VIRTUAL / REALITY:

THE DIGITALISATION OF CLINICAL TRIALS

A WHITE PAPER REPORT

- **DEFINING DECENTRALISED TRIALS, AND EXPLORING HOW THEY CAN BENEFIT YOU**
- **THE BIGGEST CHALLENGES FACING DECENTRALISED TRIALS, AND HOW TO OVERCOME THEM**
- **FACTS AND RESOURCES ON THE DATA, TECHNOLOGY AND REGULATORY ASPECTS OF VIRTUAL TRIALS**

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INTRODUCTION

Clinical Trials are an integral part of the drug development progress. Not only do they ensure a potential drug works as intended in human targets, but they can detect and diagnose any troublesome side effects or dangerous consequences that might occur. The statistics are enormous: as of March 2020, there are almost 333,000 active trials worldwide, with posted results rising 1,400% in a decade.

Even in such a well-established procedure, however, challenges remain. Those drugs which seem robust and highly efficacious during the R&D stage can fail instantly in trials - particularly human trials, where no guarantee exists that efficacy in rodents or even other primates will transfer easily to human subjects. Alongside this, trials are extremely costly and can take a considerable amount of time to develop. Moderna's recent COVID-19 vaccine, which entered human trials in late February, is not expected in the market until the end of the year.

The statistics show the issue more clearly. According to Amplion, only one in ten drugs which start the clinical trial process are eventually granted FDA approval. The cost is equally hard to bear for many pharma companies: during oncology clinical trials, according to one source, initiating a study site costs around $50,000. The same source noted that 20-30% of study sites never enroll a single patient.

The pharmaceutical industry needs, then, to change its processes. Trials must cost less. Patients must be easier to access, and receive greater communication once in the trial. Virtual and decentralised trials are one way that the industry is looking to solve the problem.

Joshua Neil, Editor,
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WHAT IS A DECENTRALISED TRIAL?

Despite existing in the sector's consciousness for a while now, the term 'virtual trial' is still a confusing one - even for leading experts in the industry. Further convoluting the issue are the numerous other terms surrounding it - decentralised trials, remote trials, hybrid trials.

A further ambiguity stems from at what point a clinical trial becomes virtual. Is it any trial that involves technology provided to patients? Must every aspect of the trial be technologically based? Is a virtual trial one where patients never meet their recruiters or healthcare experts?

Currently there is not one universally accepted term within the industry. It is largely agreed that the specific term 'virtual trial' is one in which no face-to-face interaction between the physician and the patient is had at all. A 'hybrid trial' is that trial which is not 'fully virtual' and still involves interaction with the patient by physicians, alongside some or all of the most common virtual elements of a trial: mobile technology, web-based patient diaries and wearable technologies.

Perhaps a better catch-all term that avoids the utopianism of 'virtual trial' is 'decentralised trial'. This term has been advocated by a number of subject experts. For the purposes of this report, 'hybrid trial' will be used to describe those trials which use human-to-human interaction alongside virtual elements and innovative technologies to better monitor patients. The term 'virtual trials' will apply only to those trials without physical interaction at all. 'Decentralised trials' will refer to all non-standard clinical trial models as a collective.

WHAT HAS BEEN DONE SO FAR?

The move towards virtual trials began around 2010, spurred on by soaring treatment costs due to increased trial complexity and the long-term movement towards patient-centricity by the whole pharma sector. The need to find a way to ease patient burden, as well as reduce the costs of holding trials, led obviously to an area that could facilitate both: online.

Pfizer was famously one of the first companies to run site-free trials with the help of new technologies and processes. Despite the considerable length of time since then, many pharma companies are still sticking to the old model, with take-up of even hybrid trials a slow process. In fact, it was only in 2019 that the FDA included virtual trials in its draft guidance on increasing patient diversity in research.

Despite this, a 2019 survey of industry experts conducted by Oracle found that, beyond tech suppliers and biotechs, almost no participant said they had ever been involved with a fully virtual trial.

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Gareth Powell, Patient Engagement Project Lead at The National Institute for Health Research (NIHR), said that full establishment of patient-centricity in virtual trials was not there yet, though it was getting better. He noted that return on investment was vital for the model to expand in the industry, with financial return both easier to justify and quantify for most executive boards.

Maria Palombini, Director of Communities & Opportunities Development in Life Sciences at the IEEE Standards Association, agreed. She suggested the industry has been slow to initiate real hybridised and virtual trials in pharma: "There are many factors that must be considered when considering this type of trial. One, you have to educate patients on this process from digital literacy to responsibility of personal health data management and more. You also need those patients to have sustainable access to the internet. There are so many populations that can't afford access or there is a lack of infrastructure to support it.

"Simultaneously there is a bigger market struggle of empowering patients with right to consent and manage their health data which is a significant shift away from entities who have proprietised and made money from it. Just recently (20 March 2020) the US HHS (Health and Human Services) ONC (Office of the National Coordinator) issued its final rule, pertaining to the 21st Century Cures Act, that supports seamless and secure access, exchange, and use of electronic health information enabling patients to electronically access structured and unstructured their health data at no cost (full rule details here). Therefore from the IEEE's perspective, the goal is to work with the global community of stakeholders - patients, healthcare professionals, technologists, regulators, clinicians, and others - to build consensus for developing standards providing trusted, viable and accessible solutions that would empower the patient with the right to privacy, consent and management of an important health asset - their data."

John Reites, President at THREAD Research, works with many companies including hybrid decentralised approaches in their trials and noted the acceleration in the industries' acceptance of this model compared to five years ago. "Today we see pharma, biotech and CRO customers involved across the spectrum of incorporating decentralised study designs. Some customers are on their fifth or sixth such studies, while some are still learning on their first or second attempt." He also suggested that his company expects this theme to continue as customers look to establish decentralised approaches which are fit-for-purpose for their operational designs to support specific patient populations.

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THE BENEFITS OF DECENTRALISED TRIALS

Beyond their increasing costs, virtual trials have a problem with patient recruitment. Some trials require thousands of individuals to take part, as they need to understand minor effects of treatments on a large enough scale that no adverse effects (AEs) are missed. The size of such trials is compounded by the need to have two individuals per unit of trial evidence, including a placebo or standard of care group.

But as patient-centricity increases, finding so many people becomes more and more difficult due to greater stratification and specificity. With smaller groups spread out over a greater geographic area, something must be done to make patients findable - and perhaps more importantly - engageable again.

Decentralised trials have become slowly more popular in the last few years, due to their ability to access more remote patients who may qualify for a trial but not able to come to the site. Maria Palombini suggested that the eventual end-goal of decentralised trials is to "have a more inclusive, efficient, and optimised approach to recruiting and engaging patients with trust", with an imagined endpoint of creating "a patient-driven clinical trials process."

