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# Adult neuro-oncology trials in the United States over 5 decades: Analysis of trials completion rate to guide the path forward

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**Abstract**

**Background**. Clinical trials are important to close the gap between therapeutic unmet needs and scientific advances in neuro-oncology. This study analyzes the landscape of neuro-oncology trials to identify completion rates and guide strategies for the path forward.

**Methods**. US-registered adult neuro-oncology clinical trials were extracted from www.clinicaltrials.gov (1966–2019), including funding source, trial type, scope, phase, and subjects' demographics. Completed trials defined as those that had completed participants' examinations or intervention administration for the purpose of the final collection of data for the primary outcome were dichotomized against those that failed to reach completion. Univariate and multivariate analyses were used to detect differences across factors comparing the last 2 decades (2000–2009, 2010–2019).

**Results**. Our search yielded 4522 trials, of which 1257 are eligible for this study. In 25 US states, neuro-oncology trial availability is <0.85/100,000 population. Comparing the past 2 decades, trial completion rate decreased from 88% to 64% ($P < .001$) and National Institutes of Health funding decreased from 47% to 24% ($P < .001$). Inclusion of subjects >65-year-old and women increased, while inclusion of Hispanic subjects decreased ($P < .001$). The top 2 reasons for lack of completion included accrual and operational difficulties. A larger proportion of women, non-Hispanic subjects, and older adults were enrolled in completed trials than in those that failed completion.

**Conclusions**. Our study is the first report on the neuro-oncology clinical trial landscape in the United States and supports the development of strategies to further improve access to these trials. Additionally, attention is needed to identify and modify other factors contributing to lack of completion.

## Key Points

- Neuro-oncology clinical trial completion rates have significantly decreased over the past 2 decades, from 78% to 64%.
- Fifty percent of the US population affected by neuro-oncology diseases have limited access to neuro-oncology trials.

## Importance of the Study

Our study is the first report on the overall neuro-oncology clinical trial landscape in the United States. Our study has found that the completion rate of neuro-oncology trials has significantly decreased over the past 2 decades from 78% to 64%. Examining clinical trial locations and population densities, our study also found that 50% of the US population affected by neuro-oncology diseases have limited access to trials. With increasing costs and decreasing completion rates of these trials, it is important that future trials are appropriately designed and accessible. As new trials are designed, attention is also needed to identify and modify other factors contributing to lack of completion.

Primary and secondary malignancies of the central nervous system (CNS) have significantly increased in the United States over the past 2 decades. Currently, primary CNS tumors occur in 25/100,000 population totaling 445,792 incident tumors, of which one-third are malignant.[1] As a result of better control of primary cancer and increased population longevity, the incidence of secondary or metastatic CNS tumors are also significantly increased. Metastatic CNS tumors occur in 10–40% of patients with primary cancers with a reported incidence of 10-fold that of primary malignant brain tumors.[2,3]

Glioblastoma (GBM), the most common malignant brain tumor, has an incidence of 3.4/100,000 population.[4] Patients with GBM have a median survival of 14–16 months with a 5-year survival of 7%.[5,6] The median survival for patients with metastatic brain disease ranges from 7 to 36 months, depending on the primary malignancy.[7] The therapeutic challenge and unmet needs for CNS tumors reside in their complex biology and molecular signature. In neuro-oncology, there are significant biological and clinical challenges inherent to the disease itself. For systemic therapy, the blood–brain barrier significantly affects CNS drug efficacy in both preclinical and clinical studies.[8] Clinical trials have the potential to close the gap between unmet needs and future clinical developments.

Clinical trials have played a significant role in medicine, since 1537 when Ambroise Paré conducted an unintentional trial testing a new therapy for battlefield wounds, which is now commonly noted as the first clinical trial in the history of a novel treatment.[9] In 1946, the first randomized controlled trial testing streptomycin was performed in the United Kingdom, and this trial design eventually became the standard in clinical research.[9] As the number of clinical trials increased, governments began establishing regulatory and ethical standards.[9] In 1997, the US government passed the Food and Drug Administration (FDA) Modernization Act, which established a publicly available resource (clinicaltrials.gov) with information on trials regulated by the FDA.[10] The demand for new therapeutic options drives the design of new trials focused on CNS tumors. The cost of clinical research is not insignificant. The average cost for each completed trial is estimated at $41,117 per patient and $53.1 million per study.[11] It is greater than $125,000 per patient for phase III trials.[12] Several studies have highlighted the need to improve study design to optimize the positive therapeutic success of phase III trials.[13] However, up-to-date data on trial completion rate, independent of therapeutic success, is scarce. As healthcare spending in the United States continues to rise, reaching $4.3 trillion in 2021, or $12,914 per capita, granular data on aspects linked to high cost are desirable.[14] This in turn has the potential to offer a deeper understanding of how to formulate new strategies for the path forward. The aim of this study is to analyze the completion rate of adult neuro-oncology trials in the United States to help highlight opportunities for improvement. As spoken by John Wooden, UCLA basketball coach: "*Failure isn't fatal, but failure to change might be.*"[15]

