NEXT-GEN CLINICAL DEVELOPMENT: WHY COMPANIES SHOULD INVEST IN REMOTE CLINICAL TRIALS

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The COVID-19 pandemic has forced many companies to adopt virtual or remote solutions to everyday tasks. Increasingly, pharma and biotech companies with active clinical development programs have shifted toward decentralized clinical trials that leverage telemedicine and mobile / local healthcare providers, often implemented via wearables, e-visits, home delivery of investigational therapies and other virtual data collection methods.[1]

The successful implementation of decentralized clinical trials during COVID has demonstrated that this model can represent a substantial opportunity in the future. Biopharmaceutical companies should embrace and invest in decentralized trials, especially in cases where the nature of the disease or the patient type poses obstacles to traditional trials. In this paper, we outline six cases that can benefit from remote clinical trials. They demonstrate the potential for maximizing clinical trial success by improving digital infrastructure, leveraging existing digital tools, investing in innovative technologies, seeking regulatory buy-in and partnering with decentralized solution providers.

Decentralized Trials Pre-COVID and During COVID

In 2011, Pfizer designed what is widely thought of as the first decentralized trial: the REMOTE study to investigate a new treatment for overactive bladder.[2] REMOTE allowed enrollment regardless of geographic location, required patients to self-manage the dosing and scheduling of their therapy and involved virtual results reporting. Yet while Pfizer had many volunteers, few patients matched the correct profile, and the trial was canceled due to lack of recruitment.[2] REMOTE was nonetheless key in showing how decentralized trials could be designed. However, their use remained limited pre-COVID, partly due to a few critical barriers including state-based licensing requirements that limited the ability of trial investigators to treat out-of-state patients, inconsistent availability of HIPAA-compliant telehealth infrastructure at trial sites and FDA unfamiliarity and skepticism of remote trials.[2]

The onset of COVID-19 changed that, pushing companies and regulators toward remote healthcare solutions including remote clinical trials. More than 80% of active non-COVID trials were forced to pause or terminate, resulting in considerable loss of research investment (up to $8M per day) and pipeline delays.[3,4] The debilitating halt to pharmaceutical R&D prompted the loosening of laws and regulations that previously restricted decentralized trials. These rollbacks came in various forms, such as the HHS withholding HIPAA-related penalties,[5] at least 41 states allowing in-person and telehealth treatment

by out of state physicians[6] and the FDA and EMA releasing guidance about conducting remote clinical trials during COVID-19.[7,8]

As a result, an estimated 82% of clinical trial professionals began incorporating virtual elements into their studies.[9] Further bolstering clinical trials virtualization, technologies that facilitate decentralized trials are now seeing large investment.[10] With these changes, patients and investigators are becoming more comfortable with decentralizing aspects of clinical trials.

Post-COVID-19 Opportunities for Decentralized Trials

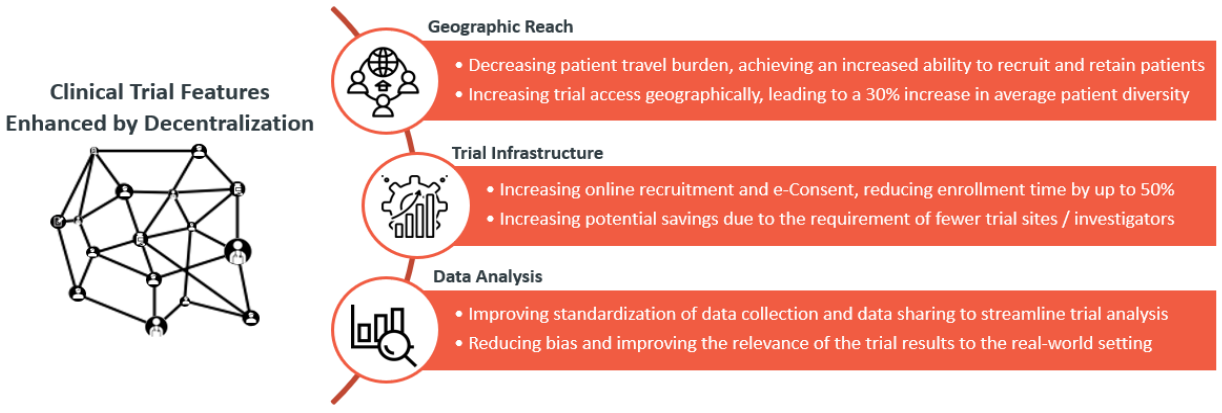
The move toward telehealth and the momentum generated by COVID-19 has been a major mover in the trend towards decentralized clinical trials.[11] It is encouraging companies to make clinical trial design smarter and implementation cheaper and faster (Figure 1). Biopharmaceutical companies should seize the opportunity to invest in decentralization and virtualization technologies for trials now, to remain at the forefront of innovation in the future.

