Nom	Email	Statut du Consentement	Date
mehdi benchoufi	benchoufi.mehdi@gmail.com		18 juillet 2016 15h1
N [redacted]	ne [redacted]		18 juillet 2016 15h2
O [redacted]	ol [redacted]		18 juillet 2016 14h39
Ol [redacted]	c [redacted]		
J [redacted]	je [redacted]		18 juillet 2016 17h41
O [redacted]	o [redacted]		18 juillet 2016 16h48
Jr [redacted]	j [redacted]		
J [redacted]	je [redacted]		19 juillet 2016 12h15

Figure 3. Investigator dashboard for blockchained consent collection website.

- 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": "2568ce846c1391d94065df6cc4a427
20369bcec9",
        "type": "pubkeyhash",
        "network": "livenet"
      }
    }
  ],
}, [
```

```

    "signature",
    "****",
    "****@aphp.fr",
    0,
    "H6qy9U3S+BNqreKwMgEnDAHiJ3wNMcq4T2+X9ax
      zx65Zd+HDy16tr03YPT4oKkGtW820so0D+0Pk
      2UTrwnXiLKs=",
    {
      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+HDy16tr03YPT4oKkGtW820so
0D+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 5](#) displays the investigator identifiers, and [Figure 6](#) reveals the consent status bound to the protocol revision version.

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.

```

[
  - {
    - link: {
      - meta: {
        - tags: [
          "method__init"
        ],
        mapId: "577f92726e27683c12a0aea9" ← Unique identifier of the protocol
        agentHash: "3263ac4e62279e355143916a5f03bd00bd3269400ad07d4900134c03d1b2e97",
        stateHash: "acdac4e2df52b79abdaa2c96545ff1e8a417d59b3eccc6131523f3fddeba166ab",
        prevLinkHash: null,
        action: "init",
        - arguments: [
          - {
            name: "1467978354664-NOTE D INFORMATION DESTINEE AU PATIENT.pdf",
            size: 154839,
            type: "application/pdf"
          }
        ]
      }
    },
    - meta: {
      linkHash: "649cc059079b0284d4fb6f7eb47aab14292fb123e7b00df6e3e0ef1c2a124e4c",
      application: "docchain",
      applicationLocation: "https://docchain.stratumn.net",
      linkLocation:
"https://docchain.stratumn.net/links/649cc059079b0284d4fb6f7eb47aab14292fb123e7b00df6e3e0ef1c2a124e4c"
    }
  }
]

```

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


```

- link: {
  - meta: {
    - tags: [
      "1467978354664-NOTE D INFORMATION DESTINEE AU PATIENT.pdf",
      "consent",
      "2c28615f6ad24dbe1f8181bd4a11d2d6f66a0dd8ad155653ee855a62b1f28ca7",
      "method__sendEmail"
    ],
    mapId: "577f92726e27683c12a0aea9",
    agentHash: "3263ac4e62279e355143916a5f03bd06bd3289400add67d4960154c85afb2e97",
    stateHash: "39a830ea6aae7997b3fa9cbabad1c33eebec59a0fbbce4cf74d7e6f23a3b0248",
    prevLinkHash: "649cc059079b0284d4fb6f7eb47aab14292fb123e7b00df6e3e0ef1c2a124e4c",
    action: "sendEmail",
  }
  - arguments: [
    - {
      Document_ID: "1467978354664-NOTE D INFORMATION DESTINEE AU PATIENT.pdf",
      Doctor_Name: [REDACTED],
      Doctor_Email: [REDACTED],
      PDF_Title: "Comparaison de l'efficacité et la tolérance de la Ledgerline versus
      Cisplatine",
      Conditions: "Nous vous proposons de participer à l'étude de recherche clinique l'Efficacité
      et la tolérance de la Ledgerline versus Cisplatine.",
      ExpiresIn: "15",
      Max_Patients: "49",
    }
  ]
}

- link: {
  - meta: {
    - tags: [
      "1467978354664-NOTE D INFORMATION DESTINEE AU PATIENT.pdf",
      "consent",
      "2c28615f6ad24dbe1f8181bd4a11d2d6f66a0dd8ad155653ee855a62b1f28ca7",
      "method__sendEmail"
    ],
    mapId: "577f92726e27683c12a0aea9",
    agentHash: "3263ac4e62279e355143916a5f03bd06bd3289400add67d4960154c85afb2e97",
    stateHash: "39a830ea6aae7997b3fa9cbabad1c33eebec59a0fbbce4cf74d7e6f23a3b0248",
    prevLinkHash: "649cc059079b0284d4fb6f7eb47aab14292fb123e7b00df6e3e0ef1c2a124e4c",
    action: "sendEmail",
  }
  - arguments: [
    - {
      Document_ID: "1467978354664-NOTE D INFORMATION DESTINEE AU PATIENT.pdf",
      Doctor_Name: "Mehdi Benchoufi",
      Doctor_Email: "benchoufi.mehdi@gmail.com",
      PDF_Title: "Comparaison de l'efficacité et la tolérance de la Ledgerline versus
      Cisplatine",
      Conditions: "Nous vous proposons de participer à l'étude de recherche clinique l'Efficacité
      et la tolérance de la Ledgerline versus Cisplatine.",
      ExpiresIn: "15",
      Max_Patients: "49",
    }
  ]
}

