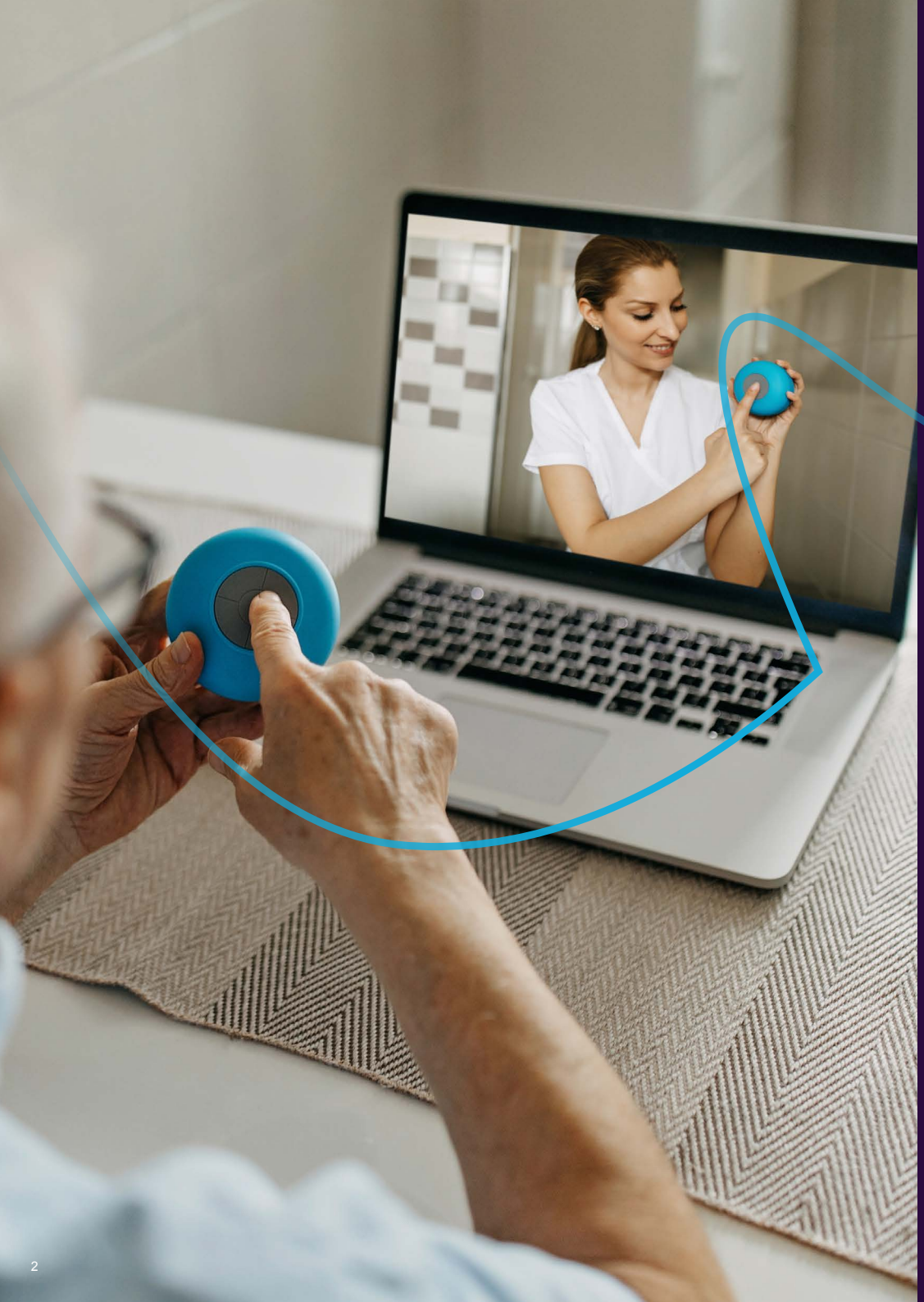
THE CLINICAL TRIAL OF THE FUTURE

Capgemini engineering



CONTENTS

Chapter 1:
Bringing digital transformation to clinical trials 6

Chapter 2:
The Opportunity 10

2.1 Optimization

Sharpening recruitment, reducing dropouts, and broadening cohort diversity 10

Trial planning and management 12

2.2 Innovations

Next-generation data science and novel endpoints 13

Harnessing intelligence from novel data and past trials 14

Chapter 3:
Making innovation work 16

3.1 Deploy new tools to capture valuable data 16

3.2 Standardize data 16

3.3 Keep data safe 19

3.4 Deploy skills to combine and model data 19

3.5 Create a culture of innovation 20

This report is based on extensive interviews with the following expert team from across Capgemini.

