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Why are clinical trials of deep brain stimulation terminated? An analysis of clinicaltrials.gov

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ABSTRACT

Background: Although deep brain stimulation (DBS) has established uses for patients with movement disorders and epilepsy, it is under consideration for a wide range of neurologic and neuropsychiatric conditions.
Objective: To review successful and unsuccessful DBS clinical trials and identify factors associated with early trial termination.
Methods: The ClinicalTrials.gov database was screened for all studies related to DBS. Information regarding condition of interest, study aim, trial design, trial success, and, if applicable, reason for failure was collected. Trials were compared and logistic regression was utilized to identify independent factors associated with trial termination.
Results: Of 325 identified trials, 79.7% were successful and 20.3% unsuccessful. Patient recruitment, sponsor decision, and device issues were the most cited reasons for termination. 242 trials (74.5%) were interventional with 78.1% successful. There was a statistically significant difference between successful and unsuccessful trials in number of funding sources ($p = 0.0375$). NIH funding was associated with successful trials while utilization of other funding sources (academic institutions and community organizations) was associated with unsuccessful trials. 83 trials (25.5%) were observational with 84.0% successful; there were no statistically significant differences between successful and unsuccessful observational trials.
Conclusion: One in five clinical trials for DBS were found to be unsuccessful, most commonly due to patient recruitment difficulties. The source of funding was the only factor associated with trial success. As DBS research continues to grow, understanding the current state of clinical trials will help design successful future studies, thereby minimizing futile expenditures of time, cost, and patient engagement.

1. Introduction

Deep brain stimulation (DBS) is an established neurosurgical intervention that enables direct modulation for a variety of dysregulated neural circuitry, including Parkinson's disease, dystonia, epilepsy, and essential tremor, with ongoing investigations examining its effectiveness in obsessive-compulsive disorder, depression, memory, and more.[1–6] To date, it is estimated that over 200,000 patients have had a DBS system implanted.[3] In recent years, there has been heightened interest in DBS as a potential treatment modality for a wide range of neurological and neuropsychiatric conditions.[3,7–9] In response, well-designed and executed clinical trials are required to determine the future directions of DBS and new implementations of this technology.

The Clinicaltrials.gov database is one of the most comprehensive publicly-available resources for information about registered clinical trials, and it has been utilized in recent cross-sectional analyses to evaluate the progress of clinical trials across a range of neurosurgical conditions[10–13] including DBS.[14] However, analyses investigating factors that correlate with trial termination or failure are scarce. Analysis of the Clinicaltrials.gov database offers a unique opportunity to investigate attributes of clinical trials especially with respect to their progress and success. There are lessons to be learned from successful and unsuccessful trials to optimize future clinical study and limit the lost financial, administrative, and physical investment associated with unsuccessful

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clinical trials.[15] Here, we review successful and unsuccessful DBS-related clinical trials and assess causes of early trial termination to identify factors associated with unsuccessful trials. We also review trials that highlight the current state of DBS for neuropsychiatric conditions.

2. Methods

A comprehensive search for all clinical trials pertaining to DBS was executed via the ClinicalTrials.gov clinical trial database. Clinical trials were identified in similar methodology as described in previous studies.[13,14] The search was conducted in December 2022 and included the terms 'deep brain stimulation' OR 'DBS'. Trials were sorted based on their recruitment status. All identified clinical trial entries were screened by two authors (AM and SB) to ensure that they pertained to DBS, and only relevant trials were retained for further analysis.

Trial characteristics were extracted from the database. Study aim (basic science, device feasibility, diagnostic, screening, supportive care, prevention, treatment, or not reported), interventional versus observational (which included imaging or neurophysiological studies), funding source (NIH /Federal, Industry, or other; "other" funding source includes academic institutions such as universities, hospitals, individuals, or community-based organizations), utilization of randomization, intervention model (crossover, single-group, parallel), utilization of blinding (including single and double blinding), number of organizations involved in the study, and trial phase were collected. Treatment condition was captured according to the specific conditions as described in trial entries, and trials that included patients with multiple conditions were also identified. Studies designated as early phase I were included as phase I trials; phase I/II studies were designated as phase II; and phase II/III studies were designated as phase III. Reason for trial termination was grouped based on a recent similar analysis.[13,16] Groups that were created include: (1) participant accrual difficulty; (2) administrative reasons; (3) financial reasons; (4) sponsor decision; (5) logistical issues; (6) device issues; (7) competing study; (8) change to standard of care; (9) other; and (10) reason not specified.

