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How COVID-19 Disrupted The Clinical Trial Status Quo

by Daniel Chancellor

As the world begins its transition into a post-pandemic existence, it becomes possible to look back on the past two years and begin to quantify the effects COVID-19 has brought. For the biopharmaceutical industry, clinical trials have been at the forefront.

From waves of infection causing inaccessible sites and reduced patient availability, through to the unprecedented development of vaccines and other therapeutics, COVID-19 has permanently changed the nature of clinical research.

Clinical trials have historically been entirely concentrated around the clinical site, typically an academic or general hospital, employing experienced investigators and site staff trained for the explicit purpose. This paradigm has prevailed over decades, despite the high associated study costs and declining enrollment performances over time. Until recently, the availability of digital technologies that enable interactions to take place virtually has had little effect on clinical trial conduct.

At its simplest, these include tools such as electronic consent and the use of home health providers. Further along the digital spectrum, modern proposals for a fully decentralized clinical trial (DCT) involve online patient recruitment, telehealth, mobile clinics, wearable medical devices and digital therapeutics, all augmented by real-time data tracking. Nevertheless, as Exhibit 1 shows, the number of such trials – regardless of the level of decentralization – has grown little through the last decade and represents a small minority of the total trial landscape. Please note that the absolute numbers are likely to be underestimates, as the identification of these trials requires specific keywords to be present in publicly available information such as titles, study designs, and endpoints.

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The COVID-19 pandemic offered clinical trial sponsors the unique opportunity to reevaluate the use of digital and virtual technologies. Initially this was carried out through necessity to mitigate disruption to ongoing clinical trials and provide continuity to patients. However, as telehealth became more prominent and patient mobility remained at lower levels, DCTs became a more attractive option. This is supported by the wide benefits that DCTs can provide, from lower costs to improved patient diversity and inclusion, claims that clinical research organizations increasingly amplify in their marketing materials.

The number of DCTs initiating each year, and the level of decentralization within each, is likely to reach an inflection point as a result of the pandemic. 2021 saw a record 35% annual increase in the number of clinical trials initiating that employ digital technologies or virtual interactions, while Pharma Intelligence's early extrapolation for 2022 suggests that this may rise a further 30%. This momentum is best exemplified by the #NoGoingBack movement, whereby clinical research professionals from across the industry have pledged to honor the lessons learned in study conduct due to COVID-19.

Master Protocols Showed Value In Pandemic Response

Vaccine trials aside, clinical research was incredibly wasteful during the pandemic. The acting FDA Commissioner at the time, Janet Woodcock, clearly laid out the scale of the problem in an article published in *Nature Reviews Drug Discovery*. In the first year, just 5% of COVID-19 clinical trial arms were randomized and sufficiently powered to detect a meaningful clinical result. Around one quarter of all enrolled patients were in these study arms, therefore the remaining three quarters participated in trials that could not inform future best clinical practice. This was a huge, missed opportunity to discover and develop (or indeed rule out) COVID-19 treatments prior to the availability of vaccines.

Conversely, there were rare examples of clinical trials that were designed incredibly efficiently and yielded rich clinical insights. Fundamental to this is the use of master protocols, which the FDA defines as: "A protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure." The same clinical trial instructions can therefore be used and reused, allowing studies to continue in perpetuity and adapting to the changing clinical landscape. In the case of COVID-19, master protocols allowed broad investigation of a range of treatment types for patients in different clinical settings, against the backdrop of an ever-improving standard-of-care.

The leading example of a successful master protocol for COVID-19 is the RECOVERY trial, set up in the UK by the University of Oxford and funded by various grants including from the National Institute for Health Research, UK Research and Innovation, and Wellcome.