- **Matt Jones**, Head of Offer Development, Hybrid Intelligence, Capgemini Engineering
- **Simon Stoddart**, Consultant, Hybrid Intelligence, Capgemini Engineering
- **Matthew Pigg**, Consultant, Hybrid Intelligence, Capgemini Engineering
- **Anniek Myatt**, Analytics consultant, Capgemini Engineering
- **David Ghesquieres**, Life Sciences Strategy & Business Development, Capgemini
- **Rachel Hirst**, Head of Offer Ownership, Hybrid Intelligence, Capgemini Engineering
- **John Whittle**, Independent project consultant

“A TRIAL OF THE FUTURE...”

A clinical trial for a novel drug commences.

It is administered to a carefully curated patient cohort, selected using demographic and medical data to recruit a population representative sample, weighted towards those most susceptible to the disease. They were recruited via social media adverts carefully tailored to them, using natural language processing to understand what messages work well with that group.

In this trial, retention is maximized through a decentralized format, with wearable sensors allowing patients to remain in their home environment, giving researchers rich, real-life and continuous data on everything from sleep to gait.

Costs are trimmed thanks to a predictive model that accurately forecasts required drug quantities by crunching data from past trials to understand retention curves.

Data collected is detailed and granular, measuring real physical and biological changes in patients as they progress through the trial, as well as traditional subjective measures. These produce data giving clear indications of efficacy, variability between populations, and advance warning of rare adverse events.

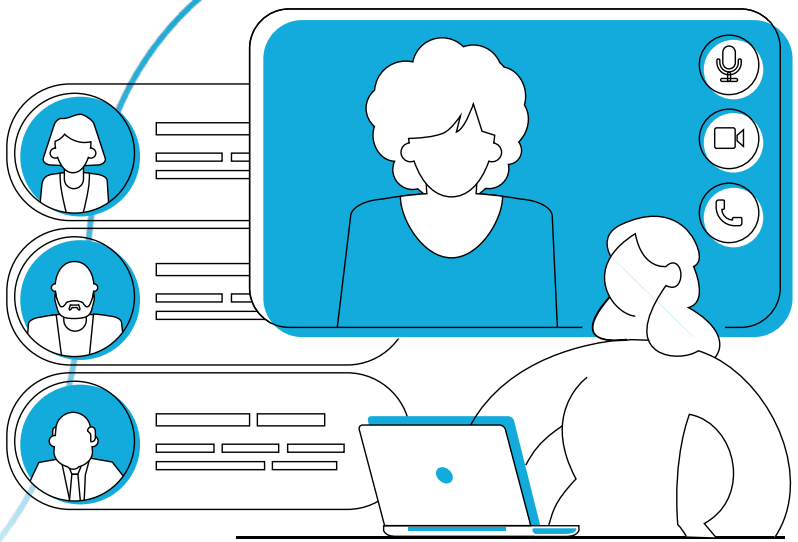
Analysis of interim data allows the sample size to be refined, doses to be altered for greater effectiveness, and alterations made to the allocation ratio to focus on patients most likely to benefit. The trial concludes early based on clear efficacy data, with clear signals on different optimal dosing regimens for different populations. This allows the medicine to reach the market sooner and lowers costs and improves profits for the company.

Thanks to higher quality data and more predictive endpoints, the trial success translates directly into real-world effectiveness, saving lives.

How can we deliver the clinical trial of the future?

CHAPTER 1:

BRINGING DIGITAL TRANSFORMATION TO CLINICAL TRIALS



The pharmaceutical industry stands at the cusp of a new chapter in clinical trials, as artificial intelligence, predictive analytics, cloud computing, and sensor technology make new approaches to trial design and delivery possible. Taken together, these technologies allow greater insight and agility in cohort selection and trial management, and understanding of the underlying mechanisms that affect efficacy, side effects and variation between individuals.

Digital innovation offers both ongoing improvements to existing trials, and whole new ways of conducting better trials in future.

These technologies bring potential benefits to all types of clinical trials. Before discussing how to harness them to deliver this transformation, it is worth considering decentralized and adaptive clinical trials, two trends that are being enabled by these technologies, and also driving interest in them (*see page 8*).