Gareth Powell agreed. He said that rather than being an end in and of itself, what decentralised trials are is an extension of the goal of patient centricity, which has been a part of the sector for ten years or more now. He said decentralised trials were a "magic bullet" for addressing key issues around recruitment and retention, reducing as they do the need to engage with site visits, the length of time spent on sites, and lessening the burden for patients. Once this was established in industry, he said, the model could be grown indefinitely and increase access for patients even further.

CASE STUDIES OF DECENTRALISED TRIALS

Famously, the first clinical trial run entirely online was the Pfizer-backed Research on Electronic Monitoring of Overactive Bladder Treatment Experience (REMOTE) trial on overactive bladder disease, run in 2011. Participants gave informed consent via e-signatures, before the drug was delivered to their homes. AEs were reported using wearable technology and web-based measurement tools.

In the REMOTE trial, Pfizer learnt a series of important lessons: first, that older populations have difficulty with technology, and that for certain populations offline channels work considerably better than online ones.

In 2015, Sage Bionetworks was able to conduct an entire study, where no product needed to be administered, through its mPower app on patient iPhones.

Another study by AOBiome showed the positive effects of running an online phase 2b trial. The study, which sought to prove the efficacy of an AOBiome acne treatment, recruited patients through social media and online adverts, screening them over the phone. During the trial all patients reported drug effects and photos on an app.

From this study, AOBiome reported that it had managed to enrol 372 patients in seven months, around half the time that a traditional trial would have been able to. The study was also able to recruit 41% minority patients, something that pharma companies have struggled with in the past. The company's CEO also said that dropout rates had been "lower than expected", with better-than-usual compliance and lower costs overall.

For a number of other useful resources around initiating decentralised trials, THREAD has uploaded a number of publications on its website relating to decentralised study approaches in clinical trials.

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The benefits to the patient of clinical trial are self-evident and profound. With no need to travel to trial sites, patients no longer need to pay out to get there; this cost is not forwarded on to the clinic. Patients with chronic pain need not move too far or put themselves out. And the associated costs and stress of sourcing childcare, taking time off work, and finding transport are minimised.

But there are many other reasons to consider the move towards virtual and decentralised trials. These include:

Decentralised trials can widen the possible pool of participants – A lack of suitable population is a huge hinderer of clinical trials: Allegedly, 85% of all clinical trials fail to recruit enough patients, with 80% delayed over recruitment and retention issues. With decentralised trials, those unable to travel - either through lack of transport, disability or distance - can participate. Decentralised trials will also receive a better quality of patient, more suited to the trial: the greater amount of data captured initially means better remote screening, making the process of finding and selecting patients faster and more accurate.

Maria Palombini agreed, noting that what pharma needs at this point is a change in the patient recruitment & retention process. She said that their primary challenge in that regard is an inability to reach the right patient populations to meet guidelines, with companies further constrained by the necessities of GDPR: in effect, this is a market need for both pharma companies and for patients.

Diversity – Similarly, more decentralised trials will allow for a broader geographic and demographic patient distribution. This not only reduces trials' tendency to use patients of a select ethnicity or sub-population, but makes it easier to find more patients of an important sub-population who might be most affected by the drug. This allows for a better knowledge of how drugs will work in diverse, real-world settings. However, there is as yet a lack of concrete studies to prove this fact concretely.

Increased retention – According to one study, as many as 30% of patients in phase 3 trials drop out or become disengaged during the process. This is sometimes for issues already discussed - the difficulty of travel or of juggling a home life with attending - but it also relates to communication and engagement. In traditional trials patients are often left in the dark about trial mechanics and how they are personally being affected. With the increased data from decentralised trials, more information exists to give to patients. Seeing their health and trial information can make a patient more interested in their participation.

Improved data quality – Following on from the last point, decentralised trials can greatly improve the data that comes out of trials. Collecting patient data using Internet of Things devices and communication platforms like WhatsApp, clinicians can access cleaner, more regular and better quality data than traditional models will allow. Automating this process for certain datasets means data can be captured in a single format at regular intervals, allowing for easier identification of cause and effect in treatment.

Where advanced data analytics tools are available, clinicians can incorporate different formats and sources of data to enrich study objectives and better understand patient experiences. This can include environmental data, exterior diseases and flus present at the time or simply historic illnesses.

Improvements for site staff, diagnostic methods and tools – Hybrid and virtual trials also offer benefits to clinical teams and sites. With a reduction in on-site visits, clinicians can talk to

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and work with a greater number of patients. With better technology and particularly automation, less form-filling and administration is required.

For patients, there is also the problem of competition for site places. The burden placed on staff of this demand, on top of the challenges of a trial, means moving to a virtual platform reduces stress considerably.

Reduced risk – Finally, decentralised trials can reduce a number of the risks associated with standard models. eConsent is a prime example of this: breaking down the legal and technical documentation into multimedia formats (e.g. videos, audio, etc) will reduce confusion and overwhelming volumes to read. This ensures the patient is better informed about the trial and what they are undertaking, and reduces the possibility of error when a physician explains trial details to a patient.

Cost – Increasing trial costs in turn raise development costs and therefore product price. In 2013, U.S. trials sponsored by biopharma cost around $10 billion total. Because of this high cost, companies are under pressure to reduce development costs and mitigate as many risks as possible. According to one survey, decentralised trials of any kind contribute to a cost reduction of 50% per participant compared to the current trial model.

Similarly, a study conducted by the U.S. Department of Health and Human Services found that testing patients at home on average reduced phase 1 study costs by 16%, phase 2 costs by 22%, and phase 3 costs by 17%.

WHEN NOT TO USE DECENTRALISED TRIALS

Decentralised trials, implemented correctly, offer a range of advantages over traditional trial models. But that is not to say that they are infallible, nor that they should be applied in every situation.

An instance where traditional trials are preferable is during phase I of a clinical trial: here, physicians need to regularly take blood from patients to determine how a drug is being metabolised: for this a highly-controlled, sterile environment is needed. This work, for now, is simply impossible without on-site meetings. While this still allows for the use of a hybrid trial system, it rules out the move to fully virtual trials. Decentralised trials are also less effective in countries without remote patient engagement support. Currently, the FDA accepts eConsent as a valid patient consent method, but many countries in the EU do not. Additionally, only select countries let central pharmacies send drugs directly to their patients.

Finally, trials which need in-hospital attention or equipment, for example trials requiring close monitoring from a specialist due to morbidity, or cancer studies measuring outcomes through diagnostic imaging.

