

CLINICAL TRIALS: HOW TECHNOLOGY IS DRIVING DIGITISATION

MEDICAL TECHNOLOGY



INTRODUCTION

The era of clinical trials as we've known them, is coming to an end. The rising costs of running a trial, coupled with the commercial risks of failure, are unsustainable. This disruptive state is driving the adoption of new technologies, and catalysing the digital transformation of clinical trials.

Clinical studies constitute the most critical stage of a drug's development, and a key activity in the calendar of any clinical trial sponsor. They are costly, with unpredictable timelines, and their outcomes influence the short and long-term future of pharma companies. To give a sense of scale, there are approximately 7,000 Phase III interventional clinical trials¹ currently active. Bearing in mind that a Phase III trial could cost tens of millions of dollars, the impact that they can have on any sponsor's balance sheet is considerable. Clinical trials attract the interest

of regulators, investors, and even patient advocacy groups. They involve multiple stakeholders, across multiple countries and their published results often make it to the mainstream press. As a result, the pressure on pharmaceutical companies to succeed is not only financial but also reputational. Here, we identify the key challenges that clinical trial sponsors face and suggest the use of digital technologies to address them. We also present the fundamental technological solutions that will catalyse the transformation of clinical trials.



¹ https://clinicaltrials.gov/ct2/results?recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=2&Search=Apply

