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Review Article

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Digital Therapeutics and Decentralized Clinical Trials Optimization in An Era of Increasing Complexities

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Clinical research is digitizing and decentralizing. Several companies have tried to catalyze this change with varying degrees of success. Although some have experienced substantial challenges in scaling, the trend will continue and it is as important now as ever for the industry to embrace the developments that will drive better patient experiences, more diverse study populations, less expensive studies, and greater capacity for the industry to conduct high-quality research [1].

Many in the industry, especially incumbents, are eager to write off the entire categories of digital therapeutics and decentralized clinical trials [2]. For example, However, key improvements to patient experience and overall execution of research dictate that DT (digital therapeutics) and DCT (decentralized clinical trials) is not just here to stay, but ever-expanding, entering its third iteration in the market, despite the general downtrend in overall sentiment. This is despite the tailwinds of COVID-19 that have reconfigured the clinical trials MedTech space, yet again, after centuries of a tried, atrophied, antiquated model on billable hours that needs another decisive push towards accelerated patient involvement in the protocol via heightened patient awareness, and in the end, higher quality of life by mitigating the burden of disease through disability-adjusted life years (or DALY's). When you bill by the hour, you have a lot of reason to believe that DCT will never work. These antediluvian revenue models incentivize less than optimized study design. For example, I have worked within the contract research organization for the past 5 years, and the billing model -billable hours - is often in direct contradiction to new financial models and pedagogies of optimizing trials. I am thinking here of cutting expenses in the budget through Functional Service Provider (FSP) which is Time and Materials vs. unit-based billing or milestone billing, using machine learning algorithms to accelerate the speed of patient enrollment, and digital technologies - such as optimization platform - to enhance patient retention. Climb is a great example of this [3].

The advent of machine learning algorithms has led to yet another iteration in clinical trials participation where Electronic Data Capture (EDC) systems can now read protocols and AI tools can seamlessly integrate into the current clinical workflow of physicians. Matchmaking algorithms can also help optimize patient engagement, recruitment, and retention.

With credit to the naysayers, however, we recognize that DCT is not a "panacea," but its inability to solve all problems for all patient populations does not mean it is not capable of delivering substantial value for many studies and across greater patient populations.

While it may be tempting to point to these and other examples to validate an industry that is rightly stuck in its ways, now is the time to double down on the modernization of the vital world of research. There are significant dialectical arguments to support the advances in DCT technologies, whether it is interoperability or accelerating patient enrollment, to the discernible drawbacks in DCT such as study protocols or the need to overcome limitations of remote patient training.

A recent survey from Applied Clinical Trials noted that 76% of 252 sponsor respondents recognized that COVID-19 accelerated adoption of decentralized clinical trials, including wearable devices, protocol redesign, and investigator-facing technologies [4]. According to Naveen Dha in "What is a Decentralized Clinical Trial," DCT can "either be fully remote or adopt a hybrid approach where some physical-site attendance is required. They are achieved with the use of remote monitoring and diagnostics, home health providers, local labs, digital capture of consent data, and direct-to-patient drug distribution. The purpose of these types of studies is to reduce or completely eliminate the requirement of face-to-face interactions between researchers and participants."

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Since 2012, DCTs have increased from 250 to 1,291 trials; there were 1,425 projected for 2022, an all-time high. In addition, we are observing strong patient retention rates of 90% in decentralized trials, a 20% reduction in patient dropout compared with traditional studies (Source: Decentralized Clinical Trials: The Way Forward Published March 1, 2021, By Taren Gro)

Also, in line with DCT trends, Seniors are happy with their virtual healthcare. The majority (89%) of adults sixty-five and older who have used virtual primary care for any healthcare need have been satisfied with their experience. In addition, (78%) of those 65+ agree that virtual primary care can be an optimal way to increase access to healthcare for people who may otherwise be unable to visit a provider in person.

Moreover, in May 2023, the FDA issued prescient guidance on decentralized clinical trials, a nonbinding recommendation to sponsors in the DCT field to, among several other considerations, strive for diversity and inclusiveness in trial populations. According to STAT News: "In one Food and Drug Administration analysis of clinical trials conducted between 2015 and 2018 showed that 78% of participants were non-Hispanic white people. More than 97% of participants in a Phase 2 trial of the Alzheimer's drug crenezumab were white and just 2.8% were Latino, even though Latino populations are 20% more likely to develop Alzheimer's" [1].