As John Reites noted, "When we discuss decentralised studies, we are not referring to ePRO or medical device/ sensor use only studies. Decentralised study designs include an array of data collection features from patient, site, home health, contact centres and other research stakeholders utilising telehealth Virtual Visits as a key to moving visits from the clinic to home when best suited based on the protocol schedule of assessments. These study designs are complex, require compliant/ validated platforms and can span from moving a couple of visits online to all visits a clinic has."

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THE MAJOR CHALLENGES FACING DECENTRALISED TRIALS

Despite their definite advantages, decentralised trials have yet to find a firm foothold in the clinical trial paradigm. On the surface, it seems strange that such a positive upgrade to standard models has yet to see widespread clinical uptake: for much of what virtual trials require, technologies and algorithms exist which can suffice. Automation of form-filling and menial tasks is present in many other areas of pharmaceuticals; wearable monitoring technologies and standardised-format messaging systems, such as WhatsApp, are ubiquitous.

LACK OF DATA INTEGRATION

The move to more internet -enabled clinical trials has meant that physicians have access to more data than ever before. While this does provide significant benefits for both clinical study and for the patients, who can now view this information to better understand their progress in the trial and their own development and treatment, problems remain.

The numerous sources of data used in clinical trials (from wearables, instant messaging platforms and e-forms) are yet to be easily integrated into a single, usable source. This disallows effective analysis, meaning that it is that much harder for trials to pass regulatory review.

According to a Tufts University impact report published last year, the amount of data from clinical trials is growing steadily through greater study scope and complexity. As this has happened, 77% of sponsors and CROs have reported difficulty loading the new data into their EDC systems for a number of reasons, in particular compatibility and integration issues and technical problems. To combat this, on average six different applications are used to contain this data.

This difficulty has a knock-on effect for trial time, with the time from "last patient, last visit" to database lock increasing from an average of 33.4 days in 2007 to 36.1 days on average in 2017.

In Oracle's 2019 survey, participants claimed that they felt like technology providers were overly focused on adding more and more functions to products, without considering whether they are interoperable with others.

Participants in the survey also suggested that having numerous technologies in a trial would slow down processes through several separate portals or log-in details. Due to the need to train staff in each technology, there is also a potentially large burden for patients averse to or inexperienced with technology.

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What can be done?

Tools that integrate multiple sources of data do exist, and are already being slowly introduced into decentralised trials. This technology allows sponsors to both aggregate and integrate data to improve efficiency. Standardising data across multiple sources also allows for much quicker analysis, a reduction on manual standardisation burden, and increased trial oversight and understanding.

While the right data integration software will vary based on company needs and circumstances, there are a number of guides already online that can narrow down the options available and make a decision considerably easier:
- The Buyers' Guide to Data Integration Software
- Bio-ITWorld's Managing and Integrating Clinical Trial Data report
- A guide to the best clinical trial management software for 2020

PATIENT INCENTIVISATION

Patient engagement is one of the major troubles facing clinical trials today. As has already been noted above, a significant percentage of patients will drop out of a clinical trial before or during phase 3. There are dozens of reasons for this: patients can feel isolated or unheard during the treatment; they can see limited feedback on their progress during the trial, or lack an understanding of what their place is in the trial; they can be put off by difficulties in any part of the process, from the burden of wearable technology to a lack of compensatory incentivisation offered.

Gareth Powell noted a central reason why clinical trials find patient engagement so difficult: "It comes down to accessibility. Clinical trials can be a burden for both patients and clinicians, with long hours and continuous visits a difficulty. Normal life gets in the way."

What can be done?

Powell suggested that as decentralised trials become more well-known and commonplace, incentivisation will occur naturally. He said that with the increase in electronic patient-reported outcomes (ePROs) capturing both healthcare and lifestyle information, such as social time, the impact of an illness on work etc, the patient is increasingly able to view their own data.

This means that they can better engage with the trial and their healthcare progress, either by seeing improvements as they occur or seeing how the data is operated. This alone gives something back to the patient and makes continuing the trial more appealing. While steps have always been made to disseminate information with the patient at the end of the trial, doing so during the process is much more engaging. For example, he pointed to LEO pharma's Imagine app. This shows snapshots across the timeline of skin condition treatment, so patients can understand the impact the medicine has had on them.

Maria Palombini noted that a number of pilot projects are currently active and onboarding patients. A majority of these projects have been focused on patients with rare diseases, as they're often highly incentivised either by potential access to a last-resort trial or to receive better therapy for quality of life.

She said that full virtualisation of trials was a fundamentally exclusionary concept. Patients who are already disillusioned with the process are unlikely to sign up to a trial which lacks human contact or inclusion. Hybridised trials, however, still have that human connection alongside the added bonus of automation and digital technologies, blockchain for data management, and increased diversity due to greater population inclusion.

LACK OF PATIENT SAFETY / ADVERSE EVENT REPORTING

Concerns have been raised that decentralising trials leads

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to a fall in patient safety, due primarily to the fact that without direct patient contact, there could be limited recognition of adverse events or dissatisfactory care.

John Reites acknowledged this as a real risk that must be mitigated: "The ability to remotely capture data, capture it more continuously and hold visits outside of the standard trial clinic visit, means that additional processes backed by experience must be setup to support patient safety as the number one focus with clear steps to support AE/SAE reporting."

What can be done?

This problem, of course, applies largely to decentralised trials that do not adapt suitably to the change with necessary or advanced technologies. While many doctors have suggested that a lack of face-to-face time with the patient could lead to missed signals, advocates of decentralising trials can point to dozens of technologies that minimise this concern.

Examples include tracking technologies, like Apple Watches, that can collect and store data, letting clinicians interpret and react to adverse reactions. Many of the more advanced types of wearable or monitoring technology can also automatically detect different forms of adverse event, such as nQ Medical's neuroQWERTY keyboard, which can predict patient disease based on how fast an individual is typing or keypad pressure and was recently awarded Breakthrough Device Designation by the FDA.

Gareth Powell elaborated on this concern: "If someone's having an AER, how can we tell? Well, if we're using Web X calls or video services, the model can work. Remote face-to-face discussions, supported by underlying data like heart rate or blood pressure that can notify of an AER, are seeing greater and greater practice. As the technology improves, we can take more and more measurements and be in a better place to analyse the data."

DEVICE SELECTION

A slighter issue with decentralised trials than those referenced above, the selection of tools and devices is also an issue brought up by some clinicians as a problem when moving to more hybrid models of trial.

Issues raised include understanding which devices and models to use, in a field that is only now beginning to develop and be better understood. Reticence to introduce variability into a necessarily structured and highly-ordered process is understandable.