## Methods

### Data Extraction and Data Mining

The ClinicalTrials.gov database was searched on March 20, 2023 using the search terms: "brain tumor", "brain metastasis", "glioma", "meningioma", and "glioblastoma". The available information for these trials were downloaded as a comma-separated value file. From the trials within this search, the following inclusion criteria were then applied: (1) trials with at least one site in the United States; (2) trials including adults (18–64 years old) and/or older adults (≥65 years old); (3) trials that have reached a primary completion date by December 31, 2019, defined as those that had completed participants' examinations and/or administration of an intervention for the purpose of the final collection of data for the primary outcome; (4) trials with a status of completed, terminated, suspended, or withdrawn. The former were included in "completed" trials, while the 3 latter in "failed to reach completion" and then dichotomized into 2 groups for comparison; and (5) trials that have a recorded study start date and primary completion date.

Using the study start date, trials were divided into 3 time periods: 1966–1999, 2000–2009, and 2010–2019. The last 2 decades were used for statistical comparison. The first time period was not included in analyses as this is largely prior to the FDA Modernization Act and therefore is not necessarily an accurate representation of the clinical trial landscape. The following parameters were compared over time: geographical location by state within the United States, trial type (interventional versus observational), funding source (National Institutes of Health (NIH), Industry, and US Federal), and study duration. US Federal funding includes federal funding from non-NIH institutions, such as the Department of Defense and the Centers for Disease Control and Prevention. Since funding sources labeled as "other" did not have details about the specifics

of the funding, trends in "other" funding sources were not analyzed. Trials that had more than one source of funding were included in counts for each funding source. Study duration was calculated as the time in weeks between the study start date and primary completion date. If the primary completion date was unavailable, final completion date was used.

For interventional trials, the following data was extracted: intervention scope (diagnostic, supportive care, treatment), intervention type (biological, device, dietary supplement, drug, genetic, procedure, or radiation), and phase. Phase is reported as early phase 1, phase 1, phase 1/2, phase 2, phase 2/3, phase 3, phase 4, and unknown phase.

### Trial Completion, Demographic, and Geospatial Data Extraction

For trials that failed to reach completion, the reason for the status of the trial (free text entry) was documented and grouped into one of the following categories (with subcategories): operational (administration difficulties, IRB decision, PI or sponsor decisions, study protocol changes, and study replacement); changes in resources (study resource unavailable and financial difficulties); accrual difficulties; intervention futility changes (risk/benefit changes and changes in standard of care); treatment toxicity; and other.

Demographic information about the study subjects were downloaded as extensible markup language files specific for each trial that had study results posted to ClinicalTrials.gov. The following demographics were analyzed: sex, ethnicity, race, and age. Trials followed the same inclusion criteria as above. Geographical population of the United States was downloaded from census.gov.[16]

### Statistical Analysis

All data was analyzed individually and as aggregate trends over time. Continuous variables were reported as mean ± standard deviation unless otherwise specified. Statistical analyses such as univariate tests (chi-square, ANOVA) were conducted to analyze differences in demographic and healthcare access variables within the cohort. Statistical analysis was used to compare the last 2 decades (2000–2009 vs 2010–2019) and was performed with chi-square tests using R (The R Group, 2013) and the packages: *tableone*. Effect sizes are reported as standardized mean differences between the 2 time periods. For failed trials, differences in failure rate among categories (funding source, phase, intervention focus and type, intervention model, and allocation) were performed in R using pairwise proportion tests with a Bonferroni correction.[17] Geospatial state-wide analysis was performed by querying the state of all trial sites. The aggregate number of trials per state and the failure percentage of those trials were calculated and plotted. Significance threshold was determined at 3 levels: $P < .05$, $P < .01$, and $P < .001$. Maps were produced using the packages *ggplot2* on R. Data from 1966 to 1999 are shown in graphs and tables for completeness.

### Ethics Statement

As this study was nonhuman subjects research, IRB review was not required, and consent was not applicable.

## Results

### Identification of Eligible Neuro-Oncology Trials

Our search yielded 4522 trials. With the application of the inclusion criteria, the final number of eligible trials for our analysis was 1257 (Figure 1) with the first start date on July 1, 1966. Of the 1257 trials, 200 included patients with metastatic tumors to the brain, and 627 included patients with primary tumors, specifically high-grade glioma (537), low-grade glioma (23), meningioma (46), and pituitary tumors (21). The remaining trials included other primary brain tumors that were unspecified.