Across studies, virtualization can be applied to video check-ins and e-consent procedures;[12] of course, not all study types are equally well suited for a decentralized trial design. Those that require infusion, difficult drug storage, invasive procedures, and isolation from other people will still require an in-person study design. Virtualization, however, can be applied to video check-ins and e-consent procedures across studies.[12] And in many cases where recruitment is traditionally difficult and remote measurements easily collected, a decentralized model could provide opportunities to speed up clinical development.

We have identified 6 use-cases that are conducive to decentralization. These are additive – the greater the number of characteristics that apply, the greater the benefit of decentralization (see Figure 2, next page).

CHARACTERISTIC 1: LOW INCIDENCE / PREVALENCE DISEASES. A decentralized design strongly benefits trials in diseases with low incidence and prevalence due to its inherent ability to circumvent traditional recruitment difficulties. In diseases with low patient volumes, sponsors often struggle to reach high enough enrollment numbers to power a clinical trial. For example, of the 22 studies, spanning 35 years, investigating disease-modifying therapies for the rare disease family of neuronal ceroid lipofuscinoses, only eight were able to recruit more than 20 participants.[13] "Site-less" trials circumvent these challenges by opening participation to what would otherwise be distant regions or potentially even new countries, thus

Figure 1. Decentralization can help speed up clinical development by increasing geographical reach, simplifying trial infrastructure, and improving data analysis.



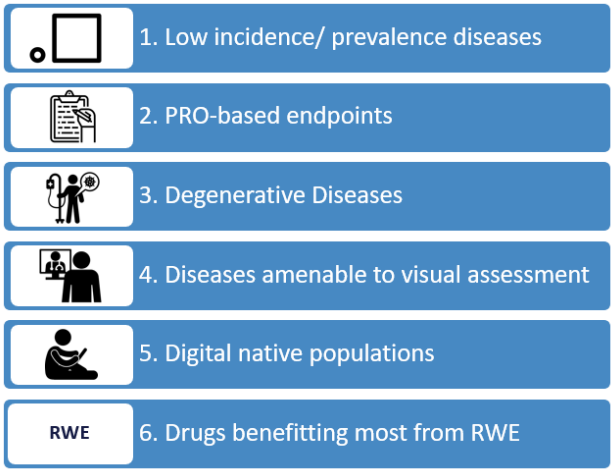
increasing recruitment speed and likelihood of reaching sufficient sample size as compared to classic trial strategies.[13,14] Increasing the number of patients surveyed improves the quality of data captured at a lower price point than a traditional clinical trial.

CHARACTERISTIC 2: PRO-BASED ENDPOINTS. Patient-reported outcome (PRO) measures are notoriously subjective: several factors may influence a patient's accurate assessment and responses. Connected technologies such as wearable devices and mobile health applications can replace or complement PROs and enable researchers to track symptoms continuously and more accurately.

Two types of diseases heavily rely on PROs and could benefit from virtualization: diseases that lead to chronic pain and behavioral/psychiatric conditions. For these diseases, many trial endpoints rely on discussions with a patient or caregiver or via daily logs.[15] In rheumatoid arthritis, for example, a disease-specific quality-of-life questionnaire combined with supplemental quantitative analysis techniques may be used to measure information, such as pain levels, that only the patient can convey.[16] These tools can be easily adapted to a remote format with minimal technological requirements beyond a digital platform and video capabilities. A decentralized trial may also enable more frequent – and potentially real-time – collection of data, which could provide a more accurate picture of patient symptoms, medication side effects, and other patient-reported data (e.g., if paired with a remote monitoring device).[17,18] These tools can be easily adapted to a remote format with minimal technological requirements beyond a digital platform and video capabilities. Furthermore, remote data has been shown to easily convert to existing clinical measures in a manner that ensures safety, validity, and usability of PRO data.[19]

CHARACTERISTIC 3: DEGENERATIVE DISEASES. Degenerative diseases often lead to severe physical impairment and decentralized trials can help avoid unnecessary travels. For these patients, even traveling short distances to a local hospital or care facility can be burdensome. For example, 80% of patients diagnosed with amyotrophic lateral sclerosis (ALS) will need a wheelchair during the course of their life, which imposes significant mobility and travel constraints (e.g., the need for a wheelchair-accessible means of transportation, a caregiver / travel companion, etc.).[20] Even those who do not need a wheelchair may experience excessive fatigue, unsteadiness, and difficulty rising from a chair and risk occasional falls.[20] Home-based solutions can reduce stress, are less exhausting and are more convenient ways to treat and manage these patients.[21] These can include home nurse visits, virtual appoints or at-home lab tests, which can easily be incorporated in remote trials. Home-health visits implemented into clinical trials can lower health risk and ease the burden of participation for degenerative diseases due to the elimination of patient travel.[22,23] In-home nurses and clinical service providers trained in their clients' study protocol and requirements can conduct a range of services,[23] from simple questionnaires and vitals assessments to more complex procedure like sample collection, blood draws, and drug administration. Companies that provide home-based trial solutions are growing quickly, capitalizing on their ability to give patients with degenerative diseases greater access to clinical trials.

