Chapter 3
Healthcare Patient and Clinical Research

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Abstract Clinical trials and research are a very involved and often lengthy process with formalities and regulations that should be adhered to. There are questions over the transparency of clinical research data from the start of the initial process of registration, informed consent, clinical outcomes and to where approval is given by post marketing and publication. These impacts suggested have manifested itself in the form of fraud, misconduct, selective reporting, bias and consequently had other effects to those taking approved drugs; some resulting in fatalities. Access to research data has also been difficult to obtain from those involved in the clinical trials such as patients and even researchers whom would be interested in the post marketing phase and pharmaceutical analysis. Evidence is presented with data extracted from credible sources that highlight the concerns in registration, informed consent and clinical research outcomes and how they are reported with recent example of how opioids misuse has ended up as a serious issue as a consequence of non-transparency. This Chapter suggests a theoretical model to propose how blockchain could present a more transparent and secure method to tackle the issues mentioned, with utilising blockchain as the mechanism/framework for clinical research institutions, regulation and non-regulation bodies, pharmaceutical organisations, drug manufacturers/suppliers and patients.

Keywords Clinical research · Clinical trials · Clinical outcomes · Fraud and misconduct · Selective reporting · Bias · Blockchain · Data integrity · Traceability · Smart wearables · Cyber-attacks · Data breaches · Opioids misuse

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H. Jahankhani et al. (eds.), *Blockchain and Clinical Trial*,
Advanced Sciences and Technologies for Security Applications,
https://doi.org/10.1007/978-3-030-11289-9_3

3.1 Introduction

Over recent years it has become clearer from research and studies undertaken that there are issues with data from clinical trials being made more transparently available; from the start of the process with registration and informed consent through to publication outcomes and drug administration. Fraud and misconduct are also reported alongside privacy of patient data concerns and the integrity of the whole process. At all points of the journey's process, it highlights suggestions or requests to improve transparency and security as explained in parts of this chapter. There has also been great technological advancement in using smart medical wearables to gather data more accurately during trials, rather than more mechanical methods of patients filling in forms when requested or next visits to the clinics. But with the advantages of valuable data comes the risk of data integrity and complexities of digital forensics. Blockchain offers a more beneficial method to seamlessly record data.

What is discussed in this Chapter is a theoretical model using blockchain as the mechanism to secure and support all processes through the data journey. This will give a more guaranteed method to provide data (which may be currently withheld) back to clinical researchers and also present data access to patients whom in some cases currently consent and undertake trials but never then gain access to results or insights of the study that they made valuable contributions to. But worryingly, there is a lot of data that is not published and studies that do not have significant results remain to be not included and may imply bias in the outcomes, Proehl and Hoyt (2017). There is also a more serious side of transparency in the full sets of raw data being available from drugs being prescribed as well as analysis on how in many cases data in the setup of the Protocol of a Trial is not matching to the clinical trial outcomes. This misalignment in outcomes can have an impact on patients from less to severe, such as fatality.

3.2 Transparency of Clinical Research/Trials and Drug Traceability

Interoperability and longitudinal data are beneficial to patients and providers, as mentioned in earlier sections and enhance both the privacy and security if run on architectures such as blockchain. However, there is also significant potential for companies involved in research to enter a new era of discovery to help better understand disease interactions, and if that data was made easily available to researchers, then the benefits would be huge; Engelhardt (2017). The access to this abundance of data is not the issue; it's often the transparency, security and privacy of that data that is the problem and blocked by many obstacles, ethics, etc. But with blockchain this will offer the patient a way to 'permission' data to be shared anonymously; with the patient being at the centre, authorising access to clinical researchers or industry.

Engelhardt (2017) makes an interesting point that not only do patients want this control, but they want their data to be useful and for researchers the value of blockchain is the immutability of the data, meaning the data is trusted not to change. This is a crucial concept in the research world that data can become more trusted.

If legacy issues are analysed it's easy to see that clinical trials are subject to many errors and fraud that undermine the whole process and can invalidate the research undertaken. Benchoufi and Ravaud (2017) specify that reproducibility is an issue (misconduct and fraud) and ideally it would be better to equip research communities with secure data sharing and a way to guarantee privacy, perhaps using blockchain. Benchoufi and Ravaud (2017) go on to solidify their case for blockchain because it 'allows for tracking, sharing and caring for data' and can be a better step towards transparency and improving trust in the research community. The research is specific on blockchain application to benefiting clinical research and worth noting the positive aspects and why to consider as follows:

- **Chronological order** – tracking can take place in the correct event order to apply a time order logic
- **Data integrity** – data falsification is as close as possible to being eliminated along with issues of embellishing
- **Traceability** – with the timestamp, a copy of the transaction is kept across the nodes ensuring no tampering of the data and provide credibility.

See Fig. 3.1 as per Benchoufi and Ravaud (2017) proposed model for explanations of the complex stages and flows of diverse data and applied metadata so keeping the data 'true' but confidential on blockchain. Smart contracts can be deployed in certain stages as that validates all previous steps.

3.3 Theoretical Model Using Blockchain to Secure Data in Clinical Research Trials

Tackling the issues of the transparency and security of healthcare data has been a difficult problem to resolve. However, with the recent advancement in blockchain application (some examples were given in the previous chapter) it now provides a tool or mechanism to support the data journey all the way, providing the benefits of blockchain.

Figure 3.2 proposes a trustless blockchain framework between clinical research institutions, regulation and non-regulation bodies, the pharmaceutical industry, drug manufacturers/suppliers and more importantly the patients.

The type of blockchain suggested could be Ethereum; since it already has significant use in healthcare applications, and speed and efficiency are known quantities in terms of transaction and processing time. But equally for future research or pilots it can be flexible to other types of blockchain. It will also be a permissioned framework, since users would need to be invited to access information where authentication

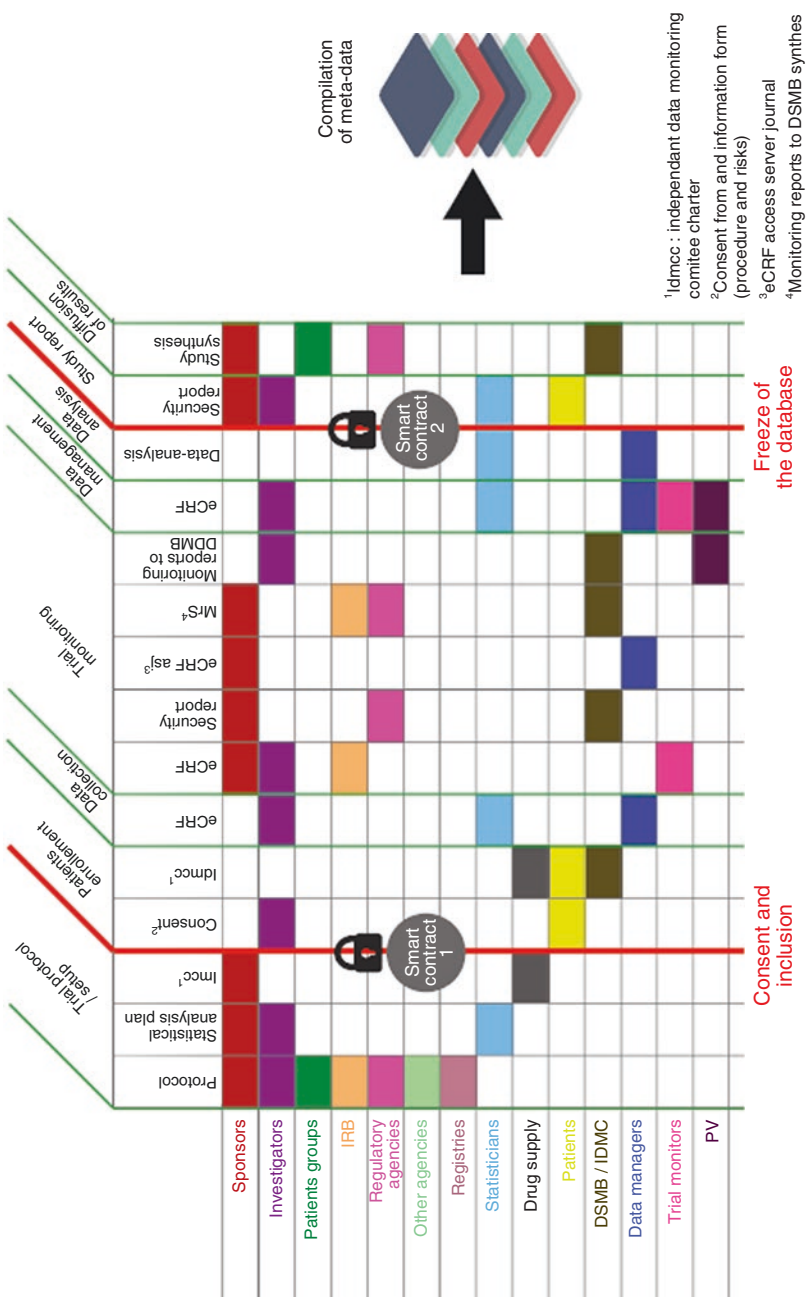

Fig. 3.1 Clinical trial data supported by benefits of blockchain. (Benchoufi and Ravaud 2017)

