LUNGEVITY

The Distribution of Non-Small Cell Lung Cancer Early Phase Clinical Trial Sites Within and Outside the United States

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EXECUTIVE SUMMARY

Background:
Recent regulatory guidance on bringing clinical trials into routine care and decentralization highlights the US FDA's charge for the applicability of trial data to real-world US patients. However, recent Oncologic Drugs Advisory Committee meetings reveal that insufficient enrollment of US patients remains an issue. Trial site saturation has been noted as a factor pushing trials ex-US.

Methods:
To contextualize recent trends, we assessed the distribution of early phase trial sites within and outside of the US over time. This descriptive assessment utilized ClinicalTrials.gov data to analyze interventional, industry-sponsored phase I trials for non-small cell lung cancer opening in January 2020-December 2024.

Results:
Overall, 555 trials opened within the study period for a total of 8,515 trial instances across all sites in 47 countries. Trials were largely located in the US (45%), China (11%), Spain (8%), Korea (5%), France (4%), and Australia (4%). While the number of trials initiated started decreasing in 2023, the number of unique trial sites and trial instances, both globally and within the US, started decreasing in 2022 and continued to decrease through 2024. Notably, the number of US sites with at least one trial opening markedly decreased during the study period (395 sites in 2020 to 223 sites in 2024). However, the sites with the highest trial volume did not see these decreases.

Conclusions:
This analysis shows a concerning trend towards trial consolidation at top performing sites in the US, further supporting concerns about site saturation and conflicting with appeals to decentralize and move trials into the community.

INTRODUCTION

Several recent publications have demonstrated the disparity between clinical trial populations and the real-world patient populations receiving the therapies after approval[1,2,3,4]. These disparities include underrepresentation of certain genders, races, ethnicities, rural populations, and other demographic factors. It is imperative that clinical trial populations reflect as closely as possible the end-user population to sufficiently determine a therapy's safety and efficacy and inform its optimal use. In response to this concern, there has been a concerted effort from United States (US) federal agencies to encourage US representativeness in clinical trials. Implementing functional efficiencies in clinical trials through pragmatic elements to lessen participant burden[5,6], adding decentralized elements to allow data collection to occur at locations more convenient for participants[7], and integrating streamlined trials into routine clinical practice to improve participant accessibility[8] have all been encouraged by the US Food and Drug Administration (FDA) as opportunities to increase access to trials and therefore facilitate enrollment of more representative patient populations and therefore more generalizable and applicable trial results.

Despite this increased attention to support US representation in clinical trials, recent FDA Oncology Drug Advisory Committee (ODAC) discussions[9,10] have emphasized trials' insufficient enrollment of US patients and underrepresentation of certain populations. The May 20-21, 2025 ODAC meeting highlighted the dearth of US patient data in a multi-regional clinical trial (MRCT) and the need to enroll representative populations to ensure the applicability of trial results to US patients. The July 17, 2025 ODAC meeting raised concerns on the low percentage of US patients (less than 5%) enrolled in the two registrational trials, and that older adults and Black/African American patients were underrepresented in the trial populations compared to the real-world affected population in the US. The high proportion of ex-US patients was also problematic according to the Agency, given the chosen control arm, as there was uncertain applicability and US relevance of the trial results as the comparator arm regimens were not used as standard of care in the US in the indicated population. Clinical trials are conducted outside of the US for a multitude of financial, temporal, and operational reasons. Among these, trial saturation and overburdening of existing US sites, compounded with the burden and time to activation of new US sites, has been cited as a factor pushing trials outside of the US[11,12,13].

To understand the broader oncology clinical trial site landscape outside of the examples highlighted by recent ODAC meetings, we assessed the distribution and frequency of early phase non-small cell lung cancer (NSCLC) clinical trial sites being opened within and outside of the US. Focusing on NSCLC provided an ideal use case given the large prevalence of NSCLC and high clinical trial volume in the patient population, allowing for evaluation of trends over time. Each trial phase has differences in regulatory goals and conduct, and we focused on only early phase trials, given their foundational evidentiary role for later trial conduct, to further narrow scope. This descriptive analysis provides the first quantitative assessment, to our knowledge, of oncology clinical trial site distribution to support the ongoing dialogue on clinical trial representation.

