 doi:10.20944/preprints202006.0310.v1

Frauds in scientific research may be overcome with distributed ledger technologies

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ABSTRACT

Frauds and misconducts have been common in the history of science. Recent events connected to the COVID-19 pandemic have highlighted how the risks and consequences of this are no longer acceptable. Two papers, addressing the treatment of COVID-19, have been published in two of the most prestigious medical journals. In both, the authors declared to have analysed

electronic records from a private corporation, which apparently collected data of tens of thousands of patients, coming from thousands of hospitals. Both papers have been retracted a few weeks later. When such events happen, the confidence of the population in scientific research is likely to be weakened.

The objective of this paper is to highlight how the current system endangers not only the reliability of scientific research, but also the very foundations of the trust system on which modern healthcare is based. Having shed the light on the dangers of a system without appropriate monitoring, we propose to improve the research process using the promising aspects of the distributed ledger technology which, thanks to the characteristics of immutability, decentralization and transparency, appears among the best solutions to avoid the repetition of the mistakes linked to the recent and past history of research.

ACKNOWLEDGMENTS

N/A

COMPETING INTERESTS

The authors declare that they have no competing interests.

FUNDING SOURCES

The authors declare that they have not received any specific funding.

 doi:10.20944/preprints202006.0310.v1

MAIN TEXT

1. Introduction

Frauds and misconducts have been common in the history of science, but recent events connected to the COVID-19 pandemic have highlighted how the risks and consequences of this are no longer acceptable, especially during a global health emergency.

The time has come to tackle the problem and to review the entire system, rethinking in particular the process of evidence creation.

The objective of this paper is to highlight how the current system endangers not only the reliability of scientific research, but also the very foundations of the trust system on which modern healthcare is based.

Having shed the light on the dangers of a system without appropriate checkpoints/monitoring, both for the scientific community and society as a whole, we propose to improve the research process using new technologies supporting control activities by public authorities. Among these solutions, we particularly evaluate the promising aspects of the distributed ledger technology which, thanks to the characteristics of immutability, decentralization and transparency, appears among the best solutions to avoid the repetition of the mistakes linked to the recent and past history of research.

2. The current concern: an excessive amount of scientific literature may lower the overall quality of COVID-19 research

The number of papers published on COVID-19 has reached the tens of thousands and is still growing. Given the massive amount of published literature, the crowd of scientists, policy makers, and physicians are facing increasing difficulty in finding those relevant to their activities, while also evaluating the quality of the scientific evidence provided. In this vast “sea of scientific literature”, those with an interest on COVID-19 are trying to keep up with all the latest news and discoveries.[1]

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COVID-19 pandemic is shaping scientific research, giving us a glimpse on how it will likely evolve in the future. To stay relevant in the current scientific landscape, researchers want to share their work in a quick, open-access fashion, in order to receive immediate feedback and praise - when deserved - by their peers. Preprint servers allows them to do so, as shown by their increased popularity: almost 4000 COVID-19 papers have been submitted to medRxiv alone.[2]

While this "torrent of preprints" surely contributed to rise the level on the aforementioned sea of literature, the major flow came from another path: most of the COVID-19 papers have already been published in refereed journals.[3] While the peer-review process is supposed to designate the researches deserving of publication, scientific journals have the responsibility to ensure that all the potential discoveries on COVID-19 are given a chance to be appropriately divulged. So, in order to cope with the overwhelming amount of submissions, many scientific journals tried to decrease the amount of time required to process, review and publish a manuscript. A recent study - ironically, a preprint that gathered a great amount of attention - shows that 14 medical journals, when compared to the pre-pandemic situation, have decreased by almost 50% the time required on average to publish a COVID-19 paper; this has been possible mainly by reducing the number of days required for the peer-review.[4]

These issues raised concerns about the quality of COVID-19 publications and, therefore, about another manifestation of the pandemic: the possible spread of misinformation and lack of scientific integrity, which are the foundations of the so called "infodemic".[5]

3. A brief introduction to recent events: the Surgisphere scandal

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It may be easy, at first, to associate this issue - an excessive amount of submissions that may lead to quicker, less accurate peer-reviews - only to the journals on the "lower end" of the Impact Factor/H-Index spectrum; that is to say, one may think that the lower the amount of resources available (represented mostly by the "stock" of editors and reviewers), the higher the chance a research of questionable quality may slip through the peer-review process and be published.

However, recent events show us how even those journals that have always been considered among the best in their sector are not immune to COVID-19 infodemic.

