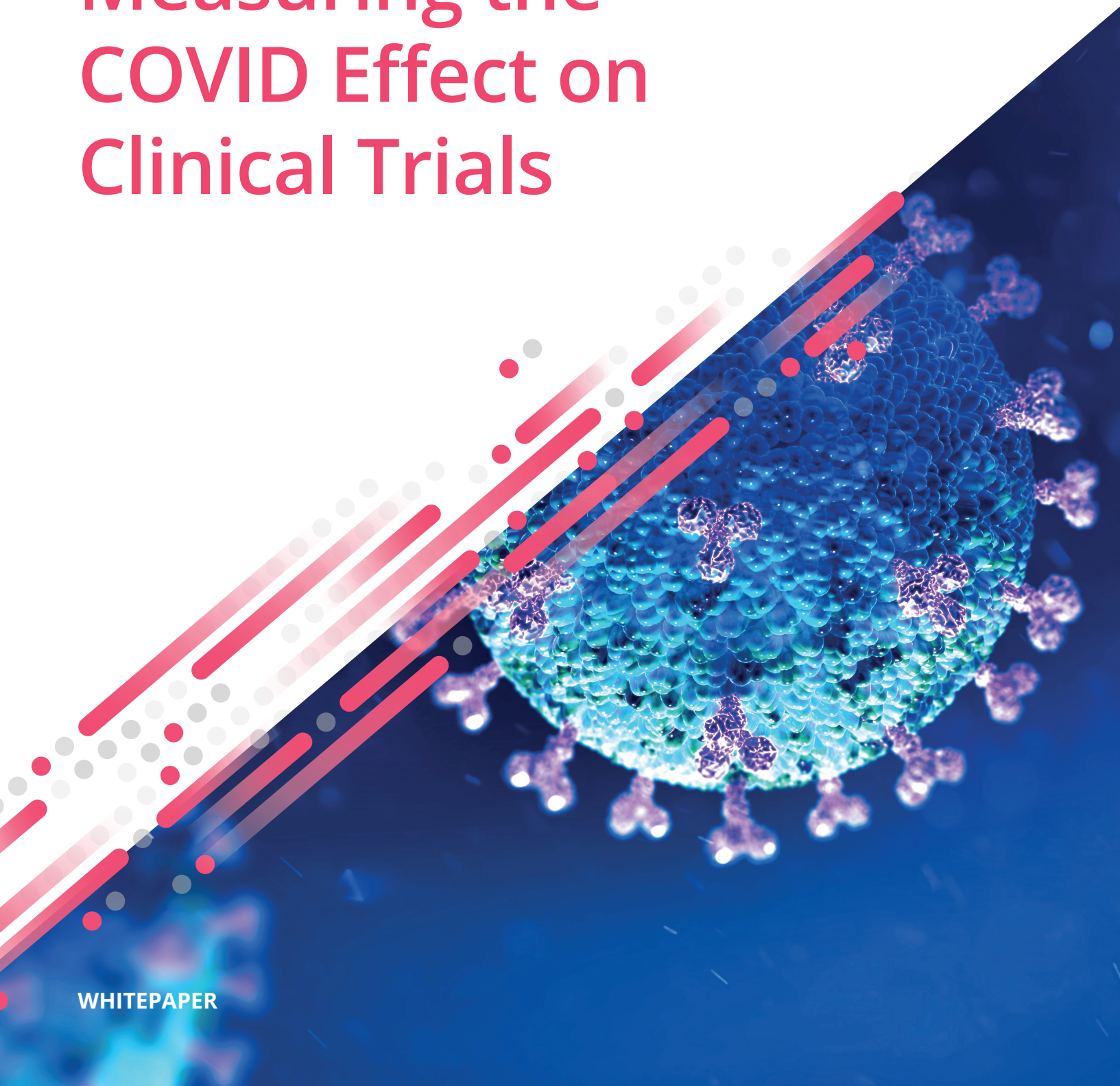
Pharma Intelligence
Informa

Measuring the COVID Effect on Clinical Trials



WHITEPAPER

Daniel Chancellor
Director, Thought Leadership and Consulting, Informa Pharma Intelligence

Introduction

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 that 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.

These positive and negative effects can be weighed for a clear-headed assessment of how well industry R&D has performed, and whether any immediate lessons have been learned. As this white paper shows, despite the incalculable cost of the pandemic, the clinical trial ecosystem has demonstrated remarkable resilience and emerged in a stronger position than ever before.

Clinical trial conduct and measures of R&D activity are at all-time highs, even when stripping out the boost provided by COVID-19 research. Furthermore, modernization initiatives such as decentralized clinical trials, patient diversity, and novel recruitment models that were underway prior to lockdowns have accelerated in line with the dramatic changes in patient behavior and healthcare delivery. Beyond these immediate and necessary changes, longer-term shifts arising from the pandemic will stretch to innovation in study design and a renewed emphasis placed on clinical trial infrastructure.

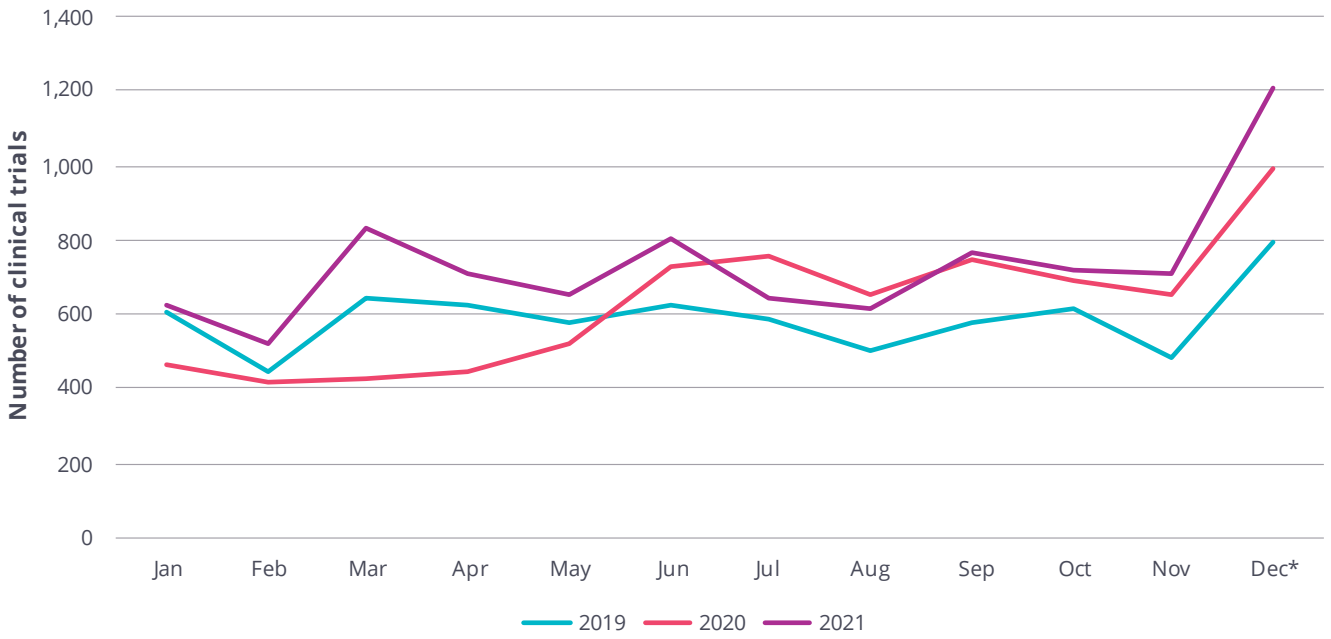
Clinical Resilience

Transient drop in new clinical starts during spring 2020 has long passed

The ability to run clinical trials is largely dependent upon capacity within hospitals and the availability of patients, investigators, and clinical sites. Each of these has been affected by the pandemic, whether that is due to reallocation of healthcare resources to intensive care units, or indirectly through social distancing measures that reduce mobility. The type of patient that is eligible for a clinical trial is also highly likely to be at risk of severe outcomes if infected, so additional shielding measures have dissuaded many from seeking face-to-face care. As a result, the initial months of the pandemic – with strict lockdown measures in place to curb exponential growth in cases – were characterized

by disruption to clinical trials.[1] Eli Lilly was the first large pharmaceutical company to publicly disclose its mitigation strategy, delaying all new trial starts, and many of its peers followed shortly thereafter.[2] The number of newly initiated clinical trials is a reliable indicator for overall clinical trial capacity. Compared to a pre-pandemic baseline in 2019, when the biopharmaceutical industry initiated approximately 600 clinical trials each month (shown in light pink in Figure 1), the first six months of 2020 saw 15% fewer new studies. This shows that the surging numbers of patients in hospital, and accompanying lockdowns, had a very clearly negative effect on overall clinical trial capacity through the spring of 2020.