What can be done?

Here more than in any other challenge to decentralised clinical trials, the answer lies in knowledge and experience, something which many companies are in short supply of. As the field progresses, physicians and site operators will by default learn more about best practices of

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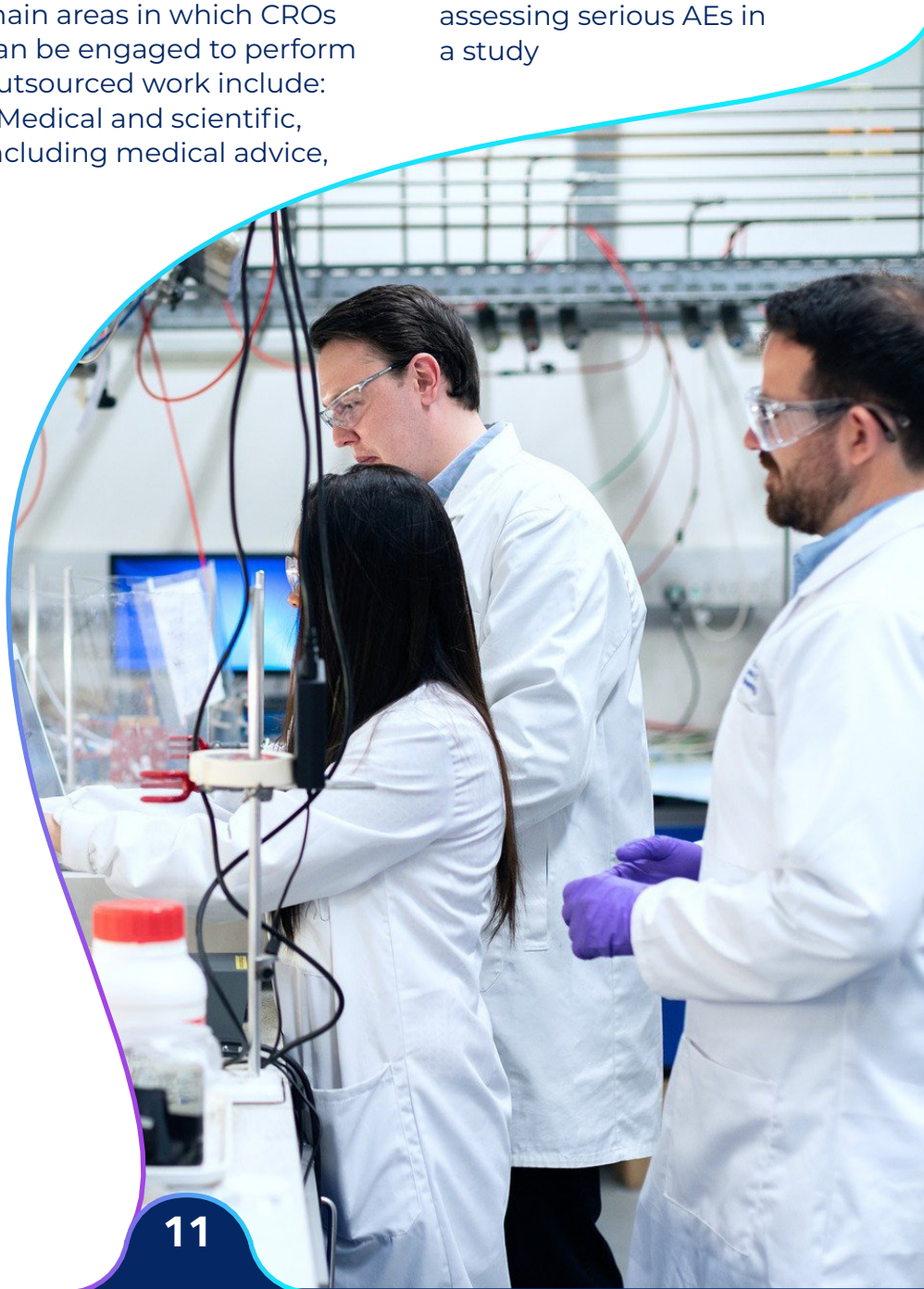
the technological aspect, and become more able to discern what will benefit both the patient and the study and what will not.

The answer to this challenge can be difficult for a company to establish on its own. The necessary equipment and processes will of course depend entirely on the trial being run, on patient population size, geographic dispersion, and the level of interaction sites wish to have with their patients.

Without any knowledge whatsoever, a CRO could be the best solution to a company's expertise needs. While some have questioned the necessity of CROs as companies gather more and more technological solutions that easily reduce outsourced work, for newer companies a CRO could be vital.

The CRO landscape now covers almost any task clinical trials need performing, from patient recruitment to working with novel or expensive technology that is more efficiently outsourced than bought and trained around. While CROs require a level of trust, co-operation and short-term expense than is otherwise found simply by internalising procedures and technology, for many companies it is the preferred option when dealing with new processes or technologies that they lack the staff for and experience in.

The use of CROs for technology, data and personnel management allows pharma companies and sites to focus on other tasks, such as developing new frameworks and building new networks with key opinion leaders. The main areas in which CROs can be engaged to perform outsourced work include:
- Medical and scientific, including medical advice, writing medical reports and legal responsibility of trial conduct.
- Statistical, including data entry into databases and statistical analysis of safety data
- Trial management, including investigator selection and recruitment and monitoring the conduct of studies and protocol compliance
- Regulatory, including compilation of technical data for regulatory agreement and interim progress reports to regulators
- Drug safety, including designing safety data collection methods, assessing the study safety profile and assessing serious AEs in a study



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TECHNOLOGY AND VIRTUAL REALITY

Decentralised trials are insupportable without the necessary technology to ensure data is captured and patients are motivated, engaged and have full knowledge of the regime and data input. As decentralised trials come more and more to prominence, so too must the technologies that enable them, either within the pharma company itself or through CROs employed to work in the company's stead.

While technology is not the prime mover of decentralised trials, it is an extremely important facilitator that enables the fundamental mechanisms to operate smoothly. In the last two decades, technology has advanced significantly in every area in which clinical trials operate, from recruiting patients to analysing trial data. This can all be leveraged to make decentralised trial implementation more fluid and easy - if a company knows where to look.

PATIENT RECRUITMENT AND ENROLLMENT

No trial can begin without onboarding patients to participate. This is widely regarded as the most time-consuming part of a trial: in a 2016 study, 18% of cancer studies between 2000 and 2011 failed to find even 50% of the necessary patients over three or more years.

