MEDIDATA | WHITE PAPER

# Insights on Clinical Trial Enrollment: Where We Are as We Head Into 2022

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# Introduction

The last two years have brought tremendous change and rapid innovation to the life sciences industry. Yet, patient enrollment persists as a critical challenge for sponsors and CROs. Currently, 80% of trials do not enroll within target enrollment timeframes and 55% of terminated trials cite low patient accrual as the main reason. [1, 2]

Since 2020, the life sciences industry faced unprecedented challenges as COVID-19 put traditional clinical trial modalities to the ultimate test. As the effects of the pandemic fluctuated, Medidata continued to monitor clinical trial developments in a series of research reports.[3] A year after our last report, we look back to assess the continued impact of the pandemic on clinical trial enrollment to help the industry navigate the dynamic landscape as we enter 2022. For the purpose of this analysis, we focus on Phase II and III studies across four therapeutic areas (TAs).

# Key Findings

- Clinical trial enrollment has recovered substantially from its low point in April 2020 during the first wave of COVID-19 cases. Across the four therapeutic areas we studied, there was a 37% decrease from the average patient enrollment per trial in December 2019, just prior to the first reported COVID-19 case. After this sharp decline, a period of recovery followed in the summer and autumn of 2020, but global clinical trial enrollment remains lower than pre-COVID-19 levels.

- Global enrollment recovery varies across TAs. Oncology trials lead enrollment recovery globally, with most countries above 80% of their pre-COVID-19 baseline. Central nervous system (CNS) and cardiovascular trials are close behind, with most countries below 75% of baseline. Immunomodulation trials lag behind in recovery, with most countries below 50% of baseline.

- These insights and the ongoing rise in COVID-19 cases due to the Omicron variant reinforce sponsors' and CROs' need to inform their operational decisions with solutions that can assess the pandemic's real-time, granular impact on trial enrollment.