Figure 1. Industry trials by actual or anticipated start date



Note: trials without an exact start date are assigned to December.

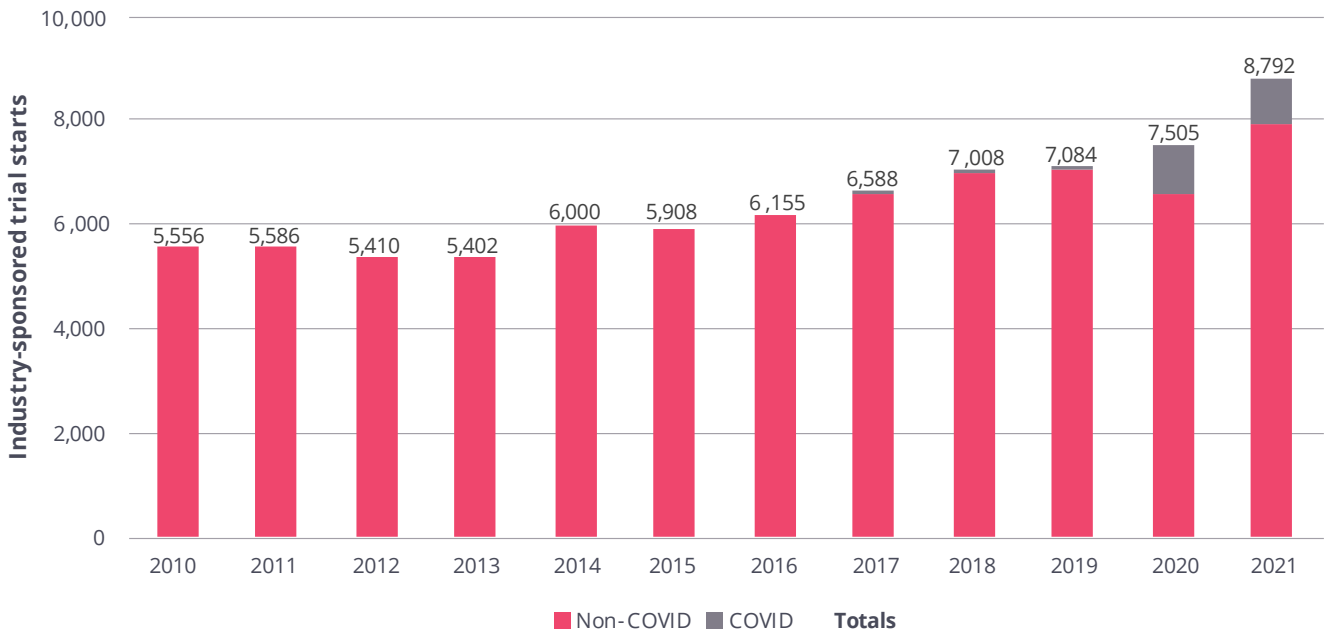
Source: Trialtrove®, March 2022

1. Informa Pharma Intelligence (2020) COVID-19 and the impact on the clinical trial space. Available from: https://pharmaintelligence.informa.com/resources/product-content/covid-19-and-the-impact-on-the-clinical-trial-space [Accessed 7 March 2022].
2. Scrip (2020) Lilly, Galapagos Put Some Trials On Hold Due To Coronavirus Concerns. Available from: https://scrip.pharmaintelligence.informa.com/SC141905/Lilly-Galapagos-Put-Some-Trials-On-Hold-Due-ToCoronavirus-Concerns [Accessed 7 March 2022].

However, by the end of June 2020, this disruption to capacity had largely passed, and the second half of 2020 showed a strong uptick in activity. The July–December 2020 period showed a 27% increase in new clinical trial starts compared to 2019, boosted by over 900 industry-sponsored trials of antivirals, vaccines, and immune modulators designed to protect against COVID-19 infection and hospitalization. Balancing out the disrupted first half with the resurgent second half, 2020 saw a 6% increase overall compared to 2019. Stripping out the influx of COVID-19 research, the corresponding growth turns into a 7% decline. Nevertheless, 2020 was remarkably resilient in light of the unprecedented challenges posed by the pandemic on healthcare systems and patients.

This resilience was converted strongly into momentum throughout 2021, as a new baseline for clinical trial activity was set. For the year as a whole, the biopharmaceutical industry initiated 24% more trials compared to the pre-pandemic baseline. 2021 saw continued clinical trials for COVID-19 therapies – approximately another 900, comparable to 2020 – as well as a strong rebound within conventional R&D. Overall growth in these areas, excluding pandemic-related studies, was an impressive 12% compared to 2019 (see Figure 2). It is apparent that the clinical trial ecosystem has been able to absorb the necessity to test new COVID-19 treatments, while retaining the capacity to meet industry demand for conventional R&D.

Figure 2. Combined biopharma clinical research, 2010–21



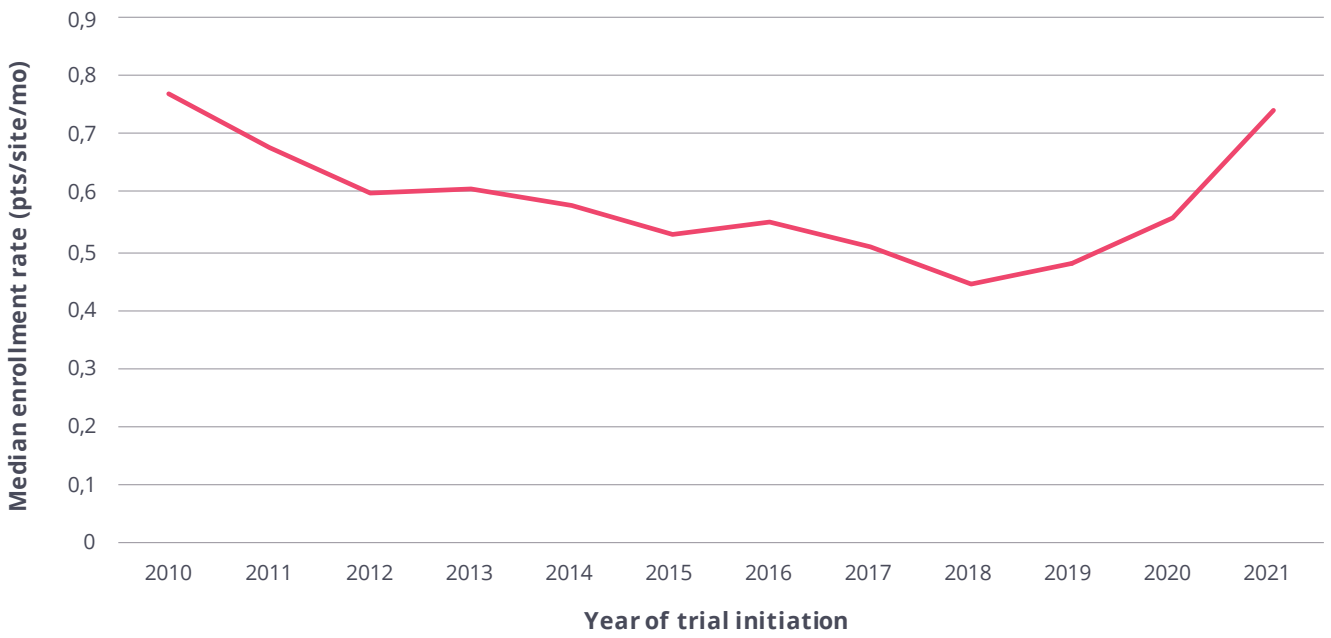
Source: Trialtrove®, March 2022

Patient recruitment rates show signs of improvement despite pandemic

Enrollment rates have steadily declined throughout the last decade, despite the best efforts of trial sponsors to optimize study design around clinical practice and patient availability. There are myriad reasons for this, ranging from intensifying competition for clinical sites and patients through to inflation in the number of eligibility criteria. Furthermore, biopharma companies are increasingly focusing their clinical efforts on oncology and rare diseases, where patients can be more difficult to find. As a result, the industry-wide enrollment rate – measured for Phase II, II/III, and III trials, excluding COVID-19 research – has steadily dropped from a high of 0.8 patients per site per month for trials initiated in 2010, down to approximately 0.5 by the end of the last decade.