### Geospatial Distribution of Neuro-Oncology Trials

Figure 2 summarizes the distribution of trials by state from 1966 to 2019. California had the greatest number of trials across all time periods, with 376 trials, followed by Texas, 328 trials, and North Carolina, 311 trials (Figure 2A). The highest trial density was found in North Dakota (6/100,000), followed by South Dakota and Northeast States (Delaware, Vermont, and New Hampshire; Figure 2B). By region, the Midwest had the highest percentage of

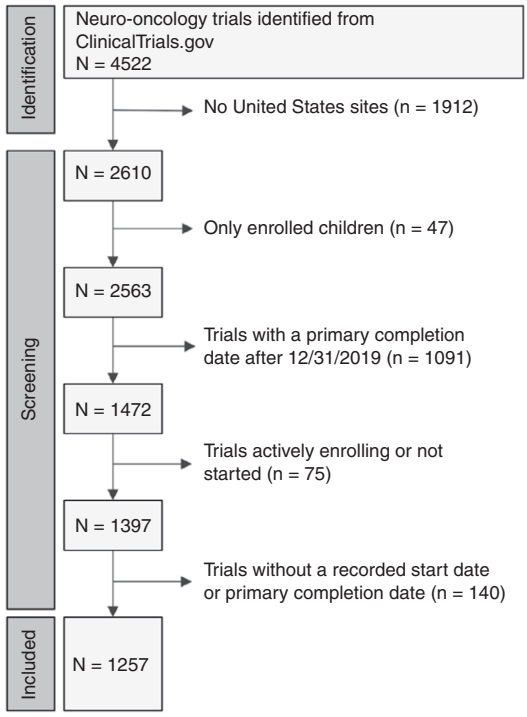


**Figure 1.** Flow diagram summarizing neuro-oncology trials' identification and inclusion/exclusion criteria.

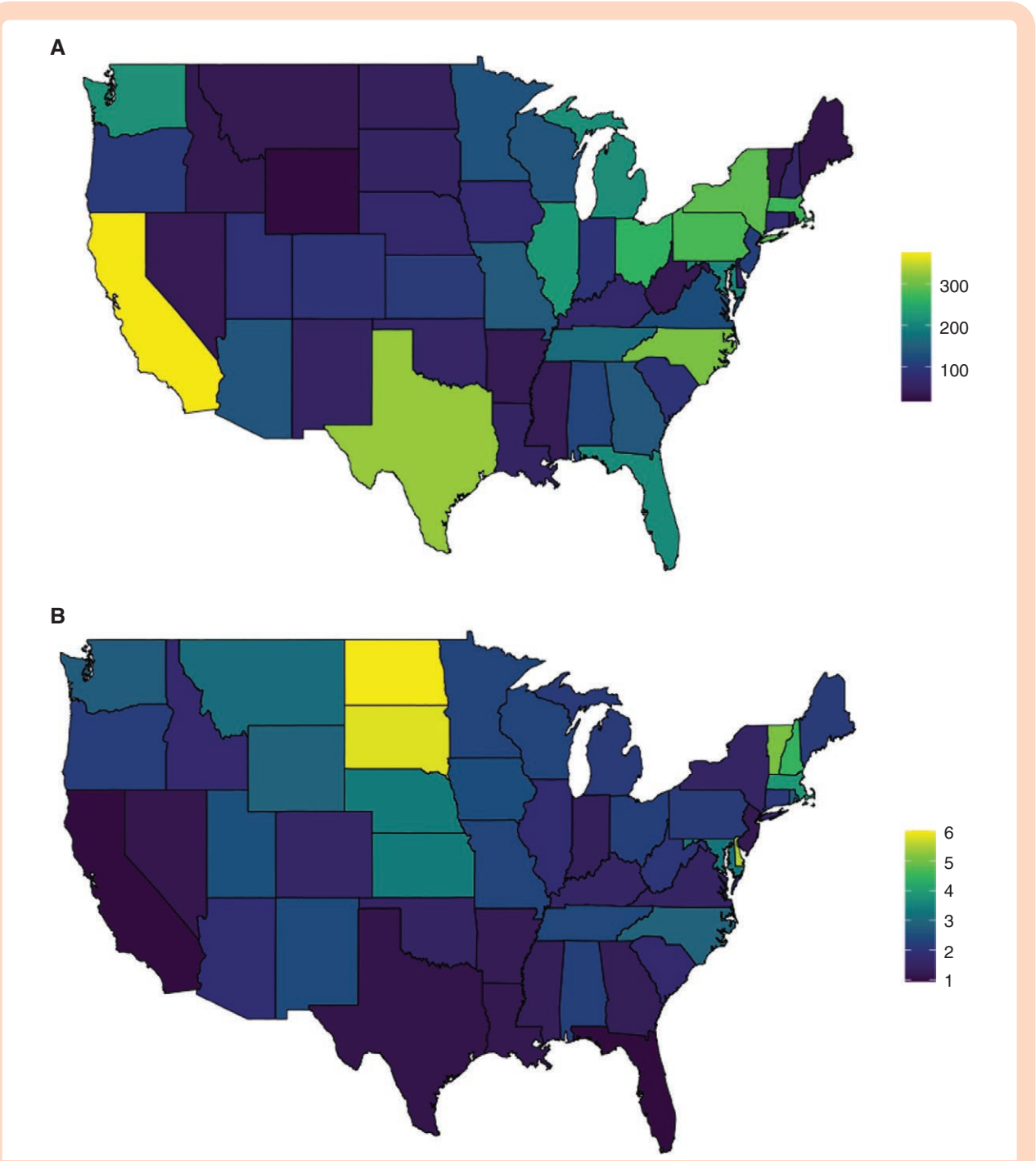


**Figure 2.** US geospatial maps showing distribution of (A) cumulative number of neuro-oncology clinical trials for the period 1966–2019 and (B) trial density (per capita).