While some companies, such as Pfizer in its early efforts, have discovered that certain populations are better engaged offline, most patients have a strong working familiarity with the internet and are open to social media and website advertisements. As the general population continues to age and technology becomes ever-more pervasive, it is likely that the tech-wary demographic will steadily shrink, and the ability to advertise online will become ever more important.

Finding and targeting patients

The very first stage in dealing with patients is finding and recruiting them. This is a well-recorded problem: cancer, liver disease, and Alzheimer's studies have all famously struggled to find patients: in serious cases, 20% of cancer clinical trials fail due to poor patient recruitment.

Outsourcing here is already a teeming market. Major companies involved in using technology to recruit patients include:

- Deep 6 AI, a company using AI to analyse data and match those data points with clinical trial criteria to better find well-matching patients
- PatientWing, a recruitment platform that allows researchers to create SEO-optimised landing pages and forms to ensure patients can quickly move through the application process
- Clinical Trial Connect, which works with charities and organisations supporting specific disease treatments, for example the National Brain Tumor Society. Clinical Trial Connect's platform, when embedded on a website, allows patients to easily find relevant studies for them.
- TrialJectory, which uses AI to

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help cancer patients find the right trial for them, staying with the patients throughout the trial process.

Some of these companies also work with patient enrollment, helping determine whether individuals meet study requirements or facilitate communication between patient and pharma.

Another is Verified Clinical Trials. The company uses a central database of patients in trials to ensure no individual enrolls in multiple clinical studies, or opens a company up to protocol violations. DocuSign allows patients to sign documents more easily online, reducing stress and drop-out rates.

Finally, ClinPal is a company particularly focused on siteless trials, with a Cloud-based platform focused on recruiting and engaging patients.

Artificial intelligence

AI algorithms are also a potentially huge boon to patient recruitment, as they are to any stage in the clinical trial process. Natural Language Processing (NLP) in particular can make a significant difference to patient recruitment.

NLP allows computers to analyse structured data, either written or spoken, and translate that data into useful information or statistics. In this case, NLP could be used on stored doctors' notes or pathology reports to find eligible patients.

The main problem for NLP's efficacy is non-standardised or unstructured datasets. Efforts are being made to bring medical records into more standardised formats, for example with the Criteria2Query open-source web tool, which allows researchers to search a database without knowing the database query language. Another, by the same authors, is DQueST, which ascanes ClinicalTrials.gov trial information and generates set questions to assess user eligibility for them. One evaluation of this tool found that after 50 questions the algorithm could determine patient eligibility up to 60% accuracy.

Online assessment

Once demographics have been targeted, prospective patients must be assessed. This can be done via video link, using Skype or a similar system to understand the patient's requirements and pathology or underlying condition. Alongside assessing the patient for suitability, this method can be used to provide all necessary information up-front and immediately, as opposed to speaking to one patient at a time with multiplying opportunities for error or accidental omission, thus saving considerable time and improving clarity.

AI and algorithms can similarly be used to whittle down patients rapidly. An example of this comes from Georgetown University, where researchers used Cloud-based computing techniques to reduce tumor profile assessment time for clinical trials from 14 days to four. According to the study's corresponding author Subha

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Madhavan, “Our platform is unique in that it integrates patient-specific data with genomic knowledge bases to provide a comprehensive report on potential trial enrollment opportunities.”

eConsent

In particular, eConsent has revolutionised online patient recruitment. This allows vast quantities of trial information to be reduced to small, understandable modules using multimedia formats. The cost and nature of eConsent will vary based on the study requirements, and are often customised based on components used. The use of remote eConsent, while challenging currently, is provided for by FDA guidance of December 2016, though if not personally witnessed by a site member this must include a method to ensure the signing patient is either participating directly in the study, or is their legal representative.

An example is FIRECREST eConsent, available from Icon, which includes interactive multimedia content to ensure patients understand commitments. Once a patient is set to take part in a trial, they can use an eSignature on a range of devices, such as smartphone or iPad. This is regulatorily compliant and allows for the real-time monitoring of the patient by site staff.

Staff training is vital when introducing eConsent to a trial to ensure correct application. It is also recommended to have a subject-matter expert on site to ensure smooth running of the technology. Regulatorily, it is also important to ensure the eConsent system follows the FDA guidance of December 2016, alongside 21 CFR Part 11, and ICH GCP E6 R2, and HIPAA and GDPR rules for the EU.

In terms of security, access to the system should generally be restricted only to those who need it, with information encrypted and backed-up in case of data loss.

Importantly, eConsent is restricted in some parts of Europe, particularly relating to signature capture. It is important to understand the full legal implications of implementing eConsent before doing so, to ensure companies are not caught out after investing time and money in the project.

PATIENT ENGAGEMENT

Once patients are onboarded, ensuring they continue with their trial to completion and adhere strictly to the procedure they must follow is key. With traditional trial models, engagement was tracked through regular meetings, diaries and forms: but as we have seen, ensuring regular completion of these and that patients would not become disincentivised was a constant struggle.

Ensuring adherence to procedure

A number of smaller companies are active in selling smart pill bottles, which can track adherence to a pill regime and notify patients of dose times, or in offering incentives based on behavioural economics. These include startups such as Towerview Health, Pillsy, Wellth and Medisafe.

Others have started to provide digital variations of directly observed therapy, where an individual or AI must observe the patient taking their medication. Research has found that patients observed in this manner complete their treatment 86-90% of the time, compared with 61% of those who are not observed.

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Reducing dropout

There are few major startups or vendor companies offering novel solutions to prevent patient dropout at this time. One of the leading businesses in the field is Brite Health, which analyses patient data and sends personalised messages to encourage flagging participants to continue the study. It can also predict when a patient is likely to drop out and notifies trial staff.

Social Listening Strategies

Acquiring patient feedback is another important focus to increase engagement. Alongside standard methods of requesting the patient participate in surveys or receiving feedback over the phone or video service, companies can enact social listening strategies. These are fairly straightforward - monitoring patient blogs or social media like Instagram or Facebook to determine their unfiltered thoughts on the trial and their participation in it.

PRA Health Sciences is one company which practices social listening. They collect public data from social media to understand how patients talk about their conditions and difficulties. In clinical trials, this information could be used for a range of uses: to better monitor and understand patient AEs; to determine morale level and drop-out risk; or to increase patient engagement by actively responding to negative aspects they mention and reinforcing positive ones.

Tips for performing such strategies well include:
- Looking for patterns to determine underlying flaws or concerns, rather than simply relying on individual comments
- Engage with a receptive audience to further understand issues and learn which alternatives would be better

DATA CAPTURE, INTEGRATION AND STORAGE

As has already been seen, mistakes or delays by either patients or site staff can result in skewed or biased data that fails to adequately reflect what is happening in the trial. Such inaccurate data has a knock-on effect for the trial, delaying its conclusion significantly.