In December 2022, Congress passed the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act, which requires Investigational New Drug (IND) and Investigational Device Exemption (IDE) applicants to report clinical trial enrollment targets by demographic subgroup, including age, race, ethnicity, and sex, and provide a rationale for those targets. By December 2023, the FDA will issue guidance on the format and content of these plans. Lastly, The Food and Drug Omnibus Reform Act (FDORA) was signed into law by President Biden on Dec. 29, 2022, which includes numerous provisions intended to modernize clinical trials, including accelerating enrollment of more diverse patient populations. This is to support the opinion that there are some identifiable public policy trends that are in alignment with modernizing, democratizing, and improving inefficiencies around study design.

Another relevant development: The FDA has introduced a fresh initiative in the form of the Digital Health Advisory Committee. This committee's primary objective is to assist the FDA in exploring the intricate scientific and technical aspects of digital health technologies (DHTs), encompassing domains such as artificial intelligence/machine learning, augmented reality, virtual reality, digital therapeutics, wearables, remote patient monitoring, and software.

Some examples of DCT companies that are changing the landscape of clinical trials are the following: Science 37, THREAD, UNLEARN AI, Curebase, Reify Health, Medable, and Climb to name a few.

The DCT movement, predating but galvanized and catapulted by the COVID-19 pandemic, rejects the notion that clinical trial activities must be completed research venue, instead favoring a fully remote or hybrid approach. With the onslaught of the COVID-19 pandemic, access to clinical trials sites was reduced by 80%, due to trial interruptions and cancellations, according to The Lancet. Since that time, sites and sponsors have adapted to remote consent, and alternative ways to manage and accelerate data collection, such as ePRO and remote monitoring after SIV.

One such example of a DCT is Curebase's collaboration with Blue Note Therapeutics in 2022 on a prescription digital therapeutics (PDT) oncology trial with a goal of maximizing recruitment efforts by screening, consenting, and navigating patients through the reporting and activities required for the study with a total of 353 patients for a fully remote trial.

Curebase is a remarkably interesting example of adjusting to the tempestuous winds of change DCT face today as it finds its footing in a post-pandemic environment. Having reduced headcount in early August 2023, Curebase has announced a shift in their business strategy focusing purely on providing software-based solutions to the industry by discontinuing more operationally intensive components of the offering. The greatest impact in the industry will come from the organizations capable of quickly embracing the rapidly changing demands of the industry. By segmenting their service offerings and fine tuning their capabilities in a vast ecosystem of sites, CRO's, and biotech "sponsors," the strongest organizations in the space will continue to accelerate their impact.

The seemingly fickle embrace of DCT throughout and after the pandemic coupled with macroeconomic trends have contributed to layoffs and shrinking valuations across the industry with virtually no exceptions. While it may be tempting to extrapolate the trend, calling these organizations down is no reason to count them out.

Reify's Care Access received substantial public scrutiny after Good Clinical Practices violations were implicated in the material changes to Pfizer's lyme study. Less widely reported were the results of an October 2023 inspection which found no FDA Form 483 observations, meaning the FDA investigator found no GCP violations by Care Access in the VALOR trial.

Another notable win for DCT is the Medable and Pluto Health partnership, which aims to accelerate clinical development, increase access to clinical research, and improve the patient experience.

Virtually every study has some remote component - the first "decentralizing" elements came decades ago by way of a remote phone screen or a paper-based diary. Modern technology now makes data collection and study protocol administration outside the view of the study team more dependable.

Aside from the ability to increase patient enrollment and retention by casting a wider recruitment net, and thereby reducing a major cost driver associated with onsite trials, perhaps the most exciting benefit of DCT is increasing the diversity of underrepresented groups. According to [5].

"Recruitment for clinical trials continues to be a challenge, as patient recruitment is the single biggest cause of trial delays. Around 80% of trials fail to meet the initial enrollment target and

timeline, and these delays can result in lost revenue of as much as US $8 million per day for drug developing companies."