states with>1.0 trial per capita at 58.3% and the South had the lowest percentage at 31.2% (Supplementary Figure 1B). With an overall disease incidence of CNS tumors in 25/100,000 population, currently in 25 US states, the neuro-oncology trial availability is <0.85/100,000 population (Supplementary Table 1). Of these 25 states, 11 (44%) are in the South, 8 (32%) are in the West, 4 (16%) are in the Midwest, and 2 (8%) are in the Northeast (Supplementary Figure 1C).

## Clinical Trials Characteristics

The funding sources of neuro-oncology trials significantly changed over time with NIH funding decreasing from 47% to 23% ($P < .001$; SMD = 0.51) and industry funding increasing from 33% to 42% ($P = .002$, SMD = 0.23; Figure 3A). US federal-funded trials remained <1% of all trials and unchanged over time. The proportion of interventional trials increased over time ($P = .034$; Figure 3B).

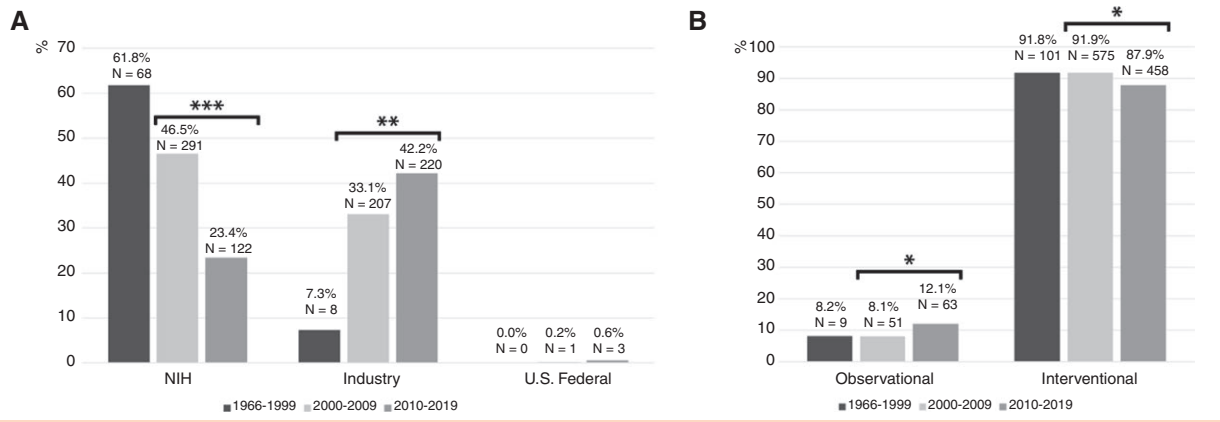


**Figure 3.** Bar graphs summarizing (A) neuro-oncology trial funding sources and (B) trial types for the period 1966–2019 divided into the 2 most recent decades and earlier. Significant *P*-values are indicated as follows: **P* < .05, ***P* < .01, ****P* < .001.

Among interventional trials, treatment trials decreased significantly from 89% to 82% (*P* = .002) over the past 2 decades (Figure 4A). Treatment trial focus showed a significant increase for trials using biological therapies and devices (*P* = .037, SMD 0.14 and *P* = .002, SMD = 0.20, respectively), while those using drug, procedure, or radiation decreased (*P* = .041, SMD = 0.13; *P* = .004, SMD = 0.19; *P* = .005, SMD = 0.18, respectively; Figure 4B). A significant increase in early phase 1 trials from 2% to 6% (*P* = .003) occurred, with a significant decrease in phase 2 and 3 trials (*P* = .026 and .003, respectively; Figure 4C).

## Demographic Characteristics of Subjects Enrolled in Neuro-Oncology Trials

Demographic information about study participants was provided by 468 trials for a total of 57,197 subjects with the earliest trial start date of July 1, 1966. A significant increase in number of women (45–50%, *P* < .001; data not shown) and subjects ≥65-year-old occurred (13–25%, *P* < .001; Figure 5A). Older adults (>65 years old) were allowed to enroll in 1044/1580 trials (66%). Over the past 2 decades, a significant decline in Hispanic participants from 8.5% to 6.5% occurred (*P* < .001; data not shown). Although slight increases for American Indian/Alaska Native (*P* = .002), Asian (*P* = .002), and more than one race (*P* < .001) were observed, each of these categories remains less than 5%. The proportion of Black subjects remained unchanged over time, around 6% (Figure 5B).

