Trial Decentralisation: The Benefits and Challenges

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Over the course of the pandemic the use of Decentralised Clinical Trials (DCT) increased significantly, with around 87% of sponsors and contract research organisations conducting or planning to conduct trials with decentralised aspects – compared to 28% prior to the pandemic.[1] The primary driver for this shift was to avoid delays in clinical trials that included vulnerable patients that were unwilling or unable to come onto site.[2]

As the adoption of trial decentralisation rises, a number of challenges have presented themselves. In this paper, we will firstly define DCTs, then discuss the expected benefits vs. those that have emerged so far, the challenges that have arisen, before finally considering where DCTs will go in the future.

1. Definition of DCT

The FDA defines a decentralised clinical trial (DCT) as one where "some or all the trial-related activities occur at a location separate from the investigator's location".[3] The EMA uses "designs that bring trials to the patients".[4] Other terminology often used includes "siteless", "virtual," and, "remote" – with "hybrid" thrown in for flavour.

A crucial factor in recognising a decentralised trial versus a virtual trial is that DCT still has patients, and it still conducts the traditional trial activities (albeit with delivery occurring in a different manner). As a result, we can avoid including approaches such as virtual trials based on computer models in the pre-clinical phase.

Our preferred definition combines this with the concept of technology or new methods of engagement: **Patient studies utilising technology or new methods of engagement to conduct some or all of the trial activities from a location other than the investigator's location.**

Current typical services that make up DCT can be divided into eight areas of varying levels of sophistication:

[1] https://www.fiercebiotech.com/cro/decentralized-clinical-trials-skyrocketed-during-pandemic-but-patient-experience-mixed-bag
[2] Stepping up the decentralization of clinical trials | McKinsey
[3] https://www.fda.gov/media/153744/download
[4] https://www.ema.europa.eu/en/documents/presentation/presentation-good-clinical-practice-fsweeney-ema_en.pdf

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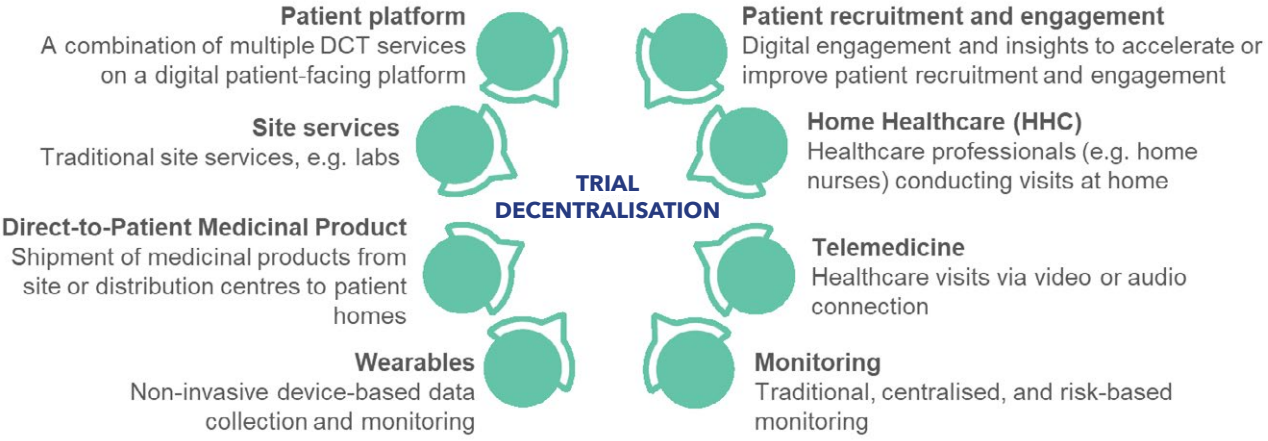

2. The Case for Trial Decentralisation

We can look at the goals of DCT in two ways: doing what has always been done, but in a more effective and/or efficient way; or doing new things, that were not possible before. For the former, we might look at telemedicine which continues the traditional contact with the investigators but at lower burden to the patient; for the latter, we might look at the potential of non-invasive imaging for dermatology to provide digital endpoints to trials.

As the majority of activity thus far has focused on traditional trial activities, this is where we will focus most of the discussion.

There are three key anticipated benefits from the use of DCT: improved patient recruitment and retention, lower costs, and better data quality. Given that implementation of DCT is in its' infancy, direct comparisons are challenging to find for accurate discussions on return on investment.

a. Recruitment and Retention

One of the key aspects of DCT is the reduction of patient burden: to reduce time-intensive and potentially costly site travel, reduce the effort to collect medication, and even sometimes reduce the effort to remember to take medication (various apps and e-reminders to ensure greater adherence). By reducing the burden of participating in trials and removing the need for frequent site visits, DCT provides an opportunity to keep patients that have had to relocate or would struggle to take significant, often costly, time away from work (potentially also benefiting the diversity profile of the trial). In one trial a DCT arm saw 89% study completion compared to 60% in the conventional arm.[5] The *n* was relatively small in this case, however, and further comparison is required to understand the impact of DCT for future studies.