Two papers, addressing the treatment of COVID-19, have been published in two of the most prestigious medical journals - The New England Journal of Medicine (NEJM) and The Lancet- only to be retracted a few weeks later. Both papers reported an analysis on drug therapies for COVID-19: one - published on NEJM on May 01, 2020 - addressed the lack of harmful effects of angiotensin-converting–enzyme inhibitors (ACE-i) and angiotensin-receptor blockers (ARBs);[6] the other - published on Lancet May 22, 2020 - focused on the potential risks of using hydroxychloroquine (HCQ) or chloroquine.[7]

These two papers are connected: they share three authors (Prof. Mandeep R. Mehra, Dr. Sepan S. Desai and Dr. Amit N. Patel) and also the source of the data analysed: Surgisphere, a data analytics company of which one of the co-authors, Dr. Sapan Desai, is also the founder.
In both papers the authors declared to have analysedSurgisphere electronic health records (EHR), which apparently collected data of tens of thousands of patients, coming from thousands of hospitals from up to six continents.[8]

Such resonating statements raised comprehensible skepticism among the readers of the journals: how was it possible for an unknown private company to obtain access to such a vast amount of international patient data? This, along concerns on the methods and results of said papers, prompted NEJM to investigate by issuing an Expression of Concern (EOC) on June 03, 2020, asking the authors *"to provide evidence that the data are reliable";*[9]the following day, Lancet also issued a

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similar EOC.[10] Exactly two days later, both journals retracted the respective publications, since *"the authors were not granted access to the raw data"* [11] and *"Surgisphere would not transfer the full dataset, client contracts, and the full ISO audit report to their servers for analysis*",[12] proving the fraudulent nature of the two researches.

4. How the lack of integrity in research influences the scientific community and our society

In the NEJM paper, the authors stated that "*the results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs*" in COVID-19 patients.[6] While not going against the current recommendations,[13,14] the paper tipped the balance in favor of one of the two sides of a still open debate.

The situation gets worse for the Lancet paper: the authors stated that the use of hydroxychloroquine or chloroquine *"was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19*".[7] Again, the paper shifted the balance in a lively discussion topic: a randomized UK trial, RECOVERY, reported a similar lack of benefit from HCQ treatment, but found no evidence of toxicity to the heart, thus not discouraging further research.[15] On the other hand, the heart toxicity reported by of Mehra et al. contributed to a global halt of the ongoing research on HCQ as a treatment for COVID-19, prompting even the World Health Organization itself to take a *"temporary pause"* of the HCQ trial.[16] After the retraction, the WHO trial, along others big clinical trials,[17] quickly restored the abruptly interrupted research activities on HCQ, but the damage had already been done.

Many researchers are worried that HCQ future as a COVID-19 treatment may be hindered, since *"the retraction won't get anywhere near as much news as the original study"*.[18] On June 05, the U.S. Food and Drug Administration (FDA) revoked the emergency use authorization (EUA) that allowed the use of chloroquine phosphate and hydroxychloroquine sulfate to treat hospitalized patients

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with COVID-19.[19] Despite the fact that the FDA report clearly states that the Mehra et al. paper has not been considered for the evaluation, it is easy to see how researchers that have been investing their time in trials on HCQ may feel like a whole month between the publication and the retraction of the paper may have been more than enough to negatively influence the opinion of public and experts alike.

A third paper was co-authored by Mehra, Desai and Patel, once again backed up by Surgisphere data. Submitted on April 06, 2020 to a preprint server, the paper - recently removed by the authors and no longer available - reported a reduced mortality in COVID-19 patients treated with ivermectin, an anti-parasitic drug.

Carlos J. Chaccour, from Barcelona Institute for Global Health,[20] explains how the preprint, despite its short life, has deeply influenced the healthcare of some Latin American countries: on May 02, 2020 a white paper encouraged the inclusion of ivermectin in Peru national treatment guidelines for COVID-19.[21] The example of Perù was quickly followed by Bolivia and Paraguay,[22] where an unsustainable demand of ivermectin brought to the use of the veterinary formulations of the drug, sold both regularly and through the black market.[23]

The preprint has been removed by the authors themselves, showing that the findings were likely inaccurate or fraudulent.

So why is this still a problem? Since this research had been divulged only as a preprint, no journal had to issue an EOC followed by a review and, eventually, by an official retraction. Hence, the legacy of this fraudulent research is still alive and kicking, and will continue to cause harm through false sense of security, possible side effects, and shortage of the drug for its appropriate application in anti-parasitic treatments.