## Trials Completion Rate and Factors Associated With Failure to Reach Completion Top Reasons for Failure to Reach Trial Completion

The overall neuro-oncology trial completion rate was 74% (924/1257). Over the past 2 decades, completed trials decreased significantly from 78% to 64% (*P* < .001, SMD = 0.35; Figure 6A and B) with an increased number of terminated trials (Figure 6B). The average time for failed trials to reach their endpoint decreased from 186.93 (±134.41) weeks in 2000–2009 to 128.03 (±76.21) weeks in 2010–2019 (data not shown). The top 2 reasons for failure to reach completion included poor accrual (40%) and operational difficulties (20%). Other reasons for trial noncompletion include changes in resources (11%), changes in intervention futility (6%), and treatment toxicity (2%). These were independent of funding source or any other parameter analyzed.

## Completion Rate and Trial Type

NIH-funded trials had a greater completion rate compared to industry-funded trials, although not statistically significant (79% vs 74%; *P* = .315; Figure 6C). Treatment trials had a higher completion rate than diagnostic (*P* = .016; Figure 6D). There were no significant differences in failure rate comparing observational versus interventional trials, type of intervention, intervention model, and design allocation.

## Completion Rate and Trial Subject Enrollment

Among studies reporting demographic characteristics, there were 344 completed trials and 124 trials that failed to reach completion (sample representative of the overall completion rate of 74%). A larger proportion of the women (*P* < .001), non-Hispanic subjects (*P* = .001), and older adult (*P* < .001) patients were enrolled in completed trials than in those failing to complete.

## Completion Rate and Geographical Location

Comparing the past 2 decades, differences in completion rate did not correlate with trial density by state (*P* = .777). Comparing the last 2 decades, states with the greatest decrease in trial completion rate included Nevada (23%), West Virginia, Alaska, and Idaho (all three 20%; Figure 6E). Florida (11%) trended toward statistical significance (*P* = .09).