These are not the only news in clinical trials, but they provide a catalyst for many of the digital changes that will disrupt the clinical trial space. Embarking on DCTs and ACTs will force pharma companies to adopt new digital technologies to collect new types of data, and embrace new approaches, technologies and skills. As they do so, and as their value becomes clear, these innovative approaches will gradually feed back into traditional trial design.

81%

OF RESPONDENTS WERE WILLING TO PARTICIPATE IN A MOBILE TRIAL COMPARED TO JUST

51%

IN A TRADITIONAL TRIAL

[1] Apostolaros, M,. Babaian, D., Corneli, A,. et al., 2020, Legal, Regulatory, and Practical Issues to Consider When Adopting Decentralized Clinical Trials: Recommendations From the Clinical Trials Transformation Initiative.

[2] Danish Medicines Agency, 2021, The Danish Medicines Agency's guidance on the implementation of decentralised elements in clinical trials with medicinal products.

[3] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6610628/

[4] Expert Interview (John Whittle) & Beauchamp et al., 2020, The Use of Wearables in Clinical Trials During Cancer Treatment: Systematic Review.

Decentralized clinical trials (DCTs)

DCTs use digital tools to monitor participants in their homes, rather than requiring regular attendance at a clinical site.[1,2] This improves patient convenience and comfort, and provides richer data.

The impact is greater willingness to participate, lower likelihood of drop out by eliminating patient fatigue, and greater diversity of participants. One study found 81% of respondents were willing to participate in a mobile trial compared to just 51% in a traditional trial.[3]

Continuous monitoring in a home environment produces more accurate data for conditions marked by fluctuations such as bowel disease, those requiring long-term monitoring of multiple outcomes like cancer, and those in which endpoints like pain, blood pressure or sleep quality can be more accurately measured in a real-world environment.[4]

"In a hospital context everything is under control, but that's not reality," says David Ghesquieres, "one of the problems with clinical trials is that they only tell you about the benefits of an intervention in a controlled context".
John Whittle adds, "You can get better results if someone can say 'my pain score right now is 7 out of 10', or if you can see in accelerometer data that their mobility is improving, rather than asking them to take a guess a week later".

Adaptive clinical trials (ACTs)

ACTs allow for prospectively planned modifications to one or more aspects of the design based on emerging data from subjects in the trial.[5] They evaluate collected data at predetermined points to make modifications, such as the termination of ineffective treatment arms or the enrichment of a study population.

This benefits patients by allowing more of them to participate in trial arms that are most likely to produce a beneficial response and to withdraw from those that are unpromising.

For researchers, it allows simultaneous analysis of multiple treatments, which is more efficient than undertaking multiple parallel studies with fixed designs.[6,7] It brings an ability to quickly adapt to changing circumstances and take early decisions to stop or refocus where results are not promising. ACTs were used extensively in Covid-19 trials as adaptive designs allow for evaluation and adaptation to changing circumstances.[8]

This all sounds like an obviously good thing to do, but meaningfully interpreting that interim data to make sensible decisions can be challenging.

[5] FDA, 2019, Adaptive Designs for Clinical Trials of Drugs and Biologics, Guidance for Industry.

[6] Mahlich, J,. Bartol, A,. Srirangan, D,. 2021, Can adaptive clinical trials help to solve the productivity crisis of the pharmaceutical industry? - a scenario analysis.

[7] https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-018-1017-7

[8] https://www.remapcap.org/pandemic-preparedness

CHAPTER 2:

THE OPPORTUNITY

INNOVATION AND OPTIMIZATION

Whether trials are decentralized, adaptive, or simply better versions of existing approaches, digital and data promise opportunities for optimization and innovation.

2.1 Optimization

Sharpening recruitment, reducing dropouts, and broadening cohort diversity

Patient recruitment is a challenge. Over 80% of trials are forced to extend or add sites due to recruitment failure, and Phase III and IV trials experience less than 40% enrolment efficiency (planned participants versus actually enrolled participants). [9,10]

The industry struggles to achieve demographic diversity of trial participants, leading to mismatches between a trial cohort and population-based prevalence of the disease. This leads to therapies optimized for those who participate in clinical trials, disproportionately white men.[11]

Data analysis can sharpen patient selection. Statistical methods applied to demographic data can identify weighted cohorts. Natural language processing can be applied to past recruitment campaigns to see which were most effective with different groups.