It would be reasonable to expect that this downwards trend would be exacerbated through the last two years, owing to the clinical burden on hospitals and general decline in health-seeking behaviors while the pandemic was still in effect. However, the median enrollment rate remarkably increases to 0.56 patients per site per month for clinical trials initiating in 2020, and leaps to 0.74 for the 2021 cohort. These are charted in Figure 3.

Figure 3. Industry-sponsored trial enrollment rates for clinical trials initiating during 2010–21



Note: recent years will be subject to revision as data availability changes.

Source: Trialtrove®, March 2022

Interpretation of these figures requires some caution, as the median enrollment rate contains a blend of clinical trials with actual confirmed rates, as well as anticipated calculations based on algorithms in Trialtrove. In particular for clinical trials in 2021, there is a heavy weighting towards these projected rates, rather than confirmed. As such, there will be larger margins of error for the more recent years and the numbers may moderate over time.

Nevertheless, the fact that these calculated enrollment rates appear to be trending upwards for the time being provides confidence in rejecting the assumption that the pandemic caused a further industry-wide decline in performance. Tantalizingly, it may appear that the opposite is true. The huge willingness of volunteers to take part in clinical research for COVID-19 vaccines, not to mention the modernization of clinical trials discussed later in this paper, may have provided a tangible boost to patient recruitment across all therapy areas and locations.

Organic growth mitigates any disruption from reshuffled pipeline priorities

Resilience in clinical trials has also been matched by the industry drug pipeline, which showed an impressive 8% increase to surpass 20,000 active development projects for the first time in 2022.[3] This is a similarly important metric to track, as the size of the pipeline is a proxy for long-term clinical trial demand, whereas new clinical trial starts and enrollment rates indicate current capacity.

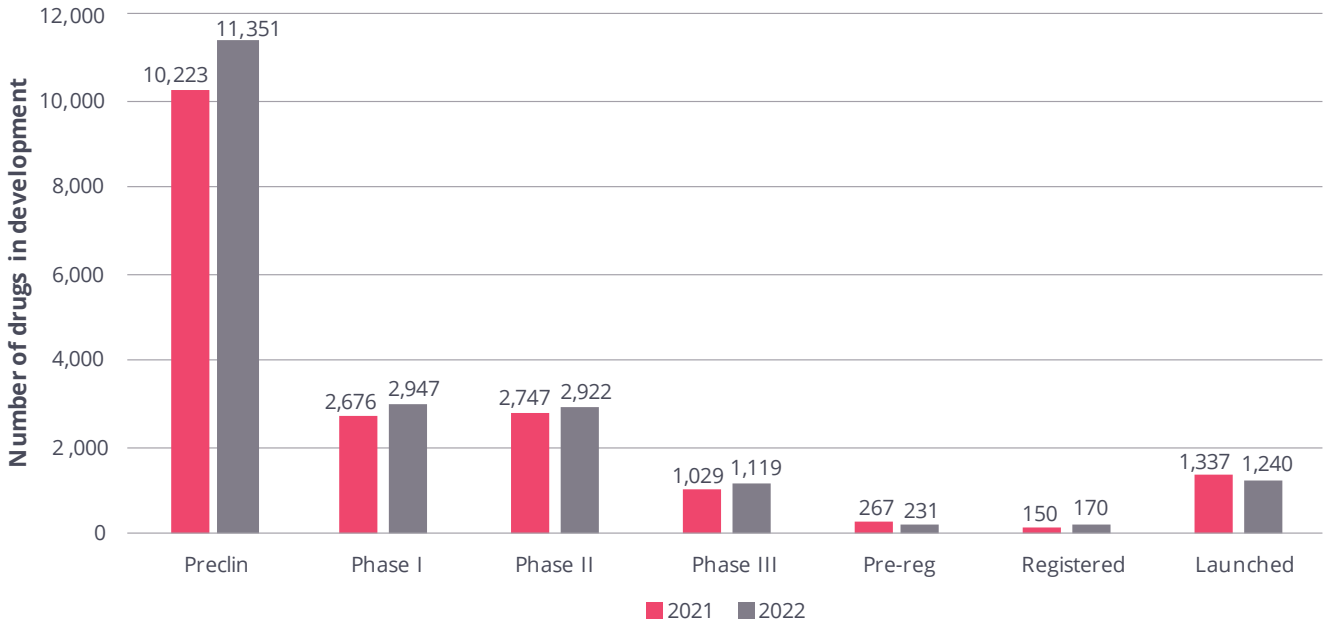
Figure 4 segments these increases in the pipeline by the highest clinical stage of the asset. Note that approved drugs are often investigated in additional indications, therefore such drugs remain classified within the pipeline and are assigned a "Registered" or "Launched" status. There were increases across each of the preclinical and clinical stages of development, with a slight dip in the number of mature drugs undergoing active lifecycle management through new clinical trials. The double-digit percentage increases in preclinical and Phase I assets bodes particularly well for the long-term demand for new clinical trials.

The increase in the number of Phase III assets from 1,029 to 1,119 in 2022 is also promising, as the number had previously reached a plateau at the 1k range lasting several years. Phase III development is the most expensive stage, therefore there is a clearer limit to the number of such assets that the industry as a whole can sustain. The fact that the biopharma industry has finally broken through this ceiling is a positive omen for the state of pipeline investment.

Hidden within these year-on-year changes to absolute totals is a considerable degree of churn, as drugs progress through clinical phases, reach the market, or have further development suspended. As Figure 5 shows, this churn has been particularly apparent in the past two years. For the past 12 months, a record 4,816 drugs were removed from the active pipeline, slightly more than the 4,699 figure of 2021 and way ahead of the 3,174 dropouts in the pre-pandemic analysis of 2020. These have been offset by record levels of asset creation, rising from 4,730 in the 12 months to 2020 to 5,544 and 6,343 in 2021 and 2022, respectively. The clear observation is that the industry R&D pipeline has been able to mitigate any disruption through high levels of growth.

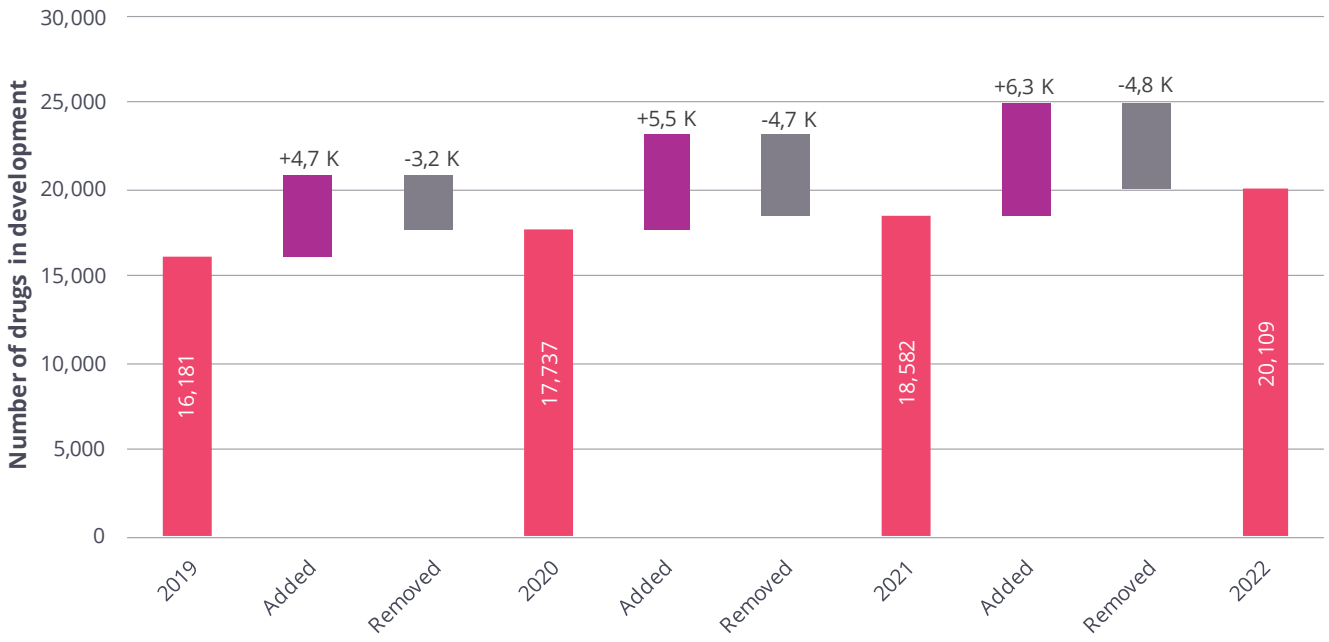
3. Informa Pharma Intelligence (2022) Pharma R&D Annual Review 2022. Available from: https://pages.pharmaintelligence.informa.com/rdreview [Accessed 23 March 2022].

