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Opinion

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

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Clinical trials typically revolve around three models: traditional, virtual, and decentralized trials. In traditional clinical research, data collection and data capture happen onsite. Virtual trials are fully remote (i.e., remote monitoring) where enrollment happens at a distance. Moreover, Decentralized trials happen when both the data collection and data capture occur outside of the traditional site.

According to Naveen Dha in "*What is a Decentralized Clinical Trial (DCT)*," 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*". Moreover, 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 by moving away from a highly manual, laborious,, byzantine approach to clinical trial design, implementation, and operationalization.[1]

One area of clinical trial automation where Machine Learning (ML) and generative artificial intelligence (GenAI) platforms can serve the highest need is right at the "tip of the spear": clinical trial enrollment and recruitment. The business and societal problem is as horrifying as it is enormous: 90% of clinical trials fail to meet their patient enrollment timelines and 30% of patients drop out before the end of the trial, resulting in billions lost in revenue.[2]

This essay will provide a discussion around the market dynamics of DCT, pros and cons of DCT, and for practical purposes incorporate a case study of various companies in industry, including my company, Icarus Therapeutics, and benchmark for the application of ML Large Language Model (LLM) and GenAI in clinical trial enrollment and recruitment. AI has forged a market that has expanded with robust players from Power, Health Match, and my Tomorrows.

From leveraging AI leveraging capabilities in natural language processing (NLP) and data analysis, to matching PHI consented data with inclusion/exclusion criteria in study protocols, GenAI will permanently change the future of clinical trials. According to Ross Jackson in Clinial Leader:

"*One of the most useful things about using AI for patient identification is its ability to process unstructured data. Patient records are often stored in various formats, including electronic health records (EHRs), handwritten notes, scanned documents, and voice recordings. Traditional software solutions struggle to interpret this diverse range of data, as they depend on structured and standardized formats — of the type that rarely exist in the real world. AI solutions can extract valuable information from these disparate sources by understanding the context and meaning of the data*".

Icarus Therapeutics is a California-based TechBio company which began in 2023 as a JLABS resident and Harvard Innovation Labs Member. Currently in a pre-seed round, Icarus was recently accepted into the Advanced Research Projects Agency for Health's (ARPA-H) Customer Experience Hub in July 2024 and presented at the San Diego Innovation Council at Scripps in

May 2024. The company removes the pain point of clinical trials enrollment for both principal investigators and patients by matching them within a defined zip code or remotely through ML and GenAI by reading inclusion/exclusion criteria in protocols, protected health information (PHI) consented data, insurance claims, application programming interface (API) from clinicaltrials.gov, and unstructured data. Moreover, Icarus offers differentiated features on the platform, such as clinical trial payment compensation for patients, and Uber/Lyft rides to sites. Icarus is the match.com of clinical trial stratification, offering a "one-stop shop" for clinical trial enrollment. By taking a population health approach thereby implementing strategic collaboration across site networks and community-health organizations, Icarus will diversify patient populations through a double verification process at the site and administrative level.

Many in the industry, especially incumbents, are eager to write off the entire categories of digital therapeutics and decentralized clinical trials.[3] For example, key improvements enhancing 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 yet another critical iteration in the market, despite the general downtrend in overall sentiment. This is despite the tailwinds of coronavirus disease 2019 (COVID-19) that have reconfigured the clinical trials MedTech space, yet again 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).

With credit to the critics and the industry contrarians, 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. AI and ML (LLM) in DCT, for example is a tool to be employed from the site up, not an end all be all for advancing clinical endpoints and I recognize the ethical implication of DCT, including "*the implications for the relationship between patients and healthcare staff, for the social dimension of the patient, for data integrity (at the source, during transmission, in the analysis phase), for personal data protection, and for the possible risks to health and safety*".[4]

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.[5]

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.[6]

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. AI in DCTs can further improve senior's patient experience, by specific type of AI technology in older adults, such as socially assistive robot technology and robotic pets.

Moreover, from a regulatory perspective 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*" (In a "*A Drive to Increase Diversity in Clinical Trials*").

On June 27th 2024, the Food and Drug Administration (FDA) a draft guidance Diversity Action Plans to Improve Enrollment of Participants from Underrepresented Populations in Clinical Studies, to assist medical product sponsors in submitting Diversity Action Plans to support certain clinical studies.

Also relevant, 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. In December 2023, the FDA issued 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 December 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. Icarus Therapeutics is a company which iterates the DCT model for patient enrollment and recruitment by going further as an end-to-end platform for the patient (demand side) and for the physician investigator (supply side) running the clinical trial. The excitement behind this company can be demonstrated through admission to ARPA-H, even winning an award as a BBB4 Good Verified Business for its commitment to social impact, community engagement, and environmental impact.

The DCT movement, predating but galvanized and catapulted by the COVID-19 pandemic, rejects the notion that clinical trial activities must be completed at a 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.[7] Since that time, sites and sponsors have adapted to remote consent, and alternative ways to manage and accelerate data collection, such as Electronic patient-reported outcome (ePRO) and remote monitoring after SIV.

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 fickle embrace of DCT throughout and after the pandemic coupled with macroeconomic trends have contributed to biotech layoffs and shrinking valuations across the industry with virtually no exceptions.[8]

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 Good Clinical Practice (GCP) violations by Care Access in the VA Lung Cancer Surgery or Stereotactic Radiotherapy (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.[9]

"*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: "*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*".[5]

• 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.5 AI and machine learning enable interoperability between EHR and EDC systems thereby accelerating drug development and improving patient outcomes. According to McKinsey partner, Alex Daverson in late 2022, AI could potentially enable the development of "*drugs in one-tenth of the time, from being discovered to being able to treat patients*".[4] One gold standard example of using AI in clinical trials is Janssen's DELPHI study for COVID-19 which accelerated site selection.

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.[2]

• 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 by applying company case studies such as Reify, Curebase, and Icarus Therapeutics, as well as presenting a regulatory framework on where the FDA stands on important DCT trends. While there is ample room for both arguments as part of a general polemical discussion in clinical trial optimization, one development post-pandemic cannot be ignored: like Gen AI, 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.

We encourage the biotech and contract research organization industry to embrace, not dismiss, vital change as public policy moves to accelerate patient involvement in trials, especially considering the rise of patient engagement platforms The move to embrace these paradigms will require greater communication - and partnerships- between the FDA, community health organizations, biotech sponsors, AI/ML platform companies, DCT and DT companies, CRO's, and patient advocacy organizations as we approach a "critical juncture" in an era of increasing trial complexities.

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