APPROACH

Study Design and Data Source

We conducted a retrospective analysis of interventional, industry-sponsored early phase NSCLC clinical trials registered on ClinicalTrials.gov and opening between January 1, 2020 to December 31, 2024. ClinicalTrials.gov, the publicly available online database of clinical research studies maintained by the National Library of Medicine, was chosen as it is currently the most comprehensive, publicly available source for information on clinical trials. Trials were included if they met the following criteria through query of ClinicalTrials.gov: (1) condition or disease specified as NSCLC; (2) study phase designated as Early Phase I or Phase I; (3) study type classified as interventional; (4) primary funding source identified as industry; and (5) study start date falling within the defined study period.

Data Collection and Processing

Trial data were extracted from ClinicalTrials.gov and subjected to a multi-step cleaning and standardization process. Each trial was individually reviewed, and trials were excluded if they represented individual-sponsored studies, Veterans Affairs (VA) system trials, or hospital system-initiated studies without industry sponsorship. Additionally, trials reporting no site locations or generic locations (e.g., "Research Site") were excluded from the analysis. All trial locations were parsed into standardized components including facility name, city, state or province, postal code (as applicable), and country.

Descriptive Statistical Analyses

Trials were aggregated by year the study started within the analysis period (2020-2024) to assess temporal site trends. The analysis examined the number of unique clinical trials opening within the study period, as well as the location of sites for these clinical trials, stratified by year. A unique clinical trial was defined by a unique NCT number listed in ClinicalTrials.gov, and the date opened was defined by the study start date. A unique site was defined as a single location where at least one clinical trial was conducted within the study period. Lastly, trial instance was used to signify the opening of a unique trial at a unique site. For each unique site, the total number of trial instances were calculated.

The geographic distribution of trial sites was analyzed by country, with the calculation of the proportion of trial instances occurring in each country. Within the United States, state-level frequencies were calculated, including the number of unique sites per state and changes over time.

For the analysis of top-performing sites, facilities were ranked by total trial instances during the study period, and the top 20 sites were identified as "top-performing". Average and median trial instances per year were calculated for the top 20 sites. Additionally, sites were stratified into low, medium, and high instance categories based on their overall trial instance volume across the study period to assess temporal trends.

A comprehensive list of NCI-designated cancer centers was obtained from the National Cancer Institute's official directory[14]. NCI Community Oncology Research Program (NCORP) sites were identified from the NCORP directory[15]. The lists were used to identify trial sites that were NCI-designated cancer centers or NCORP sites and to assess trial instance volume over time.