Machine learning can be applied to data such as medical records, past trials, insurance data, or internet searches for symptoms – as well as wider demographic and epidemiological data – to achieve risk enrichment, in which population subsets are identified. This is where we identify population subsets with desired qualities, such as those at maximum risk of a disease.[12]

"Risk enrichment was widely used in COVID-19 vaccine trials", says Matthew Pigg. "If you make good predictions about who is most at risk, you can plan your trial to give vaccines and placebos to give you the strongest possible signal from a smaller group".

A simple example of this was that many trials were run in countries with high caseloads and relaxed lockdowns. But with good data we can be much more nuanced than that.

Modeling helps you find the best cohort, recruit them, and design your trial to maximize retention, for example by deciding where to put sites or whether to run distributed arms.

OVER

80%

OF TRIALS ARE FORCED TO EXTEND OR ADD SITES DUE TO RECRUITMENT FAILURE

[9] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342339/

[10] https://www.pharmaceutical-technology.com/comment/reasons-for-clinical-trial-termination/

[11] https://www.scientificamerican.com/article/clinical-trials-have-far-too-little-racial-and-ethnic-diversity/

[12] https://www.fda.gov/files/drugs/published/Enrichment-Strategies-for-Clinical-Trials-(PDF-%E2%80%93-933KB).pdf

Trial planning and management

Clinical trials are huge managerial undertakings with plenty of scope for optimization.

Fine-tuning supply chains is one area of improvement. Drug trials involve producing pricey small batches of drugs. Insufficient drug supply undermines a trial's results, so companies tend to overorder. ***"By analysing data from past trials, especially the 'retention' curve, which shows how the patient cohort winds down over time, companies can forecast with more accuracy," says Anniek Myatt.***

AI can accelerate compliance without compromising quality, such as through algorithms that identify similar clauses and agreements previously held between clinical trials and pharmaceutical companies, to better create replica contracts based on pre-approved terms.[13]

As trials progress, cohort models can be updated to predict and plan. We have helped pharma companies model cohort progress using a Bayesian approach, which involves calculating the chance of each individual staying the course using demographic and historical recruitment data. These are updated as more information becomes available, helping predict who would sign up and when, and who would drop out and when. Such work reduces dropouts, and saves money by ensuring the right equipment and drugs are delivered to trial locations at the right time. It also helps predict when the trial is likely to deliver a result, helping plan for manufacture and marketing.

Companies can also use data modeling to deal with shocks. For example, COVID-19 significantly affected clinical trial logistics, and data modeling.

2.2 Innovation

Next-generation data science and novel endpoints

Digital innovation can enable breakthroughs in the way therapies are designed, tested and understood. There is growing excitement about new digital endpoints, which can give far deeper insights into efficacy compared to conventional metrics like mortality or patient symptom diaries.

Established endpoints, like hospitalization or mortality, are not necessarily predictive of a drug's real-world performance and often fail to capture the personal experiences of different patients. Patient-reported data, meanwhile, are subject to significant variation and measurement errors.

The ability to capture novel data through wearables and sensors allows researchers to monitor the impact of a therapy at higher resolution. Accelerometers and motion sensors can give very rich time series data to monitor how drugs impact diseases which affect movement such as Parkinson's. Ingestible sensors can pick up granular data like digestive tract acidity . A smartphone-based microphone can record coughing incidence, rather than relying on a patient trial diary.[15]

[13] https://www.epmmagazine.com/pharmaceutical-industry-insights/how-ai-is-helping-pharma-cope-with-supply-chain-disruption/

[14] https://www.medtronic.com/covidien/en-us/products/motility-testing/smartpill-motility-testing-system.html

[15] https://www.statnews.com/2019/11/06/digital-endpoints-library-clinical-trials-drug-development/

Fine motor skills, spirometry and respiration, gait, galvanic skin response and temperature are among the endpoints that digital technology can now capture in a more robust way.

AI is also creating new endpoints for measuring efficacy. Clinical trials of cancer treatments often monitor five year survival rates, an inconveniently long time. In earlier clinical phases it's more useful to monitor real-time tumor shrinkage, which is done by identifying a subset of tumors, manually measuring them with CT scans, and assuming they're representative of the whole tumor burden. But this assumption is not always correct.

An AI can learn to process the full complexity of CT imagery and measure every single tumor based on their full 3D outline – an impossible task for humans even for a single patient, let alone a whole cohort with different physiologies. These emerging tumor metrics are much more predictive of survival rates than traditional oncology endpoints, and make survival predictions possible based on data from fewer patients.

The number of digital endpoints being explored is growing, according to an online database by the Digital Medicine Society , from 34 to 166 in the fourteen months to January 2021. Growing confidence in their use is evidenced by the falling proportion which are deemed merely 'exploratory'[17].