Recruitment also benefits from the use of technology with digital engagement widening the potential patient pool and allowing for improved screening in advance of human review. These types of technologies have been in use for multiple years now, with one provider claiming 21x faster trial recruitment.[6]

[5] https://www.sciencedirect.com/science/article/pii/S2451865418300358
[6] https://www.science37.com/Offerings/Full-DCT

Increased recruitment rate is likely to be of particular interest in phase 2 and 3 trials where accelerating the time to market can have large impact on a product's revenues while still on patent. A recent study by Tufts found that the mean trial saw a 246 day reduction in trial length for phase 2 and 360 day reduction for phase 3.[7]

b. Lower Costs

Initial expectations were that DCTs would prove cheaper to run than conventional trials due to a reduction in processing costs. In practice however, some tools have not proven to be more cost effective than their in-person equivalents: e-consent and eCOA, for example. Equally, the upfront costs of telemedicine and setting up of home healthcare can prove daunting for many trialists. Poor recruitment density can rapidly increase the costs of accessing home healthcare professionals. However, the increase in recruitment rates and lower drop-out rates of patients lead to a shortened cycle time which will in turn reduce the costs of the trial. Shortened cycle times should have sufficient value to pharmaceutical companies that the upfront costs should not prove an overwhelming burden.

c. Better Quality Data

The expectation is that by going direct to electronic data, rather than through additional human interfaces the data quality will increase. In practice, data cleaning has often still proven necessary but as tools and usage increase in sophistication, this does have the potential to reduce. New forms of data remain a possibility but the processing and parsing of the potential quantity and quality of data is in early stages. Data ownership, particularly with trials run by CROs or even large technology companies, continues to be a challenging topic that will require further thought over the coming years. Nevertheless, this is likely to be where the real impact of trial decentralisation will lie, taking companies out from 'doing existing things better' and into whole new horizons.

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d. In Summary

Shortened cycle times should have sufficient value to pharmaceutical companies that the upfront costs should not prove an overwhelming burden.

[7] https://www.clinicalresearchnewsonline.com/news/2022/07/13/tufts-study-provides-first-hard-metrics-around-decentralized-clinical-trials

The reduction in patient burden is likely to provide the most value for pharmaceutical companies considering participating in decentralised trials in the near future. The impact it has on retention and recruitment, and particularly for long-running trials, should not be underestimated, even if additional data are required to formulate a reliable view on Return on Investment. The case for DCT in phase 2 and 3 trials is clear when it has such a potentially significant impact on time to market. For phase 4 - and particularly PASS - it may be worth considering for the potential impact on the long-term follow up, reducing the risk of drop-out that would impact the study results. However, differentiation may be achieved through other, less costly, approaches than interventional trials – in particular, considering the rise of interest in RWE studies.

3. Barriers to Adoption

Challenges to DCT are inevitable given its early stages of development. We consider seven barriers to be key in consideration, divided equally into internal and external factors.

a. Internal

Senior stakeholder buy-in can be challenging when the business case and ROI remains unclear as yet. Initial indications are that introducing DCT may cost more than not introducing it (setting aside the recruitment and retention benefits). It is unclear how much of the cost is to do with the first-mover burden, with partners and CROs having to build infrastructure from nothing, and uncertain patient adoption. The case for DCT often has to be built outside of traditional cost estimations and may reflect the need to invest in infrastructure that will reap dividends at a later date.

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Models of Adoption are not yet established with pharmaceutical companies being torn between build/buy/partner options. Both building and buying require high upfront investment and adaptation within the company. Buying accelerates the time to market and can provide something off-the-shelf ready to use but can have higher costs and integrating an acquisition takes significant time and effort. Partnering is cheaper and has lower resource burdens but is not free of operational implications - clear roles and responsibilities will need to be established and oversight of the new ways of working must remain with the pharmaceutical company. Additionally, while partnering may have a lower initial burden there are concerns that over-reliance on partnerships can lose the innovation opportunities, benefits, and cultural change that would otherwise be embedded within the company. Whichever method of adoption is selected, the company must commit to it as a strategic decision or risk multiple years of high cost and lack of productivity.