Successful trials were defined as trials that were completed or terminated after mid-study analysis (as a trial that was stopped after mid-study analysis did indeed yield some meaningful outcome despite not recruiting a specified number of patients). ClinicalTrials.gov defines completed trials as those that have "ended normally, and participants are no longer being examined or treated." These trials were marked as completed for analysis. Unsuccessful trials included trials that were marked as terminated or withdrawn. ClinicalTrials.gov defined terminated trials as those that "[have] stopped early and will not start again [and] participants are no longer being examined" and withdrawn trials as those that "stopped early, before enrolling its first participant." The rationale behind this decision is that it is conceptually more pragmatic to consider a trial that has met its primary endpoint as "successful" (regardless of the results, as both positive and negative results advance scientific knowledge) and a trial that either did not enroll a single participant or did not complete any mid-study analysis as "unsuccessful." The decision to consider trials that were terminated following mid-study analysis as "successful" was due to the heightened possibility that the mid-study analysis yielded *meaningful* scientific knowledge that impacted trial progression.

Due to incongruities in reported data, interventional trials and observational trials were separated for analysis. Trial characteristics (with fields containing zero-values removed from analysis) were compared by a univariate chi-square analysis. Then, a multinomial logistic regression was utilized to determine independent factors associated with trial termination. We used multinomial logistic regression because it is designed to study the independent effect of several predictor variables on a single categorical dependent variable, there was a large total number of trials available for analysis (n = 325 trials), and data for each predictor variable was available for all trials.[17,18] Trial entries were assumed to be independent of one another, with one model entry per trial, and all utilized categories were mutually exclusive. For each database entry, the provided options were considered to be exhaustive. To assess and mitigate the potential for multicollinearity (where predictor variables are correlated with each other), serial chi-square test of independence tests were performed between each predictor variable and every other predictor variable, and it was ensured that the derived chi-square value between any pair of variables exceeded a Bonferroni-corrected p-value of 0.01. For analysis, any predictors where the results would not be meaningful (e.g., the "other" or "unreported" categories) were removed. All statistical analysis were performed in MATLAB R2021a (Mathworks Inc., Natick, MA), and a cutoff of $p = 0.05$ was utilized to assign statistical significance.

3. Results

A total of 325 DBS-related trials were identified and included in analysis. Successful trials comprised 79.7% (n = 259 trials) and unsuccessful trials comprised 20.3% (n = 66). 74.5% of trials were interventional (n = 242 trials) and 25.5% of trials were observational (n = 83 trials).

3.1. Unsuccessful trials

A total of 66 trials (20.3%) were identified as unsuccessful, including 53 interventional and 13 observational trials. The most common cited cause was difficulty in patient recruitment, which was identified in 25 of 66 (37.9%) of unsuccessful studies and was the most cited cause of early termination in both interventional and observational trials. Less common causes of study termination included issues with funding (n = 7 studies, 10.6%), sponsor decision (n = 6 studies, 9.1%), and device issues (n = 5, 7.6%). There was no reason specified for 10 studies (15.2%). Counts for unsuccessful trials by cause and split by interventional and observation trials are detailed in Table 1.

3.2. Interventional trials

A total of 242 interventional trials were included in the analysis. Of this subset of trials, 189 were successful (78.1%) compared to 53 that were unsuccessful (21.9%). Trial characteristics for interventional trials are reported in Table 2. The most common primary study purpose was treatment (n = 161; 66.5%), most trials had a single funding source (n = 204; 84.3%), were single-blinded (n = 117; 48.3%) and were not multiorganizational (n = 145; 59.9%). Univariate analysis revealed statistically significant differences between successful and unsuccessful trials in the number of funding sources ($X^2(1) = 4.330$, $p = 0.0375$) while earlier trial phase showed a non-significant trend towards non-completion ($X^2(4) = 8.824$, $p = 0.066$).

Table 1
Reasons listed on clinicaltrials.gov for clinical trial termination (total n = 66 trials), including division into n = 53 interventional terminated trials and n = 13 observational trials.

	All trials (n = 66)	Interventional Trials (n = 53)	Observational trials (n = 13)
Patient accrual difficulty	25 (37.9%)	22 (41.5%)	3 (23.1%)
Financial/Funding	7 (10.6%)	4 (7.5%)	3 (23.1%)
Sponsor Decision	6 (9.1%)	5 (9.4%)	1 (7.7%)
Logistics	5 (7.6%)	4 (7.5%)	1 (7.7%)
Device issues	5 (7.6%)	5 (9.4%)	0 (0.0%)
Administrative	3 (4.5%)	2 (3.8%)	1 (7.7%)
Competing Study	2 (3.0%)	2 (3.8%)	0 (0.0%)
Other	2 (3.0%)	1 (1.9%)	1 (7.7%)
Change to standard of care	1 (1.5%)	1 (1.9%)	0 (0.0%)
Reason not specified	10 (15.2%)	7 (13.2%)	3 (23.1%)

Table 2
Reported study characteristics of n = 242 interventional trials, divided into completed trials (n = 189) and non-completed trials (n = 53). (Note: categories with a corresponding * were not included in the corresponding Chi-Square model due to actual frequency counts that include zero values.)