```

Figure 5. Consent collection master document: investigator identifiers.

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 imple-



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

mentations 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.

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.

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 materials¹⁵, readability and length of consent^{16–18}, limited awareness about clinical research or patient-physician relationship¹⁹ and momentum of consent 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://doi.org/10.5281/zenodo.237040) (https://zenodo.org/record/237040#.WHSxorYrI_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 Blockchain 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.

Grant information

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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Daniel S. Himmelstein

Systems Pharmacology and Translational Therapeutics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

Benchoufi *et al.* propose and implement a method for notarizing participant consent for clinical trials using the Bitcoin blockchain. At a minimum, such an approach must accomplish two cryptographic objectives:

1. provide participants with a fraud-resistant method to irrefutably consent to the terms of a clinical trial.
2. provide clinical trial investigators with a method to retrospectively verify participant consent at a given point in time.

I agree with the authors that cryptographically notarizing consent would be a major advance. If possible, there would be strong incentives, both ethical and practical, for investigators to implement and regulatory agencies to mandate such an approach.

By encoding a hash into the Bitcoin blockchain that derives from a "consent document", it is possible for investigators to timestamp a consent document and thereby retrospectively prove the existence of that consent document at a given point in time. However, I am not convinced that the study provides patients with a fraud-resistant, irrefutable method of consent. Specifically, I don't think the study provides a method for ensuring that a specific participant provided consent. In other words, can clinical trial investigators prove that a specific participant consented rather than just proving that some entity consented under the supposed digital identify corresponding to a specific participant?

The study uses digital signatures to attest that a participant approved a specific consent form. The implementation relies on bitcoin private keys to provide digital signatures. The problem is that bitcoin addresses (which uniquely derive from a private key) are pseudonymous. For example, anyone with access to a consent form could create an unlimited number of bitcoin private keys and use these private keys to digitally sign the consent form. How does one prove that a bitcoin address solely belonged to a single participant?

The generation of bitcoin private keys in this study occurs at <https://git.io/vSPTE>. I don't see anything in the code or manuscript that irrefutably links a participant to ownership of a given bitcoin address. Therefore, it appears to me that clinical trial investigators (or many other actors) could forge consent. In fact, the manuscript appears to concede this point with the statement:

> 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.

Linking digital identities to physical identities is difficult. However, this is a precondition to blockchain notarization of clinical trial consent. OpenPGP (the most established method for digital identity and signatures) relies on a web of trust model to link digital identities to physical identities. HTTPS relies on Certificate Authorities to link digital identities to organization identities.