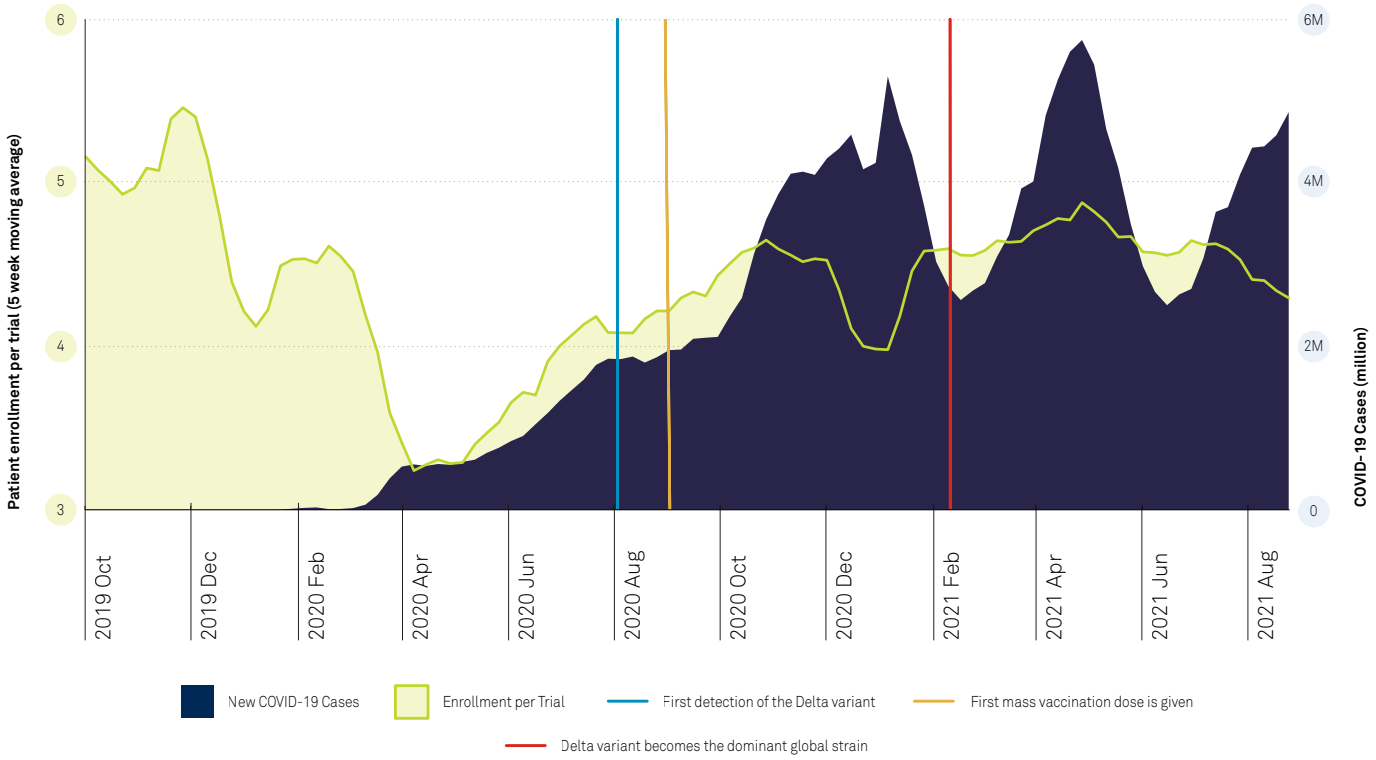
# Methodology

As Medidata continues to monitor the global impact of COVID-19 on clinical trial enrollment, we also continue to refine and improve our methodology. The convenience sample for this analysis of 504,795 patients in 2,507 studies was pulled from Medidata's proprietary real-time cross-industry dataset. Medidata Acorn AI Intelligent Trials analyzed enrollment data from Phase II and III studies in the cardiovascular, central nervous system (CNS), immunomodulation, and oncology TAs that enrolled at least one participant between January 1, 2018 and August 29, 2021.

For this analysis, patient enrollment per trial is defined as the 5-week moving average of the number of participants enrolled within a week in a country and TA, divided by the number of enrolling trials within that country and TA. Baseline is defined as the 5-week centered moving average of patient enrollment per trial between 2018-2019. For example, the baseline for the week of June 1, 2020 is the average patient enrollment per trial between May 18th and June 15th from 2018-2019.

# Global Enrollment Trends During the COVID-19 Pandemic

**Figure 1: Global trend in enrollment per trial and new COVID-19 cases**




Despite multiple global waves of COVID-19 cases and the emergence of the Delta variant, clinical trial enrollment has recovered substantially from its low point in April 2020, as the first wave of COVID-19 cases soared globally. Across the four therapeutic areas we studied, there was a 37% decrease from the average patient enrollment per trial in December 2019, just prior to the first reported COVID-19 case. As of August 2021, global clinical trial enrollment had not yet returned to pre-COVID-19 levels.