WHY CHANGE

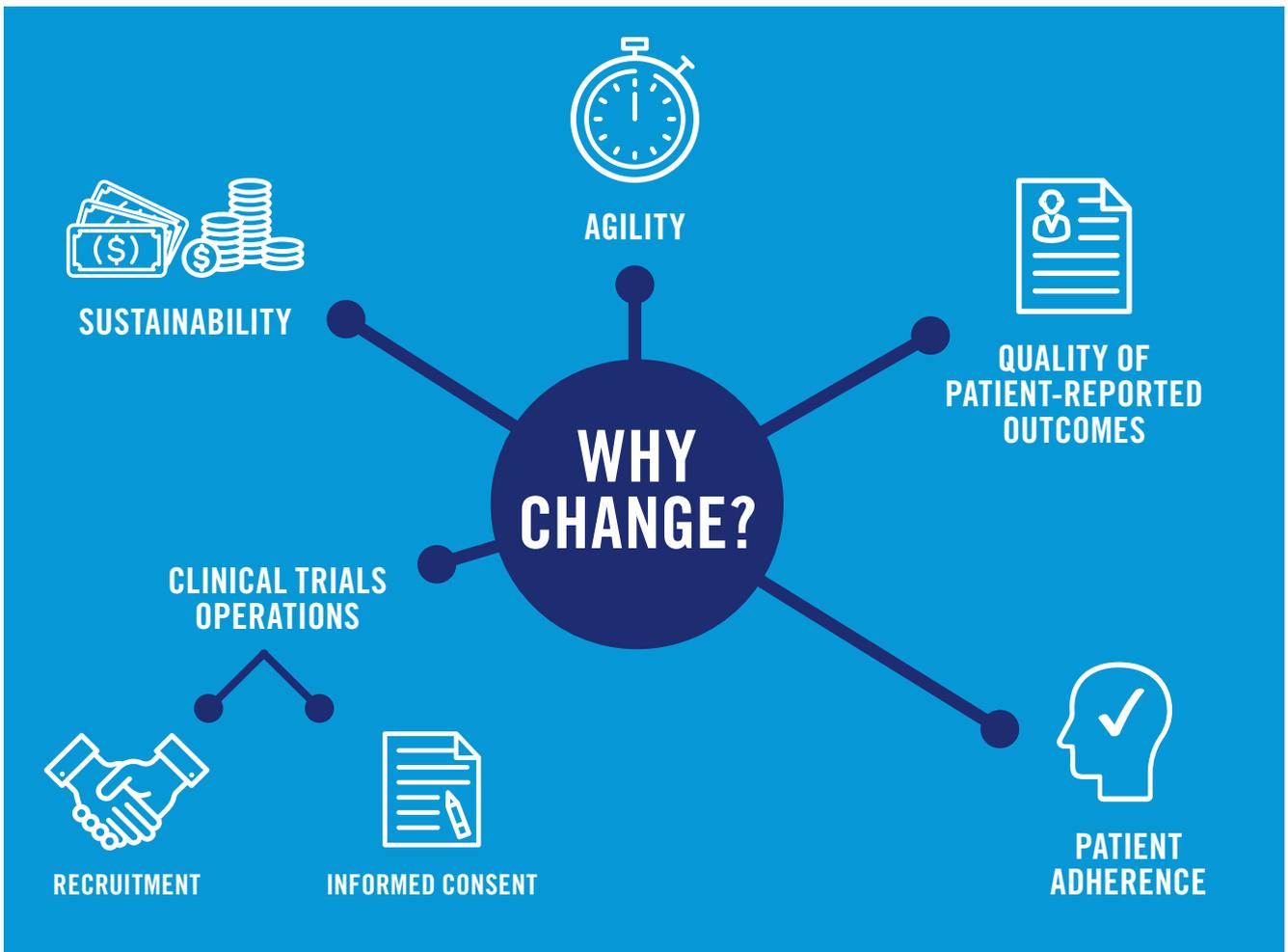
SUSTAINABILITY

Escalated clinical trial costs drive the cost of developing treatments, which in turn impacts the price of products and burdens healthcare reimbursement systems. In 2013 alone, the cost of the 6,199 biopharmaceutical sponsored clinical trials in the U.S. was calculated to be in the region of \$10 billion². The same trend applies to the complexity of running clinical studies, particularly given that the number of registered studies has quadrupled since 2009³. As a result, there is pressure on companies to reduce development costs, and justify the price of their product according to achieved

endpoints and outcomes. With so much at stake, clinical trial sponsors need to mitigate the risks, identify areas of improvement and control the spiralling costs. If sponsors do not act, it is likely that payers will.

AGILITY

Clinical trials are not dynamic in nature. Slight changes to their protocols require time to implement. Investigators often titrate treatments according to the drug's efficacy performance and the occurrence or persistence of side effects. Such



2 <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>

3 <https://clinicaltrials.gov/ct2/resources/trends>

changes rely heavily on timely access to information, so that investigators can make informed decisions. However, this usually requires a face to face meeting with a patient, which is resource demanding and takes time to organise. Similarly, it is not easy to deal with changes in a standardised way across multiple centres. There is scope for technology to close the gap and allow for more efficient and scalable data access.

QUALITY OF PATIENT-REPORTED OUTCOMES

There is a need for more efficient management of patient-reported outcomes (PRO). Patients are required to complete PRO surveys at least twice throughout the duration of a clinical trial and this is expected to take place at predetermined time points. Failure to do so impacts the quality of the data and could put patients under unnecessary safety risk. A recent study by Kyte *et al.*⁴ revealed several inconsistencies in how this process is managed across different clinical trial centres. PROs are often not completed, or completed at incorrect times. Moreover, clinical trial staff do not respond to incomplete and overdue PROs in a standardised fashion, which introduces bias to the data captured. The authors of the study also revealed that it is possible for clinical trial staff to not respond to PRO alerts in a timely and standardised manner – e.g. when evidence exists that a patient is under psychological distress. Improving standardisation levels when it comes to the completion, processing and analysis of PROs would positively impact clinical trials.

PATIENT ADHERENCE

Non-adherence is a key challenge for clinical trial sponsors as it increases costs, and impacts both outcomes and endpoints. Lack of monitoring systems for adherence could lead to misinterpretation of data on the effectiveness and safety of a treatment. There have been numerous studies that have analysed data from clinical trials and have concluded that adherence reporting is often inconsistent, causing data analyses to be biased^{5,6}. Lack of adherence, when accounted for properly at the data analysis stage, reduces the statistical power of the study sample, which automatically impacts the validity of the study. It has been reported that non-adherence to investigational medical products can be as high as 40% after just 150 days from the beginning of the clinical trial. Interestingly, there is an exponential relationship between the level of non-adherence and the number of patients that

need to be recruited to conserve the statistical power of the sample in a study. For a non-adherence level of 40%, a 200% increase in sample size⁷ is required, which makes the need to address this issue more than evident.