Since the manuscript does not sufficiently address how it links digital and physical identities, I dug a bit deeper into Stratumn, the underlying service provider. [Stratumn](#) is a French company, which aims to "secure processes between partners through blockchain technology." Stratumn focuses on "proof of process" using a JSON data structure called [chainscript](#). I had difficulty uncovering the implementation details of Stratumn's proof of process, as much of the available online material focuses on the implications of the technology rather than the technology itself. The most helpful resource I found was the [Epicenter Podcast #159](#) titled "Richard Caetano & Anuj Das Gupta: How Stratumn Secures Processes." This investigation did not answer how digital identities are linked to physical identities in Stratumn's services. The Stratumn proof-of-process [white paper](#) *does mention* identity verification under "Non-Repudiation of Source and Destination", stating:

> Non-repudiation implies that the stakeholders of the information content of each and every step should not be able to deny their involvement with the steps representing their data through the digests. The tool we will use for this is Digital Signatures.

> Both Alice and Bob need to be responsible to their respective steps in such a way they they can not repudiate their involvement if challenged. The record of their identities would be maintained by having the stakeholders digitally sign the digest of their move and then storing the signatures and public keys along with the digest in the step. The private keys will not be stored in the steps; each player hold hers separately and securely. Anyone who has access to the proof can use the public key verification to ascertain whether or not Alice or Bob can be held responsible for a step.

> In this way we enable identity management and ownership in each and every step for the proof of a process to demonstrate the Who behind each and every step.

Unfortunately, this description does not explain how digital identities are linked to physical identities. How does one know whether a digital signature is actually Alice or Bob's? Stratumn even [provides a document](#) detailing the clinical trial consent use case. However, this document does not provide an identity solution.

Conclusion

I am marking my review as *Not Approved*. **If the authors can show that it is not trivial to forge a specific participant's consent, I would be happy to revisit my decision. However, absent a reliable method to link a digital identity to a participant's physical identity, there is little benefit to cryptographic notarization of clinical trial consent.** Such an approach is only as useful as its most vulnerable step. At a minimum, the authors need to identify the trusted parties related to participant identity.

Minor points

The study could do a better job citing the relevant cryptographic literature. For example, the study cites neither the [Bitcoin white paper](#) nor the [proof-of-process white paper](#). In addition, the study should consider referencing [OriginStamp](#), [OpenTimestamps](#), and [Carlisle's 2014 blog post](#).

Figures 2 & 3 are in French. I understand that it's important to show the consent form and interface as given to the participants. However, perhaps these should be supplements with English versions in the main text.

The study states: "Smart contract: this is a contract that is algorithmically implemented and binds any change in the protocol to the patients' consent seeking renewal." However, from my understanding the study does not propose any blockchain smart contracts. Instead, the Bitcoin blockchain is only used as a timestamping service.

Positives

The study aims to replace trust with cryptography in medical research.

The study makes its source code available under a permissive open source license on [GitHub](#) ([Zenodo archive](#)).

The study understands that directly writing every document hash to a secure & immutable blockchain will be cost prohibitive, and therefore it is necessary to "group transactions", i.e. write one transactions that attests to the existence of many chainscript hashes.

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 19 Apr 2017

mehdi benchoufi, Hotel-Dieu Hospital, Paris Descartes University, France

Dear reviewer,

Thank you for drawing our attention on the questions you raised. Our answer focuses mainly on the issue related to the binding between digital identities and physical entities.

We updated the revised version accordingly to all the questions you raised.

Target of the POC and digitale identities

POC as a response to FDA raised issues

Thank you for your constructive remarks. In fact, there are two main issues regarding the consent process. The first one is related to the quality of the process itself and the second one is related to the identity of the individual consenting. Monitoring of trials by the FDA has identified serious issues in about 10% of trials, major concerns being failure to obtain written informed consent, consent document not signed or not dated, missing pages in consent document provided to subjects, failure to re-consent when new information becomes available, use of expired, non-validated or unapproved forms (reference [3,4] in the manuscript and this [link](#)). In this POC study, we aimed at fighting these issues, where existing patients were included in a study in the presence of their physician or staff. In our implementation, we ensured that all the consent process was tracked in time all along the inclusion period, that the documents made available to the

subjects were not corrupted, that they were in conformity with the current version of the protocol, and that (re-)consent was asked as many time as required. We however did not address the cases where consents were falsified by the investigating teams or where fake patients were invented for instance, which are more related to the second (identity) issue. This should be more explicit in the text, and has been emphasized in the revised manuscript.

