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Clinical Trials: Have We Finally Reached The New Normal?

by Heidi Chen

Pent-up trial demand during 2020 plus trial modernization strategies yields bumper performance in 2021 as research priorities revert to pre-pandemic trends.

The COVID-19 pandemic brought acute disruption to the clinical trials landscape in 2020. While there was an explosion of trials initiated in infectious disease, clinical trials in other therapeutic areas endured setbacks in enrollment and progression. With the uptake of vaccinations from late 2020 through 2021, and the rollercoasters of variants that dashed hopes of returns to normalcy, the entire health care industry is learning to coexist with COVID-19. Clinical research, however, has adapted more quickly and early signals of recovery have translated into an impressive full-year performance in 2021. Exploring the trends within clinical trials that initiated during 2021, contrasting against pre- and peri-pandemic themes, reveals whether a post-pandemic, new normal has now been established.

New Clinical Trial Starts Surpass 10k Mark

According to the industry-leading clinical trial database Trialtrove, 2021 saw more than 10,000 Phase I–III clinical trials initiated for the first time in a calendar year. This figure is 6% higher than 2020, which itself saw a surge in new clinical trial initiations, despite the pandemic disruption. However, within the 26% rise witnessed during 2020 was a 4% decline in traditional research priorities, hidden among the influx of almost 2,500 COVID-19 clinical trials, as shown in Exhibit 1. By contrast, 2021's top-line growth of 6% includes an incredible 22% resurgence of non-COVID-19 studies, as a new normal baseline of activity was established. By way of comparison, 2019 saw just 2% growth in the final pre-pandemic year, although this was unusually low compared to 12% in each of the two years prior.

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Trial initiations in 2021 largely comprised Phase I (37%) and Phase II (34%) research (see Exhibit 2). The exact balance between these earlier stages of clinical development has varied in the last three years, as 2020 saw an increase in mid-stage trials, presumably driven by repurposing efforts against COVID-19. The normal sequence was restored in 2021 with increases in Phase I and I/II activity. This recovery reflects projects and new research activities that resumed after being held back in 2020. By contrast, Phase III has held steady over the last three years, with such larger and more expensive studies being less affected by short-term pandemic effects.

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Oncology Reasserts Its Dominant Position

Oncology has consistently been the most active therapeutic area based on trial initiations over the last decade, although its lead in 2020 was threatened by activities from COVID-19 trials. Normal service was resumed in 2021, as oncology trials bounced back with 20% growth. With a combined 3,784 trials, oncology accounted for 36% of all clinical trials initiated in 2021.

Many of the other major therapy areas followed a similar trajectory, with 2020 showing either flat or slightly retreating trial counts, before growing strongly in 2021. Cardiovascular was one exception, with new trials growing relatively consistently despite the wider disruption in 2020. As expected, infectious diseases was a major outlier. With the addition of almost 2,500 clinical trials in a disease that only entered human circulation in late 2019, the wider infectious disease group saw over 300% growth in 2020. Trial counts only retreated a modest 9% in 2021, as the pandemic leaves a longer-lasting legacy for anti-infective research. It is highly likely that infectious diseases will be the second-ranked therapy area for a considerable period, as drug developers seek to improve upon current COVID-19 therapies, bolster pandemic preparedness efforts, and evaluate new technologies such as mRNA and viral vector vaccines against different pathogens.

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AstraZeneca Defends #1 Position, Jiangsu Hengrui Ascends

The top 10 list of leading trial sponsors in 2021 is largely consistent with that in 2020, with some minor shuffles in rankings and a modest increase of trial counts per company. *AstraZeneca PLC* kept its crown as the most active sponsor, while *GlaxoSmithKline Pharmaceuticals Ltd.* replaced *Sanofi* in the number 10 position. After claiming the top spot in 2019, *Bristol Myers Squibb Company* continues to fall through the ranks, which was a likely scenario after the consolidation of its portfolio with that of *Celgene Corporation*. As a result, BMS is now in eighth position and has the fewest new Phase III trials of its peers, counterbalanced by a bias towards early-stage research, which is also an indicator of its strong oncology focus.