A number of CROs and startups exist to capture and store data across the entirety of the clinical trial process. THREAD Research, for which John Reites works, offers a unified platform working with an array of Pharma, Biotech and CROs to allow remote data capture from both patients and trial sites and conduct Virtual Visits in place of in-clinic visits. The platform also offers eCOA/ePRO, patient engagement, sensor connectivity and retention features, and increased flexibility for sites. One of the largest digital CROs, Science 37, also offers end-to-end solutions for virtual trials, partnering with Novartis in 2018 to plan several of its siteless trials.

Certain tools exist to allow pharma organisations to determine where sites are underperforming. Trials.ai is one such platform that lets pharma see real-time feedback

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in order to correct data collection errors.

During Oracle's survey, site-based participants noted technology's use in removing layers of management, as well as assisting with increased site engagement by providing a better quality patient population.

eCOA

Electronic clinical outcome assessment (eCOA) systems capture improvements in treatment that can be fed back to patients, as well as informing clinicians of changes. The data they produce is also increasingly useful to regulators, who require such information in order to provide approvals.

There is already a significant body of evidence that suggests eCOA provides greater data quality compared with paper documents, and is not overly expensive compared with paper data collection: paper, seemingly cheap, has a number of hidden costs. eCOA, on the other hand, reduces compliance costs due to data quality and real-time data monitoring.

For those companies not wishing to invest up-front in ePRO or eCOA systems, CROs exist to outsource all needs, including, Signant Health and IQVIA. These can supply sites with smart devices, and hand sensor logistics. A number of other data capturing organisations exist that supply products to capture data from the patient: Medidata, Oracle, and eClinicalSolutions are all fairly well-known and provide a range of resources for creating and automating eCOAs and other outcome data management systems.

There are a number of other CROs specialising in transferring clinical research into the Cloud. These include Florence Healthcare and ClinicalResearch.io.

Wearables

Wearable technologies are a major facilitator of decentralised trials. With consumer devices like smartphones and internet-enabled watches, patient vitals and statistics can be tracked in-real time from home, with a range of secondary functions also possible like increased patient engagement, reduced costs and better understanding of the condition being researched. Because they measure the patient in day-to-day life rather than a clinical setting, their measurements can be more accurate and reliable than standard models.

Beyond this, wearables also allow for easy submission of this data to the clinician, removing the need for written PROs or diaries, saving the patient and the clinician time and reducing dropout because of that.

According to Gareth Powell, the vendor market for creating wearable tech is growing, with several organisations currently developing in-house

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models. He suggested the trend would move towards outsourcing these solutions, however, simply because outsourcing firms have innovation and dedicated time to create those solutions. "Obviously, large companies do too, with Janssen moving into virtual and siteless clinical trials with its work under the Global Trial Community project.

"Many vendors are supporting this, with more and more creating dedicated ePRO tools, healthcare apps and other technologies. But beyond just the tech, other groups - such as the MD Group - are doing work on things like captions and language work, using machine learning, to identify stress phrases and other pointers on when participants will drop out of trials."

John Reites mentioned the positive impact of continuous monitoring and sensor work as well. He noted it allows clinicians to see active and passive data points from medical devices and wearables in specific use-cases, capturing data beyond ePRO or surveys.

Despite these benefits, wearables do have a few drawbacks. They can increase trial costs depending on the type of wearable and what data is being drawn, as well as the number of trial participants needed.

There is also the problem of the data itself. Data issues include the potential for wearables to be used wrongly and thus supply bad readings; for misreadings of data or erroneous data entry after the information has been taken from the wearable; and the need for facilities to store greater quantities of data than have ever been handled before.

Another issue is the wearables' impact on the participant. Wearables can directly affect engagement either through over-complication, cumbersomeness or privacy intrusion. Medical-grade wearables have been particularly problematic in the past, often being too cumbersome for many to bother wearing. Now, however, new devices are entering the field.

Apple Watch and Fitbit

The two major activity trackers currently available are the Apple Watch and Fitbit, though other trackers are quickly gaining ground. In 2018, the series 4 Apple Watch received two FDA approvals for use in trials, as an EKG and a pulse monitor, though the technologies can do much more, including monitoring respiratory data, exercise and levels of movement.

Historically, these two models were deemed unfit by regulators, with clinical-grade devices used more prevalently by pharma. But with the Apple Watch's new clearance, they are being reconsidered. Commercial devices are preferable to specialist clinical ones due to their ease of use, lightweight nature, and utility.

It has generally been said that in the years to 2025, wearables will become much more widely used, with around 70% of clinical trials set to incorporate wearables by that point.

Gareth Powell summed up the need for new tech: "We're familiar with available technology now - most people have a smartphone. Even if not, there's an awareness about it, and organisations can give them devices. People are now able to more readily participate in trials where traditionally they might not have been able to. So we can use things like push notifications, gamifications, nudge theory, and associated apps as well, to retain and engage patients throughout the process.

"These technologies can help us create a more realistic and holistic view of those individuals' needs, requirements and conditions. Here's an example: a patient with severe hand arthritis could have a good day where his pain is below normal for him, but that would still be considerably more than what we'd tolerate as a 'low pain'. Relatively, he'd mark the day as low pain in his diary. But if a trial was looking for specifically high entries of pain in the pain diary, he wouldn't gain access to that

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trial, though it would be highly useful to him.

"But if we're recording that information via an app each day, you can get a much better idea of where that pain is specifically, and what the triggers and flare-ups are. Not only that, but it's also reducing the time taken to go to the clinic and hand over a diary, keeping patient engagement high. Clinicians can be more flexible and reduce patient burdens."

In order to make the most of wearables in a company, organisations are encouraged to:
- Set up a 'in fast, fail fast'model with proof-of-concepts to study feasibility of tech and learn best use cases
- Set up a team to focus on POC innovation and push best practice throughout the company
- Involve external stakeholders as quickly as possible, to understand consumer perspectives and usability
- Incorporate KPIs quickly to ensure endpoints, and how they will be used, are fully understood
- Ensure site staff have the experience to check patients are correctly using their devices, and to complete a data download (if necessary) during check-ups.

Wearables regulation

One issue with using wearables in trials is the lack of regulatory clarification at present. Acceptance of data provided by wearables has been a longstanding issue, recently brought up by FDA Commissioner Scott Gottlieb in a statement on the slow integration of real-world data into clinical research. This follows a 2018 FDA statement discussing how RWD could better inform regulatory decisions.