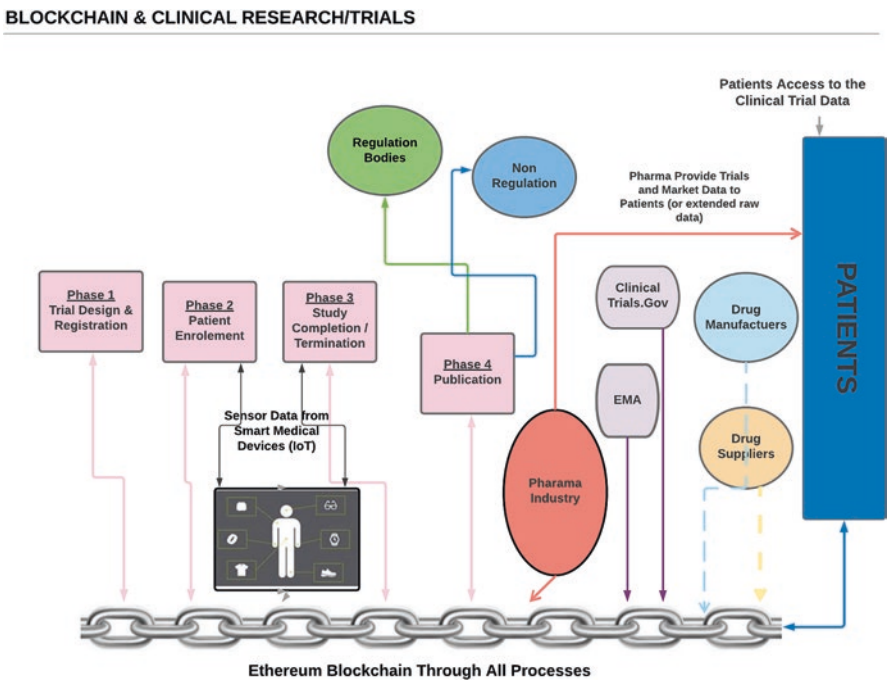

Fig. 3.2 Theoretical model using blockchain mechanism to strengthen the clinical research processes

is given (and not a permissonless public method, such as bitcoin). Ethereum also has the benefits of smart contracts as shown in the model presented by Benchoufi and Ravaud (2017) discussed earlier, where an immutable timestamp and time ordering can be achieved. Data can be stored off-chain (due to patient sensitivity and possible data size) but permissioned and authenticated via the Ethereum blockchain.

3.4 Using Blockchain for Tackling the Issues

To explain the theoretical blockchain model, this section describes the clinical data journey and how blockchain supports more transparency and strengthens the privacy of clinical and patient data. Blockchain can be the layer through the whole clinical trial journey and be used to verify, validate and sanity check all transactions and interactions that are recorded, and time stamped in a way that delivers integrity. There are many parts to the chain that can be subject to any of the issues discussed.

3.5 Clinical Trials & Research Phases

Clinical research is a very important process to facilitate new medications and improve patient outcomes and procedures that can accommodate a better way of life for many people. Clinical research is necessary to assess how treatments will work with patients, if they can be judged to be safe and lead the way to prevention based medicine. The process to undertake the research is known as trials and formulates the testing operation.

Great trust is placed in the process but at many points along the journey it is subject to data not truly being represented and a fraction of the research found in published reports, Song et al. (2010). Figure 3.3 shows the path of data and a mechanism to provide a way of immutability, from the start with the clinical phases to the provision of important feedback from the market to clinical researchers and patients who undertook the trials. The clinical trial data regarding study purposes, patient consents, registration information can all be stored on the blockchain through smart contracts giving a time ordering stamp. If any revision changes occur to the trial,

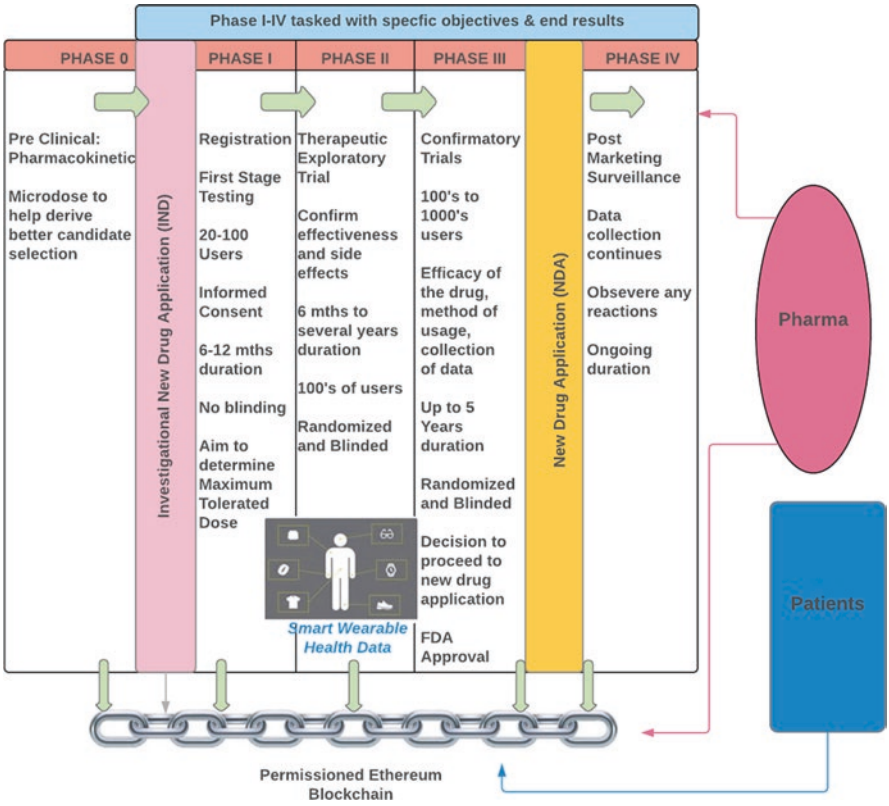

Fig. 3.3 Blockchain enhancing the privacy of data through the clinical phases

then the patient needs to give consent and it is recorded in the same fashion. This is an important aspect explained later in the data analysis in later sections as changes in any trial method could have an impact to the patient and they should have given consent to proceed on any new significant amendment. It can be seen in the data analysis given from the raw data collated in the wide gap in outcomes reported compared to the original Protocol setups.

There are many examples of where in Phase III trials, data remains unpublished after studies are completed and this can remain so for several to many years: such as gabapentin, paroxetine, pregabalin, oseltamivir and zanamivir and with oseltamivir (Tamiflu as its more known name) resulting in worldwide healthcare misdirection, Ramírez (2013). This could be avoided if data capture was an essential requirement and all data, including non-successful trials, were secured onto the blockchain model. The issue of data being cherry picked or reported selectively has a detrimental effect for researchers, physicians and patients themselves.

3.5.1 Clinical Trial Phases

As mentioned already, clinical trials compose of a number of phases all of which follows a protocol that has an intervention to arrive at understanding the safety, effectiveness/performance, safety and how the dosage would best work. Some trials can be randomised where participants are randomly selected to be given the approved treatment that is up to date or a drug that is under development. The trials are normally blinded, in essence this means the physician is not aware of which participants receive treatment. This is done to protect the integrity of the trial, so study teams are not biased or leant to one direction if they know, for example, which participant is taking the placebo treatment. Usually the trials can be conducted when all information collated on the quality of the nonclinical safety has adequately passed approvals (this can be a committee type approval).

3.5.1.1 Clinical Phase Stages

To help understand the detailed stages of clinical trials this section details a breakdown of different processes within the stages (refer also to Table 3.1). Knowing the stages can help better position why perhaps blockchain can play a significant factor to protect in each phase the multiple data points that are captured and audit trail will be more transparent. In later sections multiple issues are presented due to the current structure clinical trials operates in.

Table 3.1 Different processes within the stages of clinical trials

Types of trials	Description
Treatment	Allow testing of new synthesis of drugs or therapy approaches
Prevention	Methods to assess in preventing those that never had the particular disease or prevent return of the disease. Depending on approach will depend on including medicines, vaccines, vitamins, minerals or lifestyle changes
Diagnostic	Used to evolve better tests or procedures for diagnosing types of disease and may include those with signs or symptoms of disease/condition
Screening	To help with early detection screening is useful to help better detect signs
Quality of life	Looks at ways or methods to advance the comfort for those with chronic illnesses

3.5.1.2 Design Considerations of a Trial

It might seem detailed for a publication such as this to go into depth in clinical trial design. However, it is connected to what is delivered in the clinical outcomes as they should match to the objectives set out as part of the design and ratified in the Protocol that is approved to proceed as trial. This is evident as causing issues when analysed in later sections in this Chapter.

Objective of Trial These are what you would expect in terms of the medical questions that need answering (e.g. number of subjects, duration, etc.) but more importantly the objectives most likely are more than one and need segregating into Primary and Secondary objectives. Every trial should have primary clinical research question(s) that is not vague but is thought through after much deliberation to arrive at a particular hypothesis that can be tested according to National Center for Biotechnology Information (2018). Secondary questions are usually constructed to support primary questions.

Patient Selection To target the patient population, asset of eligibility criteria needs to be positioned as enrolment of patients can then be more specifically addressed. To set the right selection process a set of inclusion and exclusion criteria is created. In simple terms to be eligible for the trial a patient must meet all the inclusion criteria.

Control Selection It is an FDA requirement to have well controlled trials so that unbiased or non-selective evaluation of the effectiveness and safety of the drugs is carried out. If bias and selective reporting becomes part of the delivery, then a cascade of issues can arrive in Phase IV (post marketing).

Randomisation This process is derived before the intervention begins where the study participants are randomly allocated to receive one or other alternative treatments that form part of the study. Some participants receive the study treatment while others receive the standard treatment or a placebo. This is done to eliminate

any bias and allows blinding of the identity of the treatments to participants, assessors and other. Randomisation itself is subject to variations (simple, restricted, stratified and adaptive).

Blinding Also, known as masking depending on organisations where various groups involved with the trial are withheld information, such as patients, healthcare providers or researchers. This is fundamental part of the process to again protect bias from happening and there are a number of variations such as open, single, double and triple blind. Below Fig. 3.4 shows typical blinding process and procedure.

3.5.1.3 Description of Process in the Phases

Phase 0 (Pre-Clinical Trials) This phase is used to help derive a better candidate selection for the full trial by applying to a small select number of participants (or animal study) and provide a microdose. Usually before any testing in humans can begin, it should have had extensive laboratory research performed to arrive at some rational drug design, look at synthesis and purification before proceeding to animal testing. It helps rank the best pharmacokinetic (PK) pharmacodynamic (PD) parameters to decide how to take forwards the development. This can make sure to limit chances of adverse effects.