MAJOR FINDINGS

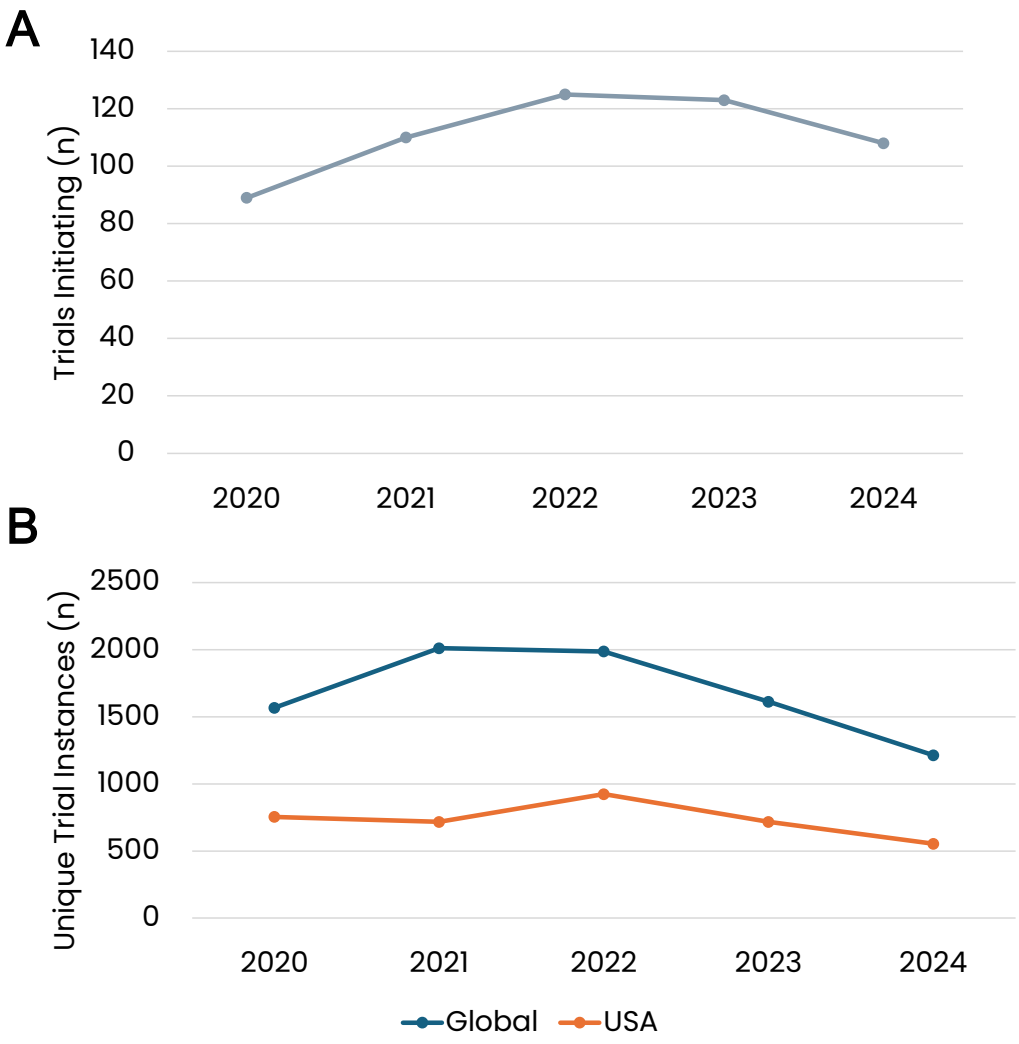
Analysis Sample Set

In the study period of January 1, 2020 to December 31, 2024, a total of 555 industry-sponsored, early phase I interventional trials for patients with NSCLC opened, based on the records from ClinicalTrials.gov. The annual number of early phase trials initiating increased from 2020 to 2023, decreasing in volume after until 2024 (Figure 1A). These 555 trials accounted for a total of 8,515 trial instances across all sites.

Global Trial Instances

Trials were initiated at sites across 47 countries. Analysis of the trial instance distribution revealed substantial geographic concentration, with the US accounting for 44.8% of all trial instances during the study period. This was followed by China (10.7%), Spain (7.8%), Korea (4.8%), France (4.5%), and Australia (4.0%). The remaining 23.4% of trial instances were distributed across other countries.

Figure 1: Temporal Trends in Initiating Early-Phase Interventional NSCLC Trials and Trial Instances across Sites.



(A) Changes in the number of unique clinical trials opening annually and (B) Changes in the number of unique trial instances for these clinical trials over time, both US-only and globally.

The number of trial instances, a measure taking into account the number of unique trial sites in which the trials were opening, decreased from 2022 through 2024, both globally and in the United States **(Figure 1B)**. The rate of this decline in trial instances in the US was half that of the decline observed globally (slope of -185 and -386.5, respectively). Of the top six countries by trial instances, only Australia saw increases in trials over time **(Table 1)**.