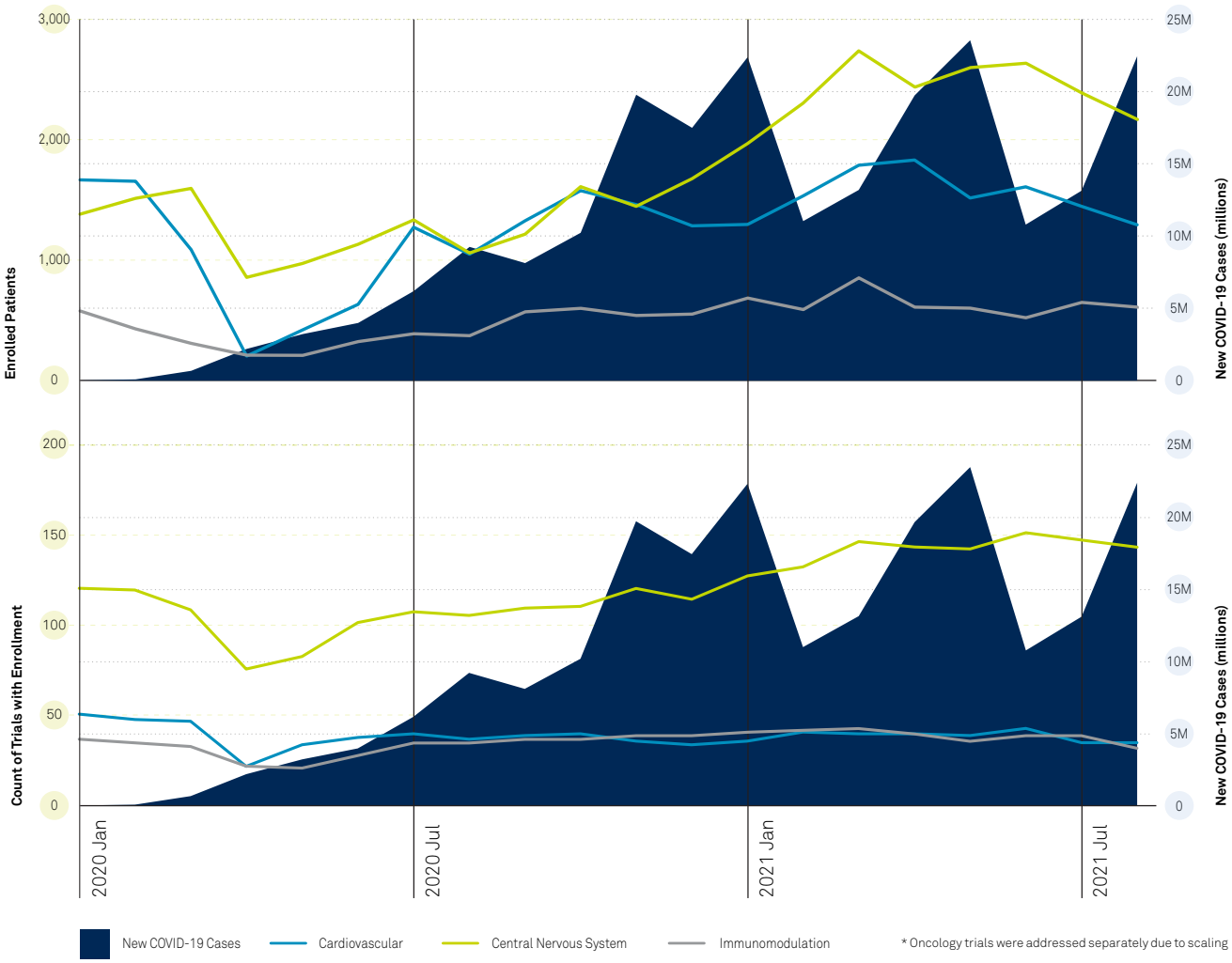
After the sharp decline in patient enrollment per trial from the start of the pandemic, a period of recovery followed in the summer and autumn of 2020. The wave of exponential growth in COVID-19 cases in October-November of 2020 coincided with a decline in clinical trial enrollment, leading to the expected seasonal decrease in trial enrollment in the weeks around the 2020 end-of-year holidays. By February 2021 case counts had fallen substantially and patient enrollment per trial returned to the level seen in October 2020. Enrollment was steady through the next wave of cases during March-April 2021. Even as the Delta variant became the dominant global COVID-19 strain during the July-August wave in cases, enrollment has not precipitously declined as compared to the start of the pandemic.[4]

These findings suggest that sponsors and CROs have adapted to post-COVID circumstances and that patients are willing and able to enroll in clinical trials again. Furthermore, the impact of later COVID-19 waves on clinical trial enrollment may be blunted by the distribution of COVID-19 vaccines. The first mass vaccination program began in the United Kingdom in December 2020. As of October 2021, almost half of the global population received at least a single dose.[5]