IND (Investigational New Drug) If Phase 0 is successful and passed successful testing, the FDA (Food and Drug Administration) is given the testing data and requests FDA approval (the IND application). If approved, a formal written protocol

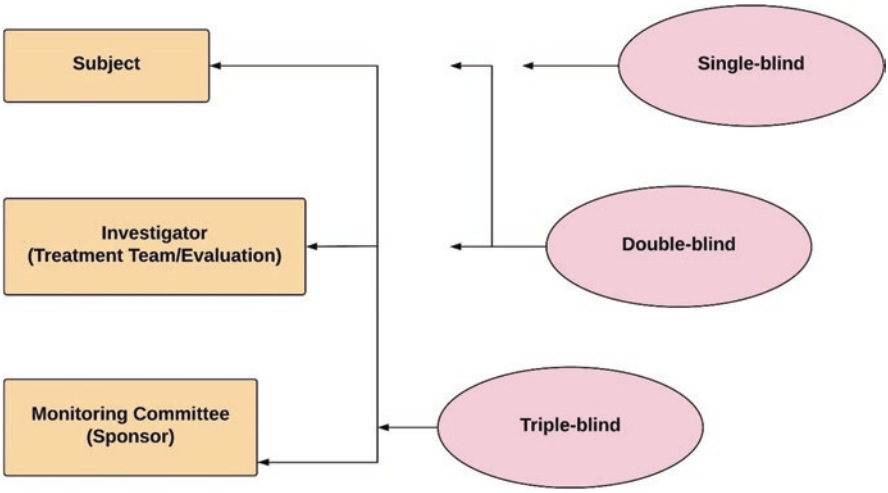

Fig. 3.4 Blinding process in clinical trials

is created, and human testing may commence. The IND application would consist of preclinical data, composition and source of drug information, chemical and manufacturing information, proposed clinical plans and protocol and ethical committee clearance.

Phase I Ensures it adheres to the Declaration of Helsinki and ICH GCP (International Conference on Harmonisation). Informed consent is required, approval by regulatory body and Protocol approved by Ethics Committee. First stage of testing in humans and designed to test safety, PD and PK of the drug and tolerance levels. There is no blind study at this stage. The aim of the trial is to assess the maximum tolerated dose (MTD) of the new treatment. The number of participants can vary from 20 to 100 and a duration of 6–12 months.

Phase II Usually a therapeutic exploratory trial, which are controlled clinical studies, to confirm the efficacy, observe safety issues/side effects and can be tested in patients that may have the disease the treatment is designed to target. Testing can be randomised, single blind (comparison with standard drugs and participants do not know if they have received placebo or standard drug) or double blind (compared with placebo standard drug and physicians and participants do not know which group received placebo or experimental drug). A duration of 6 months to several years and approximately 20–300 patients.

Phase III Designed as a therapeutic confirmatory trial testing the efficacy of the drug against existing therapy, determine optimal dosage schedules (usually termed Therapeutic Confirmatory types). A large scale randomised, controlled and blinded trial on 100's to up to 3000 patients and designed to confirm that the preliminary evidence amassed in Phase II is safe to administer in the way designed and intended recipients of the new drug. Timeline is up to 5 years and because of this can be expensive, difficult to run and therefore collation of data is important to validate all. At the end of Phase III, a decision is made as to either proceed to file for a NDA or terminate.

NDA (New Drug Application) This is the formal proposal for approval to making a new drug for sale and the NDA contains all the necessary data from preclinical to Phase III.

FDA Approval There is a process for the FDA to review and may take 2–3 years. The evidence to sway approval should be that the drug is safe and effective, benefits are more heavily weighted and proposed labelling is correct.

Marketing Permission The drug will undergo a marketing phase.

Phase IV (Post Marketing Phase) The drug is out in the market and studies continue on data collation, analyse any adverse effects/reactions and if harmful effects are found the drug can be no longer sold or restricted. The phase may also involve

safety monitoring, called Pharmacovigilance and any support such as technical. Further evaluations are undertaken on cost/benefit analysis (Pharmacoeconomics).

3.6 Smart Wearable Health Devices in Clinical Trials

Some years before the invention of smart wearable devices the data collection was a manual process and could be managed by interviewing the users involved in the trial. This may not achieve the most accurate results, since it's based on experience and memory and subject to bias in the patient's interpretation. There is also the question of privacy and security of how these data records are kept.

More advanced development of smart health wearable devices (IoMT) has taken out the unpredictability of capturing accurate data or having to plug devices to download to computers. These devices can come in a multitude of types and use cases ranging from activity trackers, pacemakers, monitoring, etc. Data can be transmitted in real time to researchers without any additional practical requirements from those participating in the trials. Data is captured seamlessly, uploaded and synchronised to cloud and blockchain acting as the authentication piece. All associated data on the patient can be stored and connected in a timestamp ordering manner on the blockchain and connected to patient healthcare records. This gives complete accuracy as chronological ordering and can be adhered to several smart contracts as milestone points in trials. It also takes care of the silo issues of containing data in separate locations which comes with the problem of cyber security breach risks; interoperability is a key aspect here. Liang et al. (2017) explain a similar process in their presentation of integrating blockchain with healthcare wearables.

One of the other concerns that blockchain can remedy is a way to store and protect the huge growth anticipated in healthcare wearables and its associated data coming from Wireless Body Area Networks (WBAN). This concern, as mentioned previously regarding healthcare being a primary target for cyber hackers and data breach. If alternative mechanisms such as blockchain are not considered, then there is a greater risk of more data being breached through the increase in attack surface with the volumes of heath wearable data now also considered a target for cyber-attackers. The patient is the most vulnerable in this current cycle with no control, access or understanding of where the data is kept or even if the breach has happened, although GDPR is designed to at least give notification within 72 h of breach occurrence; however, this does not help the patient if security was not taken care of. Wearable technology is a significant evidence addition to the trial process and blockchain is the underlying support to all parts of the trial chain.

3.7 Publication and Post Marketing Effects and Issues

When it comes to Phase IV, post marketing, it is a very crucial stage of the phase. Hopefully if all has been carried out diligently in Phase 1–3 and all data collated (whether positive or negative) then when the drugs are available in the market it will not have any adverse and unexpected effects or results. However, as explained in more detail later in this Chapter, if processes are not followed and data is not collected in correct manner there are a spiral of issues that can cascade from serious, such as fatalities, downwards. This can be a lot to do with the way reports are presented and distort the information given for evaluation or approval. In the true sense there should not be any 'bad' information as even negative results are valuable to all associated in the trials process.

Publication bias, cherry picking, and selective reporting are issues in the current trials process. The annual spend by pharmaceutical industry on clinical trials is circa 90 billion USD and as example of the scale of activity, Roche and Novartis in April 2013 declared activity in 1000 clinical trials, Public Eye (2013). A lot is at stake for these companies and why there is public pressure for a method to increase higher transparency to ensure that evidence-based processes avoid the affliction the clinical research industry suffers in the form of selective publishing that can distort the clinical outcomes by obscuring relevant data to researchers and patients, Ross et al. (2012). There appears to be a lack of accountability, marketing involvement and practise of seeding trials, particularly in industry sponsored trials. As Ross et al. (2012) outline in their research that seeding trials does not inform on all objectives to patients and researchers and effects patients from making fully informed consent decisions. In this Chapter included are some examples of litigations undertaken on pharmaceutical companies who have placed cherry picking, misconduct and fraud as a part of the clinical trial process in order to achieve hidden objectives and highly unethical practices that go largely unreported.

The blockchain model proposed would handle every part of the research process including any published effects and feedback from the market place, so researchers can gain extended understanding to align on new or other trials. This can be said for any unpublished data and seems a reasonable request to allow all data to be accessible.

3.8 Regulation/Non-regulation and Pharmaceutical Behaviours

The role of regulatory bodies, such as in the UK the Medicines and Healthcare products Regulatory Agency (MHRA), takes care on approval of regulating medicines, medical devices and associated equipment with its main aim to safeguard public health. There are many international regulatory bodies around the world and they often collaborate with each other e.g., Food and Drug Administration (FDA).

In the case of, for example, MHRA they would issue a licence (marketing authorisation) to allow issue of medicines for treatment once full assessment has been undertaken by an evaluation team of experts. Testing of the drugs is the process through clinical trials and will have had to meet strict criteria.

However, even with an approval process undertaken with regulatory bodies there looks to be a number of issues. John Castellani, of PhRMA (Pharmaceutical Research and Manufacturers of America) was quoted to give opinion that if regulators viewed all trials data behind closed doors then it would be good enough, Goldacre (2013). But this implies a mistrust, no chances to review all sets of data in a transparent manner and in more direct terms, which Goldacre (2013) makes good point on, is that the serious implications to patients with exposure to drugs that may be more harmful or of no effect at all. In certain cases, regulatory bodies have not identified the data inconsistencies that previous independent parties have seen. It would benefit all if whole data sets, including raw data which can be thousands of pages long, were authenticated through blockchain so many independent eyes from all parts of the process can validate and test the theories as does in normal world of academic science.

Whilst it appears pharmaceutical companies look to present data in a selective way there are some in the industry that are looking to offer a more transparent access to all trial raw data sets. GlaxoSmithKline signed up to AllTrials (started in 2013 as advocating open access on all trials research) with an open declaration of transparency; AllTrials (2013). This can only benefit patients and allow then access and protect privacy through blockchain.

3.9 Drug Manufacturers and Suppliers

Since this research presents a holistic solution for all parts of the trials process with blockchain as the model to encourage transparency and protect privacy, then it is also good that blockchain can also offer a secure method for drug traceability. It is mostly about strong chain of custody in the manufacturing and supply of drugs to a patient and blockchain heralds itself as the answer to the issue where things have gone wrong and acts as the block to fake drugs entering the supply chain. As it stands counterfeit drugs are estimated to be at 50% in low income countries with a global market range of $200 billion (DrugPatentWatch 2017). As well as counterfeit drugs being a failure to treat the patient, it may also kill/harm the patient. Blockchain will create the place where the ecosystem of a supply chain would interact and record all transactions without being able to tamper the records. The result is a transparent method to secure the chain of custody and data.