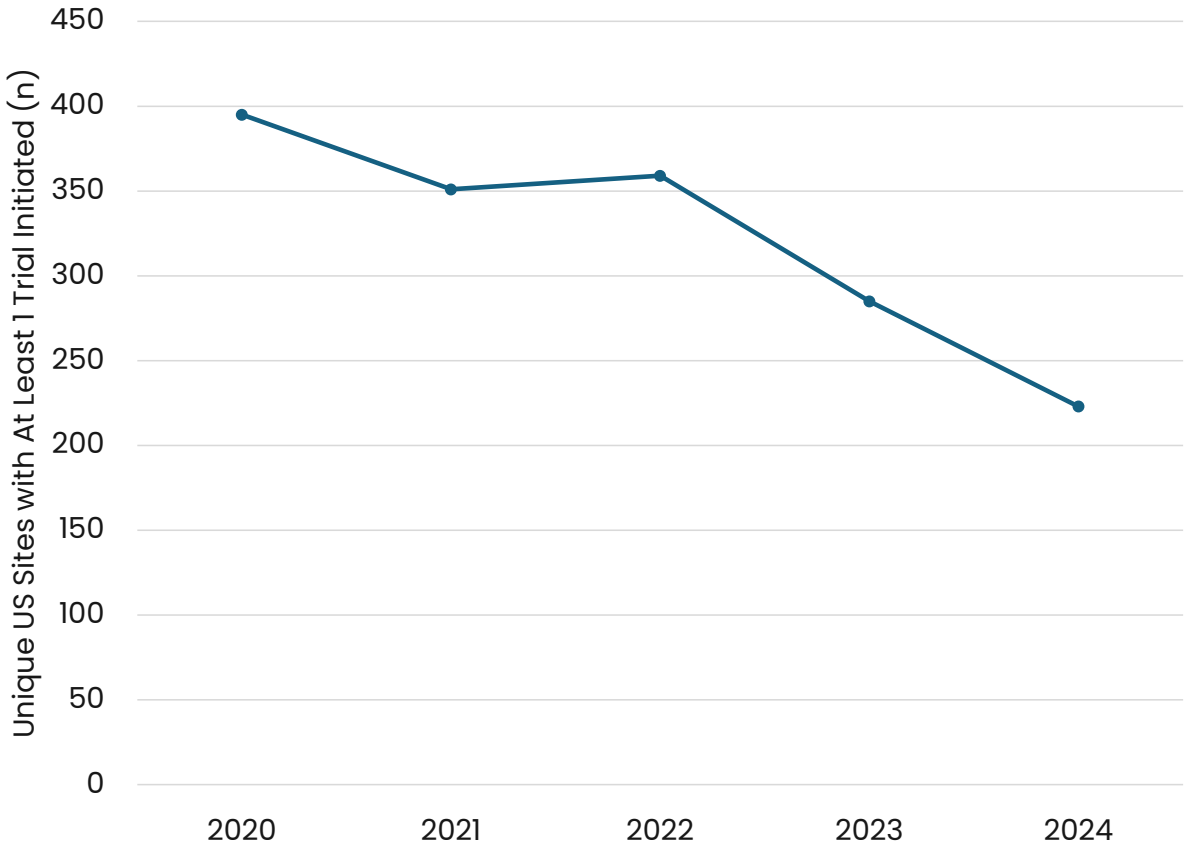
Table 1: Trial Instance Distribution Across Top Countries Over Time.

	2020	2021	2022	2023	2024
US	819	738	955	736	566
China	196	222	267	133	95
Spain	105	170	153	152	80
Korea	80	124	61	76	66
France	48	111	82	93	47
Australia	64	59	64	75	76

Distribution of US Trial Sites

We further evaluated the number of unique US sites participating in early phase NSCLC trials **(Figure 2)**. The total number of unique US sites initiating an early phase trial was 854. The count of unique US sites with at least one trial initiating decreased from 395 sites in 2020 to 223 sites in 2024, a 43.5% reduction in sites initiating early phase clinical trials and a resulting 172 fewer sites at the end of the study period than the start. Notably, 39 out of 50 (78%) states had fewer unique sites where trials were initiating in 2024 compared to any other year in the study period, highlighting a loss of new clinical trial opportunities.

Figure 2: Decreases in US Sites Initiating Early-Phase NSCLC Trials Over Time.