This partly stems from a lack of data quality from many wearables. The difficulty of truly identifying the data originator or source is a particular issue, addressed several times by the FDA. There are also concerns around the security and c onfidentiality of wearables, which many regulators consider only a storage site for the data, with an audit trail beginning only after the data enters a sponsor's EDC system.

The Critical Path Institute's ePRO Consortium has offered relief in this area, however, with 2018 recommendations on selecting wearables and assessing their suitability for measuring relevant endpoints. Other guidance has been written by the Clinical Trials Transformation Initiative (CTTI).

This situation is still ongoing: despite regulators' enthusiasm for technologies which expedite pharmaceutical processes and make lives better for patients, as yet the beneficial applications stemming from wearables are simply not satisfactory for a real green light from regulators. This needs to change soon if wearables are to see rapid uptake and approval.

Data-sensing and digital biomarker-collecting technologies

Digital biomarker collectors, which collect behavioral and physical data from patients, are one type of wearable. Many CROs supply such collectors and the systems which integrate their data, such as Actigraph. Google's Verily medicare company is doing the same with its Study Watch, and Vivify Health provides 'kits' including a tablet featuring an in-built wireless vitals monitor.

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With advancing technology comes the potential for sensors to be created that need limited skin contact - even for such functions as heart rate monitoring and breath effort. These sensors include passive tags woven into clothes around the chest and wrists.

VR Equipment

Another technology that's seen limited discussion compared to wearable tech or apps is that of virtual reality (VR) equipment. The market for VR equipment in pharma is growing: in the five years to 2017, VR and augmented reality (AR) in healthcare rose $451 million, and is expected to see around 54.5% annual growth up to 2023 and beyond.

While VR is being primarily used in hospitals and other healthcare centres to increase patient understanding and reduce stress rates, it does have strong application in clinical trials too. As an Interactive Journal of Medical Research (IJMR) studyshowed, 94% of patients undergoing a VR experience on how HIV medication protects the body's blood cells self-reported as more closely following treatment regimes, with follow-up tests supporting this fact.

Operationality, not Technology

John Reites stressed the importance of focusing on the operations of decentralised studies as equally as the technology for clinical trials. He noted that technology should work well and be seamless to support all the study stakeholders as the enabler of study operations.

To counter possible setbacks around technology - device failures or incorrect patient usage - Janssen has created an internal ring-fenced team and budget to ensure compliance. One spokesperson for the company mentioned that such problem-solving teams need to be extremely agile to take in multiple revisions to plans as and when they occur.

> "It has generally been said that in the years to 2025, wearables will become much more widely used, with around 70% ofclinical trials set to incorporate wearables by that point.

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John Reites noted that data collection is important in decentralised trials and that the source from which it comes from is equally as important; “one of the advantages of decentralised study approaches is that data can increasingly be provided directly by the source during the Virtual Visit as opposed to entry from a source into another system. This supports the ability to reduce the amount of data and time requiring monitoring and supports highly quality data due to the lack of transfer needed from one system/paper into another system.

THE NEED TO IMPROVE DATA QUALITY

Historically, collecting data via paper surveys and diaries is liable to inaccuracy and poor quality of data, not only from routine human errors but from the necessity of ensuring patient availability at certain times and at certain places in order to complete PROs. A number of studies on trials have found that patients often experience delays or do not show up to sites at all.

In addition to this, it has been found that there are generally a number of inconsistencies in how PROs are managed across different clinical trial centres, with clinical trial staff sometimes failing to respond correctly to these incomplete or overdue PROs, introducing biases to the data.

Standardisation and better data quality are a must if the clinical trial model is to function at all.

As has already been mentioned, the FDA has at length discussed the need for greater data quality in clinical trials, particularly around wearable tech, and has in the last few years published guidelines on electronic signatures and mobile technology.

Gareth Powell pointed out the ramifications of failing to improve data quality and safety: “So far, the whole idea of patient data and how that’s handled hasn’t been done entirely well. There are still a lot of questions around the issue. Historically, patients didn’t feel that they were being informed where their data was going. When Google began accessing data at Moorfields Eye Hospital, for example, and using machine learning to predictively analyse de-personalised eyes for signs of eye disease, the hospital was criticised for handing data over to Google without a firm understanding of that data’s ownership.

“On the other side of that, we see patients keenly provide healthcare data to companies like 23andMe to directly support clinical research. So the desire to provide healthcare data is there, as long as individuals have control over that data and understand what it’s being used for.”

Maria Palombini argued that decentralising trials improved a patient’s right to privacy, and ability to consent more clearly on what they want to share in exchange for some transactional benefit.

The current state of patient health data brings many complexities including the trial process. She raised the common issue of standardisation,

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with no taxonomies set up for health data: “current health data sits in a data swamp, not a data lake.” It would be very difficult and perhaps not very beneficial (from time or financial perspective) to try and clean up the “historical data baggage." It would be more beneficial to adopt approaches and technical and data standards utilising technologies such as machine learning and open application program interfaces (APIs) to make health data portable with trusted applications and validated endpoints.

She stressed it is important for all of the industry’s stakeholders to engage and have a 'voice' in the development of technical standards. In highly complex regulatory environments such as pharma, regulators need to be included in the process in the development of the standard not only to contribute their expertise but to understand the nuances of how it can deliver a trust and viable approach to the problem.

Regarding the safety of patients’ data, many of the same problems remain as are found in regular trials, compounded further by greater quantities of data being taken and stored, and greater automation leading to a weakening of data ownership. Powell noted that, with the entrance of GDPR, clinicians are extremely wary of how they use patient data, especially when using more and more vendors to manage that process. Problems still remain, however, on how that information can be decentralised and stored safely.

Blockchain

One recent innovation pharmaceutical companies are looking to integrate into their trial processes is the private blockchain model. Unlike the more well-known public model, used by cryptocurrencies like Bitcoin, the private model is more controlled and permission-oriented.

Due to the control relevant parties have over information, blockchain could prove particularly useful during the earlier stages of a trial, for example in monitoring consent. One study has set out the ideal open consent form using blockchain.

Maria Palombini noted that blockchain/distributed ledger technologies (DLTs) offer a significantly reduced risk to hacking depending how the application is deployed (public versus private) and consensus algorithms utilised (proof of work (PoW) vs proof of stake (PoS). “Right now, someone can hack a healthcare system and find a treasure of detail on 100,000 patient records or more. With an appropriately deployed decentralised DLT approach, if one patient’s device is hacked, then only that one patient would have been hacked!”

Beyond safety, blockchain has promise with regard to trial data and feedback. Currently, certain therapeutic states simply cannot be mobile or virtual, as patients will always need to go on-site to be treated. But currently, Internet of Things devices and autonomous data collectors on-site don’t get tied back to the patient’s home data profile.