3.10 Patients and Clinical Researchers

Perhaps the most important part and central to all the transparency and privacy of the data theme are patients and researchers. As it currently stands along the clinical research data flow explained in earlier sections, if some information is excluded or selectively positioned for the reasons mentioned then the most impact is conveyed to the patient and researchers. There seems a trust given by patients to the clinical research providers that their information gained from trials will help advance medical outcomes. This trust is extended down the line with regulatory bodies to approve to release to the public and the pharmaceutical industry to share the full clinical data sets. Consenting in this trial process usually to a patient means being exposed more understanding of the results. It is stated in the Declaration of Helsinki that participants should be advised of the results. However, the placement of this trust looks in many cases to misguided as many participants/patients are not given access to results or further understanding; Logvinov (2014). In the previous Chapter (Digital Transformation of Healthcare) patient centric data was discussed and the benefits to place patients in the centre of all activities. This clearly makes a more transparent model in terms of clinical trials as the patient can be more directly engaged and also learn more on the trial they undertook, and any other data sets outside their own. They can also understand further from pharmaceutical companies what the wider effects or analysis are after Phase IV when the drugs are publicly available.

Researchers have the issue of not accessing all data impacts in the post marketing phase that pharmaceuticals may chose or not chose to report, and so science may develop in a direction that is either stifled or led in alternative routes. Patients have no control over their data and where and what is held. If blockchain can facilitate as a mechanism to safely share data, then there are more opportunities available to researchers than just curing the interoperability issue. A network of patients, scientists, researchers, clinicians, etc., could actively share data across the board to help advance research in a more dynamic fashion. If all the data is recorded and audited and permissions given to access, then potentially this can go a long way to resolve selective reporting. Intervention data exaggerated, misconstrued or negative results hidden are causing the effects mentioned later in this Chapter.

3.11 Clinical Trials Processes

The clinical trials data flow and its associations with interoperability, privacy and security of the healthcare data makes a very captivating model to analyse. The purpose of the next few sections is to review the following:

- Survey data from leading industry organisations taking a global perspective regarding if blockchain is ready for adoption to healthcare initiatives.
- Analyse some key data points in the clinical trials process, which are Trial Registration, Informed Consent, Trial Outcomes and healthcare cyber security

breaches. This helps determine, with other evidence found in previous sections and in critical discussion later in this Chapter, that there is a real need to look at a mechanism to support transparency, security and privacy of healthcare data and will help validate the urgency of this need.

3.12 Clinical Registration Analysis

It is difficult to assess globally how many trials go unregistered and unpublished and is thought-provoking to imagine that to some extent there is a lot of wastage of expenditure and any knowledge that could have been gained and shared with other researchers or groups. Prayle et al. (2012) took an in-depth review of registered and interventional clinical trials and discovered that only 22% of trials that were mandatory to post results actually did. It raises the question of how monitoring is taking place. Also, another interesting fact is that 40% of industry sponsored trials reported their results compared to 9% in non -industry sponsored trials.

Whilst the outcomes of clinical trials are clearly measurable factors and issues revolving around are explained in this Chapter, it's also recognised that a lot can be said for the accuracy in how clinical data is registered and over the years the quality has been noted as being poor, Viergever et al. (2014). The analysis compared a previous 2009 study by Viergever and Ghersi (2011) against a 400 randomised records sample in 2013 (taken from 23,046 interventional trials) on registration data, interventions and outcome. The analysis showed increasing trial registration/quality issues and needed improvement. Half of industry funded trials did not input the primary contact name and in non-industry funded trials it was nearer to 95%. Contact information appears to be removed by those undertaking trials when the study is completed or for some reason stopped. Other issues show retrospective registration, which can cast bias to results. There are driving factors of registration in the form of legal, regulatory, ethics, funding policies, etc., and as Viergever et al. (2014) point out that even though there are these important considerations, some trials still go on to be unregistered. In the assessment they also found that the primary outcome was only reported in 66% of registered trials and other details such as medication dosage., etc. was reported in 70% of registered trials, Viergever and Ghersi (2011). It seems from the research that besides just increasing the percentage of trials registered, if some enforceable measures for quality assurance could also be considered (this would be how to record/capture data and look at what controls to enhance the process).

The irregularity of the method and way registration is undertaken adds to the publication bias explained later in this section and a further look into why is it that there are some organisations that require registration but do not enforce it; or as best practice than mandatory. An interesting quantitative and qualitative analysis was undertaken by Wager et al. (2013) and reviewed a random sample of 200 journals from a list of 3512 journals.

The quantitative study shows:

– 142 journals require no registration (71%)
– 55 require registration (28%)
– 3 were encouraged to register (2%)

It's interesting to also understand the qualitative study Wager et al. (2013) did where interviews with 15 editors of a selection of 31 journals were undertaken to understand reasons trial registration was not required and as follows the main points:

– Competition; in the way of concerns of failing to rival journals who are not themselves imposing process of registration
– Primary papers; perhaps as a smaller or mid-level journal not requiring submitting papers
– Lack of clinical trials papers; in case some organisations might not publish many clinical trials to formalise registration
– Small trials; if the trial was a small research project there were feelings that registration would probably be not a necessary factor
– Effectiveness of registration; doubts whether negative trials would be published, even if registered
– Developing regions; trial registration in emerging countries may not have enforced registration so requesting requiring this for papers may create issues if there is no registration in the country or origin.

Table 3.2 from Wager et al. (2013) shows over a period of time (including their sample selection) of analysing different random journals that requiring to register is more or less of same percentage. This could be an additional ingredient to publication bias and adding to the problem in a cumulative way.

3.13 Informed Consent and Privacy

Informed consent sits well with the flow of data with regards to this research and transparency. The role of participants is strategically important to the clinical trials study process and therefore should have assurances on the ethics, respect privacy, inform participants on any changes and generally involve them at all points. Hence transparency is the key theme here. There is a process that should be followed from the first agreement/consent to ongoing periodic checking with participants that they still bear willingness to continue. Where it can be of issue, in terms of transparency and privacy, is when new information comes to light and a new consent form should be agreed. This is especially important if, for example, to highlight new side-effects.

There are current issues in informed consent. As example, a FDA report into 57 clinical trials found that over 53% failed to protect the participant interests and issues in the process of informed consent; Seife (2015). Ethical safeguards are in place with reference to the Declaration of Helsinki as per World Medical Association (2018) so at least the guidance and operational framework is there. But it needs a

Table 3.2 Comparison over the years of 'required registration'. (Wager et al. 2013)

			Source	Registration		
Study	Search date	Journals		No in sample	Required	Encouraged
Matarese	2008	Italian; UK	Medline; Medline	76; 76	0; 21 (28)	—; —
Meerpohl	2010	Paediatric	*Journal Citation Report*	69	11 (16)	5 (7)
Meerpohl	2011	Open access paediatric	*Directory of Open Access Journals*	41	9 (22)	4 (10)
Krleza-Jeric	2009	WAME members	WAME membership list	102	35 (34)	—
Kunath	2011	Urology	*Journal Citation Report*	55	18 (33)	2 (4)
Wager	2012	Random sample	Cochrane CENTRAL database	200	55 (28)	3 (2)

diligent approach from clinical organisations and as per this research, a model that can be applied onto blockchain to secure all stages of consent; that is all notifications of checking to proceed, any new trial protocol amendments, etc. If applied as a smart contract, then privacy is respected and data capture of any event time-stamped in order.

3.14 Clinical Outcomes Data Analysis

Clinical outcomes are the measuring tool to determine the baseline objective that patients will undergo to assess the drug efficacy and treatment process and success ratios. In the case of clinical trials, before commencement a Protocol/Registry is designed that lists the parameters i.e. types of participants, procedures, medications, duration, outcomes, etc. It's expected to conform to CONSORT (Consolidated Standards of Reporting Trials) which gives a minimum check list specification to aid transparent reporting. It's of high importance since this is the central piece to the whole chain of events. If poorly documented or inadequate validation against the outcomes is given, or worse if selective reporting is applied leading to misconduct and fraud, then potential impacts are cascaded to patients, from minimal issues to loss of life. Therefore, the data analysis in this part of the data flow in clinical trials looks to be essential in what is captured, reported and possible effects (these can only be validated from patient use in post marketing of which seems sufficient and growing in evidence and explained in later section).

3.15 Global Aspect of Clinical Trials

If the number of trials/studies enrolled in ClinicalTrials.gov (the largest of clinical trials database run by US National Library of Medicine) is currently, as of May 30, 2018, at 274,416 then the sample selection of data analysed in this section presents a worrying concern on the current state of affairs; (ClinicalTrials.gov 2018). See Table 3.3 for the global percentage breakdown, Fig. 3.5 for the perspective growth of Trials over time and Trials results posted in Fig. 3.6.

It is also worth understanding the breakup of types of studies undertaken and what results are posted on ClinicalTrials.gov as in Table 3.4:

3.16 Clinical Outcomes Data Concerns

Given the prospect that there is a potentially large amount of data that could be reviewed and extracted; for the purposes of assessment for this research a smaller subset is reviewed and validated with original Protocols and its delivered outcomes. It suggests a more extensive study can be undertaken outside of this research for larger data sets and analysis to see if there is a more substantial problem than envisaged.

COMPare (CEBM Outcome Monitoring Project) is an organisation that monitors clinical trials and has a mantra to alert on misreported outcomes and are monitoring the top 5 medical journals (The Lancet, Annals of Internal Medicine, JAMA, BMJ and NEJM). They analyse the trial protocol/registry entry (as per CONSORT) and any outcomes that are switched are reported and letters sent to editors to notify; COMPare Trials Project (2016). It's important to measure against the protocol set, so to avoid a false positive by random chance. When the trial is complete there should be a match to see where reported outcomes are different from pre-trial. It should be declared and explained so unbiased representation is given.