The challenge in all of these is getting a meaningful signal from the data about the disease. It's one thing to collect vast amounts of time series data or high dimensional 3D scans, but that will be vast, complex and full of noise. It needs expertise to dig into and understand the meaningful signal. Sometimes the measurement itself needs significant modeling before it can offer anything meaningful. For example we helped a company look at voltage data from nerve impulse signals, using adapted radar-tracking algorithms, to create metrics of pain.

Knowing what the data is telling you requires sophisticated data analysis guided by a knowledge of what you're looking for, and a reliable baseline to compare it to.

Harnessing intelligence from novel data and past trials

Data science can help the industry predict risk in ways that could transform trial decision-making.

Adverse events are one area of important progress. A wide range of resources including post-marketing safety data, genomic data and even social media and online discussion forums, are being used to guide probabilistic adverse event predictions[18].

Secondary use of data – reusing data from a trial beyond its original purpose – can inform study design and identify best practices.[19,20] Secondary use of data can inform clinical research where a randomized trial format may be infeasible. It can also enable the pooling of data from different trials and sites, which could help R&D in conditions with small patient groups, as with rare diseases .

Data can have important re-use cases such as developing trial cost-effectiveness analyses. A collaboration between Genentech, universities, and hospitals, conducted cost analyses using data from the Vista International Stroke Trials Archive (VISTA), which hosts a central database of clinical trial data related to strokes. The study contributed to cost-effectiveness analyses of acute stroke interventions which would be impossible without access to VISTA.[22]

Simon Stoddart notes that "Natural language processing of patient consent forms can play a role in helping researchers identify usable data from older trial data with consent terms that were not as specific as they tend to be today with regards secondary use permissions."

Artificial intelligence can analyse secondary data to evaluate existing data sources to generate new hypotheses, and potentially inform drug re-purposing.[23]

Researchers can use AI to find links based on existing patient data sets and clinically approved drugs, by constructing medical knowledge graphs and harnessing machine learning to analyse the several million entities that medical knowledge graphs output.[24] Secondary use could also help understand the relationship between diseases. Capgemini has used existing data sets to cluster the sequence of diseases people frequently develop, and this could enable predictions of future disease sequences, and support more preventative or mitigating interventions before patients are diagnosed.

[16] https://www.dimesociety.org/communication-education/library-of-digital-endpoints/

[17] https://medium.com/digital-medicine-society-dime/the-rapid-evolution-of-digital-endpoints-are-we-headed-in-the-right-direction-c25bbcb32eee