Linking digital identities and physical entities

We then agree with the reviewer that the second issue is important in the context of a real clinical trial. This relates to the question of pairing digital identification with physical persons. In our implementation of the POC study, the link between a participant and his/her digital identity is done through his/her email address. A participant cannot simply generate any Bitcoin address and use it to sign, because the private key is created on the server by the agent (but not saved on the server), then is sent to the email address. So the only guarantee is that the participant had access to that email address. This is pretty light, but seemed to be satisfactory given the scope and focus of the POC. 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 subject—would actually participate to the study. However, in a production application we must implement a more secure mechanism, and we thank the reviewer again for outlining the possibilities. There are indeed several solution to secure the digital identity of participants.

First, we can mention that KYC processes are now quite widespread and there are plenty of examples where digital identities are linked to physical entities or human beings in the context of sensitive data: in most western countries the fiscal administration allows online service for taxpayers to declare their income and proceed to related operations, banking services also provides their services online such as bank transfer, account consultation. All these examples have in common that users (taxpayers, bank clients) are given a physical material, often by sending a document by regular postal service, or by giving a first card or document by hand. These documents carry an identification number. This approach could be implemented in production.

Second, even in regular off-line consent process, ensuring that the patient really signed the document is not without carrying problems. We have in mind that the patient must meet the medical doctor and receive by hand their consent document. So that, when they go back to the medical doctor with the signed document, there is no way to prove that it was signed by the patients himself or that the patient was not influenced at the time of signing the consent form. Regarding a possible implementation of our blockchained consent process in a real clinical trial, we can provide, at the moment the patient meets the doctor, authentication cards with an identification number and so strengthen the binding between the electronic signature id and the physical one. Let's mention that some bitcoin companies also provide material keys, such as USB keys, that hold the cryptographic signature, which can be unlocked by an easy-to-remember code. This can be an excellent candidate to get stronger digital-physical binding. These issues are now covered in the revised discussion.

Besides, we think that full online consent collection process raises more the issue to reach subjects that the one related to ensuring the targeted patient is really the one consenting.

Patients invention

Going further, we can summarily refer to the extreme case of patients invention. Unfortunately, there is almost no way to prevent data invention. And there are some documented case in the medical literature, fortunately very rare, where clinical trial patients and all related clinical data were invented from end to end. Let's notice here that, in the first implementation of our POC, we timestamped an extensive part of interactions between the subjects and the online email and web platform : time of the email sending, reception, time email was opened, the links being clicked on. We then validated the transactions into the blockchain, this way we could at least detect anomalies if such data appear grouped in time, so that it does not prevent from invention but higher the barrier to fraud.

Further technical improvements

On a more technical side, Stratumn's technology, via proof-of-process, provide an implementation that would allow one to create an audit trail of the the different steps that happened until the participant provided enough evidence to convince the verifier of his/her identity, which is quite an upgrade to current KYC processes, because there would be a permanent record of what happened, and the process would impose rules that must be respected to the letter (by computer code) before moving to the next step. In short, this is not a complete out-of-the-box solution to linking digital identities, but Stratumn has the tools to build one. While implementing such a verification process with the technology is possible, this was beyond the scope of the POC.

Smart Contracts

Indeed, we did not implement it in our setting, we meant to mention that Smart Contract can bind the modifications occurred in the protocol and some to be defined events on which parties can agree.

Besides, we did not detail or implement in the article all the advantages that can be derived from the algorithmic nature of the Smart Contracts: the way consent process is monitored, the way the related informations are shared between the stakeholders, the investigators and the IRB or building Smart contracts with the condition patients will only be included when the enrolment is complete or building one checking the whole consistency between the data and the blockchained proof of data, preventing from the whole hassle of gathering the documents and checking them by hand

Figures

Indeed, some figures are in french and we complied to the F1000 policy that invited us to proceed so.

Bibliography

We thank the reviewer for the precious remarks about bibliography and to have brought to the knowledge of the authors two of them, namely the one referred as `OriginStamp` and the Carlisle blogpost. We add and referenced them in the revised document.