The following Fig. 3.7 shows high level report created from the raw data as per site COMPare Trials Project (2016). It's a quantitative analysis from period October 2015 to January 2016 undertaken by coders who audited, checked and advise the pre-specified outcomes. Also, if it was reported and if new outcomes were added.

Table 3.3 Number of global registered studies. (ClinicalTrials.gov 2018)

Region	Percentage of Registered Studies
Non-U.S. only	130,418 (48%)
U.S. only	96,663 (35%)
Both U.S. and non-U.S.	14,845 (5%)
Not provided	32,490 (12%)
Total	**274,416 (100%)**

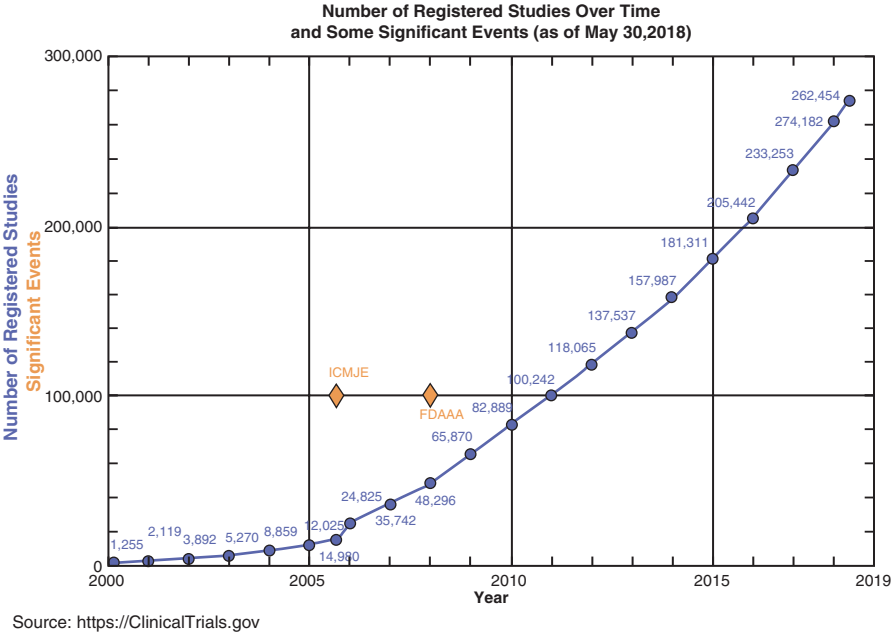

Fig. 3.5 ClinicalTrials first posting since 2000. (ClinicalTrials.gov 2018)

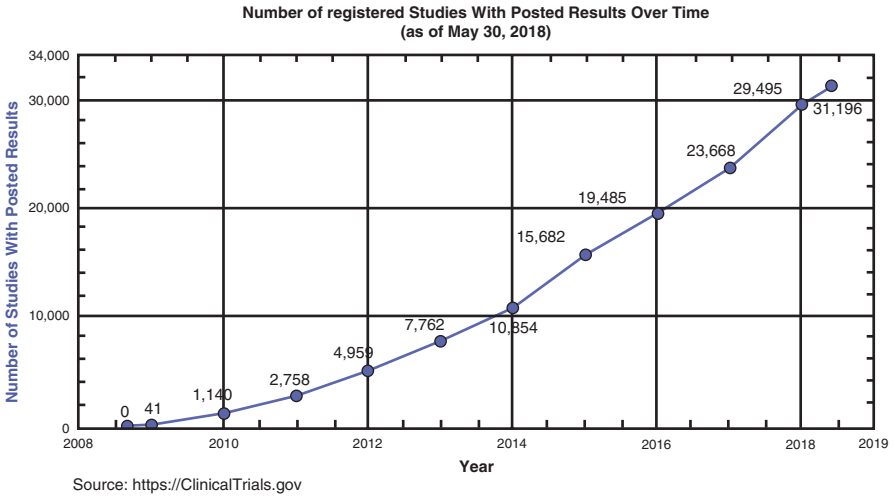

Fig. 3.6 Number of registered studies with results posted. (ClinicalTrials.gov 2018)

Table 3.4 Types of registered studies. (ClinicalTrials.gov 2018)

Study and intervention type (as of May 30, 2018)		Number of registered studies and percentage of total	Number of studies with posted results and percentage of total
Total		274,416	31,217
Interventional		218,243 (80%)	29,376 (94%)
Type of intervention	Drug or biologic	128,004	23,415
	Behavioural, other	67,229	5207
	Surgical procedure	23,245	1610
	Device	26,870	3643
Observational		54,919 (20%)	1841 (6%)
Expanded access		481	N/A

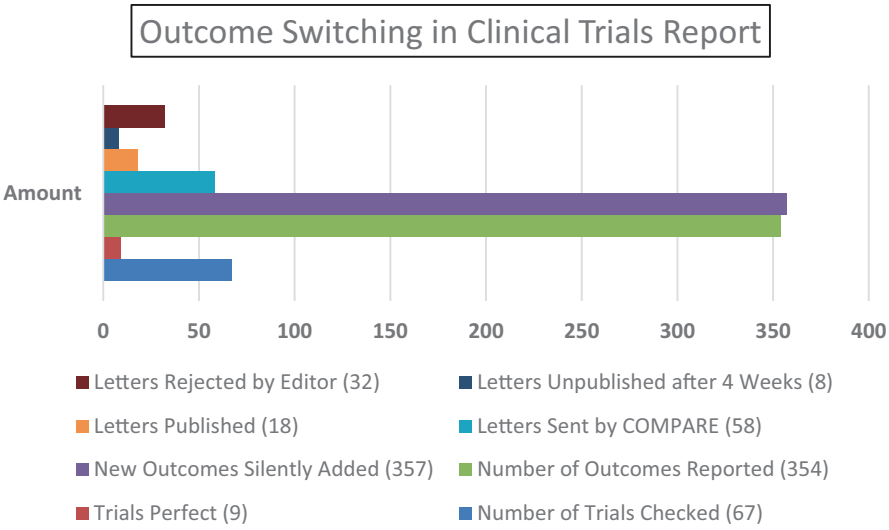

Fig. 3.7 Outcome switching in clinical trials report. (Data sourced from COMPare Trials Project 2016)

Full sets of raw data can be located at the COMPare Trials Project (2016) and links to the full assessment sheet for each trial to ensure transparency of the analysis.

Figure 3.8 shows 67 trials were reviewed from October 2015 to January 2016. Only 9 Trials were found to be perfectly correct whilst it was found 354 outcomes were not reported. However, noted were 357 new outcomes that had been silently added. COMPare have followed up by sending 58 letters of which 18 letters were published. If a mean average is calculated it only presents each trial as reporting 58.2% of its outcomes from original specification. The average of silently added

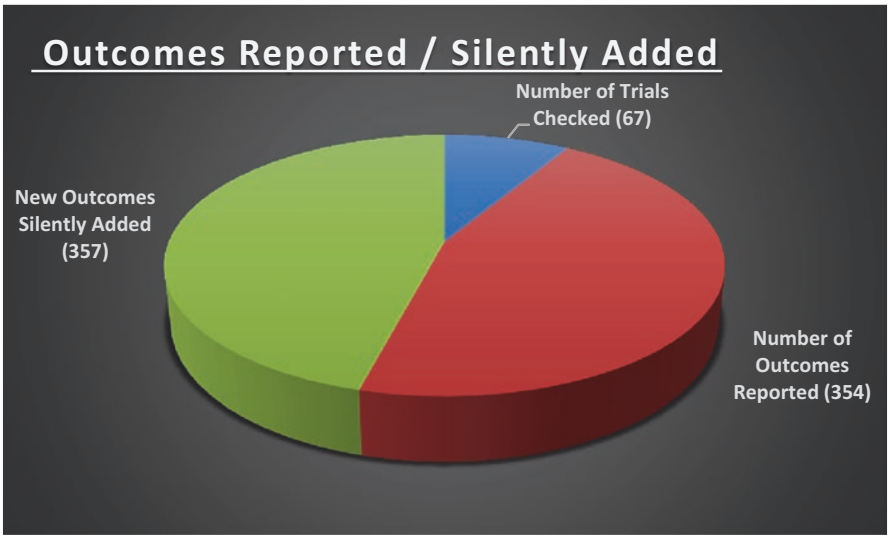

Fig. 3.8 Trials outcomes reported vs trials outcomes silently added. (Data sourced from COMPare Trials Project 2016)

outcomes is 5.3. COMPare is currently assessing this first set of findings as an academic submission but provides useful deliberation and concern for this research regarding transparency, security and privacy of data. It also suggests more work in this area and a more transparent method of monitoring the Protocol and outcomes delivered; blockchain could assist in this deliberation by using smart contracts making review easier over a period of time.

Table 3.5 shows a slice of the COMPare Trials Project (2016) of 67 Trials reviewed which are showing the pre-portion of pre-specified outcomes as correct, which should show 100% and the new undeclared non-prespecified outcomes that were added and for a correctly reported paper that should be zero. Table 3.6 describes the higher undeclared non-prespecified outcomes and a snapshot of the top sample of data taken from a full data set.