Pfizer Inc. and *Jiangsu Hengrui Medicine Co., Ltd.* are also heavy on early-phase trials, with over half of their 2021 trials being Phase I or I/II. Pfizer has consistently placed in the top five, although Jiangsu Hengrui has extended its remarkable rise from 69 trials in 2019 to 130 trials in 2021, overtaking Pfizer into fourth place. Such a rise reflects the growing influence of Chinese biopharmaceutical companies on the global stage, and it would not be a surprise if Jiangsu Hengrui – or one of its peers – were to claim the top spot in future editions of this analysis.

Of all the companies in the 2021 top 10, *Novartis AG* has the largest share (and absolute number) of trials at Phase III. Like its peers, Novartis places a strong emphasis within oncology, although its late-stage clinical activity is diversified across a range of therapy areas, also including immunology, cardiovascular, metabolic/endocrinology, CNS and ophthalmology. Such an investment is difficult to maintain in the long-term: 2020's Phase III leader *Roche Holding AG* has pivoted strongly towards earlier-stage clinical trials with its 2021 portfolio.

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China Overtakes US As A Trial Location For The First Time

In prior years, the US and China have contended for the top two spots in terms of most new studies. For 2021, China finally reigned as the number one destination for trials, with 3,795 new clinical trials initiated in the year, compared to 3,310 in the US. 6% annual growth in new clinical trials in the US was greatly overshadowed by a remarkable 37% increase in Chinese trials, with this considerable momentum expected to create a growing gap in future years.

The major European countries of France, Germany, Italy, Spain, and the UK, alongside Canada, Japan, and Australia, constitute the rest of the top 10 locations for clinical trials initiated in 2021. This top 10 is highly consistent, with the same countries appearing in the 2019 and 2020 lists (except for a pandemic-boosted Iran replacing Italy in 2020).

Exhibit 5 additionally compares the top 10 countries by therapeutic area from 2019–2021, and shows that most of the top countries are largely consistent with prior years, with steady year-on-year growth. There is a clear and definite trend of decreased trial volumes in 2020 across most

therapeutic areas, the major exception being Infectious Disease. Trial volumes in 2021 exhibited resilient recovery, many exceeding pre-pandemic levels in countries that suffered significant setbacks with trial enrollment and delays.

Notable datapoints include 80% and 79% year-on-year increases in the numbers of CNS trials in China and the UK, respectively. The number of oncology trials in China also jumped sharply, rising 46%. Coincidentally, 46% is also the total share of all clinical trial activity for oncology in China. The top 10 locations for infectious disease trials sees the greatest deviation from the overall top 10 rankings, with India, Iran, Brazil, and Russia all featuring. Clinical trial infrastructure established in these countries during the pandemic may have a legacy to provide the foundations for these regions to become more internationally competitive across other therapeutic areas in the future.

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Are We Back To The New Normal?

Any disruption observed to the clinical trial landscape in 2020 proved to be short-lived, as 2021 saw a resilient recovery of clinical trial activity across all therapeutic areas. Not only did 2021 trials show a strong return, but we witnessed all-time high trial volumes. This is partly due to the influx of COVID-19-related clinical research, but also aided by the broader resumption of normal R&D priorities, in particular for the major oncology indications, other high-burden chronic and rare diseases, and encouragingly, new Phase I programs.

Although the main sponsors, disease priorities, and locations for trials in 2021 are generally similar to the pre-pandemic observations, there is a broader shift in progress. Namely, China is becoming a dominant force in the clinical trial landscape. More studies were initiated in China than any other country in 2021, and the leading domestic sponsor, Jiangsu Hengrui, is beginning to challenge the largest multinational pharmaceutical companies for R&D activity. Meanwhile, the established companies are continuing to coalesce around similar research priorities, with intense clinical activity in solid tumor indications.

Underpinning all of these trends is the strength of the clinical trial ecosystem. Technological advances in digital health, clinical trial decentralization, improved patient engagement, and an emphasis on diversity have allowed the industry to successfully navigate through the challenges of the pandemic and enter 2022 with considerable momentum. We can confidently conclude that – in the world of clinical trials, at least – we have reached a new normal and the lingering effects of the pandemic are behind us. The future appears brighter than ever.

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This article has been adapted from a white paper, 2021 Clinical Trials Round-Up, using Citeline's gold-standard clinical trials intelligence solution Trialtrove. To read the white paper in full, and to learn more about Trialtrove, please visit https://pharmaintelligence.informa.com/resources/product-content/2022/10/06/13/24/the-clinical-trials-landscape.