Best regards,

Competing Interests: No competing interests were disclosed

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Mike Clarke

Northern Ireland Methodology Hub, Centre for Public Health, Queen's University Belfast, Belfast, Ireland

This is an important article, worthy of publication in F1000Research. There are some places in the article where the writing could be tidied up (e.g. references 1 and 10 are the same) but my main comments relate to questions that prompted in my mind, which the authors might wish to address if they revise it:

Proof of concept, blockchain and the study generally

1. Is the reported study a "proof of concept" for the use in a real trial, or simply a demonstration that blockchain can be used for a series of sequential "signings"? If the latter, had that not been shown previously?
2. Are there any plans to test this in a real trial, perhaps as a SWAT[1] and to include it in Trial Forge[2]?
3. How would this system be used if patients cannot get online personally?
4. How would the system cope if someone's email addresses changes? (I raise this because I am currently locked out of my Twitter account because the email I used to set it up is no longer active following my move away from that institution.)
5. Can you reflect more on the challenges of doing online trials?
6. Do you believe that this system will be applicable to all trials, a majority or a minority? You seem very enthusiastic about the use of this system and the article might benefit from the addition of more caution about its general applicability. For example, you write "we evoked a possible improvement in the enrolment rate, by empowering patients and granting them information and control over the enrolment phase." but say little of the possible negatives (such as concerns about security of the data (see below); fear or discomfort with technology; and whether empowerment might come more from the ability to talk to a human being about the trial and the consent process).
7. Who will ensure that blockchain is future proof? Might people need to print or export a copy of the electronic record for long-term storage?
8. Does blockchain allow for "workarounds" (e.g. to move to the next step without completing the previous one if for some reason this is necessary)?
9. What do you mean by "transparency" in relation to the new system? If a potential participant thinks this means that others can see that they gave their consent, might this discourage them from joining the study?

Consent in general

10. How would this system cope with differences between the process for obtaining consent to take part in prospective research in different countries and cultures? For example, what if someone other than the patient might need to give consent?
11. Would patients be able to request that their ongoing consent is presumed without needing to be contacted again when there is a change in the trial? It might discourage patients from joining a trial if they are told that they will have to be contacted each time there is a change (especially if that change does not affect them personally).
12. What protocol changes should lead to new consent (e.g. should it only be those that directly affect the patient, or should it be those that might have influenced their decision to join?)
13. Would a patient need to be asked for their renewed consent if the change can no longer affect them? For example, if they have already completed treatment and are now on follow-up, do they need to be informed about changes in the evidence base about a side effect if they can no longer suffer that side effect?
14. Should patients be asked to consent again, or be asked if they want to withdraw? What assumption would be made if they do not reply?
15. Might it be worth discussing this new system in the context of other research into recruitment and retention (for example, as brought together in Cochrane Reviews [3,4,5,6])?
16. Is a lack of informed consent a source of bias (or might it be closer to the "truth" if patients don't realise that they are being studied) or bad ethical practice?
17. Might it be worth discussing the double standards of needing written consent for someone to receive a treatment in a trial but not needing it if they are given the treatment as part of "routine practice"?
18. How important is "written consent"? Is this unfair or difficult to reach populations who struggle to read or write?

Electronic consent

19. How would you ensure that the appropriate person "signed" the consent form if you do not see them do so? Is it easier to submit someone's electronic key, than to forge their signature?

Security

20. Might patients' concerns over the security of their data and the importance of confidentiality make them cautious about joining a trial if they had to use this system? How worried might they be

because of news stories about data from banks and other supposedly secure systems being hacked and leaked?

21. Might it be worth writing something about how patients may think that paper consent forms locked in a filing cabinet are more difficult to access and make available to everyone online, than documents that are already available to the research team from anywhere on the internet.

Language

22. The words "subject" and "participant" are used to refer to people who take part in trials. I prefer to avoid "subject".

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Competing Interests: I am involved in several initiatives to improve the quality and conduct of clinical trials.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 19 Apr 2017

mehdi benchoufi, Hotel-Dieu Hospital, Paris Descartes University, France

Proof of concept, blockchain and the study generally

Dear reviewer,

Here are some responses to the questions that were raised. Besides, thank you for your remark related to the bibliography and the reference duplicate.