3.17 Research Misconduct, Fraud and Selective Reporting Impacts

Fraud, misconduct and selective reporting all have negative and serious impacts, but it is worth distinguishing the difference to understand what the drivers are. It may be assumed fraud and misconduct could be classified as being the same activities and definitions, when in fact there are clear differences. According to Gupta (2013) fraud has some form of deliberate action whilst misconduct may be a case of a

Table 3.5 Correctly added pre-specified incomes. (COMPare Trials Project 2016)

Journal	Trial title	Trial published	Prespecified outcomes reported	Undeclared non-prespecified outcomes reported
BMJ	Liraglutide in people treated for type 2 diabetes with multiple daily insulin injections: randomised clinical trial (MDI Liraglutide trial)	28/10/2015	19/19 (100%)	0
JAMA	Effect of vericiguat, a soluble guanylate cyclase stimulator, on natriuretic peptide levels in patients with worsening chronic heart failure and reduced ejection fraction: the SOCRATES-REDUCED randomized trial	08/11/2015	2/2 (100%)	0
JAMA	Naproxen with cyclobenzaprine, oxycodone/acetaminophen, or placebo for treating acute low Back pain	20/10/2015	1/1 (100%)	0
Lancet	Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial	21/11/2015	2/2 (100%)	0
NEJM	A randomized trial of progesterone in women with recurrent miscarriages	26/11/2015	9/9 (100%)	0
NEJM	A study in older subjects to evaluate the safety and ability of andexanet alfa to reverse the anticoagulation effect of apixaban or rivaroxiban	09/11/2015	20/20 (100%)	0
Lancet	Skin antisepsis with chlorhexidine–alcohol versus povidone iodine–alcohol, with and without skin scrubbing, for prevention of intravascular-catheter-related infection (CLEAN): an open-label, multicentre, randomised, controlled, two-by-two factorial trial	21/11/2015	7/8 (87.5%)	0
Lancet	Extended pre-exposure prophylaxis with lopinavir–ritonavir versus lamivudine to prevent HIV-1 transmission through breastfeeding up to 50 weeks in infants in Africa (ANRS 12174): a randomised controlled trial	18/11/2015	3/5 (60%	0
NEJM	Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer	22/10/2015	3/5 (60%)	0
NEJM	Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis	16/11/2015	5/9 (55.6%)	0

(continued)

Table 3.5 (continued)

Journal	Trial title	Trial published	Prespecified outcomes reported	Undeclared non-prespecified outcomes reported
NEJM	A phase 3 randomized trial of nicotinamide for skin-Cancer chemoprevention	22/10/2015	5/11 (45.5%)	0
NEJM	Cabozantinib versus everolimus in advanced renal-cell carcinoma	05/11/2015	4/16 (25%)	0

Table 3.6 Analysis of higher undeclared non-prespecified outcomes. (COMPare Trials Project 2016)

Journal	Trial title	Trial published	Prespecified outcomes reported	Undeclared non-prespecified outcomes reported
Lancet	An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial	24/10/2015	0/12 (0%)	17
Lancet	Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term (PPROMT trial): a randomised controlled trial	09/11/2015	17/35 (48.6%)	17
Lancet	A randomized, open-label, multi-center, active-controlled, parallel group study to determine the efficacy and safety of the REG1 anticoagulation system compared to bivalirudin in patients undergoing percutaneous coronary intervention	04/11/2015	1/1 (100%)	21
BMJ	Stepped care for depression and anxiety in visually impaired older adults: multicentre randomised controlled trial	23/11/2015	0/8 (0%)	22
Lancet	Neurodevelopmental outcome at 2 years of age after GA or awake-regional anaesthesia in infancy	04/11/2015	0/3 (0%)	26

failure to follow structured and well established protocols. Fraud has the intentional and planned actions to cause deception for personal gain by fabricating research data and misleading reporting of the results. With misconduct it may not be intentional actions or more a case of poor management to follow structure and processes that in set in place. The Medical Research Council makes clear its statement in its code on fraud and misconduct and has clear distinction on deliberate, dangerous and

negligent actions that deviate from accepted practices and protocols. This will not include honest errors and mistakes, and even poor research that has not the intention to deceive.

3.17.1 Types of Fraud and Misconduct in Clinical Research

Fabrication New data sets and records may be created. One area of the clinical research workflow that may be prone to this deception is at the various stages of Informed Consent, mostly in Informed Consent forms. Here data could be fabricated if some amends to the trials were made, then to imply consent was acknowledged by the patient.

Falsification Data is altered in any records so deliberately implying a different version of outcomes or perhaps hiding negative data.

Plagiarism Other person's work/ideas may be taken and acknowledged as one's own work.

Deception The intentional obscuration or inclusion of data that may create a bias or lead to selectively represent misleading directions.

The motivations to any of the above can be due to a number of reasons, some for personal gain and others for professional ambitions or just inadequate disciplines to ensure that the protocols and procedures are diligently followed taking in consideration Medical Research Council codes of conduct and the overall importance of accuracy. If any of the above consequences suffer the actions of the types of fraud and misconduct, then it can have a myriad of effects and some examples explored in later examples.

An interesting report method by Seife (2015) looked at 57 published clinical trials (due to redactions many trials were not identifiable and hence only the 57 were selected) from 600 clinical trials and identified several issues. The chart analysis below (Fig. 3.9) summaries the research results, Seife (2015) and based on data it shows that 22 trials were falsified; 14 trials had issues with adverse events reporting; 42 trials had protocol violations; 35 trials had inadequate/inaccurate record keeping; 30 trials had a failure to protect patient safety and issues with the Informed Consent process; and 20 trials where violations were there but not categorized. Only 3 publications of a total of 78 publications that were outputs of the trials disclosed a picture of violations or malpractice in the trials. In others there were no expressions of these concerns and types of violations explained which presents a picture that the publications had successful trial process with no concerns.

This lack of transparency with the quantitative data examples gives validated reasons to look at blockchain as the framework to control all and ensure a better way

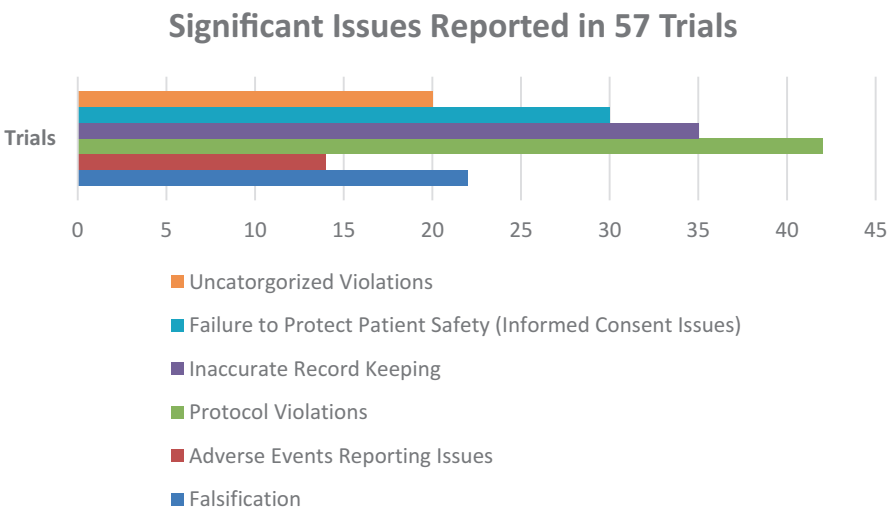

Fig. 3.9 57 Trials selected showing significant issues. (Data sourced from Seife 2015)

to modulate the data. However, the interesting aspect to these results is more than just the clear violations, inaccuracies, falsifications, etc., but more the fact of the range of potential impacts to patients. The research that was produced by Seife (2015) shines a torch on a few case studies and where, for example, falsification of laboratory results of chemotherapy regimens resulted in the researcher falsifying the lab results; this obscured the facts that the patient had impaired liver/kidney functions and was exposed to the first dose which was fatal. The researcher was found criminally negligent (a custodial sentence applied) yet no details of this appeared in the peer-reviewed content that tie-in to the chemotherapy trials the patient was deceased from.

The concerning aspect is how many trials are there where the data/outcomes are misconstrued or covered up; be it for the gain in the market edge, competitor pressure or in one's belief that showing only 'interesting' selective data is acceptable and only worth recording. The smart contracts feature of blockchain would allow a clear and transparent model to base all data and archived in a time stamp method with time ordering so bolstering integrity to the whole process. This should capture most aspects including all raw data, so situations such as the case described above can be transparently analysed by all those permissioned on the blockchain. This can ensure even the negative results or some results that do not match the positioned post marketing effects are kept in compliance and sanity checked by those unbiased and qualified to assess. Hopefully, the effects of a transparent model will lessen the occurrences of falsification, fraud, deception, etc. and more adherence to medical ethics and greater integrity.

3.17.2 Publishing Clinical Trial Data – Noncompliance

The previous sections go into a deep dive of the various stages of processes and the potential failure points. Another area to consider is the completed clinical trial publishing aspect which leaves a question mark on its conformity and compliance to publish the data. The previous sections covered where the data may be cherry picked or selectively reported, etc., but this question is more about the time to publish from completing the trial. Some cross-sectional analysis has been undertaken by Ross et al. (2012) and who reviewed compliance with FDAAA (FDA Amendment Act of 2007) on funded trials by National Institutes of Health (NIH). The analysis concluded that 46% of 635 registered and completed trials had published the results in peer-reviewed journals within 30 months of trial completion. The target is aimed at 1 year so 30 months is a long way from this target date recommended by FDAAA. Another fact is after 5 years one third of completed trials are still unpublished. This lack of diligence to publish can suggest publication bias but more importantly does not factor in consumer safety.

More analysis by Bourgeois et al. (2010) talks about observing 546 drug trials registered in ClinicalTrials.gov and discovered 66% had published their trials but again late on delivering publication and not within the requested publishing window. Just 32% of industry-funded trials had their results published within 24 months of completed trial. A larger review shows more gross noncompliance, undertaken by Zarin et al. (2011) of 79,143 records in ClinicalTrial.gov recorded that 52% of registered/completed trials had published within 2 years. There is a common theme across the analysis undertaken that noncompliance adds to the dangers and issues created when drugs are publicly available. There may be significant issues that could be stopped before widely being distributed if data was shared much earlier and transparently. Also, if perhaps other groups of researchers had access to these published results then it might add reflection to their study that would allow a change of tact or repeating unnecessarily what may not have worked first time or potentially causing harm to participants. Goldacre (2013) makes stronger comments that the number of clinical trials ignoring FDAAA requirements is more like 60–90%. It is suggested this might be due to publication rules being more relaxed with having to prove clinical trial registration.