Figure 2. Six use-cases are conducive to clinical trial decentralization



CHARACTERISTIC 4: DISEASES AMENABLE TO VISUAL ASSESSMENT. Conditions that can be monitored visually are well suited for decentralized

trials. Dermatological conditions, which rarely involve the need for hospital-based care and where diagnosis is principally through visual examination and patient description of symptoms, is one such example.[24] In fact, a recent study of lower disease severity psoriasis patients determined that the online clinical research model was superior to care provided via the in-person care model.[24,25] By incorporating remote assessment through video, photographs, or other imaging technologies, these conditions could be monitored over time in a virtual setting. In this way, investigators can collect the necessary data points for analysis of the efficacy of a drug in a decentralized clinical trial design.

CHARACTERISTIC 5: DIGITAL NATIVE POPULATIONS. Younger, more tech-savvy candidates tend to be highly adaptable to changing technologies. They are "digital natives" – natural candidates for enrollment in decentralized clinical trials and patients with diseases that have long been associated with digital interventions.

Trials involving young adult or pediatric populations may be particularly viable candidates for decentralization due to the patients' familiarity and comfort with technology. Indeed, a recent study found that patients who ultimately enrolled in fully decentralized trials were more likely to be younger.[26] Patients who grew up using digital technologies are more likely to be able to adapt to virtual trial formats and understand complex digital interfaces, without the need for extensive training.[26] However, efforts must be made to ensure that younger, tech-savvy patients are not overrepresented in trials that require patients across a range of ages.[26,27]

Similarly, diseases for which remote patient monitoring is already part of routine clinical practice can be suitable candidates for decentralized trials. Studies of diabetes patients have shown improvement in glycemic control with the use of mobile devices, electronic logbooks, and other technologies.[28] Further, the proliferation of mobile applications to review blood glucose data also represents an opportunity to better manage glycemic-related complications. For example, in the "VERKKO" study, Sanofi demonstrated that use of a 3G-enabled wireless blood glucose meter allowed patients to collect their glucose data 22% faster with 18% fewer attempts than those using standard glucose monitoring technology. The study site itself required 66% less time for study coordination activities compared to the traditional non-remote trials.[29]

CHARACTERISTIC 6: THERAPIES THAT ARE MOST BENEFITED BY RWE. The final archetype for a decentralized trial are therapies that would benefit from remote collection of real-world evidence (RWE) using electronic health records. With new RWE policies being announced by the FDA, there is an expectation that RWE studies will allow drugs/biologics to be approved more efficiently and have their indications expanded on a showing of good post-market performance.[30] Pfizer's Ibrance, for example, was first approved based at least in part on real world evidence.[31] Representatives from the FDA recognized that multiple RWE endpoints were key in this drug receiving approval, including analysis of "physical exams, symptom improvement, and pathology reports, which were used to supplement descriptions of radiology findings in the overall clinicians' assessment of response."[31] Real-world data (RWD) from electronic health records also played a substantial role in Ibrance later receiving a supplemental approval in male breast cancer. The rarity of breast cancer in males limited the feasibility of conducting a prospective clinical study, and limited evidence existed to help guide treatment decisions. FDA therefore deemed the use of RWD sufficient to support the labeling indication in males. That said, the Ibrance trial could have further benefited from decentralization as the format better merges the clinical efficacy, safety, and RWE assessments into a single study, saving money, time, and resources.

The ability to demonstrate a drug's benefit outside the structured setting of a traditional clinical trial would also add value and impact with respect to what can be expected in the commercial setting.[32] Because decentralized trials put much of the onus on patients, achieved results may be more akin to outcomes observed once the drug becomes commercially available, which may lead to a greater

confidence from physicians on the benefits of the drug when prescribed.

Key Action Items for Biopharmaceutical R&D

In order to capitalize on decentralized trials, pharmaceutical and biotech companies can initiate five key actions to maximize chances of success:

I. **EXPAND DIGITAL INFRASTRUCTURE.** Biopharmaceutical companies should grow internal infrastructure for telehealth and invest in the maintenance and development of digital infrastructure at key clinical trial sites. This should include deploying connected digital products and platforms that enable remote patient monitoring and data collection. Most importantly, digital infrastructure should allow for the integration of data from a variety of platforms to maintain flexibility and enable secure remote review of data in compliance with data privacy laws. Regardless of whether the infrastructure is developed in-house or obtained by way of partnership, it is a key platform component that must be in place to capitalize on clinical trial decentralization.