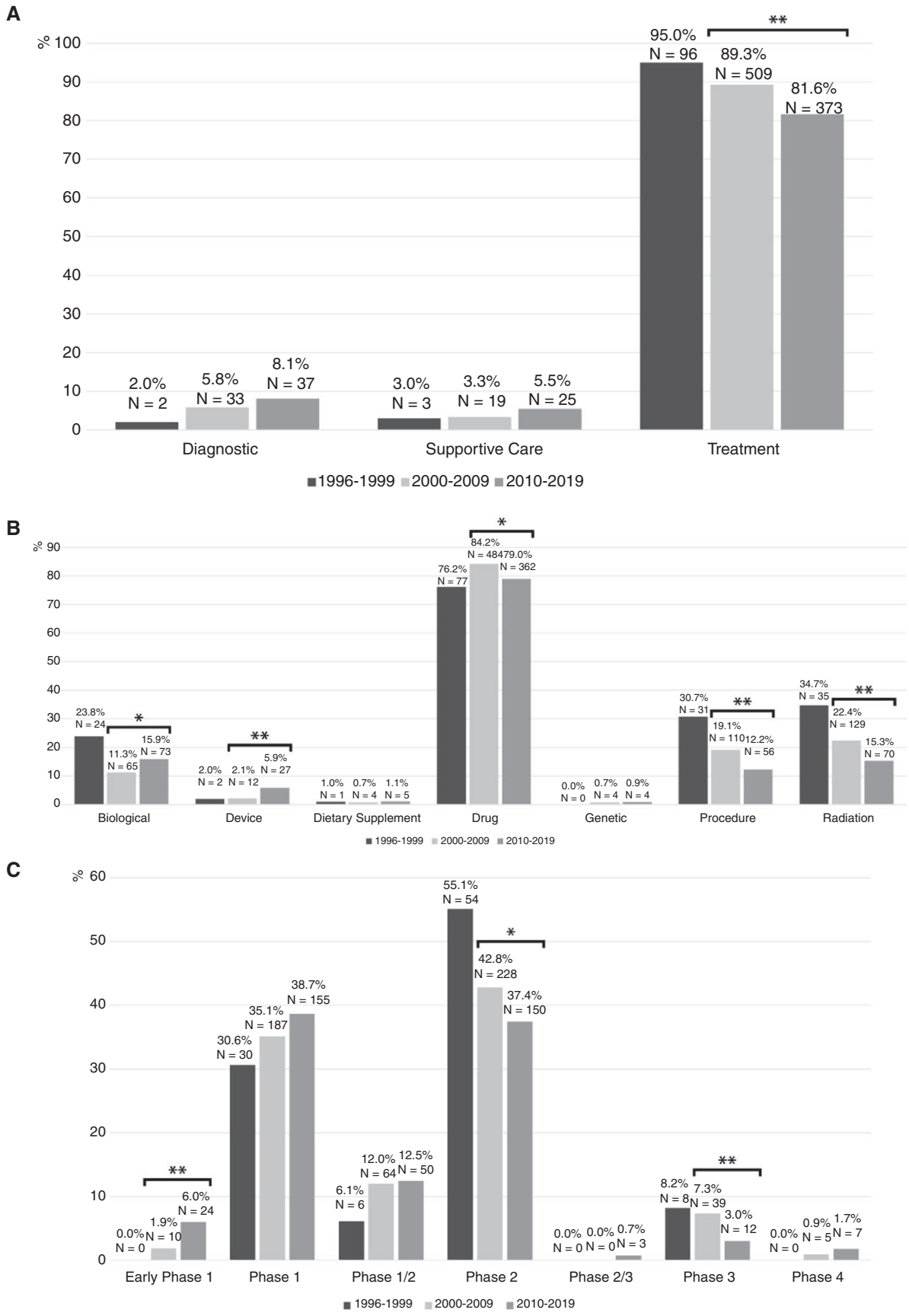


**Figure 4.** Bar graphs summarizing neuro-oncology clinical trial characteristics and changes over 3 time periods for (A) interventional trial phases; (B) treatment trial focus; and (C) trial phases. Significant *P*-values are indicated as follows: *$P < .05$, **$P < .01$.

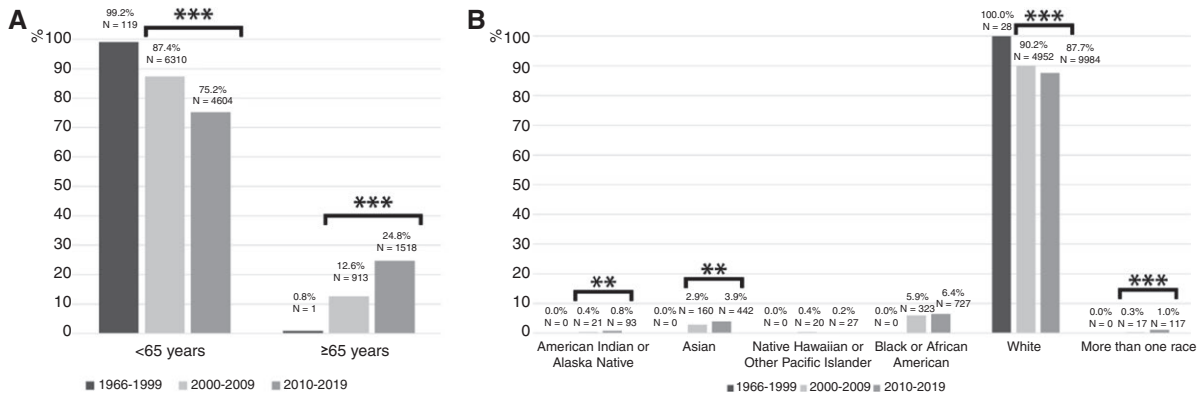


**Figure 5.** Bar graphs summarizing neuro-oncology clinical trial enrolled subjects' characteristics over time (A) age <65-year-old versus ≥65-year-old and (B) race. Significant *P*-values are indicated as follows:*$P < .05$, **$P < .01$, ***$P < .001$.

## Discussion

This is the first study to report on US-registered clinical trials in neuro-oncology, including both observational and interventional trials, providing an analysis and its current landscape since database inception in 1966. Clinical trials are valuable and essential to exploring novel therapeutics and evaluating the comparative efficacy of the existing treatment modalities, and ensuring that they are performed effectively and equitably is a priority in the field. However, trials require significant investments necessitating granular analysis to formulate strategies to guide future resource allocation. In this study, we report an alarming significant decrease in completed neuro-oncology trials with a rate of 64% in the past decade compared to 78% in the previous. Our analysis offers helpful data to formulate strategies for the path forward.

The 2 main reasons attributed to current trial failures included poor accrual and operational difficulties. Accrual difficulties are multifactorial. Previous studies have highlighted strict eligibility criteria and complexity of trial design.[3,18,19] Our study provides evidence that currently in 25 US states, the availability of adult neuro-oncology trials is <0.85/100,000 population despite an overall disease incidence of 25/100,000. This suggests that challenges in recruiting participants for these trials may also be attributed to limited access as 50% of the US population affected by neuro-oncology diseases have minimal trial availability. Strategies aimed at assessing if opening trials in underserved areas might be considered and weighted against the cost of building the necessary infrastructure to conduct the trials. Alternatively, facilitating "long-distance" accrual could be more within reach. Most centers require on-site visits to determine patient's eligibility, which is difficult to accomplish for many reasons including finances, logistics, and fatigue secondary to the cancer and its treatment.[20] Incorporating modern technology, such as mobile phone apps and/or solutions utilizing artificial intelligence-driven solutions, can serve the purpose of initial eligibility screening, thereby streamlining the accrual process. Ultimately, this approach has the potential to boost the rate of trial completion.