	Completed trials (n = 189)	Non-completed trials (n = 53)	Total (n = 242)	p-value
Primary Study Aim				
Basic Science	28	4	32	0.597
Device Feasibility	7	3	10	
Diagnostic	7	1	8	
Screening*	1	0	1	
Supportive Care	8	2	10	
Prevention*	1	0	1	
Treatment	121	40	161	
Not Reported	16	3	19	
Funding Source				
Industry	42	10	52	0.823
NIH	22	4	26	
Other	167	43	210	
Number of funding sources				
Multiple	38	4	42	0.0375
Single	155	49	204	
Randomization				
Randomized	109	36	145	0.306
Not randomized	20	7	27	
Not applicable	54	10	64	
Not reported*	6	0	6	
Intervention Model				
Crossover	53	15	68	0.92
Single-group	83	21	104	
Parallel	48	15	63	
Not reported	5	2	7	
Blinding				
Double	32	8	40	0.738
Single-group	93	24	117	
None/Not reported	64	21	85	
Multi-organizational				
Yes	73	24	97	0.382
No	116	29	145	
Phase				
1	13	9	22	0.066
2	21	8	29	
3	15	7	22	
4	7	2	9	
Not applicable	133	27	160	
Condition				
Parkinson's Disease	80	24	104	
Essential Tremor	13	3	16	
Dystonia	12	3	15	
Obsessive-Compulsive Disorder	12	1	13	
Bipolar Disorder	1	1	2	
Neuralgia	0	1	1	
Epilepsy	6	4	10	
Major Depressive Disorder	10	4	14	
Alcohol Use Disorder	0	1	1	
Spinal Cord Injury	0	1	1	
Schizophrenia	1	1	2	
Obesity	3	0	3	
Pain	2	0	2	
Autonomic/ Urinary Tract Failure	1	0	1	
Tinnitus	2	0	2	
Traumatic Brain Injury	2	0	2	
Alzheimer's Disease	6	0	6	
Huntington's Disease	2	0	2	
Anorexia	1	0	1	
Multiple Sclerosis	1	0	1	
Cluster Headache	2	0	2	
Multiple/ Nonspecific Procedural (No specified condition)	28	9	37	
Anesthesia	1	0	1	
Caffeine	2	0	2	
Wound Infection Prevention	1	0	1	

Most interventional trials recruited patients with Parkinson's Disease (n = 104; 43.0% of all interventional trials), followed by essential tremor (n = 16; 6.6%) and dystonia (n = 15; 6.2%). There were also trials for major depressive disorder (n = 14; 5.8%), obsessive-compulsive disorder (n = 13; 5.4%), and Alzheimer's disease (n = 6; 2.5%). Thirty-seven trials were classified as multiple or nonspecific conditions such as "movement disorders" (15.3%) (Table 2). Trials for conditions with FDA-approved application of DBS (i.e., Parkinson's Disease, Essential Tremor, dystonia, and epilepsy) comprised 145 trials (59.9% of all interventional trials) of which 111 were successful (76.6%) while experimental conditions comprised 56 trials (23.1% of all interventional trials), of which 46 were successful (82.1%).

Multinomial logistic regression analysis was executed to analyze interventional trial characteristics that are associated with unsuccessful trials. Trials that exclusively utilized NIH funding were associated with success (OR = 0.321, 95% CI 0.108–0.952, $p = 0.040$), whereas those that exclusively utilized "other" funding (academic institutions such as universities or hospitals, and community-based organizations) were more likely to be unsuccessful (OR = 6.095, 95% CI 1.078–34.478, $p = 0.041$). No other characteristics were found to be associated with trial success. The results of the regression analysis are summarized in Fig. 1.

3.3. Observational trials

A total of 83 observational trials were included in analysis. Of this subset of trials, 70 were successful (84.3%) compared to 13 that were unsuccessful (15.7%). Trial characteristics for interventional trials are reported in Table 3. These trials were primarily single organizational (n = 56; 67.5% of all observational trials) and with a single funding source (n = 63; 75.9%). In univariate analysis, there was no significant difference between successful and unsuccessful trials in any of the collected measures (Table 3).

Most observational trials were those that recruited patients with Parkinson's Disease (n = 43; 51.8% of all observational trials), followed by essential tremor (n = 5; 6.0%). There were also trials for obsessive-compulsive disorder (n = 4, 4.8%) and major depressive disorder (n = 2, 2.4%). Twenty trials were classified as multiple or nonspecific (24.1%) (Table 3). Trials for FDA-approved conditions comprised 55 trials (66.3% of all observational trials) of which 48 were successful (87.3%) while experimental conditions comprised 8 trials (9.6% of all observational trials), of which 6 were successful (75.0%).