It's clear that compliance falls short in the process as per cross-sectional studies undertaken by those mentioned in previous sections and is not in sync with FDAAA requirements. The suggestion is full disclosure and transparency on the results would provide an invaluable resource to clinicians and researchers to understand the risks/fundamental points of new drugs regarding safety and efficacy, Logvinov (2014).

There is some concern mentioned in other reports of allowing full disclosure but looks to be more a case of how something should be packaged and presented for consumption by the pubic and all. Logvinov (2014) mentions that dumping huge volumes of data into a database may not be helpful to consumers. But this can be more effectively managed via authentication on blockchain by giving permissions

to all or certain parts of data (but at least the whole data sets are there for usage). It makes sense that participants can discuss results with providers/investigators. It will also support and help the general cause of clinical research enrolment and ensure there is still interesting to participate. If blockchain can help facilitate a closer relationship between investigators and participants, then they may feel more consulted and empowered with information they receive. Pharmaceutical organisations have argued that divulging all can be a risk to their intellectual property and erode a competitive edge (especially in emerging markets that may reproduce very similar drugs on the back of the pharmaceutical bulk of research work. It is a difficult balance but likely the more important angle will sit in public health and safety than preservation of intellectual property and commercial aspects. But the Trade-Related Aspects of Intellectual Property Rights (TRIPS) does offer a protection clause (Article 39, para 3) to pharmaceutical in their right to protect opening up undisclosed data unless a threat to public health, Logvinov (2014).

3.18 Cyber Risks to Clinical Healthcare Data

Under the current methods that healthcare data is stored in presents a serious risk to the CIA triangle (Confidentiality, Integrity and availability). It is of major concern and connected to the clinical research flow of data as whilst there are substantial benefits to all in the advancement of healthcare technology; be it wearables, machinery, drugs to assist better and more targeted healthcare, etc., it also means the data will exponentially increase and needs to be a more sophisticated method to protect healthcare data. Also, it requires clearer transparency to protect the worst effects of data breach for any patient of identity theft and possible victimisation that normally follows. Fig. 3.10 below highlights this widescale breach of data across industries but clearly demonstrates that healthcare has the highest levels of attacks.

Gemalto is an organisation that collates and aggregates worldwide data breaches in various industries and proactively monitor this through the *Breachlevelindex.com*. The report is useful as is also backed by where the weblink data source originated from and so can be validated as high quality, quantitative data. It makes measurement of the data in terms of data records lost/stolen, type of breach, source of breach and filtered into the industry sectors. Gemalto apply a scoring system to value the risk factor of the breach. So, a scoring measurement of the risk impact is as follows:

- 1–2.9 (minimal)
- 3–4.9 (moderate)
- 5–6.9 (critical)
- 7–8.9 (severe)
- 9–10 (catastrophic)

When analysing the healthcare industry, the data makes interesting discoveries. In 2017, there was a 27.3% increase in records breached compared to the year of

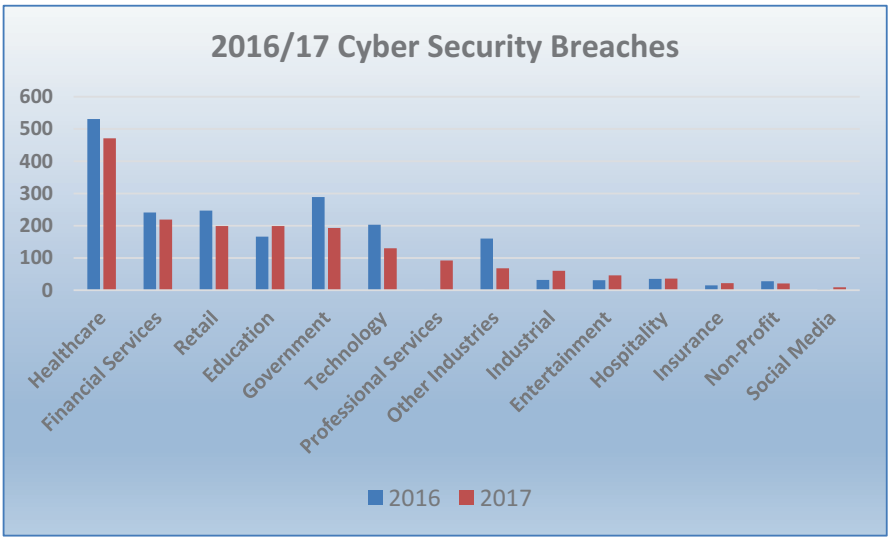

Fig. 3.10 Cyber security breaches 2017 industry comparison. (Data sourced from Breachlevelindex.com 2018)

Table 3.7 Breakdown of 473 healthcare breaches of 2017. (Breachlevelindex.com 2018)

Source of breach	Breach volume
Malicious outsider	322
Malicious insider	68
Accidental loss	82
Hacktivist	1
Type of breach	**Breach volume**
Identity theft	414
Nuisance	19
Account access	18
Existential data	11
Financial access	8
Financial loss	3

2016 (33,717,772 from 26,467,715 records in 2016). There were 473 organisation healthcare data breach incidents in 2017 (see Table 3.7 for the breakdown of categories) and the full raw data sets extracted from the *Breachlevelindex.com*.

A snapshot of the top 10 incidents can be seen in Table 3.8 where the top incident had a catastrophic breach exposing 26 million records and given a rating risk score of 9.0.

However, it is also worth to analyse and compare where the type of breach and source of breach occurs most. Figs. 3.11 and 3.12 show a dangerous correlation mix

Table 3.8 Top ten healthcare cyber security breaches in 2017. (Breachlevelindex.com 2018)

Rank	Organisation breached	Records breached	Data of breach	Type of breach	Source of breach	Location	Risk score	Weblink to site of data source
13	**National Healthy Service (NHS)**	**26,000,000**	17/03/2017	Identity Theft	Accidental Loss	UK	9	https://www.telegraph.co.uk/news/2017/03/17/security-breach-fears-26-million-nhs-patients/
36	**Commonwealth Health Corportation**	**697,800**	01/03/2017	Identity Theft	Malicious Outsider	USA	8	https://ocrportal.hhs.gov/ocr/breach/breach_report.jsf
37	**Airway Oxygen**	**500,000**	18/04/2017	Identity Theft	Malicious Outsider	USA	7.9	http://www.healthcareitnews.com/news/500000-affected-ransomware-attack-home-medical-equipment-supplier
45	**Urology Austin**	**279,663**	27/02/2017	Identity Theft	Malicious Outsider	USA	7.9	http://www.kxan.com/news/local/austin/ransomware-attack-on-urology-austin-gets-patient-information/994849601
46	**Women's Healthcare Group of Pennsylvania**	**300,000**	01/01/2017	Identity Theft	Malicious Outsider	USA	7.7	https://www.nbcphiladelphia.com/news/local/Womens-Health-Care-Group-Pennsylvania-Hackers-Medical-Information-Stolen-Data-Breach-436635983.html
66	**Med Center Health**	**160,000**	19/03/2017	Identity Theft	Malicious Outsider	USA	7.4	http://www.wbko.com/content/news/Med-Center-Health-416769003.html
72	**HealthNow Networks**	**918,000**	10/04/2017	Identity Theft	Accidental Loss	USA	7.3	https://www.hipaajournal.com/918000-patients-sensitive-information-exposed-online-8762/
74	**Pacific Alliance Medical Center**	**266,123**	14/06/2017	Identity Theft	Malicious Outsider	USA	7.3	https://www.hipaajournal.com/pacific-alliance-medical-center-announces-ransomware-attack-8925/
75	**Retina-X and Flexispy**	**130,000**	12/04/2017	Identity Theft	Malicious Outsider	USA	7.3	https://motherboard.vice.com/en_us/article/53vkba/a-week-later-hacked-spyware-vendors-havent-warned-their-130000-customers
79	**Arkansas Oral & Facial Surgery Center**	**128,000**	26/07/2017	Financial Loss	Malicious Outsider	USA	7.2	https://www.tripwire.com/state-of-security/latest-security-news/oral-surgery-center-notifies-128k-patients-ransomware-attack/

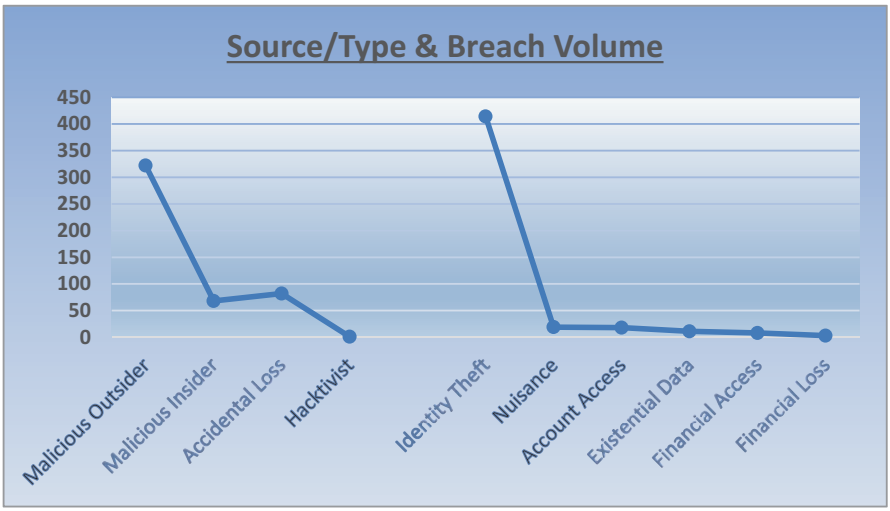

Fig. 3.11 Correlation mix of malicious outsider/identity theft. (Breachlevelindex.com 2018)

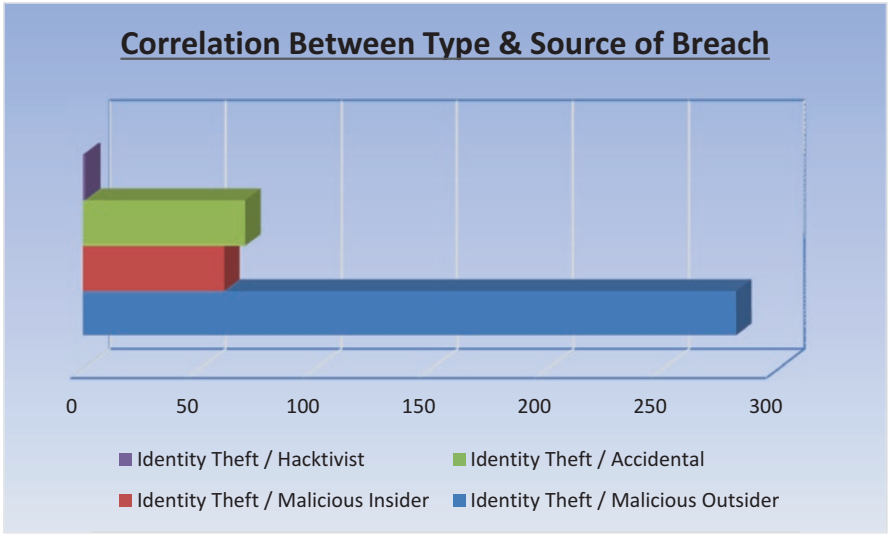

Fig. 3.12 Type and source of breach. (Breachlevelindex.com 2018)

between the worst type of breach (identity theft) and the source of breach as malicious outsider.