[18] https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-020-3509-7

[19] https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-019-3627-6

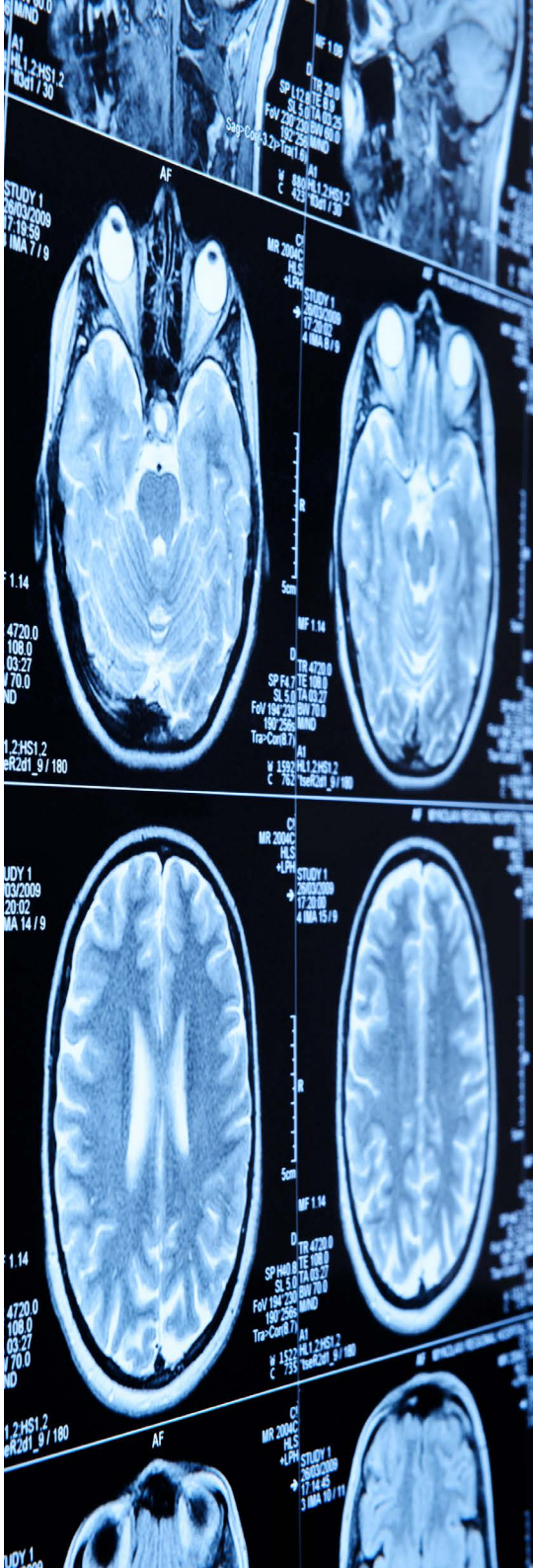
[20] Expert Interview - Simon Stoddart

[21] https://www.jmir.org/2021/6/e26631

[22] https://journals.sagepub.com/doi/pdf/10.1177/2396987316683780

[23] https://www.jmir.org/2021/6/e26631/

[24] https://www.thelancet.com/journals/landig/article/PIIS2589-7500(20)30192-8/fulltext



CHAPTER 3:

HOW TO PREPARE YOUR ORGANIZATION FOR DATA DRIVEN CLINICAL TRIALS

Digital technology, combined with data science, has already delivered impressive successes in raising quality of clinical trials. But the pharmaceutical industry has plenty of room to do more to improve current approaches, whilst moving towards more wholesale shifts that embrace adaptive, decentralized and innovative data driven trials.

How can companies take hold of the opportunities now available to them? In this chapter, we outline principles and approaches to move in this direction.

3.1 Deploy new tools to capture valuable data

New sensors and measurement tools can capture better data. This may involve deploying new sensors to measure safety and efficacy in new ways, or finding signals in biological or physical data from medical tests.

The key is do this strategically, not leap on the latest technology. Think about the right tool for the job. This means paying attention to what the most valuable data would be to deliver the insight you want – and considering the range of options for capturing that. It also means thinking through what that means – the data you want may be messy and have limitations, so consider how much effort will be needed to make sense of it, and what additional skills and technologies you will need to do that. Only by thinking through the whole process can you make the right decisions that will capture data that will give you what you want.

3.2 Standardize data capture, upgrade old data, and build an architecture to handle data-driven innovation

Fundamental changes to the design or management of a clinical trial may require a new approach to data management and legacy infrastructures. Inconsistent formatting and data silos constrain the creation of an open data landscape, which in turn limits the reach of techniques like AI to find patterns across disparate or complex data sets.

"A lot of the data in clinical trials is traditionally written down manually, rather than captured in consistent formats, despite predefined formats being available," says Andrew Koubatis. "Now we're seeing the management of a lot more data especially in the context of wearables and devices, it is essential that we have the infrastructure and processes to manage that."

Data quality from devices could be harmonized through an industry-wide approach to the types of wearables used, and definitions of outcome and adherence

measures which would improve the data's capacity to be generalizable and scalable[25].

Companies should look to create a holistic data strategy to allow data to be re-used and shared more easily and consistently and to synthesize legacy systems with new technologies.

Set up a storage and data architecture to feed data captured into an anonymized database where it can be easily piped to data science teams. Add in metadata – a layer beyond the raw data file, making it easier to understand and combine for further analysis by data scientists. Use intelligent indexing and query systems to ensure data sets are easy for all users to find, interrogate, and integrate into models.

3.3 Keep data safe

Pharmaceutical companies must, of course, protect against poor data practices, unauthorized access and use, or leaks in the new environment.[26,27] New risks can emerge in adaptive trials, such as insider trading that result from interim trial data being accessed by unscrupulous actors. DCTs mean data capture leaves the perimeter of the organisation, so new systems must be put in place to ensure it is transmitted securely.

3.4 Deploy skills to combine and model data

As more data types are used, including many not necessarily designed for clinical trials, there is a growing need to combine complicated and diverse data sets. This needs people who can pull relevant data sets from the database, or other sources, and combine them into models – eg statistical models of populations, or biological models of humans and diseases.

A major strategic challenge for pharmaceutical companies is to understand which of the emerging tools, capabilities and data skills can help them, in which contexts they are best applied, and what partners can best help them flourish.