CLINICAL TRIAL OPERATIONS

RECRUITMENT

Randomised, controlled clinical trial patient samples are not representative of the patient types that HCPs treat under real world conditions, and in many cases would not pass an external validity or generalisability test. There is a need to recruit patients across more geographies and demographics and for patients that better represent the clinical scenarios under which a treatment will be used. By default, the introduction of more screening criteria will make the recruitment process more resource demanding, costly and lengthy. There are many limitations that clinical trial sponsors need to overcome in order to make the recruitment process more efficient. One such barrier is making the proposition of joining a clinical trial more attractive to patients. For example, patients can often be sceptical about the fate of the data generated during clinical trials⁸ and the effectiveness of data security mechanisms employed. Moreover, patients do not appreciate the fact that data they generate cannot be accessed by healthcare professionals of their choice, or become part of their standard health record. There is scope to make participating in clinical trials more attractive.

INFORMED CONSENT

Patient informed consent is the cornerstone of clinical trials and failure to diligently satisfy consent requirements can have a catastrophic impact on the validity of the study. The current process comprises extensive paperwork, can be confusing and burdensome, tests the commitment of patients and does not represent a robust system. Considering that satisfying consent requirements is not a single event in the clinical trial calendar but a more open-ended process (e.g. a patient can withdraw consent at any point), it causes frustration, leading to oversights and improper practice. It has been reported that a significant percentage of clinical trials assessed by the FDA exhibit consent collection issues⁹. Clinical trials will benefit from streamlining the process of consent, making it less labour intensive and more effective to manage. The process would benefit from a more transparent system that allows for constant monitoring by all stakeholders.

4 <http://bmjopen.bmj.com/content/6/10/e012281>

5 <https://www.ncbi.nlm.nih.gov/pubmed/22709676>

6 <https://www.ncbi.nlm.nih.gov/pubmed/26797242>

7 <http://www.appliedclinicaltrials.com/non-adherence-direct-influence-clinical-trial-duration-and-cost>

8 Personal communication with clinical trials patients

9 <https://www.ncbi.nlm.nih.gov/pubmed/25664866>

HOW CLOSE ARE WE TO CHANGING CLINICAL TRIALS?

Clinical trials are a necessity for pharmaceutical companies, as they need to comply with the demand for safe and effective treatments at justifiable prices. With so much at stake, the time has come to improve the efficiencies of clinical trials, and there is evidence that this change is underway.

Firstly, over the last 10 years, the Clinical Trials Transformation Initiative (CTTI) – a public-private collaboration – has systematically promoted the need to increase the efficiency and quality of clinical trials. The CTTI's recommendations on endpoints, and how digital services and tools can create a new gold standard clinical trial design, have been critical in transforming clinical trials.

Secondly, the global e-clinical solution software market, is expected to grow to \$10.6 billion by 2024, growing at a CAGR of 13.4% from 2016 to 2024¹⁰. The growth of software for clinical trials will be fuelled by the need to manage an increasing number of clinical trials. The larger number of clinical trials will exacerbate the challenges faced by sponsors today, including the complex recruitment requirements across multiple centres and countries. The growth of software is also associated with the sponsors' increased appetite for outsourcing studies, while containing the otherwise bursting costs.

It should then be no surprise that the amount of Venture Capital funding invested in this area has increased over the years, while companies specialising in clinical trial software solutions have achieved significant fund-raising successes. One such example is Bio-Optronics, a developer of software for clinical trials, that claims to allow regulatory compliance flexibility and efficiency. Recently, it attracted \$30 million in funding from Mainsail partners¹¹. Equally successful in raising funds has been goBalto¹², which since its inception 10 years ago has raised more than \$35 million. These two examples represent just the tip of the iceberg.