It is clear from the quantitative analysis that identity theft is the major objective which correlates with it being a malicious outsider orchestrating the attack. However, other sources of breach such as accidental loss are on the increase so there is likely a requirement of ongoing training programmes, better defences, etc. Whilst that is a necessity, there should be a more direct mechanism to help protect the patient when records are breached and therefore makes a strong case for blockchain application. The identity theft is the major concern since it is a well-known fact on why malicious attackers chose the healthcare industry as next section will explain.

3.19 Case Studies: Marketing Ineffective/Dangerous Drugs – Opioids Study, Breast Cancer Screening – Interoperability Study, etc

3.19.1 Opioids Misuse

Continuing with the theme of patients being at the most vulnerable position is perhaps interesting to look at the prescription opioids scandal; as this highlights the whole question on how drugs are passed through into the market with positive/selective reporting and publication. Prescriptive opioid effectiveness has been reported in the BMJ as having a very high failure rate of over 90%; Moore et al. (2013). In the report, the opioid oxycodone has a failure rate of 100% and quoted as less useful than a placebo. This appeal through the published report, to regulators such as MHRA and large pharmaceutical companies, was done to try and generate an outlook to transparency but so far did not make any impact. Whilst drugs being ineffective is not helpful to solving patient pain, the problem lies in many reports of drugs being harmful to patients, causing addiction and even fatal outcomes. There are numerous risk factors associated with Opioid use and there can't be too many positive outcomes if risk is shown to lead to hospitalisation, criminality and mortality.

Perhaps the more recent and well-known case of Purdue Pharma, that manufactures the OxyContin painkiller, is valid to demonstrate the non-transparent and misconducted way a drug was brought to market and has been associated with causing 200,000 deaths in the US whilst making £26 billion; Cohen (2018a, b). Lawsuits and litigations are the natural response but the accusations of deception in the marketing process, place serious doubts on the current system of how data and information is accessed and regulated; Bellon (2018). Figure 3.13, through the Cohen (2018a, b) report, shows the extent in the UK of how the addiction and opioid admission is growing in the UK, a worrying aspect as it follows a path already taken in the US with the UK as the largest consumer of painkillers in Europe. Prescriptions are surging (£263 million spent annually in England, Cohen 2018a, b) and the

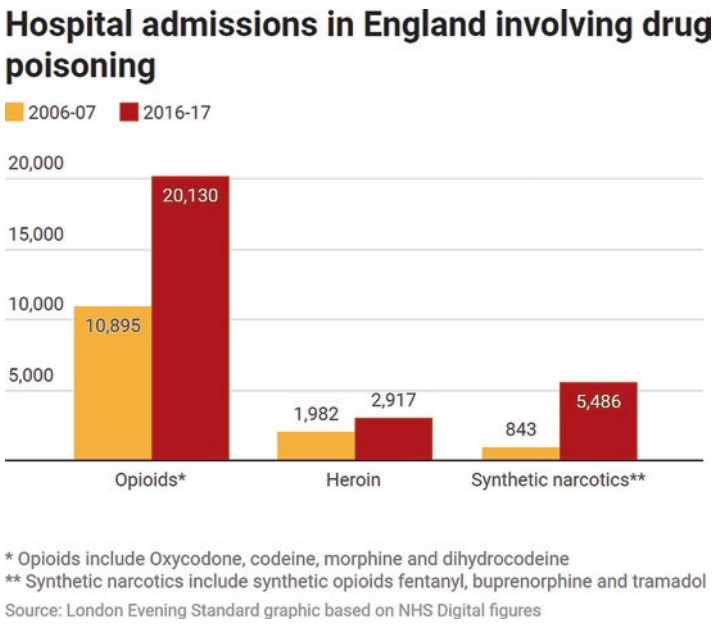

Fig. 3.13 The growth of opioid admissions. (Cohen 2018a, b)

effects are starting to become more published as opioid fatalities increase to 2038 in 2016 attributed to opioid abuse; Hurley (2017). Figure 3.14 shows the rise in opioid deaths and useful as a graphic to understand in relation to growth over the two time periods.

There are many real-life cases of effects to patients who started off with a prescribed opioid drug from their GP for pain relief for medical injuries with all beginning in good stead but then the patient having to increase to higher dosage amounts and eventually becoming a drug addict and purchasing higher quantities illegally. The destruction caused can be anything from major impacts to work, home, family and even fatality; a story that is similar to Philip Hopwood in damage to all these things but fortunately not his life; Cohen (2018a, b).

With a history of over 200,000 deaths in the US and seemingly aggressively growing in the UK there are question marks over regulators like MHRA and Big Pharma companies. There have been both quantitative and qualitative data analysed previously which can bring sense to proposing a validated model such as blockchain as to the many good reasons explained throughout this publication. However, just as important as looking at the effects of selective reporting, bias and misconduct is the importance of transparency so that ethics and trust can be held in more confidence. There's almost an inborn trust most patients have in taking advice from the medical profession in prescription of drugs but as shown in the example of opioids it can potentially cause a reverse of all good intentions, from criminalising an individual

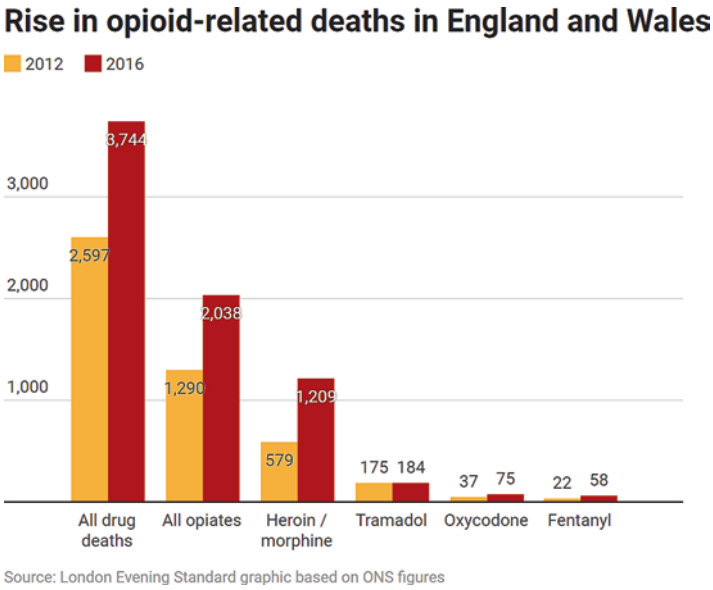

Fig. 3.14 The rise in opioid deaths according to ONS. (Cohen 2018a, b)

into illegal drug purchase to losing one's life. The inborn trust now needs a more validated model as proposed in this research that although is trustless, is the purpose to make this more transparent since no single entity has total control and can be selective in its approach. The patient is put in the centre of control and at least has the knowledge to make more informed decisions.

3.19.2 Breast Cancer Screening – Interoperability Study

Another example is of how perhaps blockchain could have helped avoid IT mishaps due to interoperability issues where a technical issue that dated to 2009, was only picked up in 2018. There appears a question mark in this case of how 450,000 women missed being sent breast screening check-up letters and resulted with up to 270 women dying, Matthews-King (2018).

The IT glitch affected only women aged between 68 and 71 as screening occurs every 3 years for women aged 50–70 years old. The glitch was picked up when the national screening IT system underwent an upgrade and discovered that women involved in a particular study (AgeX trial managed by Oxford University) were not receiving final screening at the 70 age mark. When a much wider review was launched it discovered a similar situation replicated in other parts of England. The problem looks to be the length of time before the glitch was picked up (almost 10 years).

Whilst errors can happen it may have been a better placed model to secure all healthcare records on blockchain and milestone screening results and next due dates all captured and accessible by patients and all parties that need be involved. Perhaps this could have made the system more transparent and operate in a proactive way.

3.20 Conclusions

The clinical trials theoretical model presented in this research makes an interesting example of how healthcare data can be made more transparent, privacy strengthened and how to make best use of blockchain through its time stamp, time ordering, smart contracts and immutability. It offers the benefits just outlined above but opens up a very serious debate and question on potential harm caused by bias, selective reporting, misconduct and fraud, which currently appears to have many gaps in its clinical process, as the example data analysis leads to suggest. Blockchain can tighten up these processes and offer a balanced framework so confidence is restored and reduce the issues described, as the example provided in the case of opioids abuse. There appears a range of destructive issues to a patient that can lead to fatalities. This alone should help qualify the next steps and additional research be committed to make a more trust worthy framework centred on blockchain. Healthcare looks to need the offering of the tangible benefits of interoperability, longitudinal medical data, more privacy protection against cyber breach/identity theft and more protection of the unforeseen damages caused by not having a method of transparency through the whole process of clinical trials research.

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