RECOVERY is an example of a platform trial, in which a single master protocol governs the

evaluation of multiple treatments simultaneously. Given the nature of the pandemic, it was designed to be adaptive, with new arms being added and removed as evidence matured and the broader clinical context demanded. Two years after it was first conceived, RECOVERY has randomized nearly 50,000 patients across 200 different clinical sites, producing conclusive recommendations for 10 separate therapeutic strategies. The first clinical recommendation for dexamethasone was generated within 100 days of trial initiation, and it continues to yield new treatment insights. The huge wealth of information produced by the platform trial comes at a fraction of the cost of conventional clinical evidence, with an estimated total spend of less than $10m.

There are features in the design of RECOVERY, and the health care system within the UK, that provided the unique opportunity to capture vast amounts of clinical data with such efficiency. These are not generalizable across the entire clinical trial ecosystem but can provide a template upon which other countries and collaborators may seek to adapt and innovate to suit their own needs.

The example set by RECOVERY is impossible to ignore, even if there is relatively little precedent for platform trials in non-COVID settings. Exhibit 2 charts the number of platform trials that can be identified within Trialtrove according to the year of initiation, based on a keyword searching methodology. As can be seen, the numbers are very low, and the increases in 2020 and 2021 are largely driven by pandemic research. Nevertheless, the small but growing number of platform trials in conventional areas of clinical research will help to raise confidence, added to recent regulatory guidance to support further industry investments.

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New Entrants May Disrupt Status Quo

The increasing recognition of the importance of clinical trials, and new paradigms for generating clinical evidence, provides opportunities for new entrants that may disrupt the status quo between biopharma companies and contract research organizations. One such example, the UK-based Protas, led by RECOVERY trial co-lead Sir Martin Landray, has been clearly inspired by the lessons of the pandemic. The company ethos is that randomized clinical trials remain the gold standard for demonstrating the efficacy and safety of treatments, but that they must be made more simple, practical and scalable. Announcing its first collaboration with *Sanofi*, Protas claims, “By conducting high quality trials at a fraction of current costs, Protas will radically readjust the economics of late-stage randomized clinical trials.” To achieve these goals, the clinical trials that Protas designs and executes will strip down on unnecessary endpoints and exclusion criteria, integrating within conventional healthcare delivery and using digital solutions to maximize patient convenience.

Protas's initial focus will be within the UK, which is in the top five leading locations for clinical trials. Its studies will capitalize on the infrastructure already established within the NHS, which has proven highly amenable to the type of approach that Protas espouses. It is noteworthy that the company is set up as a non-profit organization, which will limit its scale and geographical reach. Applying the same approach to different, more fragmented health care systems presents a much larger challenge, and one in which a considerable footprint is merited. Considering the growth potential of CROs, and the continued creation of new assets within the drug pipeline, this area is ripe for investment.

Private equity is already involved for established players, but the area may also draw venture capital attention. As a sign of what may follow, the influential investor Robert Nelsen at ARCH Venture Partners has teased that one of his priorities for 2022 is to reinvent clinical trials. Start-up innovation is not just limited to science-based biotech companies, but also to the broader ecosystem around the biopharmaceutical industry, such as contract manufacturing and clinical research.

A range of other organizations will also invest in building greater clinical trial capabilities, from governments and academia through to health care providers and hospital networks. While the response to the COVID-19 pandemic set new precedents for the speed at which new treatments could be evaluated and distributed, it also highlighted chronic underinvestment in pandemic preparedness. The Coalition for Epidemic Preparedness Innovations (CEPI) has called on its collaborators, including governments and health care providers, to support a 100-day strategy for vaccinating against the next emerging pandemic threat.

Looking Ahead

The longer-term shifts in clinical research priorities may not become apparent for many years, although one likely legacy is the recognition of the value that adaptive platform trials provide. They have been an incredibly rich source for clinical information in managing COVID-19, enabling evidence generation at pace and scale.

As with any disruption to the trial paradigm, there are opportunities for newcomers to displace incumbent clinical leaders. These may come in the form of non-profits, venture capital-backed start-ups, and strengthened hospital networks boosted by government funding.

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