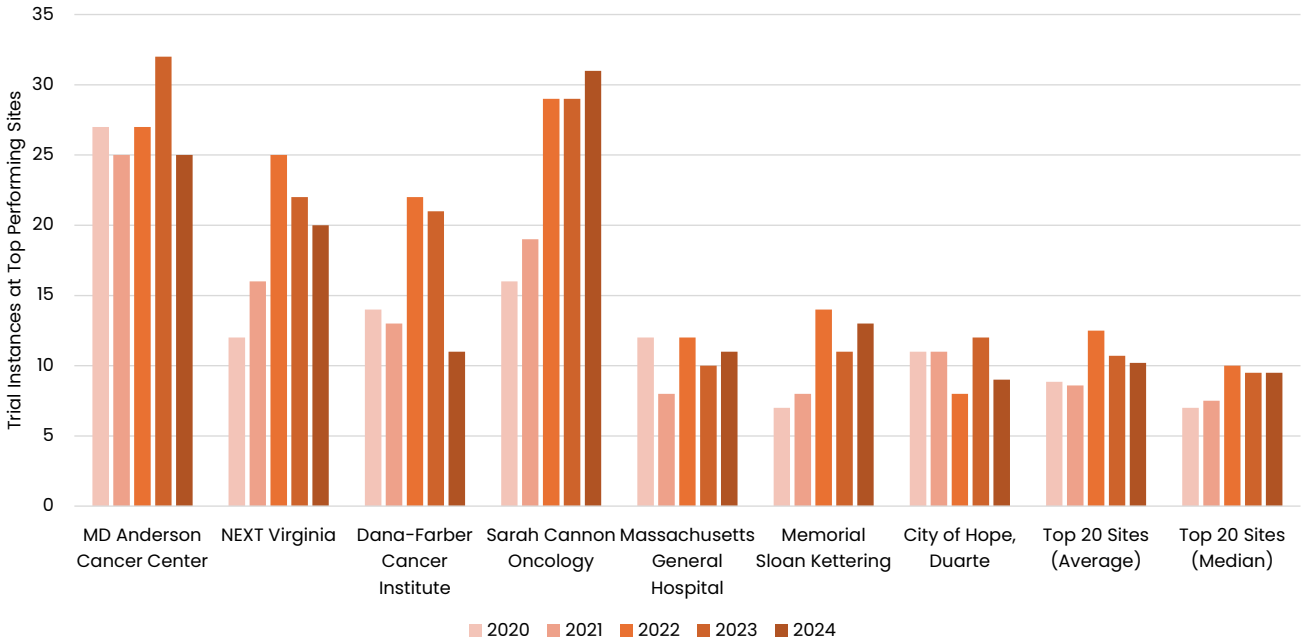


Within the study period (2020-2024), the number of US sites initiating a clinical trial within the year decreased.

Associations with Site Trial Volume

However, these trends were not consistently seen across all US sites, but varied according to site capacity. The top 20 performing sites, determined by initiating trial volume, all had at least 27 trial instances during the study period. The average and median annual trial instances at these top 20 sites did not show major decreases over time **(Figure 3)**, with a median between 7 and 9.5 trials initiating annually over the study period. The highest volume site was MD Anderson Cancer Center, with 25 or more early-phase trials initiated every year.

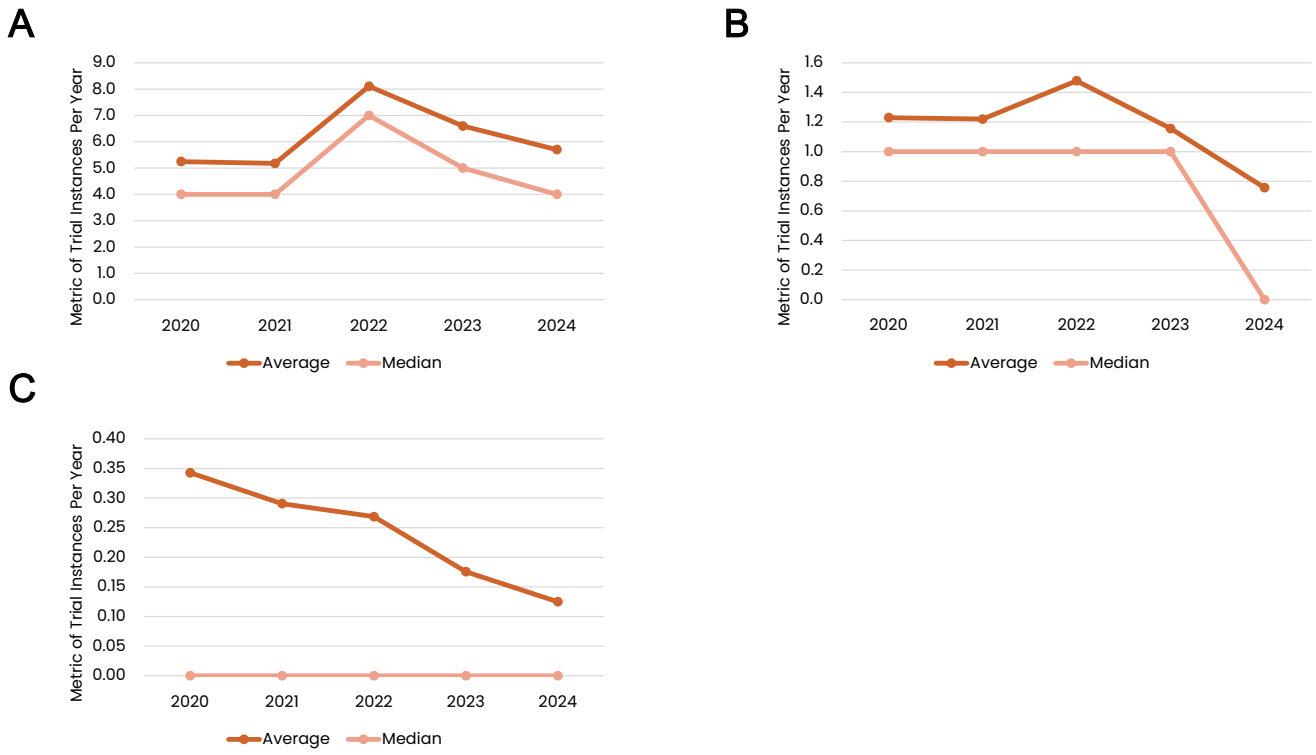
Figure 3: Trial Instances at Top Performing Clinical Trial Sites by Year.