# Enrollment Trends Broken Down by Therapeutic Area

Figure 2: Global trends in patient enrollment by therapeutic area

Figure 3: Global trends in enrolling trial counts by therapeutic area



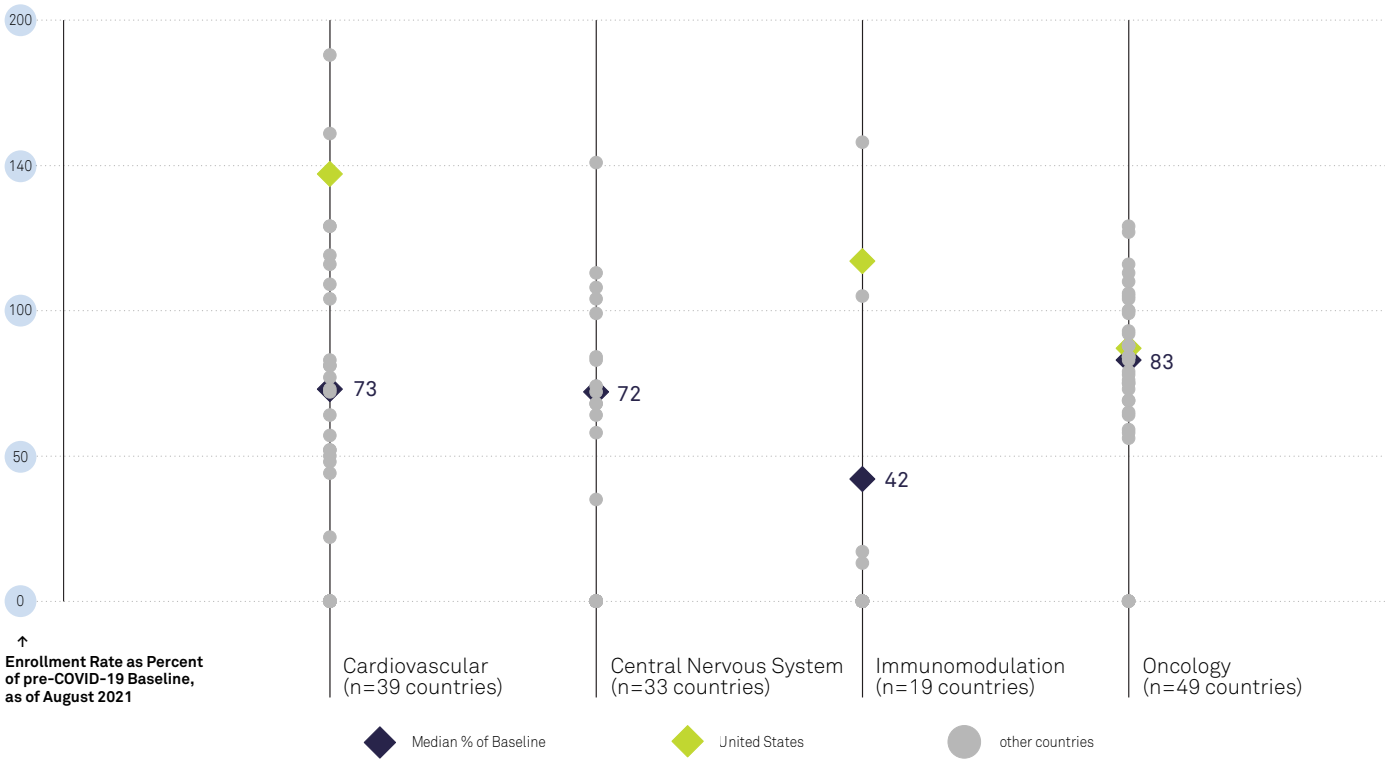

Enrollment trends for both total enrollment and the count of enrolling trials show that the first wave of COVID-19 cases had a differential impact among individual TAs. As of August 2021, recovery in enrollment also varies by TA.

**CNS trials** reached their lowest levels for both patient enrollment and trial counts in April 2020. Since then, both figures have been steadily trending upward, with enrollment surpassing levels since January 2020.

**Cardiovascular trials** also reached their lowest levels for both patient enrollment and trial counts in April 2020. After a brief recovery in July, the count of enrolling cardiovascular trials trended downwards in the second half of 2020 and beyond. Total enrollment has trended downward since April 2021.

**Immunomodulation trials** reached their lowest levels in May 2020, and exhibit a shallower recovery than CNS and cardiovascular trials.