Build

- High upfront cost
- High resource requirements
- Often time-intensive
- Meets company's needs exactly
- Embeds innovation

Buy

- High upfront cost
- Requires integration (time/resource requirements)
- Accelerates time to market
- Embeds innovation

Partner

- Lower upfront cost
- Minimum integration required
- Minimum resource required
- Higher ongoing costs
- Potential partnership risks (resourcing, etc.)
- Reduces internal innovation

Resistance to Change is always a challenge to the adoption of new ways of working; concerns for employees will be the additional training burden, the potential extra work, and the company line on acceptable risk which can be inconsistent across compliance and legal. There is a possibility that DCT becomes seen as a "ClinOps challenge" which means that the expertise and buy-in would remain in the operational side of the business. Bringing in SMEs from other functions as DCT is integrated within the organisation is generally positive; while this can provide resource challenges, it is necessary to widely circulate the opportunities created by DCT capabilities, the benefits it can bring, and the changes necessary to accommodate it. Senior stakeholder buy-in and encouragement will be vital to overcome organisational resistance and legal and compliance teams should be brought in from the planning stages to prevent late-stage challenges to new ways of working causing high-impact delays. Companies should typically expect DCT to impact SOPs and adjust time expectations for implementation accordingly.

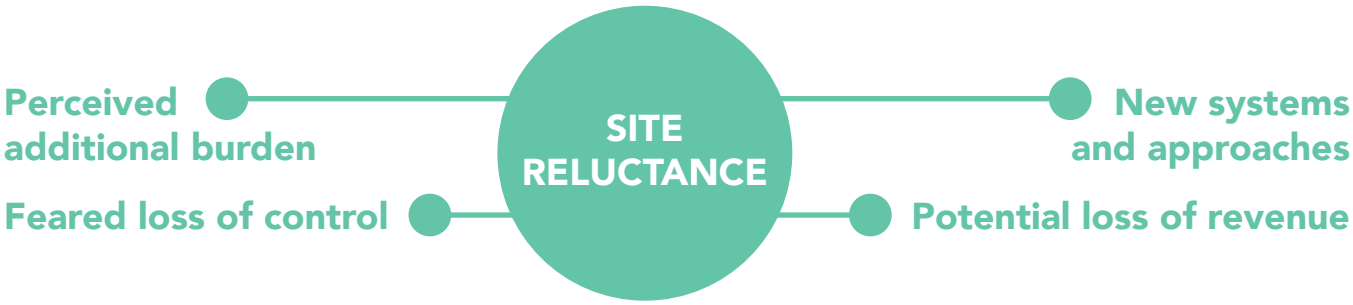
> **Senior stakeholder buy-in and encouragement will be vital to overcome organisational resistance**

[8] https://florencehc.com/learn/blog-posts/what-do-patients-think-about-decentralized-clinical-trials
[9] Anonymised interview; top ten pharma

b. External

Adoption Among External Stakeholders is not a given; although DCT is expected to alleviate patient burden, sponsors have seen a mixed reaction. In one trial, "78% of patients preferred a decentralised trial to a traditional one".[8] Some sponsors have identified more "trepidation" among patients, who were "used to a more personal touch".[9] Most pharmaceutical companies acknowledge that not enough has been done on user friendliness, or to engage with patients on a larger scale which may result in DCT being 'imposed' on the patient rather than willingly adopted. To prevent loss of potential recruitment, optionality through hybrid models is typically discussed as preferable but it is currently unclear whether this might introduce bias to trial data. Patients who choose to engage in technology-led options may be less diverse than the overall population - or may trend younger, or to wealthier demographics, all of which would bias the reporting arms. Options requiring, for example, good internet connection for telehealth or for auto-reporting of data may exclude particular rural populations. Availability of different languages is also typically limited within apps. All the above factors have the potential to bias or affect outcomes reported.

Sites are typically challenging when it comes to the adoption of DCT. There can be a reluctance to adopt for a variety of reasons - perceived additional burden, requirement to learn new systems and approaches, feared loss of control from the investigator, and in some cases, potential loss of revenue from patients not coming on-site. The perceived additional burden, including new systems and training requirements is particularly acute when sites might be participating in multiple trials with multiple companies and CROs, each of whom are using their own systems and tools. In some situations, sites have developed their own tools and are reluctant to switch away, necessitating costly systems integrations - this is particularly applicable in the case of telehealth where many sites have solutions that they are using and are familiar with.



Further coordination as an industry may be beneficial to ensure that the case for change is convincing for sites. While pharmaceutical companies may be motivated by the return on investment brought about by faster recruitment and higher retention rates, the recruitment and retention is fundamentally driven by the increased patient benefit and the reduced burden for

participating patients.
Emphasising the benefits to the patients with clear case studies and examples is likely to prove beneficial in persuading future sites to adopt DCT capabilities. Similarly, the more the industry can drive towards inter-operability where sites may continue to use their preferred systems and solutions rather than learning new systems for every trial, the less burden sites are likely to see in the adoption of technology.