The top seven trial sites, based on total trials initiated at the site during the study period, with trial instances over time, as well as the median and average trial instances for the top 20 performing sites.

All US sites were further stratified into low, medium, and high trial instance volume categories based on their overall trial instance volume in the entire study period **(Figure 4)**. Medium instance sites had a median of 1 trial (average slightly above 1) initiating at their site per year each year in the study period until a drop to a median of 0 (average of 0.8) in 2024 **(Figure 4B)**. Alternatively, the high-volume sites started in 2020 with a median of 4 trials (average of 5.2 trials) initiating annually that never dropped lower in the study period **(Figure 4A)**. The low volume sites, however, maintained a medium of zero trials initiated annually, highlighting that these sites did not regularly participate in trials, with the average trial instance steadily decreasing over time **(Figure 4C)**.

Figure 4: Associations of Changes in Trial Instances Over Time with Trial Site Volume.

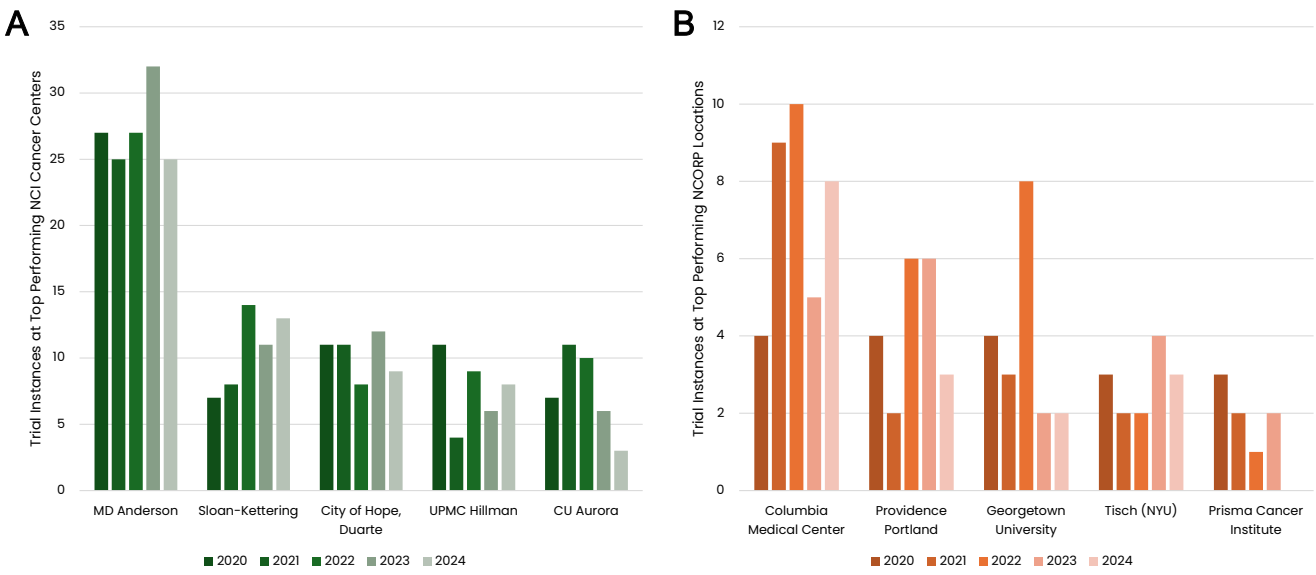


The median and average number of trial instances per year across US sites stratified by (A) the high volume sites, (B) the middle volume sites, and (C) the low volume sites over the study period.