Figure 4. Industry pipeline by stage of development, 2021 vs 2022



Source: Informa Pharma Intelligence, 2022 Pharma R&D Annual Review

Figure 5. Churn in the pharma R&D pipeline, 2019–22



Source: Informa Pharma Intelligence, 2022 Pharma R&D Annual Review

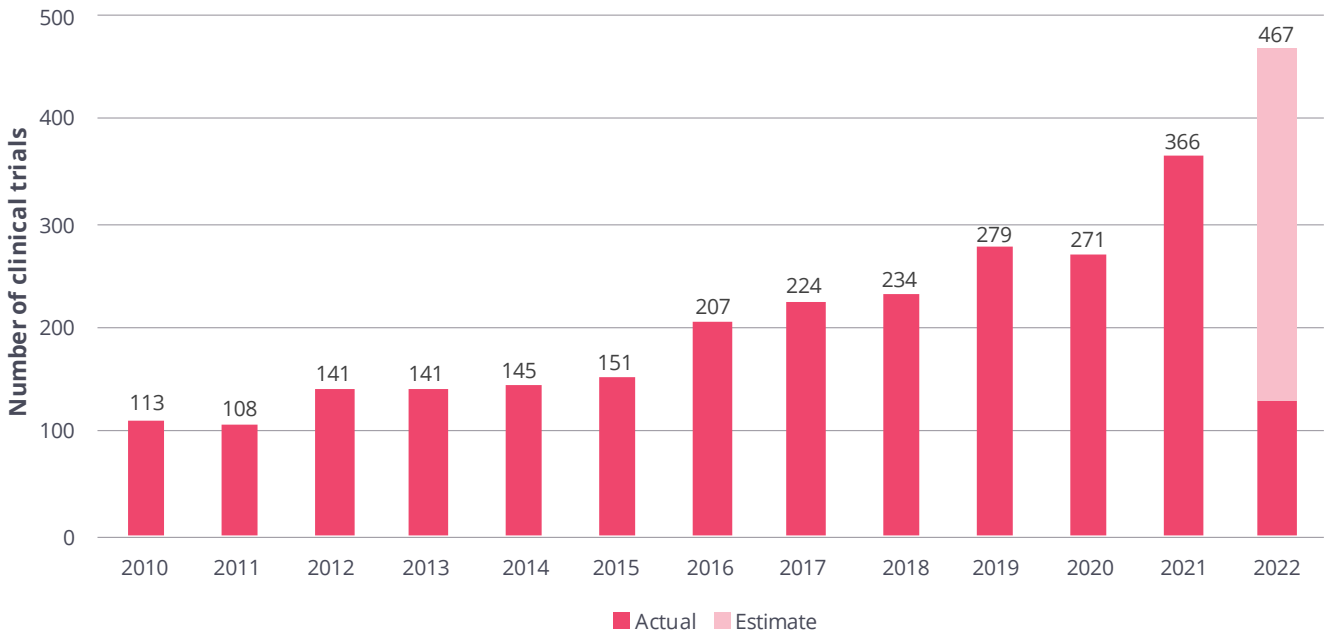
Industry Modernization

Inflection point reached in clinical decentralization

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, in spite of the high associated study costs and declining enrollment performances over time as shown in Figure 3. 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 Figure 6 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.

Figure 6. Disclosed clinical trials employing digital technologies or virtual interactions, by start year



Source: Trialtrove®, March 2022

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 in order 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.

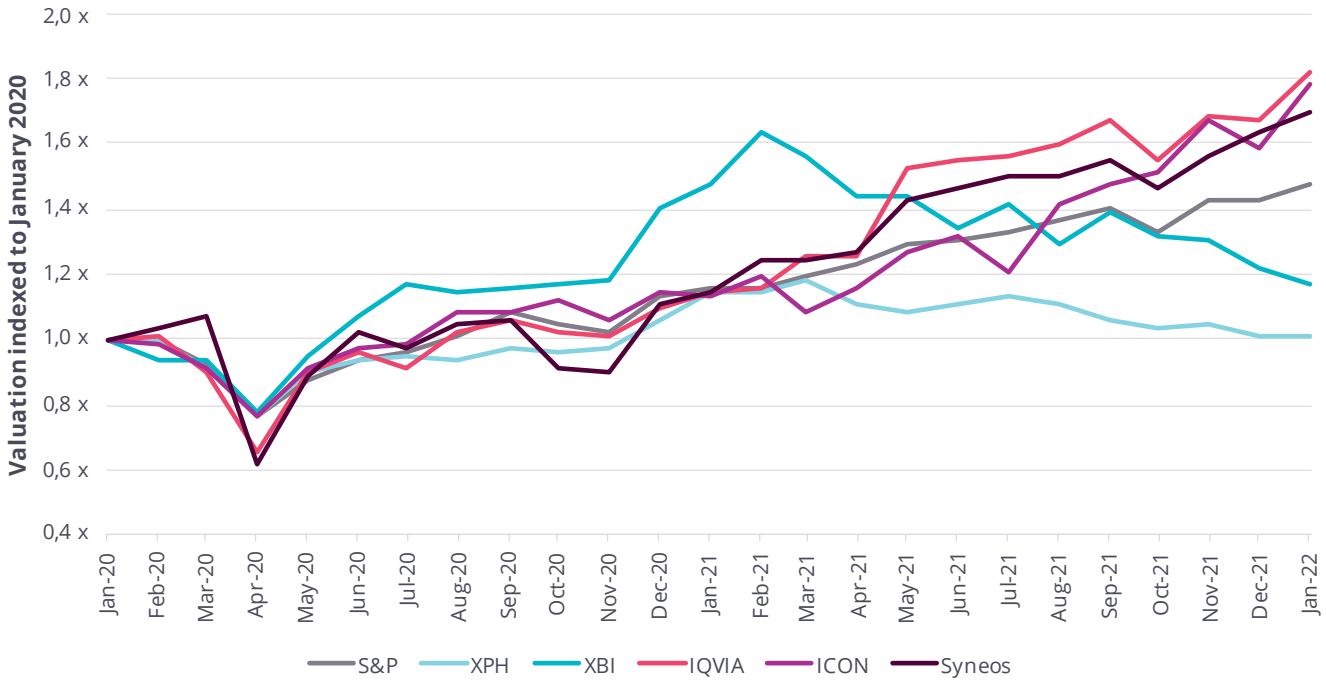
The number of DCTs initiating each year, and the level of decentralization within each, is likely to reach an inflection point as a result of the pandemic. 2021 saw a record 35% annual increase in the number of clinical trials initiating that employ digital technologies or virtual interactions, while 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.

Rise in CRO valuations outpaces biopharma and broader market

As well as technological advances in the clinical trial ecosystem, the financial importance of clinical research players has also accelerated at a faster-than-expected pace. This can be viewed through the lens of the stock market and valuations of leading clinical research organizations (CROs) compared to relevant benchmarks. Admittedly this analysis is highly reductionist and belies important patient-centricity advances that will be discussed subsequently, although it provides an impartial answer to the question as to whether clinical trials are perceived to be more or less valuable exiting the pandemic.

Figure 7 shows the share price performance of the three leading publicly traded CROs (IQVIA, ICON, and Syneos Health) since January 2020, compared to three popular exchange-traded funds that serve as industry benchmarks. Two of these refer to the customer base of CROs – the pharmaceutical (XPH) and biotech (XBI) industries – while the broader market (SPY) can be assessed via the performance of the S&P 500.

Figure 7. Valuation of public CROs against select benchmarks



Source: Yahoo Finance

In this analysis, the CRO subset clearly outperforms all of the relevant benchmarks in terms of share price gains since January 2020. While initially hard-hit by the pandemic in Spring 2020, these major CROs each more than doubled from this low, delivering 20–30% higher returns than the broader market over the two-year period – 50% above biotechs, and 70% greater than large pharmaceutical companies. Drawing contrasts between biotech's surging performance and subsequent decline, the CRO industry very much provides the picks and shovels to the gold rush led by biotech and early-stage drug discovery. This performance reflects the long-term revenue potential and strategic importance attached to the delivery of clinical trials.