With blockchain however, one record of truth can be established that is fundamental to the patient and to the trial. Unlike current informed consent processes, where multiple copies exist on multiple platforms and changes made to one may not necessarily be carried over to others, leading to confusion, blockchain technology provides a constant, immutable source of true data.

Blockchain, quite simply, improves trial data integrity via secure, autonomous data collection. Clinicians do not have to worry about hacking or tampering. The potential for fraud is eliminated.

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One difficulty still remains, however. The private model of blockchain means that patients who want to remove their data from a chain will find it extremely difficult to access the right permissions.

REGULATORY GUIDANCE AND ACCEPTANCE

By all accounts, regulators are not averse to the innovations virtual trials can bring: the opportunities for strengthening diversity and increasing access for patients are too good to ignore. While regulation around this area is still minimal, the FDA has discussed the area with the CTTI and with sponsors, and has issued some guidance (as highlighted earlier in this white paper). In 2015 it also published a draft guidance document on using electronic informed consent in clinical investigations to specify how regulators will let companies use online media like interactive websites to push forward informed consent.

In more general regulation, the American 21st Century Cures Act suggests mobile technologies are a useful technology, and encourages regulation to better advance innovative therapies and improve patient-centricity. The FDA is currently aligning its policies with this mandate.

The FDA's Center for Devices and Radiological Health has also been working on the impact technologies can have on medical products. In July 2017 it released a Digital Health Innovation Action Plan that committed the FDA to address barriers to use of mobile technology in clinical trials. It set out the FDA's intention to update its policies and issue guidance clarifying the 21st Century Cures Act software provision. Another piece of guidance on FDA policy.

The European Medicines Agency has not yet published specific guidance for virtual trials. it has, however, set out its draft strategy plan, Regulatory Science to 2025, which was created to encourage collaboration around improving evaluation quality. The plan recommends developing a framework to revise oversight, in order to create wearables methodologies and allow decentralised trials which directly collect data. Draft guidance on electronic source direct data capture was also published in July 2019.

John Reites noted from his personal experience that regulators are open and inviting to have conversations on decentralised study designs with sponsors. He also noted that one of the most important insights THREAD has learned from these conversations is that sponsors should provide regulators with clear process information on the context of use with decentralised approaches. This includes detailing how the telehealth Virtual Visit will be utilised, how this approach will support the fit-for-purpose use on the study, how the assessment retains its validation when being conducted remotely, describing what will not be done via telehealth, etc.

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WILL DECENTRALISED TRIALS EVER BE STANDARD?

Gareth Powell suggested that at least in the long-term, fully-virtual trials would be a reality. “Even now we’re talking about wearable technologies, capturing real world evidence from this, sending medication by post. Worries still exist, but right now we’re beginning to see benefits, too.

“Of course, there has been some pushback. But the patients using the service in young, metropolitan populations like London - as opposed to GPs - enjoy the benefits of decentralised trials.”

John Reites believed more specifically that decentralised trials would become a standard approach in the 'toolbox' for sponsors to utilise on studies.

“This means that not every study should be fully decentralised - maybe only a small percentage of full decentralised designs will exist over the coming years. What is happening today and what I see is the evolutionary step the industry is making now, utilising hybrid decentralised designs that are applied to study designs in a fit-for-purpose way. The hybrid decentralised approaches are providing value to patients/sites, offering balance to sites/patients in how their interact on studies (i.e. mix of virtual and on-site) and enabling more modern study designs for sponsors to utilise.

> A study conducted by the U.S. Department of Health and Human Services found that testing patients at home on average reduced phase 1 study costs by 16%, phase 2 costs by 22%, and phase 3 costs by 17%.

5.1 CONCLUSION

As a whole, participants in the Oracle survey agreed that decentralised trials increase patient retention and enrollment, as well as making clinical trials more convenient for all parties.

Gareth Powell said that while limited implementation of hybridised trials is evident now, first impressions have shown that reception to them is varied: “We need to be more flexible. Right now we’re making assumptions that this is what every patient needs, and assuming these trials will solve everything. But some patients value going into the clinic and seeing the clinician, for example where people say home visits are invasive or unwelcome. Flexibility is the key to ensure all parties are happy when the roll-out finally occurs.”

John Reites concluded by stating that while the discussion around decentralised trials has been largely North American based so far, the model is being utilised globally in Asia Pacific, Europe and South American countries.

It is indisputable that integrating new, efficacious technologies and patient-centric processes into the long-established clinical trial model will have a profound impact on how patients are recruited, treated and analysed. But pharmaceutical companies need to learn a lesson from the slow take-up of such trials across the sector. Until the fundamental issues around standardisation of technology, manageability of data quantities, and balance of technology versus in-person meetings are addressed, we will move only slowly towards a future where clinical trials cost less and take up less time, and pharma companies learn far more.

> “The progression of a decentralised study approach is not that you fully decentralise every single study - maybe for a small percentage that can be done. But more often it means taking those hybrid elements that work for the specific trial and making them work for you.

5.2 UPCOMING STRATEGY MEETINGS

PROVENTA INTERNATIONAL

2 JUNE	- Chemistry Manufacturing Control | Regulatory Affairs -	ONLINE
3 JUNE	- Biomanufacturing | Cell and Gene Therapy -	ONLINE
25 JUNE	- Clinical Operations | Clinical Trial Supply Chain | Pharmacovigilance -	ONLINE
29 JUNE	- Biology | Medicinal Chemistry -	ONLINE
30 JUNE	- Oncology | Bioinformatics -	ONLINE
5 OCT	- Clinical Operations | Clinical Trial Supply Chain | Pharmacovigilance -	ZURICH
6 OCT	- Biomanufacturing | Cell and Gene Therapy -	ZURICH
7 OCT	- Regulatory Affairs | Chemistry Manufacturing Control -	ZURICH
2 NOV	- Oncology | Bioinformatics -	SAN FRAN
3 NOV	- Medicinal Chemistry | Biology -	SAN FRAN
5 NOV	- Medicinal Chemistry | Biology -	SAN DIEGO
9 NOV	- Pharmacovigilance -	BOSTON
10 NOV	- Clinical Operations -	BOSTON
11 NOV	- Clinical Trial Supply Chain -	BOSTON
16 NOV	- Oncology -	BOSTON
17 NOV	- Bioinformatics -	BOSTON
18 NOV	- Biology -	BOSTON
19 NOV	- Medicinal Chemistry -	BOSTON
23 NOV	- Biology | Medicinal Chemistry -	LONDON
24 NOV	- Oncology | Bioinformatics -	LONDON