Associations with NCI Resourcing

Among the 854 total US sites analyzed, 51 were NCI-designated cancer centers that collectively initiated 703 trials. Alternatively, 42 sites were NCORP sites, opening 164 trials at their locations. Although the number of sites was relatively the same between NCI-designated cancer centers and NCORP sites, unsurprisingly the NCI-designated cancer centers conducted significantly more trials, included many of the top performing sites, and continued with initiating trials throughout the study period **(Figure 5A)**. Interestingly, NCORP sites demonstrated relative stability in trial instances over time compared to other lower-capacity sites, as seen in the top five performing NCORP sites **(Figure 5B)**.

Figure 5: Trial Instances at Top Performing NCI-Designated Cancer Centers and NCORP Sites by Year.



The total number of trials initiated each year at the top five (by total trial volume) sites for (A) NCI-designated cancer centers and (B) NCORP sites.

CONCLUSIONS AND IMPLICATIONS

Our analysis of early phase, industry-sponsored interventional NSCLC trial site distribution from 2020 to 2024 reveals a concerning pattern of consolidation that may have significant implications for clinical trial representativeness and generalizability. The number of unique US sites participating in these trials declined precipitously, with high-capacity sites and those supported by NCI infrastructure maintaining or expanding activity while smaller volume sites experienced a decline in trials initiating. This consolidation to a smaller number of institutions creates a geographically concentrated clinical trial landscape that may result in more limited access to clinical trials for patients who cannot travel to these centers. These overall results run counter to federal efforts to enhance trial accessibility and representativeness in the US.

This work provides additional quantitative context to support some of the concerns raised at the recent FDA ODAC meetings regarding the representativeness of oncology clinical trial populations to the US population. While we found that the US still has the largest volume of trials initiating, the loss of US trial sites over time will only exacerbate the issue. The NCORP sites, while smaller volume sites, maintained relative stability in opening trials over time, suggesting that the infrastructure support and integration into research networks may be able to buffer these community sites against the forces driving consolidation.

This analysis has several limitations. Our focus on industry-sponsored early phase NSCLC trials, while providing a well-defined cohort, may not fully represent patterns in investigator-initiated and/or late-phase trials. Later phase (e.g., phase III) trials, in which the safety and efficacy profile profile of the investigational agent has become more established due to earlier phase trials, may allow for broader participation by less experienced sites, compared to early phase trials in which

less-experienced, lower volume sites may be less sought after due to potential unforeseen safety events. Therefore, a study of phase III trends in site distribution would be of interest to compare to our findings. Additionally, this analysis only examined trial instances, rather than patient enrollment numbers, as enrollment volume at each site is not publicly available. However, while a site may have a trial open, this does not mean enrollment occurs at the site, and therefore the number of actively enrolling sites is likely even smaller than seen herein. Therefore, future analyses examining enrollment trends across sites would provide valuable complementary insights.

Despite these limitations, our findings document a clear trend toward consolidation of early phase oncology trials. Several factors likely contribute to the observed consolidation. The increasing complexity of trial protocols and the novelty of new oncology modalities with accompanying safety profiles create substantial infrastructure and expertise requirements that may be prohibitive for smaller sites. Additionally, regulatory and compliance burdens associated with trial activation and conduct have increased. The competitive oncology landscape for trial enrollment may favor established sites with proven track records, creating a self-reinforcing cycle where high-performing sites attract more trials, develop greater expertise, and become increasingly preferred by sponsors—while lower-volume sites struggle to maintain the infrastructure and expertise needed to compete for trials. Addressing this consolidation and ensuring identification of the appropriate sites for clinical research will require coordinated efforts to reduce site activation barriers, provide infrastructure support, and potentially implement policy incentives that encourage diversification of trial portfolios within the US. Additional discussions with policymakers, regulatory agencies, drug developers, investigators and site staff, and patient advocates are needed to understand the complexity of the driving factors for these trends. With such efforts, trial populations may better reflect real-world populations to support the generalizability and representativeness of clinical trial results.

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