1. Is the reported study a "proof of concept" for the use in a real trial, or simply a demonstration that blockchain can be used for a series of sequential "signings"? If the latter, had that not been shown previously?

In the idea of establishing all the consent process in real conditions, we claim it is a proof of concept. We developed a complete and realistic set of interactions between fake patients and stakeholders, and we paired consent status and protocol revision through blockchain held by a single master document accounting for the whole process.

2. Are there any plans to test this in a real trial, perhaps as a SWAT[1] and to include it in Trial Forge[2]?

For the moment, we have no specific plan to implement in a real trial but our POC is precisely a preparation to go further to a real setting.

We have no expertise in SWAT or in using Trail Forge platform, but it should comply with no difficulty with our implementation.

3. How would this system be used if patients cannot get online personally?

This is more a problem related to online consent than a blockchain related question. In situations where patients cannot get online personally, then the medical doctor should provide the consent form to the subjects by hand. Besides, let's indicate that in most countries, the written consent is legally mandatory.

There are other situations where the online access is not possible, related for example to disabilities, then either the legal representative should be given access to the online consent form, or written consent should be sought.

4. How would the system cope if someone's email addresses changes? (I raise this because I am currently locked out of my Twitter account because the email I used to set it up is no longer active following my move away from that institution.)

In a real clinical trial, we would set multiple ways to reach a patient : digitally, phone number, postal mail. For sure, email is not sufficient, and we would use a stronger identifying system than email, i.e. material objects storing cryptographic keys, such as a USB key. We could also build a Smart Contract triggered by a destination email error callback. Then, when this condition is met, Smart Contract would cause the other reaching methods to be proceeded. Since Smart Contract are pieces of code, this automatized processed can be customized at will.

However, although this is not the situation you are pointing to, this procedure may find a limit: there is no way to distinguish between the situation where an email has been sent without response, and the one where the email is still maintained by the institution with no access anymore for the previous account holder. But, we think this very case looks quite exceptional.

5. Can you reflect more on the challenges of doing online trials?

There are some challenges regarding online trials:

- people that are not in a condition to access an online platform: severe conditions, lack of consciousness, learning disability, no access to internet or people not friendly to online tools
- the current state of technologies do not allow interventional trials. However, the explosion of IoT, miniaturization could lead to imagine some specific interventional trials to be conducted online. In this respect, we mention the existence of blockchain systems specifically dedicated to connected objects.
- ensuring that the person consenting is effectively the one pretending to be: this should lead to use a strong identifier, and at minimum use KYC process (Know Your Customer) implemented to bind digital identities to physical entities in the case of sensitive data. Fiscal administration, Banks makes use of that.

It is worth noting that from a blockchain point of view, the email is by no mean a method to identify. In our settings, we generate identifiers for each patient which consists in complex cryptographic strings. It would be possible in addition of these informations stored in the local machine of the subject, to duplicate this information on a USB key or identifier cards on the model of KYC procedure. Let's state that there are some companies providing material supports to keep the blockchain id's.

6. Do you believe that this system will be applicable to all trials, a majority or a minority? You seem very enthusiastic about the use of this system and the article might benefit from the addition of more caution about its general applicability. For example, you write "we evoked a possible improvement in the enrolment rate, by empowering patients and granting them information and control over the enrolment phase." but say little of the possible negatives (such as concerns about security of the data (see below); fear or discomfort with technology; and whether empowerment might come more from the ability to talk to a human being about the trial and the consent process).

Indeed, blockchain is not without carrying some issues. Our point was to put in a perspective a trend. Every new technological gap raises some fears, as the internet at its very beginning, but the overall trend is that usages have imposed. It is worth noting that users shape also technologies and their fear pushes the improvement of technologies conducting these to take more account of their needs and apprehensions.

Besides, our idea is not to rely on a technology by itself but to complete the blockchain network ability to ensure data consistency by a strong human support at any step of the clinical trial, first and foremost the consent process.