"*The damage to public health continues, fuelled by unbalanced media reporting and an ineffective response from government, researchers, journals, and the medical profession*[...]".

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This statement, very fitting to the ivermectin/COVID-19 situation, was issued in 2011 by the British Medical Journal, quickly after former-doctor Andrew J. Wakefield incrimination.[24]

On February 28, 1998, Wakefield published a study in The Lancet reporting a link between measles, mumps, and rubella vaccination and a syndrome of autism and bowel disease in 12 children.[25]

In the years that followed, countless epidemiological studies found no evidence of this link;[24] however, the study was retracted only 12 years later, in 2010, when "t*he claims in the original paper that children were consecutively referred and that investigations were approved by the local ethics committee have been proven to be false*".[26] These, however, are just narrower misconducts that do not describe the Wakefield case in all its gravity: altered medical histories, misreporting, failed investigations, conflicts of interest, and enormous scientific flaws.[27,28]

Between 1998 and 2010, Wakefield fraud caused an incommensurable, long lasting damage, through diminished vaccination rates and general distrust of the healthcare authorities, sentiments that are still lingering today, despite the pandemic.[29]

Recent events show that, even after more than 20 years, scientific research is still susceptible to this kind of misconduct, at the expense of the scientific community and our society as a whole.

5. Weakness in the data process

The Surgisphere scandal has definitely brought to light the enormous criticalities in the world of scientific research and scientific publishing. However, what happened is not an anomaly or a novelty. To understand how this kind of misconduct has been possible, now and in the past, we must consider what the process of the data (e.g. clinical data) is, from when it is created on a patient to when it is analyzed and reported in the literature, to end up within the guidelines and indications for clinical practice, for instance. While This is clearly country by country dependent, there are some common points.[30]

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The data is generated by one individual (e.g. a patient) in a healthcare setting (Figure 1). An "intermediary" usually collects, cleans, sorts, and analyzes it (e.g. a researcher). Then, the results of this analysis must be shared and reported to be used by the rest of the scientific community and beyond. To do this it is necessary to publish in a scientific journal (divulger). Finally, the public or private authorities (WHO, Ministry of Health, other hospitals) receive the information and put into practice the new evidence (e.g. indicate mandatory PPEs) that returns as a benefit to the end user (again the patient/citizen).

This should be a virtuous circle (Figure 1). However, what has been brutally highlighted by the recent events is that there is a number (unknown) and a type (unknown) of intermediaries, more or less official, who collect and often analyze huge volumes of digitized data, in particular the so-called real world data, from electronic health records, claims and administrative data flows, to cite a few examples. What determines an increased risk of process failure is not knowing who these subjects are, their interests, and, above all, the ways in which they collect, store, analyze and share data. As previously outlined - and confirmed by recent events - data collected during a research phase can be altered *ex post*, in order to bring out the expected outcomes,[31] or for other reasons. In particular, researchers, or other subjects involved in the research, can be led to review some of the results already collected, in the light of newly acquired results, in order to confirm the expected results. At best, such data alteration, manipulation or falsification can determine the grave consequences described before. In worst case scenarios, the falsification of data leads to the commercialization of potentially harmful products, with serious consequences for patients' health, related ethical and legal problems, and also economic and social issues.

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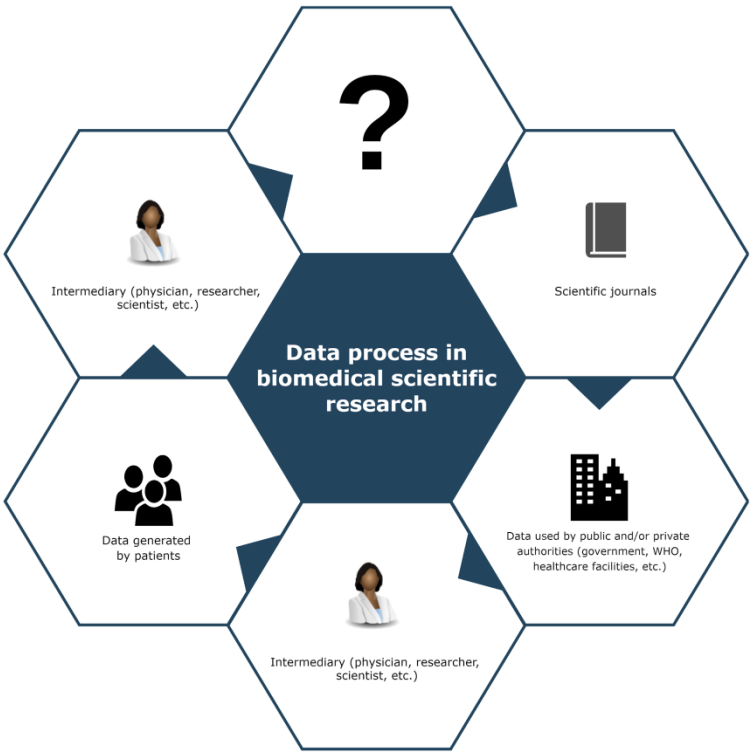