II. **SECURE AND ULTIMATELY LEVERAGE EMR DATA.** Electronic Medical Records (EMR) are an underutilized trial monitoring resource. Today, most trials use data collected on trial registers;[33] however, a wealth of additional information included in the EMR could be beneficial for further analyses. Clinical researchers are exploring ways to address privacy concerns by granting research monitors read-only access to the medical records of clinical study patients who have consented.[34,35] Data privacy violations, such as through the publication of DNA sequences, and medical malfeasance in past clinical studies, such as Tuskegee, have limited engagement in clinical trials by minority groups.[36,37]Minimizing the privacy concerns associated with decentralized clinical trials could not only increase participant engagement during the study but also further expand the pool of the population willing to take part in a decentralized trial, which in turn could increase recruitment number and diversity.

III. **SEEK REGULATORY BUY-IN.** Regulators have demonstrated flexibility and progressivism around decentralized trials during COVID, and these attitudes are unlikely to disappear in the post-COVID world.[38] However, without regulatory support, decentralized trials will not be possible; therefore, it is important for biopharmaceutical companies to engage in conversations with key government bodies such as the FDA or EMA and understand upcoming regulatory changes and requirements for the design of compliant trials.

One way to do this is by joining consortia working to grow decentralization practices. Over 50 companies, including pharma, biotech, and digital health companies,[39] have joined to form the Decentralized Trials & Research Alliance (DTRA).[40] DTRA, as well as other similar organizations, such as the EU-based Association of Clinical Research Organisations' Decentralized Clinical Trials Working Party (ACRO DCT WP),[41] are fostering inter-pharmaceutical collaboration, in order to bring together pharmaceutical / healthcare companies and further the adoption of decentralized clinical trials across the globe.[41]

Regulators are not expected to represent a significant barrier to decentralization moving forward, but a continued dialog is essential. In a recent qualitative study on the impact of COVID-19 on clinical trials, over half of the pharmaceutical and biotechnology executives interviewed perceived the FDA as responsive, flexible, and supportive of decentralized trials.[42] The largest perceived barrier moving forward was a need for greater clarity on whether data collected remotely would be accepted

or whether validation trials would be needed to show equivalence with traditional collection methods.[42]

Consequentially, investment in clinical trials that validate remote endpoints and biomarkers may be needed for FDA buy-in.[34,43]

IV. **DESIGN PIPELINE STRATEGY.** A detailed understanding of how decentralized trials fit into each company's pipeline is critical for designing a comprehensive future clinical trial strategy. Companies should also investigate the appeal of incorporating data strategies such as virtual control arms or aggregated clinical datasets. Virtual control arms use predictive statistical data to replace the control group that receives the placebo, and aggregated clinical datasets may improve the comparison between traditional versus decentralized trials.[43] This is likely to decrease the level of uncertainty when measuring the benefit of a new treatment. Furthermore, reducing the amount of necessary control patients -- or eliminating them entirely --and instituting a synthetic control arm can increase efficiency, reduce delays, lower trial costs, and decrease the often arduously long timeline for a therapy to reach the market.[44] Finally, the incorporation of virtual control arms also allows for further use of real world data, which not only increases the field of real world data itself, but also simultaneously eliminates the risk of patients avoiding a trial because they fear being assigned to placebo -- one of the top reasons patients do not participate in potentially lifesaving relevant clinical trials.[45]

V. **CAPITALIZE ON DIGITAL INNOVATION.** At least three types of digital innovators are now operating within the context of decentralized trials: clinical trial companies providing end-to-end management of in-home trials; start-ups leveraging community doctors to help ensure a diverse principal investigator pool; and platform-as-a-service technologies that integrate the range of clinical research processes into a centralized ecosystem.[43] These companies are disrupting the way trials are performed and can be new partners for biopharmaceutical companies who seek to leverage decentralized trials without the requirement to build the entire infrastructure.

Conclusion

The current healthcare environment is ripe with opportunities for pharmaceutical companies to enter the arena of decentralized clinical trials. Choosing the appropriate design, population, or indication for such studies will be key. Making the right infrastructure and financial investments will play a critical role in driving healthcare innovation in a post-COVID world.

As the dust settles around these changes and decentralization uptake continues to ramp up, it will be critical for pharmaceuticals to find their footing and take advantage of this new arena, lest they miss out on significant clinical and commercial opportunity.

Let's talk.

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