Another sign of change is the investment that pharmaceutical companies are making in novel technologies. Many of the top-tier companies are actively seeking solutions that will re-shape the way they conduct clinical trials and give them competitive advantage over their competition. Companies such as Novartis, Otsuka and Janssen often feature in industry news related to the adoption of innovations that could disrupt the way clinical trials are conducted¹³. Their partnerships with Science 37 – a technology enabled clinical research company that offers decentralised clinical trials – is one example^{14,15,16}.

WHAT PHARMA NEEDS TO DO TO STAY ON TOP OF THIS CHANGE

DEVICE
CONNECTIVITY AND
ULTRA-LOW COST IOT



BLOCKCHAIN



SENSING
TECHNOLOGIES



DATA ANALYTICS
AND ARTIFICIAL
INTELLIGENCE



¹⁰ <https://www.variantmarketresearch.com/report-categories/pharmaceuticals/e-clinical-solution-software-market>

¹¹ <https://bio-optronics.com/blog/press/bio-optronics-announces-30-million-growth-investment-mainsail-partners/>

¹² <https://www.gobalto.com/>

¹³ <https://www.forbes.com/sites/matthewherper/2018/03/26/ai-telemedicine-quantum-new-novartis-boss-says-tech-will-finally-change-the-drug-biz/#172c83c36b54>

¹⁴ <https://www.science37.com/science-37-novartis-sign-strategic-alliance-advance-decentralized-clinical-trials/>

¹⁵ <https://www.science37.com/science-37-otsuka-pharmaceutical-collaborate-advance-digital-health-innovation-focus-technology-enabled-clinical-trials-home/>

¹⁶ <https://www.science37.com/science-37-sanofi-introduce-new-partnership/>

WHAT PHARMA NEEDS TO DO TO STAY ON TOP OF THIS CHANGE

Disruption in clinical trials requires the masterful convergence of multiple technologies and technical capabilities. Their combination will reinvent the way data is captured, analysed and processed and, in doing so, re-define the role of the patient in a clinical study. Below, we outline the technologies and tools that will drive this change¹⁷.

DEVICE CONNECTIVITY AND ULTRA-LOW COST IOT

Connected drug delivery devices and smart primary packaging are both disrupting the way patient adherence data is being captured. Connected devices will help overcome the misinterpretation of data when it comes to the impact of drug dose related side effects, outcomes and the patients' general well-being. A great deal has been done to enable the connectivity of drug delivery devices for both respiratory and parenteral devices. One example comes from Novartis, with the introduction of the connected BreezHaler¹⁸ to closely monitor patients' drug intake during clinical trials. Information can be shared in real time, and allows clinical trial sponsors to respond and tackle low levels of adherence. Another example of investment in device connectivity involves Janssen¹⁹, which recently invested in a novel clinical trial system that uses smart blister packs.

Ultra-low cost connectivity components, coupled with direct-to-cloud technologies, such as NB-IoT/LTE-M, will fuel the transformation towards fully connected and digitised clinical trials. Drastically reducing the cost of IoT devices will remove a key barrier towards the adoption of not only connected drug delivery devices but also wearable sensors. To date, the cost of a radio has been determined by its analogue components, but work to replace the analogue component with a fully digital radio transceiver has progressed. Cambridge Consultants' Pizzicato enables flexible software-defined radios that can change frequency, bandwidth or radio standard in an instant, allowing a much more dynamic use of the radio spectrum. Such systems could justify economically the use of connected wearable sensors and even connected low-cost drug delivery devices, such as syringes.