In exploring new way of designing and delivering clinical trials, pharmaceutical companies should identify their own unrivalled capabilities, identifying where they need to upskill their R&D teams in emerging digital technologies and data capabilities to support these capabilities, and finding areas where an outside partner can help.

All that said, companies need to take their time to avoid being overwhelmed as more and more vendors pile into clinical trials. ***"We're seeing clients that are a bit lost amongst these new offerings, because they're unsure if it's a pure technology offering, or technology plus services, which is a sector that's also growing" Ghesquieres explains.***

A historical challenge of AI has been that companies not versed in the technology went for the 'safe option' and bought the most recognizable technology brand, only to find it was overhyped and designed for general applications rather than their bespoke needs. Due diligence, sometimes with the help of vendor neutral external experts, is a good starting point for technology, data science, and support selection.

[25] https://mhealth.jmir.org/2020/11/e22006/

[26] https://ojrd.biomedcentral.com/articles/10.1186/s13023-021-01806-4

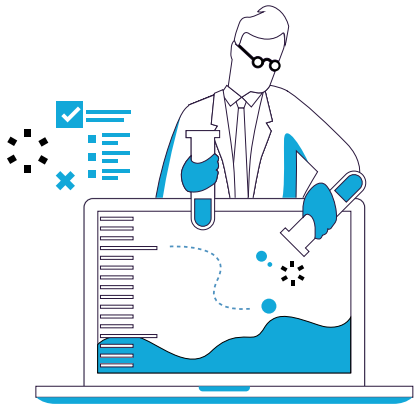
[27] https://www.outsourcing-pharma.com/Article/2019/06/28/Information-exchange-a-top-priority-as-sponsors-CROs-accelerate-move-to-modern-systems-Report

3.5 Create a culture of innovation

The 'human factor' is just as important as technology and data. Risk aversion, mindsets, and resistance to change can all obstruct progress towards more dynamic clinical trial formats and get in the way of technical reforms.

Risk aversion is understandable in an industry where failure is high stakes. ***"There's a tendency not to change something that is not broken, even if it's not optimal," says Andrew Koubatis. "There's this fear that if we're going to implement something new, are we thereby introducing new risks, and do regulations cover it? Decision-makers are reluctant to simultaneously develop a new therapy and a new way of capturing, managing, or analysing the data"***

However, the status quo is hardly optimal. Between January 2017 and September 2019, 195 drugs and 34 medical devices were recalled by the FDA.[28,29] Digital innovation, far from introducing new risks, can reduce failure rates through, for instance, using AI to improve prediction of adverse events.



To foster a culture of responsible innovation, companies should focus on incremental change rather than big bang reform.

We recommend starting with a readiness assessment exercise – a short discovery process that asks, 'how valuable would it be to adopt a new approach' (eg measuring how arthritis drugs affect patients' daily lives), and 'can we get the data to do it well' (eg do we have good enough sensors, data architecture, and modeling skills). If so, move on to a proof of concept, and if that works trial it, and ultimately move to full deployment.

At each stage, evaluate whether it is working. If not, ask whether it would work with better data and different skills, and whether getting those is worth the investment to deliver the intended outcome.

Processes like this – which can be run in parallel across multiple projects, with the best taken forward – allow safe experimentation and institutionalize innovation, allowing projects to be quickly tried out, with the best ones progressed and unpromising ones stopped before they become expensive.

[28] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7395820/#:~:text=There%20were%20195%20(85.2%25),consensus%20top%2020%20pharmaceutical%20company.

[29] https://www.fdanews.com/articles/201621-fda-drug-recalls-rise-in-2020-new-report-says?v=preview