**Figure 4: Enrollment recovery among countries as percent of baseline by therapeutic area**



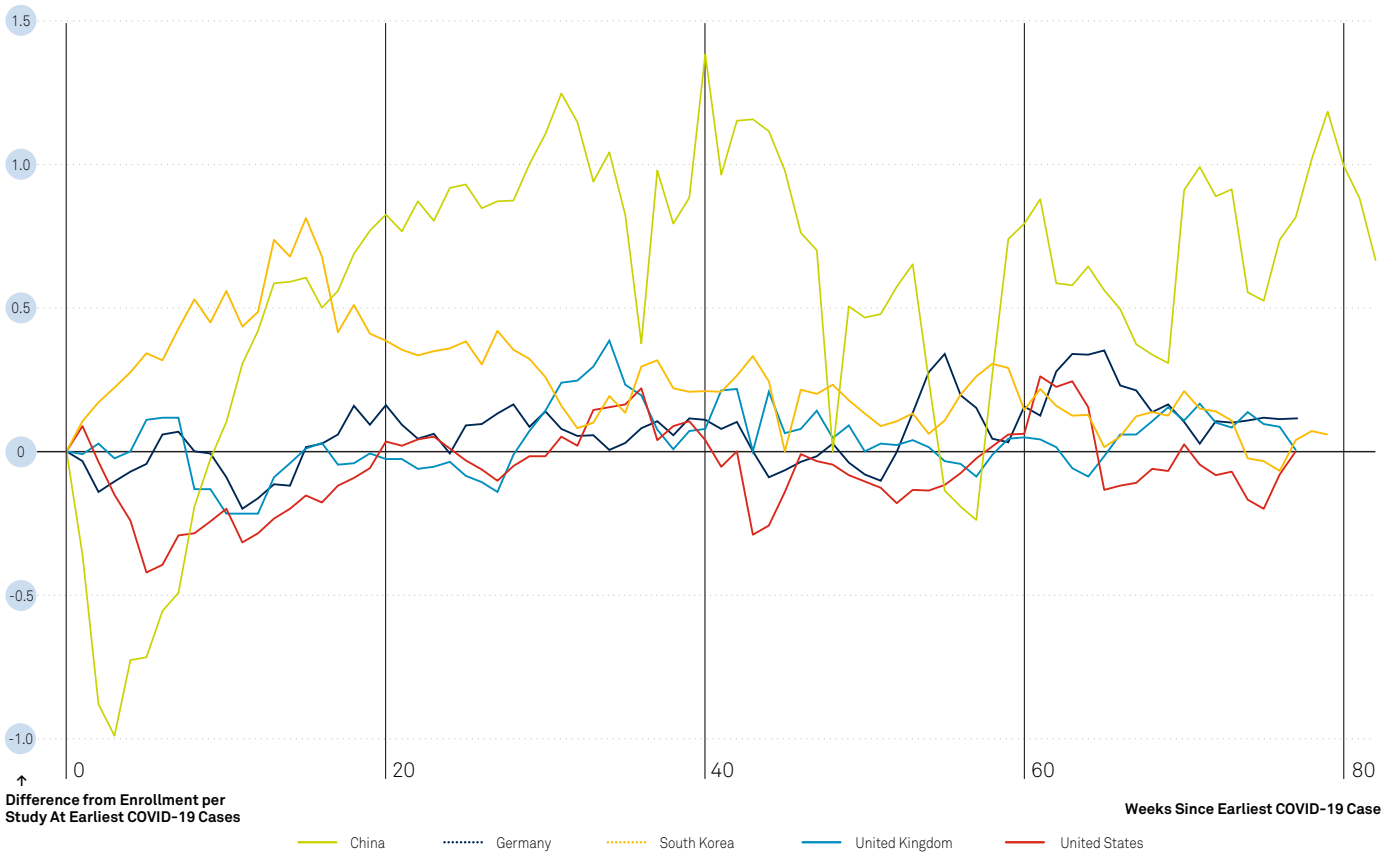

We also continue to see stark differences in recovery across the globe. To assess recent clinical trial performance, we compared current enrollment rates to each country's baseline historical performance. This baseline is a seasonally adjusted average of recorded enrollment rates during the pre-COVID-19 era.

Oncology trials lead global enrollment recovery, with the median country patient enrollment performance at 83% of pre-COVID-19 baseline. The percent of baseline is also tightly grouped across countries, showing that most countries running oncology trials are returning to their pre-COVID-19 enrollment rates.

CNS and cardiovascular trials are not far behind. Several countries are leading in recovery with enrollment rates above 100% of baseline, whereas the median percentage is just below 75%. Both TAs show a large difference in percent of baseline between leading and lagging countries, meaning that CNS and cardiovascular trial enrollment is heavily influenced by country selection.

Immunomodulation trials are lagging behind other TAs in recovery, with the median country patient enrollment performance at only 42% of baseline. However, some countries, like the United States, strongly lead within immunomodulation trials and are above their historical baseline rate. As noted in Figures 2 and 3, the nadir in enrollment for immunomodulation was a month after the other TAs. This differential impact on enrollment for immunomodulation trials may be due to the risk of contracting COVID-19. Exposure to COVID-19 has a known association with cytokine response, which may cause patients to refrain from enrolling in trials.[6,7]

**Figure 5: Recovery curves for oncology as difference from enrollment per study at earliest COVID-19 cases**




If we dive further into geographic performance over time, we find that clusters of countries generally follow two distinct paths of recovery. The trends for China, the United States, the United Kingdom, and Germany are emblematic of these paths. In our analysis, we chose to focus on oncology trials, as these exhibited the strongest recovery amongst the TAs assessed.