Let us identify the potential benefits and drawbacks to DCT:

- Greater enrollment flexibility with increase in generalizability of trial inclusion by mitigating the need for onsite visits and promoting hybrid site monitoring with first SIV.
- Potentially significant cost savings for sponsors.
- Increased study adherence and lower dropout rates. For example, "strong patient retention rates of 90% in decentralized trials, a 20% reduction in patient dropout compared with traditional studies" [6]. Another example: "Clinical trials that leverage digital connectivity between the patient and physician can lead to increased engagement and more consistent access to critical study data," Mr. Costello says. "With more sophisticated, patient-centric tools, DCTs have more potential than ever to provide a broader and deeper view of the patient. Patient insights and feedback need to be baked into each level of the clinical trial process, from study design and burden to the use of technology" [4].
- Improving rates of follow-up
- More interaction with patients can translate to a better "continuous" patient experience and better outcomes in case of side effects/emergency.
- Potentially higher data quality/data capture., for example some EDC's can now read protocols through AI [4].
- With the emerging increase in DCT technologies, there will invariably be an increase in patient awareness over time. For example, by the end of 2023 thirteen new cell or gene therapies could be approved in the US, Europe, or both, however the need for patients to become aware of these approved therapies has never been greater. The advent of more approved personalized medicine, with the increasing complexity of telehealth visits and/or self-administration in outpatient settings, especially in local communities, should lead to a positive effect on clinical trial awareness, and thus, a positive net effect on enrollment and retention.
- Ability for real-time "continuous monitoring" of patients.
- Potential increase in diversity of underrepresented groups with new next generation platforms which increase "patientricity" which will, in turn, turn the archetypal panopticon on its head. That is, the typical inefficient site selection/feasibility process will be replaced with patients having more (not less) choice, and thus, more power over the site selection process. AI platforms such as Mytomorrows and Providence's Trial Connect are terrific examples.

Now let us examine potential disadvantages or drawbacks of DCT:

- Lowering the frequency of onsite visits can also, with it, bring potentially less adherence to patient safety, if patients are self-administering at home.
- Greater reliance on technology training both for DCT trial participants and for the staff administering these technologies.
- Data security and privacy concerns around data breaches and patient confidentiality. This includes potentially compromising both the quality and reliability of data collection.
- Regulatory concerns
- Technological barriers since this assumes access to technological platforms is a given. According to the FDA prescient guidance from May 2023, sponsor is supposed to provide Digital Health Technology to all participants (if participants do not want to use or do not have their own device). But what about the additional cost for the sponsor (buying devices for all participants) and the ecological/ environmental impact of all these devices (are they re-used?)
- Therapy and disease limitations – DCT does not capture every condition or illness due to technical requirements.
- Hidden costs associated with new technological platforms, also known as "passthrough" or third-party vendor costs.
- Some clients prefer brick-and-mortar sites depending on the inclusion/exclusion criteria, and thus a particular study might be a better "fit" for onsite analysis, data collection, and monitoring. For example, depending on the clinical study design, some studies require clinical monitoring visits onsite.

This discussion has focused on both the positive and negative net effects of DCT. While there is ample room for both arguments as part of a general polemical discussion in clinical trial optimization, one thing cannot be ignored: DCT is here to stay. To quote Luca Issi, from Genetic Medicine Leads a Surge of Innovation in Biotech, "We believe the ultimate 'winner' in this field may not necessarily be the companies with the most attention-grabbing technology, but those that can successfully target the right indications and cleverly design clinical trials." Or to take it one step further and paraphrase Charles Darwin, who could have replaced the epochal tone about evolution with redesigning clinical trials, "It is not the strongest of the species that survives, nor the most intelligent. It is the one that is most adaptable to change." Resistance is good, contrarian opinions will force solutions to improve but that resistance should be focused on making DCT better for patients, sponsors, and study teams, not on making DCT go away [7].

We call on the biotech and contract research organization industry to embrace, not block, vital change as public policy moves to accelerate patient involvement in trials, especially considering the rise of patient engagement platforms and also the willingness of the clinical trials industry to embrace alternative models with more embedded efficiencies such as Functional Service Provider (FSP), a methodology with higher cost savings to sponsor without compromising quality, higher degrees of scalability, study flexibility, and higher visibility of CRAs, and thus, more effective site relationships [8]. The move to embrace these paradigms will require greater communication - and partnerships- between biotech sponsors, DCT and DT companies, CRO's, and patient advocacy organizations as we approach a "critical juncture" in an era of increasing trial complexities [9].

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