2021 has also been noteworthy for the CRO landscape as it witnessed considerable M&A activity, undoubtedly triggered by the increasing attractiveness of investing in the clinical space. Three of the top 10 largest acquisitions for the entire biopharma ecosystem involved CROs, which is unprecedented against the usual backdrop of aggressive Big Pharma dealmaking. Thermo Fisher secured the single largest deal of 2021 in its $20.4bn purchase of PPD, ahead of ICON's $12.0bn consolidation with PRA Health Sciences. Parexel also exchanged one private equity owner for another in a transaction worth $8.5bn. The raised level of investment within CROs promises to further expedite the development of new

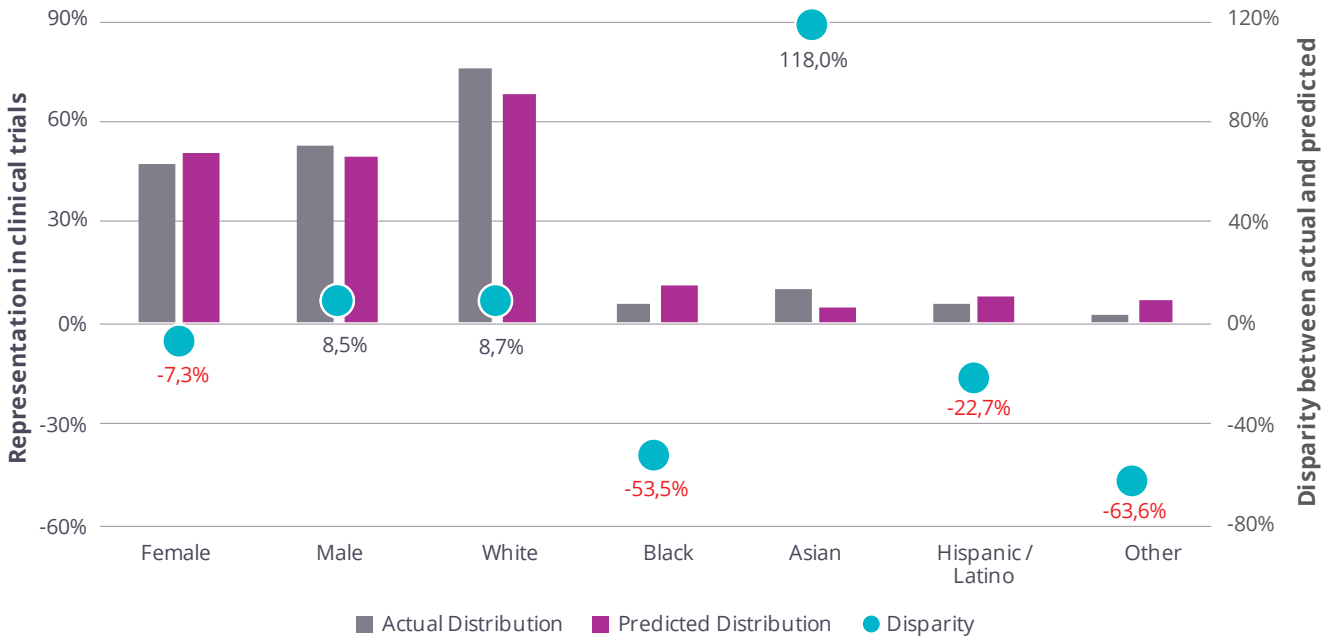
clinical capabilities. However, one note of caution; at the time of writing, the early months of 2022 have seen a notable market pullback affecting CROs, biotechs, and pharmaceuticals equally.

Diversity in clinical trials is now a primary consideration

For many years, clinical trials have underserved certain communities based on social determinants of health, such as age, gender, education, income, and ethnic background. The centralization of clinical trial sites in more affluent areas, and the barriers to participation that many patients face, enforce these biases at a structural level.

Analysis by the Tufts Center for the Study of Drug Development, described in Figure 8, shows the overrepresentation of males, and stark underrepresentation of black participants, or participants of African descent in US trials.[4] Disparities in the expected number of Hispanic or Latino volunteers, and the "Other" category comprising Native American, Native Alaskan, and Hawaiian or Pacific Islander participants, were also notable. Data were gathered by comparing reporting of patient subgroups in clinical trials submitted as part of 341 NDAs or BLAs over the 2007–17 period to the expected enrollment based purely on epidemiology and census data. With participant subgroup reporting optional, these disparity calculations may even be underestimates of the true picture.

Figure 8. Clinical trial representation by demographic



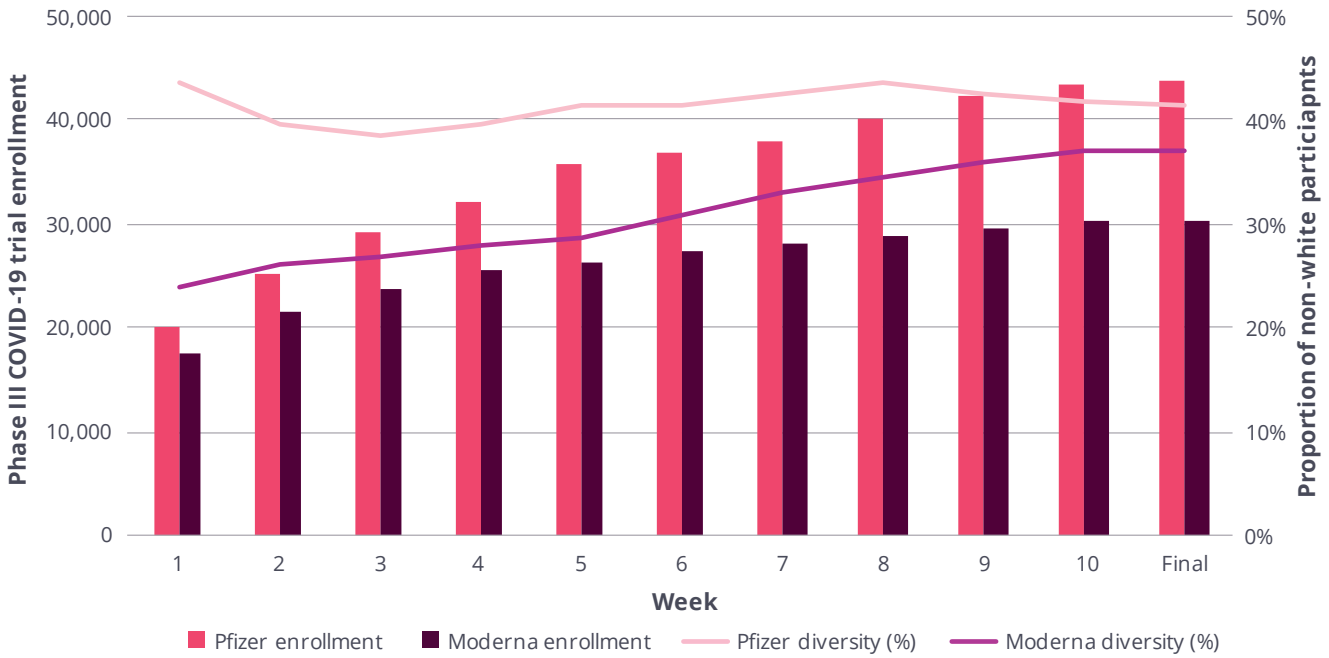
Source: Tufts Center for the Study of Drug Development

4. In Vivo (2020) Expanding The Tent: Improving Trial Participation Among Under-Represented Patient Populations. Available from: https://invivo.pharmaintelligence.informa.com/IV124476/Expanding-The-Tent-Improving-Trial-Participation-Among-Under-Represented-Patient-Populations [Accessed 10 March 2022].

The industry's long-standing failure to create diverse and inclusive trials has prevailed despite being widely recognized. The FDA launched a five-year action plan in 2015, although there has been no discernible effect as per data recorded in Drug Trials Snapshots, one component aimed to improve transparency and reporting.[5] Simply put, regulators have had limited ability to incentivize and enforce diversity, and clinical trial sponsors have not gone far enough on a voluntary basis. However, the COVID-19 pandemic and the health inequalities it laid bare created the momentum behind clinical trial diversity becoming a strategic imperative. While Pfizer and Moderna led the way with their approach to COVID-19 vaccine development and the need to counter hesitancy, the ramifications extend to all aspects of clinical research.

Both Pfizer and Moderna voluntarily published the full story protocols in the interests of transparency, and publicly reported real-time enrollment metrics. This included the proportion of participants that were from diverse backgrounds, as shown in Figure 9. This unprecedented degree of accountability allowed Moderna to take the unusual step of stopping enrolling further Caucasian participants, prioritizing a representative study population at the expense of overall speed. This is remarkable considering the intense timeline pressures that these companies were under. As described by

Figure 9. Phase III vaccine trial enrollment and diversity



Source: In Vivo

5. Green AK, et al. (2022) Despite The FDA's Five-Year Plan, Black Patients Remain Inadequately Represented In Clinical Trials For Drugs. Health Affairs, 41(3), 368–74.