Capgemini Engineering's Data Science Partnership

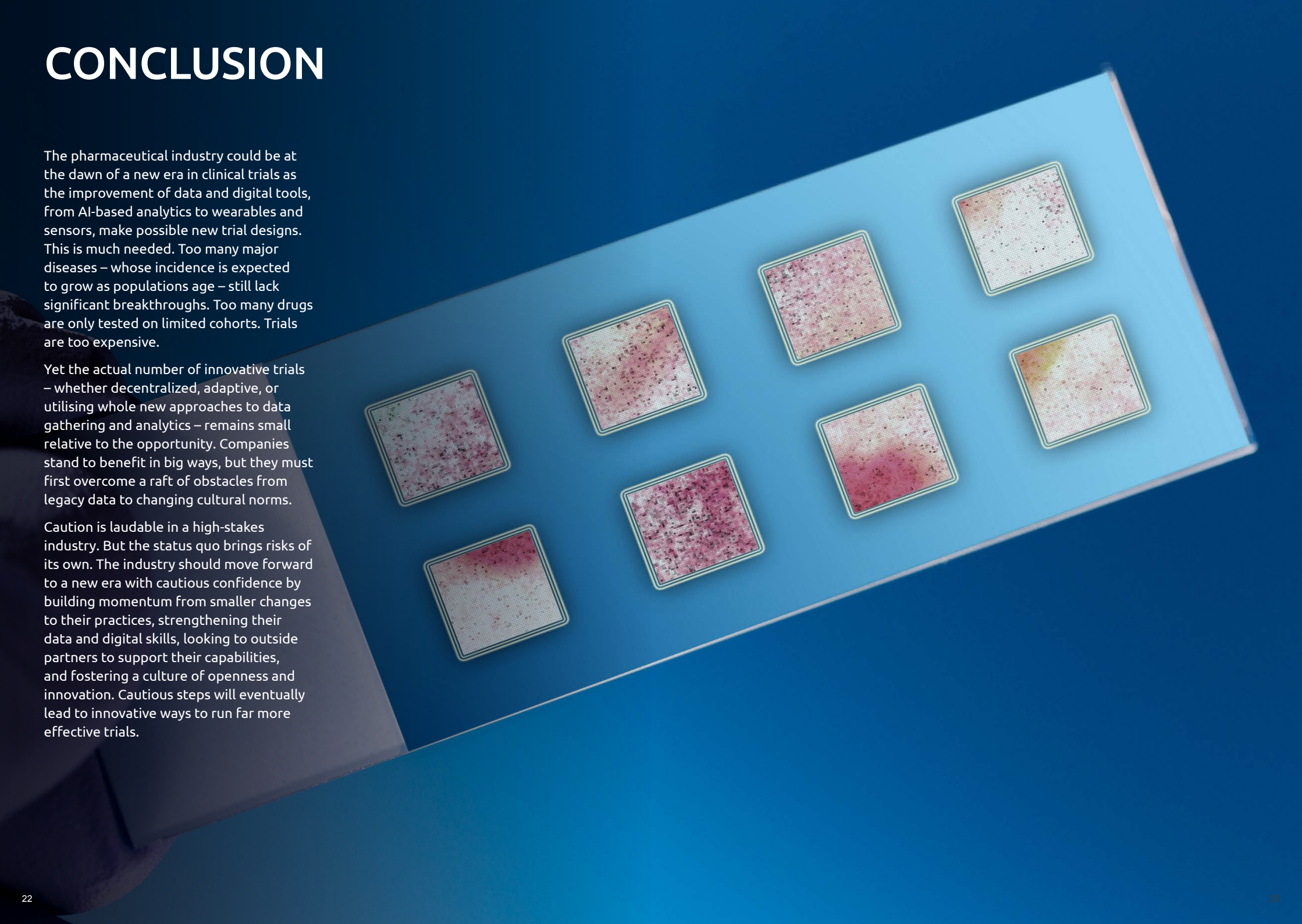
Clinical trial data innovation is a journey, not a destination. Companies' needs and capacities evolve as they build out their digital and data capabilities. Capgemini Engineering works with clients across every step. We start by building up capabilities and delivering value through data science knowledge and as an organisation matures in its data science capability, our role evolves. We can then offer expertise for more challenging, high-end skill requirements, supporting an organisation from only undertaking one data science project to fifty projects.

CONCLUSION

The pharmaceutical industry could be at the dawn of a new era in clinical trials as the improvement of data and digital tools, from AI-based analytics to wearables and sensors, make possible new trial designs. This is much needed. Too many major diseases – whose incidence is expected to grow as populations age – still lack significant breakthroughs. Too many drugs are only tested on limited cohorts. Trials are too expensive.

Yet the actual number of innovative trials – whether decentralized, adaptive, or utilising whole new approaches to data gathering and analytics – remains small relative to the opportunity. Companies stand to benefit in big ways, but they must first overcome a raft of obstacles from legacy data to changing cultural norms.

Caution is laudable in a high-stakes industry. But the status quo brings risks of its own. The industry should move forward to a new era with cautious confidence by building momentum from smaller changes to their practices, strengthening their data and digital skills, looking to outside partners to support their capabilities, and fostering a culture of openness and innovation. Cautious steps will eventually lead to innovative ways to run far more effective trials.



Capgemini engineering