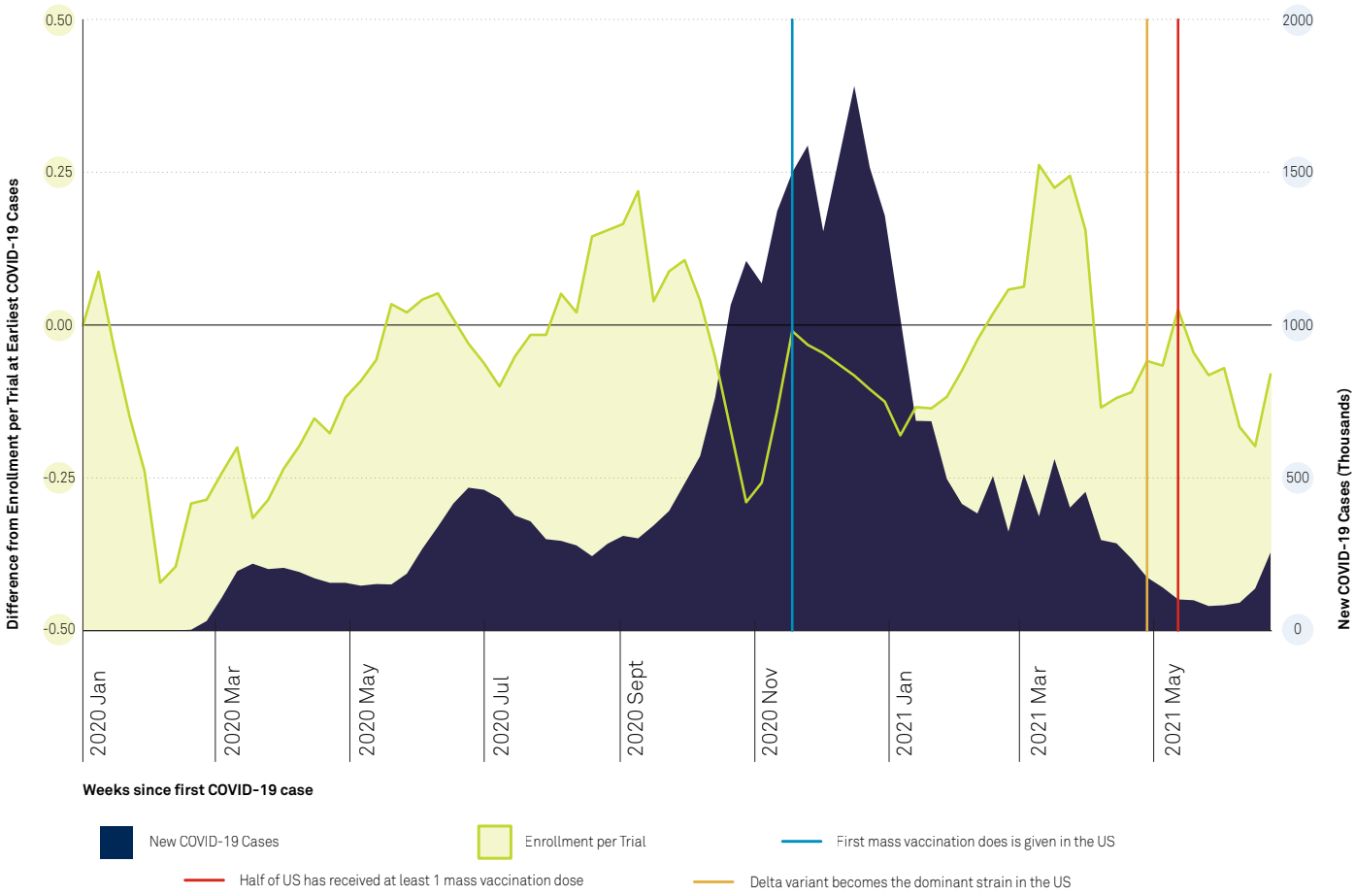
To assess the impact of COVID-19 over time, we created a country-level view of weekly oncology enrollment rates. For each country, we compared the enrollment rate at the earliest COVID-19 cases with rates in the subsequent weeks.[8]

China had a steep initial decline and a subsequent rapid recovery outpacing pre-COVID-19 levels. According to COVID-19 case and death rates, China contained the pandemic more successfully than other countries. Their subsequent high performance may indicate some shifts in site selection from sponsors and CROs. Some countries with similar recovery curves included Israel, Japan, and Portugal.