Moderna's chief development officer Melanie Ivarsson, "It took us a week or two to implement because… we wanted to be very respectful of those who had already approached the site about being screened and were scheduled in to come for a visit. So, we allowed those individuals regardless of race or ethnicity to come for their visit, and then once that had been done, we requested the sites to offer up all remaining slots to people from communities of color."

This example has reset expectations on what clinical trial sponsors should deliver, and is inspiring companies from across the spectrum to assign strategic importance to diversity and inclusion. As examples, Bristol Myers Squibb has pledged $100m to train and develop new clinical investigators from ethnically diverse groups,[6] while J&J has a similar $100m commitment with the broader goal of promoting health equity solutions.[7] Diversity has become a key consideration for environmental, social, and corporate governance (ESG) scores, and where such initiatives lead, regulations may eventually catch up.

For the time being, diverse trials are not enshrined in approval pathways, although the recent FDA rejection of Eli Lilly/Innovent's PD-1 inhibitor sintilimab based on a China-only trial suggests that this is the direction of travel. Tellingly, the FDA commented that the accompanying clinical evidence "does not align with broad initiatives and renewed commitment across the pharmaceutical industry for equitable representation in clinical trials." As such, there are growing incentives to be ahead of the curve in adopting diversity and inclusion best practices in clinical research.

6. Bristol Myers Squibb (2020) The Bristol Myers Squibb Foundation and National Medical Fellowships Launch $100 Million Program to Help Increase Diversity and Inclusion in Clinical Trials. Available from: https://news.bms.com/news/details/2020/The-Bristol-Myers-Squibb-Foundation-and-National-Medical-Fellowships-Launch-100-Million-Program-to-Help-Increase-Diversity-and-Inclusion-in-Clinical-Trials/default.aspx [Accessed 10 March 2022].
7. Johnson & Johnson (2020) Johnson & Johnson to Address Racial and Social Injustice Through Platform that Aims to Eliminate Health Inequities for People of Color. Available from: https://www.jnj.com/johnson-johnson-to-address-racial-and-social-injustice-through-platform-that-aims-to-eliminate-health-inequities-for-people-of-color [Accessed 10 March 2022].

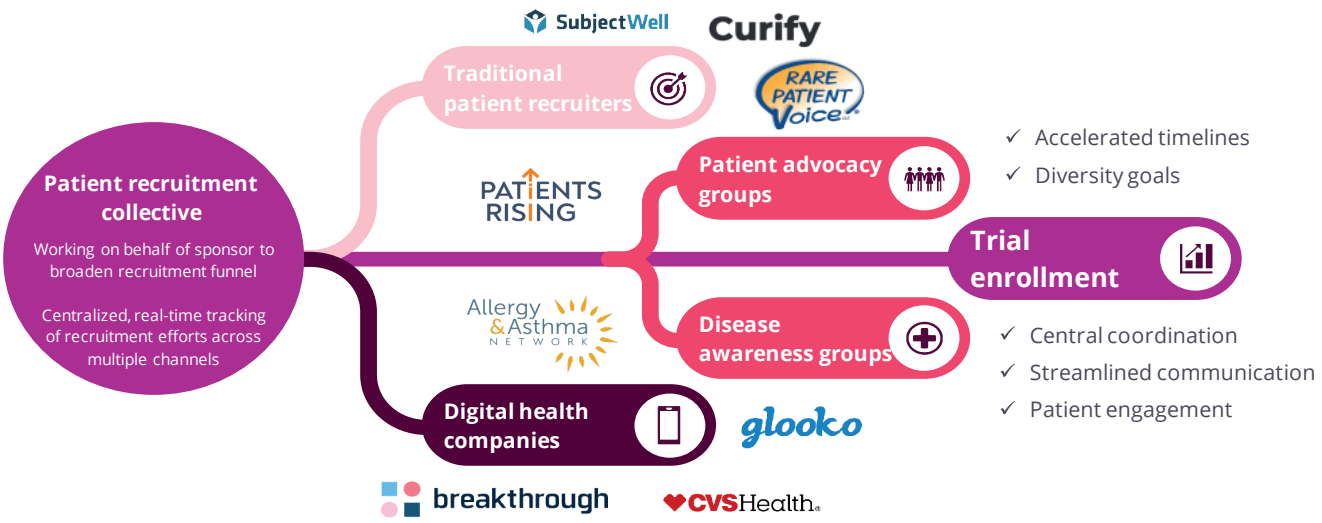
Patient recruitment collectives can accelerate trial timelines and promote diversity

Biopharmaceutical companies have a range of tools to employ in order to achieve diversity goals, from optimizing study protocols through decentralization to minimize bias and working with investigators at clinical sites with access to diverse populations. The proliferation in digital channels and the growing number of patient-facing organizations that can act as recruitment partners can also be utilized to improve study diversity. This has been harnessed in a new model for industry's approach to clinical trial recruitment – the patient recruitment collective.

Through a centralized platform, a variety of patient-facing organizations can be brought together, from traditional recruitment partners through to disease awareness organizations, patient advocacy groups, pharmacies, and even diagnostic service providers, as shown in Figure 10. By creating and tapping into a network of validated partners that can steer patients in the direction of clinical trials, study sponsors can cast the net far wider and more equitably.

This one-to-many approach has substantial advantages over working with select traditional recruitment partners, which have failed to address declining enrollment rates over the last decade, and reinforce a lack of diverse participation. Patient advocacy and disease awareness groups have a particularly important role in this new paradigm. According to a joint Pharma Intelligence-Rare Patient Voice survey that gathered over 900 opinions on participation or intent to participate in clinical trials,[8] these groups emerge as the preferred and most valuable source of clinical trial information. Their involvement helps to engender trust in the overall clinical trial process, not to mention broadening the reach for potential patient referrals.

Figure 10. Patient recruitment collective model



Source: Biomedtracker, February 2022

8. Informa Pharma Intelligence (2021) Patient Perspectives on Clinical Trial Participation Report. Available from: https://pharmaintelligence.informa.com/resources/product-content/2021/07/22/16/07/patient-perspectives-on-clinical-trial-participation-report [Accessed 11 March 2022].

The pandemic and the need to enroll large numbers of patients in record time, while meeting diversity goals, meant that Moderna pioneered the patient recruitment collective model in its Phase III COVE study of Spikevax for the prevention of COVID-19 infection. By using Citeline Connect's network of recruitment partners, the referral collective was able to pre-screen more than 200,000 potential applicants, leading to 85,000 referrals, and ultimately over 6,000 patients randomized, the first of which was delivered within just four days.[9]

With this proof-of-concept, there is now much broader interest among trial sponsors in recruitment collectives, rather than relying on a smaller number of traditional recruitment partners. This extends beyond the pandemic setting, where clinical necessity and patient engagement were unnaturally high, and encompasses a range of therapeutic areas. In particular, the collective model is transformative for clinical trials in rare diseases. When such patients are difficult to identify through conventional channels, sponsors need to create the broadest possible outreach and be agnostic in their choice of recruitment partners.

9. Citeline Connect (2021) COVID-19 Trial Recruitment at Warp Speed. Available from: https://pharmaintelligence.informa.com/resources/product-content/covid-19-trial-recruitment-at-warp-speed [Accessed 11 March 2022].

Predicting Longer-Term Shifts

Master protocols showed tremendous 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.[10] In the first year, just 5% of 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) treatments prior to the availability of vaccines that protect well against severe outcomes.