Figure 1. Schematization of the data process in scientific research. The "?" is intended to show how possible intermediaries can participate in the process and undermine its reliability.

6. Public (dis)trust in the data process: undermining trust in healthcare and scientific research

In modern societies trust of the general public in healthcare and scientific research is based, *inter alia*, on the credibility of the *data process in biomedical scientific research* described above. Such a process is usually quite difficult for the non-technical population to understand. The general population is thus normally informed by scientific news sources and the mass media, which have the important task of translating the scientific results achieved by researchers into a language intelligible to everyone.

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The results of the above described process therefore gains credibility in the eyes of the population both because of the credibility of the researchers, and in light of the actual outcomes, including patient satisfaction.[32]

However, if the results actually produced are not in line with expectations, or worse, turn out to be based on fraudulent data, the confidence of the population in the aforementioned process is likely to be weakened. Where this malfunction is occasional or in any case sporadic, the responsibility for errors might only be attributed to individual persons. Conversely, where a certain dysfunction is repeated, and occurs independently of the subjects involved, the distrust might shift towards the process itself. This second hypothesis is particularly dangerous because in this case the solution to the problem perceived by the population is no longer the simple replacement of the subjects in charge. In such cases, the effectiveness of the process as a whole might be questioned.

This is what could happen in relation to the phenomenon of falsification, or in any case manipulation, of health data. As explained above, numerous cases have already occurred in which it was ascertained that the data on which certain scientific evidences were based were in whole or in part false, or in any case were not entirely accurate. Therefore, the repetition of these events can have the consequence of undermining the credibility of the process as a whole. The population, considered as a whole, does not have the knowledge and the means to tell apart reliable and unreliable scientific news. As a consequence, repeated instances in which it has been demonstrated the unreliability of well-established sources have the effect of leaving the general public with the doubt of what information can actually be trusted.[33] The more this happens, the more grows the distrust of the population towards scientific news sources and the mass media, and, consequently, towards healthcare and scientific research processes.

In order to avoid this loss of confidence, we must evaluate how this dysfunction can be resolved. In order to avoid a complete reform of modern scientific processes, we can rather support their activities with new tools, to make up for their current shortcomings.

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The tools that more than any other appear to be appropriate and that are already helping to support scientific research are those offered by new digital technologies. In this perspective, the technologies that we are interested in taking into consideration can be divided between cloud-based systems and Distributed Ledger Technologies (DLTs). It is therefore necessary to underline the characteristics that these systems must have in order to respond to the problems highlighted above.

In this perspective, we want to focus on DLTs, for two reasons. First of all, cloud technologies are those on which the vast majority of IT systems have so far been based, without the problems mentioned above being avoided. Secondly, DLTs have on the contrary shown to offer guarantees of traceability, immutability and transparency which seem particularly suitable for overcoming the problems described so far.

7. Distributed Ledger Technologies supporting the data process in scientific research

The scientific community has for some time been pushing towards the adoption of control tools, and new technologies that allow data to be shared between geographically distant subjects.[34,35,36,37] The capacity and the ease of safe data sharing represent fundamental conditions for guaranteeing quality scientific research. A panoply of services and apps is available to create, collect and share different types of data.[38,39]

Data may originate from clinical records, current or ad hoc data flows (e.g. registries of pathology, claims data, etc.), directly from patients (e.g. surveys, questionnaires and scales to report patient reported outcomes, PROMs) or from published studies (systematic reviews and meta-analyses).

With the advent of new digital technologies, scientific research must face new technical, ethical and legal challenges. Current softwares for the management of data and documents in scientific research are mainly based on cloud-based or DLTs.

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Surgisphere itself, after an initial business based on medical guides and textbooks, over time have shifted its efforts into developing a cloud-based database of hospital records that could be used for research.[40,41]

The facts evidently corroborate the idea that the cloud is not totally sufficient to guarantee reliability in the data process, and it is probably necessary to evaluate new options.