BLOCKCHAIN

Blockchain has already proven its value in building a transparent transaction network between parties who do not necessarily trust each other. Blockchain-based solutions may also hold the key to providing more efficient ways of handling the early stages of clinical trials, particularly in relation to recruitment. As blockchain provides a controlled way of accessing proof of the existence of an entity, it may be used for monitoring the existence of consent. This could be of key value to clinical trial stakeholders across multi-centred studies. It means that investigators, sponsors and regulators will all be able to share consent information and better manage re-consent requirements for each batch of patient data corresponding to a specific version of a trial protocol. A mechanism like this would warrant proof of existence for consent and would be timestamped before sharing any data. Benchoufi *et al.*²⁰ have described a gold-standard, open and secure consent collection form, using blockchain.

As a shared ledger, blockchain can be used to enable and monitor access to clinical trial data, allowing a transparent yet controlled way of sharing patient information. A system like this may help patients to access their data – often held in data silos – and benefit by sharing it with their healthcare professionals (e.g. their GPs). Being able to share personal data and potentially even use it to update patient health records means that patients may be more incentivised to take part in clinical trials, and keep high levels of engagement when it comes to taking part in the different activities and assessments planned.

SENSING TECHNOLOGIES

There are many advances in the field of sensing technology that could disrupt data collection for clinical trials. The types of sensors, and what they can monitor, has advanced and sensors could feasibly replace manual surveys and assessments. Moreover, sensors are becoming smaller, easier to integrate and use continuously without interfering with a patient's everyday life.

17 Clinical trial management solutions for siteless studies are outside the scope of this report and not covered here.

18 Colthorpe et al. Adding Electronics to the Breezhaler®: Satisfying the Needs of Patients and Regulators, Respiratory Drug Delivery 2018, in press

19 <http://www.mobihealthnews.com/content/janssen-set-launch-clinical-trial-system-uses-smartphone-app-smart-blister-packs>

20 <https://f1000research.com/articles/6-66/v1#ref-11>

For example, contactless sensing may play a key role in how data is collected. Typically, vital sign monitoring requires on-body electrodes, which of course need direct skin contact and often some sort of skin preparation to reduce interference. Today there is evidence that even for vital sign monitoring – with the use of near field coherent sensing (NCS) – it is possible to avoid skin contact. Hui *et al.*²¹ demonstrated that such systems could be used to monitor heart rate, blood pressure, respiration rate and breath effort. The system tested comprised passive tags which were integrated into garments at the chest and wrist areas. This type of sensing could revolutionise the way physiological and PRO data is gathered during clinical trials. Innovation in this space will address not only data quality issues but also catalyse an improvement in patient engagement.

Advances in materials will also boost efforts to improve sensing technology. With the use of graphene and metal nanowires²², a Korean team developed prototype contact lenses that measure glucose levels and intraocular pressure. “Invisible” sensing will play a key role in the creation of sensing systems that gather multi-parameter data and allow the holistic quantification of an individual’s disease status, including that person’s response to treatment during a clinical trial.

DATA ANALYTICS & ARTIFICIAL INTELLIGENCE

Connected devices, connected wearables and the possibility of continuous monitoring during clinical trials open new avenues in terms of the quality of data captured and the overall insights that could be generated. Nevertheless, to generate these insights, we will need to deal with very large datasets, derived from diverse patient populations. Accounting for diversity is particularly important as the manifestation of complex conditions and their symptoms differs among individuals. This will require “diverse” and personalised benchmarks against which a person’s progress can be assessed. For example, let’s assume that activity levels are considered an important indicator for the wellness of a patient in a clinical trial. Measuring activity is easy, but analysing the data and associating it with that patient’s disease state is far more challenging. For the data to make sense, we must be able to determine how closely it is correlated with the disease, the clinical trial intervention and, hence, validate those correlations before generalising any findings.

Data analytics platforms will make or break how impactful the clinical trial connected ecosystem can be. This may involve systems that can be calibrated to reflect the weighted contribution of an individual’s ‘ecology’. Similarly, using AI it will become possible to filter out any data generated by the individual’s environment, and remove any unwanted biases. Such objective data analytics platforms will be able to calculate reasonable benchmarks against which individual patients will be assessed. Gathering meaningful data for a medical assessment in a non-controlled environment is a significant challenge and is key in providing trustworthy and impactful insights.