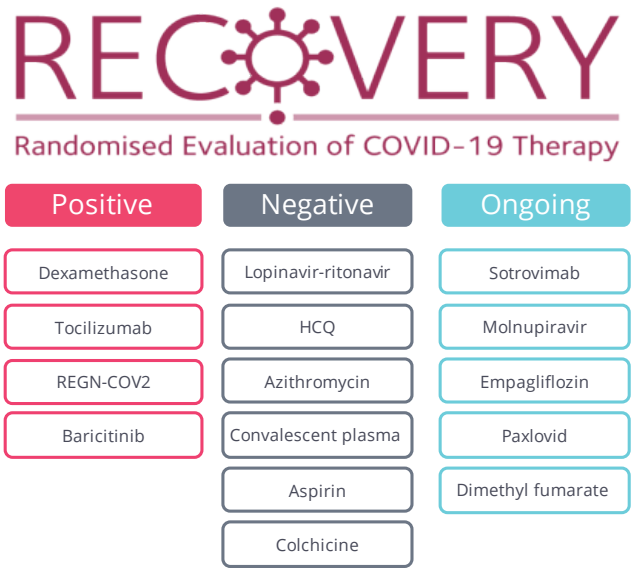
Conversely, there were rare examples of clinical trials that were designed incredibly efficiently and yielded rich clinical insights. Fundamental to this is the use of master protocols, which the FDA defines as: "A protocol designed with multiple substudies, which may have different objectives and involve coordinated efforts to evaluate one or more investigational drugs in one or more disease subtypes within the overall trial structure."[11] 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.[12] 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.[13]

10. Bugin K, Woodcock J (2021) Trends in COVID-19 therapeutic clinical trials. Available from: https://www.nature.com/articles/d41573-021-00037-3 [Accessed 15 March 2022].
11. FDA (2022) Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics. Guidance for Industry. Available from: https://www.fda.gov/media/120721/download [Accessed 15 March 2022].
12. RECOVERY trial (2022) RECOVERY Randomized Evaluation of COVID-19 Therapy. Available from: https://www.recoverytrial.net/ [Accessed 15 March 2022].
13. STAT News (2022) They built a smarter approach to Covid clinical trials. Now they want to do the same for other diseases. Available from: https://www.statnews.com/2022/01/24/building-on-study-of-covid-drugs-scientists-launch-effort-to-accelerate-clinical-trials/ [Accessed 15 March 2022].

Figure 11. RECOVERY trial evidence summary

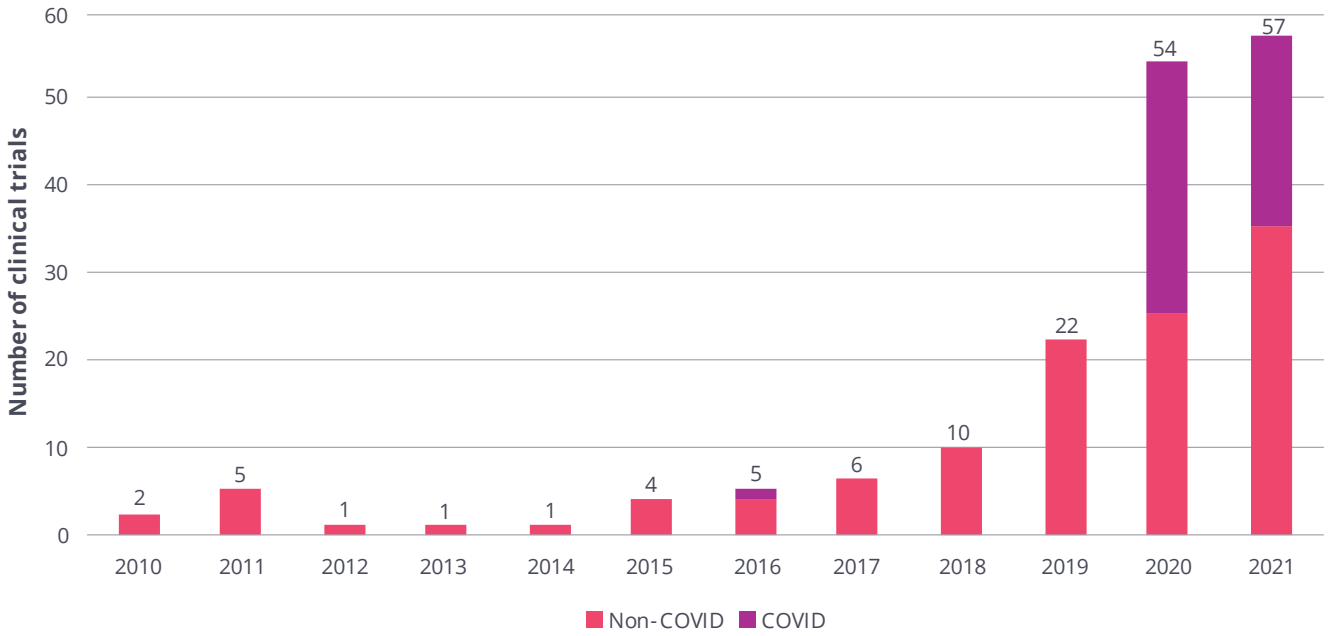


There are features in the design of RECOVERY, and the healthcare system within the UK, that provided the unique opportunity to capture vast amounts of clinical data with such efficiency. These are not generalizable across the entire clinical trial ecosystem, but can provide a template upon which other countries and collaborators may seek to adapt and innovate to suit their own needs. Primarily, there is a large degree of interconnectivity in the National Health Service, whereby patients can be effectively triaged to available treatment options based on electronic health records and test-and-trace protocols. With the number of treatment arms being evaluated simultaneously, a large proportion of patients would be eligible and could be directed to study teams working in the hospitals. The study itself was designed in such a way to minimize unnecessary complexity, allowing medical professionals to incorporate it into their clinical practice without additional burden. Lastly, being coordinated by an academic group without the influence of government or the pharmaceutical industry, it could operate without commercial or political conflicts of interest, focusing purely on discovering the most effective interventions for patients with COVID-19.

Modern trial designs will supplement traditional RCTs in other diseases

The example set by RECOVERY is impossible to ignore, even if there is relatively little precedent for platform trials in non-COVID settings. Figure 12 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. In particular, oncology is often the breeding ground for innovation in trial design – another trial design based on master protocols, the umbrella trial, is now commonplace to detect efficacy signals across a range of patient groups. It will also be in oncology that platform trials continue to demonstrate their utility. Even accounting for the influx of pandemic-related platform trials, oncology is the current leading therapy area for such trials. This is owing to the rise of precision oncology and the increasingly complex ways in which patients can be segmented and treated. This relies on biomarker-driven definitions of cancer and next-generation sequencing techniques that can support these diagnoses.