Emerging DLTs technologies offer alternative solutions for the management and sharing of data in scientific research and might represent a useful tool for data sharing and management in modern scientific research.

DLTs have already been successfully implemented for issuing and circulating whealth in the form of cryptocurrencies.

Public (Permissionless Ledger) and private (Permissioned Ledger) DLT solutions have been proposed. Public DLT solutions, of which the most famous and widespread example is represented by the Bitcoin's Blockchain, are open, do not have a "property" or a third party authorization and are designed not to be controlled by any single entity. The purpose of public DLTs is to allow everyone to contribute to updating data on the Ledger and to have, as a participant, all immutable copies of all operations. That is, to have all the identical copies of everything that is recorded and approved on the Ledger. This DLT model prevents any form of censorship, no one is in a position to prevent or erase an operation on the ledger once such operation has been approved through the consensus mechanism of the DLT model.

However, this solution has some disadvantages. Public DLTs can be used as a global database for all those documents that need to be absolutely immutable over time, except for updates that require security and privacy. They require that all data, or its representation through the so called hashes, are made available to a large number of users. They also require considerable computing power and consequent proportional energy consumption. This implies that current DLT techniques cannot

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be used in contexts in which the data must be kept confidential and / or the number of users is very limited, such in research studies.[42]

On the contrary, private DLTs rely on private or closed networks. Private DLTs are populated by a series of actors who must rigorously share the same rules. In scientific research applications, a private DLT solution seems to represent a better alternative. It can be used for secure data collection, management, and sharing. For instance, several decentralized data management solutions have been proposed, for example to share electronic medical records between patients and providers. Choudhury et al. developed a decentralized framework for consent management and secondary use of research data.[43] Recently, a study on a blockchain-based software solution for clinical trials was conducted at Stanford University.[44]

8. Practical use of DLTs in scientific research

Practical uses of DLTs solutions for enhancing the scientific research process' reliability have already been suggested, and some adopted. [42,43,44]

Among the practical uses, pathology registries, clinical databases or databases of electronic healthcare records, as the one under accusation of Surgisphere, are possible targets.

Large regional, national and supranational databases of patients' electronic medical records are increasingly used in scientific research. Currently these databases are usually stored on the device of a single individual, of a research structure or of a healthcare system, where it is "fed" by different,geographically distant subjects. In addition to the problem of data reliability highlighted by the cases of the Lancet and NEJM, this system also has the drawback that researchers often do not have access to the full database when they need to because they cannot access the device on which the full database is stored. By using DLTs this problem can be fully overcome. The entire database can be stored on the device of each participant in the research project. At each data or file

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change the database is continuously updated on all devices, so that all data is always synchronized. And since this mechanism can be based on a DLT, everything happens in a secure way on a peer-to-peer basis.

Alternatively, to solve the problems discussed above, DLTs can allow complete traceability of the data (anonymized at the source), with creation/modification date, location and subject that originated the data, or possibly altered it. This can give a "license of reliability" to the data, as long as from the early stages of the collection it is all managed through DLTs platforms. On this aspect, the editorial groups or the final stakeholders of Figure 1 should incentivize researchers to adopt DLTs' systems, right from the research protocol drafting, for example by privileging for publication studies with "license of reliability".

9. Conclusions

The Surgisphere scandal highlights some serious concerns on the scientific integrity of today's publication system. This situation, which is certainly not the first of its kind - and unlikely to be the last - confirms that ensuring data integrity (validation, accuracy, consistency and quality) is a professional and ethical obligation, aimed at providing reliable results to healthcare systems, regulatory authorities and supranational bodies.

In other words, it is essential to implement a secure and reliable system, one that can be deployed within any research environment, that can ensure the traceability of all activities performed on medical scientific research and beyond. Such a system should ensure that data is not altered, manipulated or falsified, and that - in case any of these actions are performed - it is possible to identify exactly who manipulated the data, by also tracing when and how.

The entire process of creation, collection and sharing of scientific research data, as well as the editorial one, should be reviewed. To do this, Distributed Ledger Technologies can be one implementable and rapidly scalable solution. Thanks to the DLTs, the system can ensure data

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integrity in all phases of research, while ensuring the traceability and constant monitoring of data. This can help increase confidence and trust in the data and resulting evidence, both by the scientific community and the general public.

It is therefore essential to take advantage of recent events to rethink the scientific research system, starting in the biomedical field, by adopting processes and technologies aimed to reduce the risk that this kind of situation will happen again, undermining the credibility of science itself.

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