Besides, from the data security point of view, we positively think that it is much better ensured by blockchain-like technologies than the one currently used : first, because of the strong crypto-oriented transaction validation, second the distributed nature of the network prevent from the "single point of failure" problem related to centralized data collection. By the way, we can take the Bitcoin network as an example, which carries sensitive money data and which is proving to be resistant for almost ten years.

7. Who will ensure that blockchain is future proof? Might people need to print or export a copy of the electronic record for long-term storage?

Blockchain consist of a network of peers, anybody involved in the network storing in his computer the archive of all the history of transactions, i.e. the public ledger. So that, even if the network had to fail for one or other reason, any single node can restore the last state of the network. Moreover, if necessary, depending on the design of the blockchain implementation, we might enable the only stakeholders or if we want any participant, to export and print the copy of electronic transactions. We may have in mind that data stored are "proof of data" that can be checked to match the true

data on any dedicated public website.

8. Does blockchain allow for "workarounds" (e.g. to move to the next step without completing the previous one if for some reason this is necessary)?

Yes, one core functionality of blockchain technologies, is Smart Contract. They allow to write algorithmically any set of conditions that modules the execution of some instructions.

But, we stress the fact the system can be "fault-tolerant" but there are no "roll-back" possibility. So, suppose that someone stores some informations but has mistaken, then he'll be able to add the new corrected information (that's what we can call a "fork"), but the first errored information is still accessible in the blockchain.

9. What do you mean by "transparency" in relation to the new system? If a potential participant thinks this means that others can see that they gave their consent, might this discourage them from joining the study?

We mean by transparency that the rules are clear for anybody taking part in the process. This is the very role of the Smart Contract we already mentioned.

Besides, the perimeter of the people sharing the data can be controlled : we can decide that data can be shared by the only stakeholders, or decide that participants will be able to share access to their data with persons of trust. All this fine-grained control can be powered on the top of blockchain.

Consent in general

10. How would this system cope with differences between the process for obtaining consent to take part in prospective research in different countries and cultures? For example, what if someone other than the patient might need to give consent?

Differences between cultures, countries need to be tackled one by one. So that we need true implementation of clinical trials to face with those kinds of issues. I don't think there is a one general answer.

Online tools can help orienting the participant regarding to their specific situation. Moreover, we believe chat support should be provided in order to take account of specific situations

11. Would patients be able to request that their ongoing consent is presumed without needing to be contacted again when there is a change in the trial? It might discourage patients from joining a trial if they are told that they will have to be contacted each time there is a change (especially if that change does not affect them personally).

Indeed, there is no need to overwhelm patients with a flood of informations. However, from a general point of view, patients association often complain about lack of informations regarding the clinical trial progress, so that some calibrated informations can be delivered conveniently to the patients.

Moreover, in case of a major change in the protocol, they should be specifically targeted to get an email asking to consent again.

12. What protocol changes should lead to new consent (e.g. should it only be those that directly affect the patient, or should it be those that might have influenced their decision to join?)

There is heavy literature about this. We refer it in the article: [10,11,12] in our bibliography and we mentioned these links detailing the protocol changes that should lead to renew the consent:
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>;
<http://www.yale.edu/hrpp/policies/documents/Reconsentingguidance.pdf>)

13. Would a patient need to be asked for their renewed consent if the change can no longer affect them? For example, if they have already completed treatment and are now on follow-up, do they need to be informed about changes in the evidence base about a side effect if they can no longer suffer that side effect?

Yes, these kind of new informations should be given to patients and require to ask for a renewed consent again, even if they are not supposed to suffer this side effect thereafter.

14. Should patients be asked to consent again, or be asked if they want to withdraw? What assumption would be made if they do not reply?

If patients want to withdraw, they should not be asked again.

When patients do not reply, and after ensuring by other means (emails, mail, phone call if available) that they do not provide an answer, then they should be considered as consenting because they already gave their consent.

Besides, this kind of situation can be advantageously scheduled in a Blockchain Smart Contract, that can be adapted to local legal contexts.

15. Might it be worth discussing this new system in the context of other research into recruitment and retention (for example, as brought together in Cochrane Reviews [3,4,5,6])?