The United States, United Kingdom, and Germany showed an early decrease followed by a shallow recovery, bringing the enrollment rate to a level similar to the week of the earliest COVID-19 cases. Some countries with similar recovery curves included France, Italy, and Turkey.

In contrast with the two paths above, South Korea showed no observable adverse impact of COVID-19 for the oncology TA.[9]

**Figure 6: US oncology recovery curve as difference from enrollment per trial at earliest COVID-19 cases**




A deeper look at oncology patient enrollment performance in the US reveals the dynamic nature of enrollment during the pandemic and the distinctness of country-level trends. To observe this, we overlaid oncology trial enrollment, COVID-19 cases, and milestone events in the United States. The surge in COVID-19 cases starting October 2020 coincided with a steep decline in enrollment, in part due to the seasonal US holiday, which was not seen globally. However, the start of vaccinations in December 2020 and the decline in cases were accompanied by a peak in enrollment rates in April 2021. As Delta became the dominant strain in the US in June 2021, enrollment began to decline again.

# Summary

After multiple waves of new cases, the emergence of variants, and the rollout of mass vaccination campaigns, the COVID-19 pandemic continues to negatively affect clinical trial enrollment. The impact on enrollment rates varies across TAs and geographies, with some leading in recovery toward pre-pandemic levels, while others lag behind.

These insights, and the ongoing rise in COVID-19 cases due to the Omicron variant, reinforce the need to inform clinical trial operational decisions with an understanding of the pandemic's real-time, granular impact on trial enrollment.

As the clinical trial landscape grows more complex, past success and practices are no longer sufficient predictors of future success. Medidata Acorn AI Intelligent Trials uses AI-enabled technology and advanced analytics based on real-time performance data to help sponsors and CROs meet the challenges of this ever-changing landscape. Our clinical trial analytics solution brings together cross-industry real-time performance metrics, predictive models, and forecasting capabilities to give companies a competitive edge in trial planning and execution.

# Footnotes

1. Clinical trial delays: America's patient recruitment dilemma. Clinical Trials Arena (2012).
2. Desai, M. Recruitment and retention of participants in clinical studies: Critical issues and challenges. Perspectives in clinical research (2020). Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7342339/.
3. COVID-19 and Clinical Trials: The Medidata Perspective Release 8.0. (2020).
4. Shu Y, McCauley J. (2017) GISAID: Global initiative on sharing all influenza data – from vision to reality. EuroSurveillance, 22(13) DOI:10.2807/1560-7917.ES.2017.22.13.30494 PMCID: PMC5388101
5. Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. Nat Hum Behav (2021). https://doi.org/10.1038/s41562-021-01122-8. Data provided subject to the Creative Commons Attribution CC BY standard.
6. Fajgenbaum DC, June CH. Cytokine Storm. N Engl J Med. 2020;383(23):2255-2273. doi:10.1056/NEJMra2026131
7. Excludes countries without clinical trial enrollment in August 2021.
8. The first week when 0.5 new COVID-19 cases per 100,000 population is reached.
9. Only data points that pass Medidata's data sharing rules are shown. Weeks where the metric cannot be shown are replaced with an interpolated line.

## DATA SOURCES

1. Source for COVID-19 cases: European Centre for Disease Prevention and Control. Data provided subject to license available at: https://www.ecdc.europa.eu/en/copyright
2. Source for population data: The World Bank. Data provided subject to the Creative Commons Attribution CC BY standard.
3. Source for Delta variant: Shu Y, McCauley J. (2017) GISAID: Global initiative on sharing all influenza data – from vision to reality. EuroSurveillance, 22(13) DOI:10.2807/1560-7917.ES.2017.22.13.30494 PMCID: PMC5388101. Data provided subject to the Creative Commons Attribution CC BY standard.
4. Source for vaccinations: Mathieu E, Ritchie H, Ortiz-Ospina E, et al. A global database of COVID-19 vaccinations. Nat Hum Behav (2021). https://doi.org/10.1038/s41562-021-01122-8. Data provided subject to the Creative Commons Attribution CC BY standard.