The use of AI will not be limited to data analysis solutions. Instead, we envisage that AI will play a key role in establishing centre-less clinical trials. It will drive recruitment, patient engagement and will allow trials to run remotely with less intervention from clinical trial staff. One such technology example is Orbita’s voice-based home health assistant²³, which claims to provide a more user-friendly way of completing clinical assessments at home. There is great potential in this space, which could drive clinical trials beyond the need for a clinical trial centre.

²¹ <https://www.nature.com/articles/s41928-017-0001-0>

²² <https://www.medgadget.com/2018/01/soft-transparent-comfortable-contact-lens-measures-glucose-intraocular-pressure.html>

²³ <http://adigaskell.org/2017/07/03/voice-technology-deployed-in-clinical-trials/>

AND SOMETHING ELSE

There is strong evidence of escalating costs for running clinical trials and a clear need to improve certain processes. Clinical trial digitisation offers a solution for most of the challenges that need to be addressed, but how easy is it to integrate new technologies and digitise clinical trials?

Could the cost of developing and adopting clinical trials prove to be a barrier in making the switch to digital? When assessing the positive impact of digital technologies on recruitment, patient engagement, quality of data, adjusting treatments and protocols, and improving the agility of studies, it is easy to recognise the value these changes will bring. The average cost of a patient in a clinical trial is approximately \$38,000²⁴. We can assume that the cost of introducing digital tools – that will be used again and again, even in commercial settings post development – will only be a fraction of that total. If anything, it is likely that the digitisation of clinical trials will introduce many cost efficiencies. More importantly, the cost of a failed or mismanaged clinical trial will always be far more significant than the cost of digitisation. To that point, a report commissioned by the U.S. Department of Health and Human Services concluded that home testing alone could, on average, reduce the cost of a Phase I study by 16%, a Phase II study by 22%, and a Phase III study by 17%. The impact on net cost for each phase is significant, considering that in the same report the average cost of a phase trial was estimated to be \$20 million²⁵.

Clinical trials are slowly changing in order to address concerns around their efficiency. These changes have the potential to offer competitive advantage to clinical trial sponsors. Companies can streamline their clinical trials, improve their R&D efficiency, cut costs and minimise the risk of development. They will be able to increase the number of their clinical studies, develop and test more treatments simultaneously, reach remote and even smaller patient groups and create better protocols to test their treatments. To do so they will need to demonstrate an appetite for adopting new technologies. Failure to do so could have a long-term impact on their business.

WHY DIGITAL TECHNOLOGIES WILL DISRUPT CLINICAL TRIALS

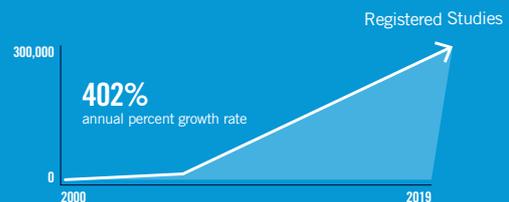
There is a **NEED** for more clinical trials across more sites

Studies **267,888**



35% are US only

The **NEED** will continue to grow



This increase comes at a significant **COST**

In 2013 only, biopharma **INVESTED \$10billion** in trials in the US



COSTS can be managed if we tackle **INEFFICIENCIES**

- Recruitment
- Patient engagement
- Data quality and data sharing
- Agility in planning & execution
- Compliance
- Consent

Digital technologies could reduce trial **COSTS** and the **BENEFITS** could be significant

PHASE 1 **16%**

PHASE 2 **22%**

PHASE 3 **17%**

²⁴ <http://phrma-docs.phrma.org/sites/default/files/pdf/biopharmaceutical-industry-sponsored-clinical-trials-impact-on-state-economies.pdf>

²⁵ <https://aspe.hhs.gov/report/examination-clinical-trial-costs-and-barriers-drug-development>

About Cambridge Consultants

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