Indeed, we might implement some Smart Contracts, checking the recruitment and retention process. So Cochrane reviewers could have an insight about whether this process was done conformally to standard procedures. However, we notice that the code of the Smart Contract should also be reviewed, so that an experienced developer should be required.

16. Is a lack of informed consent a source of bias (or might it be closer to the "truth" if patients don't realise that they are being studied) or bad ethical practice?

Lack of informed consent is for sure a bad ethical practice, in a strict contradiction to Helsinki declaration, Nuremberg declaration and good clinical practices.

Regarding the matter of generalisability bias, the latter is more related to the setting of inclusive criteriae than related to consent.

17. Might it be worth discussing the double standards of needing written consent for someone to receive a treatment in a trial but not needing it if they are given the treatment as part of "routine practice"?

In any case, the participant to a clinical trial must to sign the consent form, even he is already taking the medication for which the consent form is seeking his/her consent. At this occasion, the patients may be informed of actual informations related to the treatment, for example new side effects of a drug.

18. *How important is "written consent"? Is this unfair or difficult to reach populations who struggle to read or write?*

The written status of the consent by opposition of the electronic has not by itself more credit. However, depending on the local legal context, "written consent" is mandatory. Besides, collecting consent of people with reading, writing or learning disabilities needs care. The person collecting the consent must assess the ability of the person to understand correctly the informations and to make a decision. The information must be given orally and to the legal representative if any. Some ethics committees allow the mediation of families or other supports at this stage.

Electronic consent

19. *How would you ensure that the appropriate person "signed" the consent form if you do not see them do so? Is it easier to submit someone's electronic key, than to forge their signature?*

In this POC, we generated cryptographic keys for each patient. So, in this design indeed, we can't ensure that the person consenting is the person he or she pretends to be. This can be improved in different manner.

At least, using KYC standard procedures, i.e. doubling the electronic identification by one related to a physical object holding some number code. One step further would be to provide patients with an objects storing USB key storing the cryptographic signature and unlocked by a easy-to-remember id.

Security

20. *Might patients' concerns over the security of their data and the importance of confidentiality make them cautious about joining a trial if they had to use this system? How worried might they be because of news stories about data from banks and other supposedly secure systems being hacked and leaked?*

We refer to the question 6 on the notion of "single point of failure", which answers at some level the raised issue.

In any case, patients are very sensitive to the security and the privacy of their data and this system addresses precisely this issue. Indeed, the decentralized structure of the blockchain, the involvement of anyone as a peer on the network, the ability to finegrain the data sharing perimeter, allows more control of the patients over the data workflow.

However, we are conscious that this system is very new and needs some pedagogical support. Anyway, Bitcoin is now a widespread, trusted electronic currency, available on payment platform of a wide range of websites such as Amazon, Apple's App Store. An implementation of such processes in a real clinical trial should be the occasion to add different media support : documents, videos in order to inform patient of the benefit of using such technologies .

For the second part of the question, see the response to question 6. of the present reviewing question list.

21. *Might it be worth writing something about how patients may think that paper consent forms*

locked in a filing cabinet are more difficult to access and make available to everyone online, than documents that are already available to the research team from anywhere on the internet.

Absolutely it might be very interesting.

Language

22. The words "subject" and "participant" are used to refer to people who take part in trials. I prefer to avoid "subject".

We substituted the usage of "subjects" by "participants" in the revised document.

Best regards,

Competing Interests: No competing interests were disclosed

Discuss this Article

Version 1

Reader Comment (*Member of the F1000 Faculty and F1000Research Advisory Board Member*) 02 Feb 2017

Pierre-Marie Lledo, Perception and Memory Laboratory, Institut Pasteur, France

As clinical research has to face an ongoing lack of trust, this article comes at a right moment to address key issues such as transparency, reproducibility and eventually a more reliable methodology. Blockchain technology provides interesting proof of data and therefore a trustworthy environment in order to exchange clinical data. It can lead to a substantial breakthrough which will help to set up health communities with common ethics and patients empowerment.

Competing Interests: No conflict of interest.