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While building new processes, clear thought should be put into the amount of burden that is being put on the site. This is particularly relevant when it comes to direct-to-patient medicinal product where depot-site-patient models were at least initially in use during the pandemic. With sites being required to do multiple checks prior to dispatch of medication, often the burden can begin to become unwieldy. Additionally, if preparation of products is required to adapt to patient needs, stability information and similar must further be considered as current information available is typically inadequate.

Regulatory Requirements are still an area of consideration. During the pandemic, regulatory authorities were seen as being "accommodating" with regards to trial design. It remains to be seen whether this permissive attitude will continue with COVID restriction beginning to be relaxed. Additional guidance is expected from the FDA soon on trial decentralisation.

While trial design is currently being accommodated , privacy constraints are seen as more challenging - with particular reference to GDPR in Europe. Technology companies have run into challenges with patient data, particularly when country borders are brought into play for telemedicine and e-Consent. Remote source data verification is of limited use in the EU, for example, due to privacy provisions. GDPR requires the data controller (in this case, the trial sponsor) to be fully accountable for the appropriate technical and organisation measures to meet data protection rules.

EU CTR goes further in the sponsor responsibilities, all of which can cause internal compliance teams to be extremely cautious in their vendor approvals. Highly explicit consent forms are likely to prove their value and ability to re-consent patients for future use of their data will prove important in making efficient use of available data. EFPIA has developed a draft code to aid in consistency and clarity and intends for formal submission to the European Data Protection Board in the future.

The final challenge we believe necessary to highlight are the **vendors**, if a company choses to partner. Identifying and selecting vendors is generally seen as problematic, with pharmaceutical companies seeing the landscape as crowded. Audit requirements for the vendors put high burden on quality and compliance, particularly in combination with uncertain regulatory requirements.
Even when a vendor has been selected, scaling can prove problematic – in the COVID-19 environment, HHC was in high demand and lead times to activate new locations once a patient had been identified could be several months, undermining the value of DCT in speeding up recruitment. Technology companies push their solutions and capability to manage data but often poorly understand the regulatory environment of the pharmaceutical industry; CRO solutions can be less user-friendly, with the CRO themselves keen to exploit the benefits of new technologies without the pharmaceutical company gaining from the innovation.

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Data ownership with vendors is a tricky topic, with all stakeholders involved keen to leverage the data they gather from clinical trials, which makes having a clear internal data strategy for the pharmaceutical company key prior to beginning contracting and negotiations with any potential vendors.

In Summary

The implementation of DCT has not been without its challenges. Clear strategic direction and understanding of the potential pitfalls is vital to overcome internal challenges; external factors are likely to be addressed by time, including vendors consolidating and scaling where necessary. Industry-wide collaborations can help to accelerate adoption among sites and patients and increase clarity around regulatory requirements, but sharing best practice is likely to benefit the pharmaceutical industry as a whole.

4. DCT in the Future

The rapid adoption of DCT over the course of the pandemic has created a trend that is not easily reversible. While the benefits are still being proven out, earlier indicators suggest that the impact on overall study cycle times is sufficient to prove convincing in pivotal studies. The barriers in place will require time and effort to overcome; in particular, clear strategic

direction internally is required to avoid costly failures and redirections.
Data challenges and regulatory requirements are likely to be tested out in collaboration with regulatory authorities over the next few years and there is already a strong push from industry to reduce uncertainty through the publication of additional guidance.

> **Clear strategic direction internally is required to avoid costly failures and redirections.**

As adoption accelerates, the business case for DCT is likely to increase in value; it may become an expectation for patients that they should not be unnecessarily disrupted by site visits and data entry, in which case lagging companies are more likely to be disadvantaged by their lack of DCT capabilities. Data quality is likely to increase as sites and patients become more accustomed to the tools in use and user experience is improved through regular testing and updates.

Once existing capabilities are well-established, it is likely that both pharmaceutical companies and vendors will begin investigating the potential future uses of DCT – in particular, how new forms of data and larger quantities of good quality data will impact study conclusions. Patient reported outcomes may become more important as regular patient inputs become feasible through apps and frequent, low-burden connection points. Digital endpoints utilising sensor-reported datasets can bring trials closer to real world evidence, as well as allowing greater granularity in the breakdown of symptom management and treatment. Quality of life differentiators become more feasible with the additional data, allowing HCPs and patients to make more informed decisions regarding treatment. This kind of data can impact pricing decisions as well as potentially linking to outcomes- or value-based pricing.

COVID-19 has created an environment in which the value of decentralised trials can be seen. The barriers to adoption are reducing over time and momentum suggests this will continue post-pandemic, improving outcomes for both patients and sponsors. To take advantage of the current impetus, companies should be looking now to consolidate their approach towards DCT. From previous work, we are well aware of the necessity of clear strategic direction and development of effective internal operating structures. Without these factors, companies can find themselves partnering ineffectively, duplicating effort across TAs and functions, and involving themselves in costly miss-steps in both time and resource.

Interested in speaking further?

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