With an increased global life expectancy, currently at 76 years in the United States, it is essential that new therapeutic options are tried in the overall population.[21] Our analysis showed a rise in the number of trials enrolling adults 65 years and older. However, it is worth noting that 75% of trials continue to exclude subjects ≥65 years old. This can in part be secondary to the nature of the disease as some trials are focused on tumors that are predominant in the population younger than 65 years, like low-grade gliomas. Interestingly, completed trials had a larger percentage of older subjects than those that failed to reach completion, suggesting that strategies to enroll older patients might be beneficial 2-fold. First, by providing information about the overall aging population and, second, by contributing to successful trial completion.

The decline of enrolled Hispanic subjects and stagnant low number of Black subjects reported in our study is not unique to neuro-oncology.[22,23] Strategies to improve minority accrual have been presented.[18] Prospective data analysis will be helpful in ascertaining the impact of these strategies on trial completion rates.

With healthcare costs continuing to soar in the United States, it is important to closely analyze areas associated with major expenses.[14] It has been estimated that the cost of a phase 1, 2, and 3 clinical trial is US$ 4, 13, and 20 million, respectively.[11] We have shown that failed trials are approximately 30% shorter in duration than completed trials. Although trial costs are multifactorial including a number of enrolled subjects, study duration could be used as a surrogate to approximate the cost. Over the past decade, with 251 trials failing to reach completion ($N = 120$ for phase 1 or phase 1/2, $N = 113$ for phase 2 or phase 2/3, $N = 14$ for phase 3, and $N = 4$ for phase 4), the approximate estimated cost of trials failing to reach completion is nearly US$ 1.5 billion. This observation coupled with the steep decline in NIH funding from 47% to 24% over the most 2 recent decades underscores the need to identify strategies aimed at improving trials' completion rate. In addition, there is an intrinsic unpredictability with industry-funded trials. As smaller companies depend on rounds of funding to continue trial operations, the financial stability of these companies can change in a moment.