Figure 12. Platform clinical trials initiated each year, 2010–21



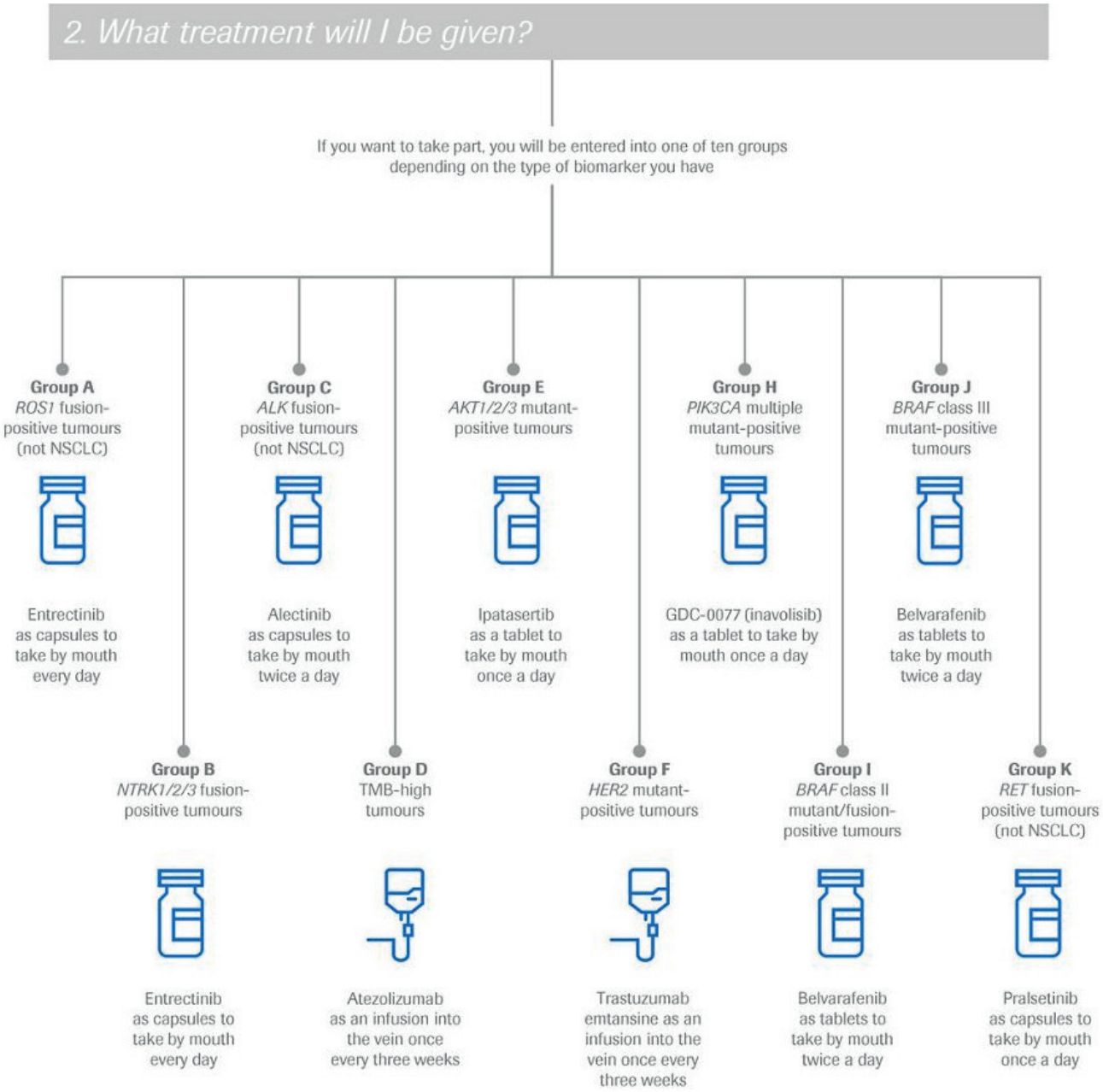
Source: Trialtrove®, March 2022

Roche's TAPISTRY trial is an interesting case study for the use of platform clinical trials in precision oncology.[14] As the largest oncology drug developer, Roche is uniquely positioned to run such a trial, in which patients with solid tumors are randomized to one of 10 different treatment arms dependent upon their biomarker status, as shown in Figure 13. Half of these treatment arms are established, whereas the remainder are investigational. Individually, each one of these experimental arms would require a large number of patients owing to the rarity of some of the biomarkers in question. A large majority of patients would be ineligible after undergoing screening and next-generation sequencing.

However, in the case of TAPISTRY, Roche is able to offer a much larger proportion of patients an appropriate targeted- or immuno-oncology-based drug regimen because it boasts such a broad commercial and investigational drug portfolio. This setting mirrors real clinical practice much more closely, where patients can rapidly receive drug treatment based on their precise diagnosis. The platform trial subsequently supports the further investigation of individual cohorts in which the open-label treatment shows promise. In this way, platform clinical trials are entirely complementary with conventional randomized clinical trials, which will remain the gold-standard for supporting product approval.

14. Roche (2022) A clinical trial to understand how genetic testing can help doctors to decide which treatment is best for patients with solid tumours (TAPISTRY). Available from: https://forpatients.roche.com/en/trials/cancer/solid-tumors/tumor-agnostic-precision-immuno-oncology-and-somatic-ta-50851.html [Accessed 15 March 2022].

Figure 13. Treatment arms in the TAPISTRY platform trial



Source: Roche

Another setting where platform clinical trials show promise is for rare diseases, where alternative development pathways may help to encourage and incentivize R&D that otherwise may not be funded. The HEALEY ALS platform trial is a prime example of a non-industry-funded study that may support smaller biopharmaceutical companies in their path to market. The premise of the trial, hosted by Massachusetts General Hospital, is to accelerate the path-to-market for new ALS therapies by testing multiple treatments at once, reducing the cost of research by 30%, decreasing the trial time by 50%, and increasing patient participation by 67%.[15] The trial has selected five different investigational treatments from smaller biopharmaceutical companies, each forming a separate treatment arm with 160 patients randomized 3:1 to the study drug or placebo. Depending upon the data produced, these drug companies will be able to file for regulatory approval based on data from this platform trial. Without the HEALEY ALS study, they may not have had sufficient resources or expertise to complete pivotal clinical trials without a large development partner.

New entrants may disrupt the 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 CROs. 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."[16] 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 healthcare 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

15. Mass General (2022) HEALEY ALS Platform Trial. Available from: https://www.massgeneral.org/neurology/als/research/platform-trial [Accessed 15 March 2022].
16. Protas (2022) Protas launches today and announces Sanofi as its first partner. Available from: https://protas.co.uk/protas-launches-today-and-announces-sanofi-as-its-first-partner/ [Accessed 16 March 2022].

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 healthcare 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 healthcare providers, to support a 100-day strategy for vaccinating against the next emerging pandemic threat.[17]

A large part of achieving this goal depends on the ability to mobilize clinical trials at scale, or rather establishing this global network before it is required. Janet Woodcock has often spoken of the need to build a stockpile of clinical trials for pandemic preparedness, in much the same way that therapeutics are stockpiled ahead of time. There are pandemic examples where established adaptive platform trials such as the I-SPY breast cancer trial and REMAP-CAP for pneumonia could be harnessed rapidly to generate COVID-19 evidence.[18,19] Similarly, community-based clinical trial networks built in the name of pandemic preparedness can also work in reverse and benefit drug development across the therapeutic landscape.

Key Takeaways

The pandemic has shown the clinical trial ecosystem to be incredibly resilient, as any short-term disruption has been replaced by renewed R&D impetus. The transient slowdown in new trial activity has been replaced by surging activity both in COVID-19 and conventional areas of research, while there are early signs that clinical sites are able to recruit patients faster than ever owing to increased patient engagement with the trial process. Furthermore, with the growth in the industry pipeline turbocharged by the pandemic, future demand for trials is set to flourish.

Much of this response to the pandemic has been facilitated by technological and patient-centric shifts in the approach to clinical research. Initiatives that were in place prior to the pandemic have been accelerated by years,

17. CEPI (2021) Developing pandemic-busting vaccines in 100 days. Available from: https://100days.cepi.net/100-days/ [Accessed 17 March 2022].
18. Esserman L (2020) Adaptive Platform Trials: Scalable from Breast Cancer to COVID. Available from: https://rethinkingclinicaltrials.org/news/august-21-2020-adaptive-platform-trials-scalable-from-breast-cancer-to-covid-laura-esserman-md-mba/ [Accessed 17 March 2022].
19. Angus D (2020) Optimized Learning While Doing: The REMAP-CAP Adaptive Platform. Available from: https://rethinkingclinicaltrials.org/news/may-15-2020-optimized-learning-while-doing-the-remap-cap-adaptive-platform-trial-derek-angus-md-mph/ [Accessed 17 March 2022].

such as decentralized trials and digital health solutions. Patient diversity has been cast in an uncomfortable, but necessary, spotlight and new approaches to recruitment will facilitate a more inclusive approach to clinical research. Lastly, underpinning the modernization and optimism around clinical research has been buoyant valuations for the major players in the space, as investors place considerable value in these much-needed capabilities.

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. Investment in pandemic preparedness will surely focus on strengthening platform capabilities, both to the benefit of public health initiatives and research across the therapy area spectrum. 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 startups, and strengthened hospital networks boosted by government funding.

About The Author

Daniel Chancellor

Director, Thought Leadership and Consulting, Informa Pharma Intelligence

Daniel has over a decade of experience as an analyst in the biopharma industry, spanning roles in drug discovery, market analysis, competitive intelligence, and strategic consulting. He now develops and leads Informa Pharma Intelligence's Thought Leadership program, producing materials that help clients across a range of hot topics in the biopharma industry. As part of this, Daniel regularly participates in webinars, conferences, and other speaking arrangements, and he has provided expert insights across a wide range of leading industry and business publications. Prior to joining Informa, Daniel worked as a medicinal chemist at the UK biotech company Summit Therapeutics and graduated with First Class Honours in Natural Sciences from the University of Bath.

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Accurate and timely intelligence about the drug development pipeline is vital to understanding the opportunities and risks in today's biopharmaceutical marketplace—whether you are targeting an unmet medical need, investigating promising new therapies or researching drug development historical trends and treatment patterns. If you are providing contract research or other services in the pharma industry, you need to stand out. A solid understanding of your potential clients' pipelines and competition will help you leave a lasting impression.

Contact us at pharma@informa.com

United States
605 Third Avenue
Floor 20-22
New York
NY 10158
USA
+1 908 547 2200
+1 888 670 8900

United Kingdom
Blue Fin Building
110 Southwark Street
London
SE1 0SU
United Kingdom
+44 20 337 73737

Japan
21st Floor, Otemachi
Financial City North Tower
1-9-5, Otemachi
Chiyoda-ku
Tokyo
100-0004
+81 3 6273 4260

China
23rd Floor
16F Nexxus Building
41 Connaught Road
Hong Kong
China
+85 239 667 222

Australia
Level 4
24 York Street
Sydney
NSW, 2000
+61 (0)2 8705 6968