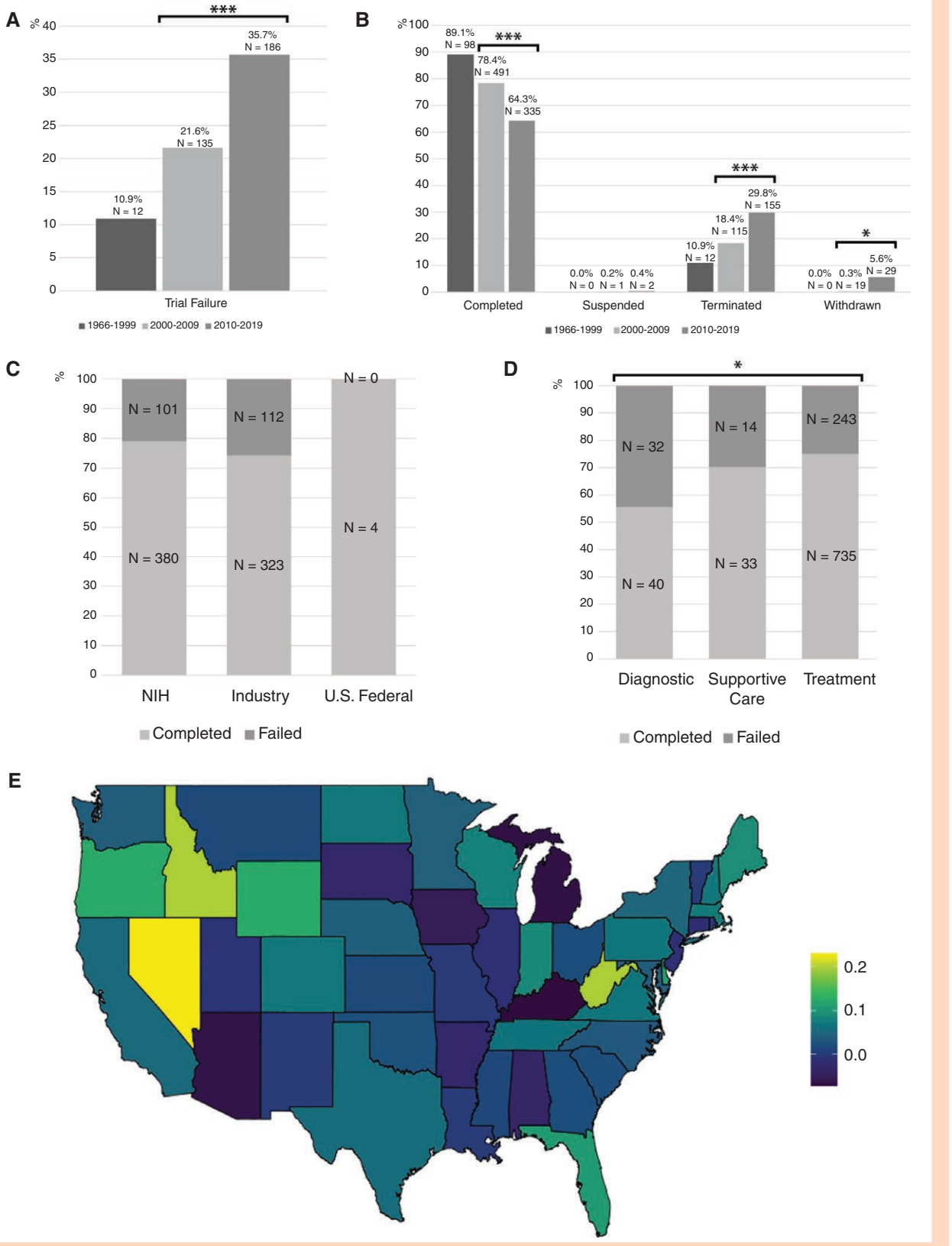


**Figure 6.** Bar graphs summarizing trial completion rate (A) over 3 time periods; (B) compared to completed trials; (C) by trial funding source; (D) by study intervention type; (E) geospatial map summarizing trial failures difference change in each state comparing the last 2 decades. Significant *P*-values are indicated as follows: **P* < .05, ***P* < .01, ****P* < .001.

Although our analysis did not find that association between trial design and changes in completion rates, it is important to note that trial design has previously been linked to influencing the clinical therapeutic success of trials. Specifically, multicenter and/or trials with a control arm have a higher potential to result in therapeutic success.[24] Taken together, our data supports the concept that well-designed trials should be sought. Currently, novel and potentially more efficient trial designs such as platform trials with sharing of control arms and Bayesian adaptive randomization such as INSIGhT and GBM AGILE are being evaluated.[25,26]

Study limitations should be highlighted. First, the 10 key issues limiting the use of the clinicaltrials.gov database have been previously summarized.[27] Pertinent to our study is the accuracy in recording start/end dates, data entry for subject enrollment demographics, and reporting reasons considered important for lack of trial completion. This accuracy depends on the compliance of the study investigators and sponsors, with a study from 2015 finding that industry sponsored trials are the most likely to report results in a timely fashion.[28] In our analysis, 54.9% of the glioma trials, 17.7% of the metastases trials, and 27.4% of the other or unspecified pathology trials were industry funded (Supplementary Table 2). Additionally, funding sources were broadly grouped into 4 categories: Industry, NIH, US Federal, and other. While clinicaltrials.gov is the most complete database of past and current trials that is publicly available, not all trials are required to register with this database. The FDA Amendments Act of 2007 and the Public Health Service Act of 2017 require applicable clinical trials to be registered. Applicable clinical trials are defined as controlled clinical investigations of any FDA-regulated drug or biological product and certain studies involving medical devices, which generally include most interventional trials.[29]

First, investigator-initiated studies were categorized based on the source of their funding, including philanthropic and foundation-funded support (categorized as other) unless they also received additional funding from industry, NIH, or US federal sources. Second, the US population data is derived from census information with known limitations. Third, the currently available data is not sufficiently granular and requires more details to allow a more precise estimation of the cost associated with trials that fail to reach completion. Finally, although lack of accrual was listed as the primary reason contributing to the failure of trial completion in 40% of cases, 20% attributed it to operational difficulties without providing sufficient details to differentiate the specific administrative, regulatory, and/or other financial issues that might have been associated with trial's lack of success in completion.

In conclusion, the alarming decrease in the completion rate of clinical trials in neuro-oncology, dropping from 78% to 64% over the past 2 decades, highlights the necessity to investigate the factors associated with trials failing to reach completion. Our study provided valuable data regarding the current landscape of neuro-oncology trials in the United States, including enrollment demographics. To facilitate the trial completion rate, it is critical to implement strategies focused at streamlining the accrual process, particularly in areas where 50% of the US population have limited access to trials. Additionally, acquiring a more granular understanding of administrative, regulatory, and other aspects might contribute to increase trial completion rates as part of an overall strategy.

## Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/neuro-oncology).


## Keywords

clinical trial design | clinical trial outcomes | neuro-oncology clinical trials

## Funding

None declared.


## Conflict of interest statement

None declared.

## Authorship statement

Study conception was performed by E.J.S., A.N., and I.M.G. The methodology was performed by E.J.S. and A.N. Data collection was performed by E.J.S., A.N., and M.G. Data analysis and interpretation were performed by E.J.S., A.N., and I.M.G. Manuscript writing was performed by E.J.S., A.N., M.G., and I.M.G. Manuscript revision was performed by P.Y.W., M.L., and S.M.C. All authors approved the final manuscript submission.

## Data availability

The data used in this study are publicly available on ClinicalTrials.gov and Census.gov. Additional information about how to obtain this data will be made available upon reasonable request.

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