4. Discussion

Deep brain stimulation is an established treatment modality, with ongoing investigations to optimize its use and to expand indications. Clinical trials are crucial to advance our knowledge of disease processes and establish the efficacy of DBS for these conditions. However, these studies involve substantial investments (including financial, administrative, and physical resources), and unsuccessful ones represent both a

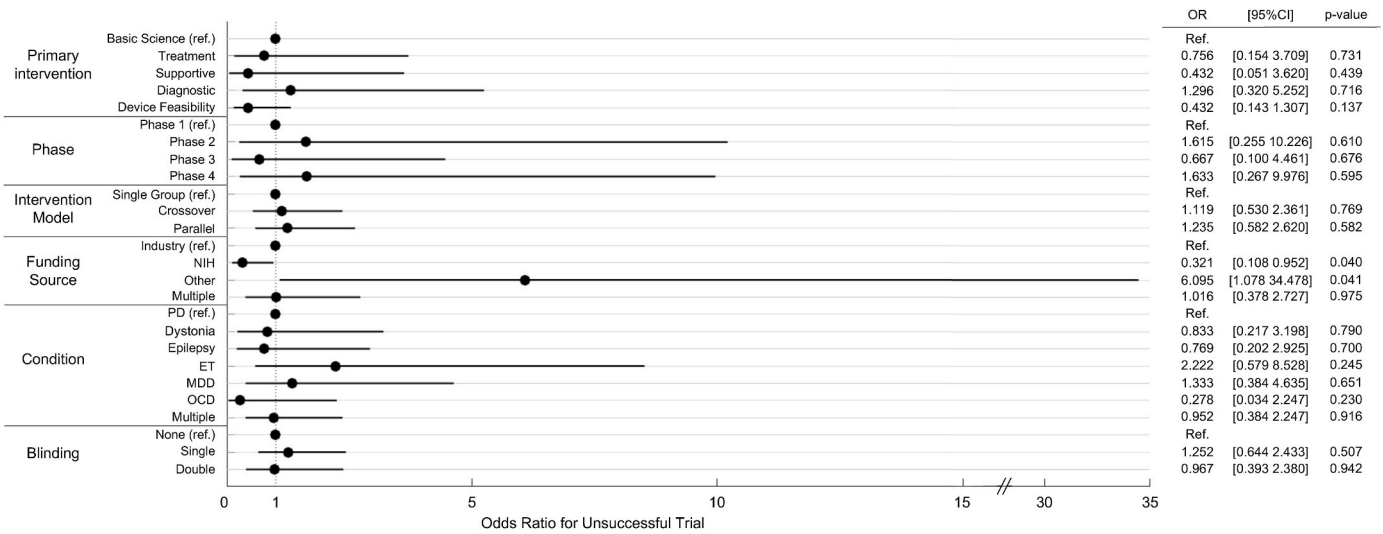

Fig. 1. Forest plot illustrating odds ratio and confidence interval for unsuccessful DBS clinical trials alongside *p*-values for each predictive factor. "Other" funding sources include academic institutions, individuals, and community-based organizations. Reference values for each characteristic are stated as (ref.)
ref, Reference; NIH, National Institutes of Health; PD, Parkinson's Disease; ET, Essential Tremor; MDD, Major Depressive Disorder; OCD, Obsessive-Compulsive Disorder; OR, odds ratio; CI, confidence interval.

Table 3
Reported study characteristics of n = 83 observational trials, divided into completed trials (n = 70) and non-completed trials (n = 13).

	Completed trials (n = 70)	Non-completed trials (n = 13)	Total (n = 83)	p-value
Funding Source				
Industry	21	3	24	0.76
NIH	11	3	14	
Other	56	10	66	
Number of funding sources				
Multiple	17	3	20	0.925
Single	53	10	63	
Multi-organizational				
Yes	22	5	27	0.619
No	48	8	56	
Condition				
Parkinson's Disease	38	5	43	
Essential Tremor	3	2	5	
Dystonia	3	0	3	
Obsessive-Compulsive Disorder	2	2	4	
Bipolar Disorder	1	0	1	
Epilepsy	4	0	4	
Major Depressive Disorder	2	0	2	
Autonomic/ Urinary Tract Failure	1	0	1	
Multiple/ Nonspecific	16	4	20	

burden and lost opportunity. We identified and categorized 325 successful and unsuccessful trials involving deep brain stimulation, and reviewed trial characteristics that may be associated with trial termination.

Of all closed DBS trials identified on ClinicalTrials.gov, 20.3% were identified as unsuccessful. This is higher than the 12% trial termination rate noted across all ClinicalTrials.gov entries,[19] the 19.8% termination rate reported for glioblastoma multiforme trials[13] and the 14% termination rate for spinal procedure trials.[12] In this study, trials were most often terminated due to participant recruitment difficulties (38% of terminated trials),which was also noted to be the most common cause of termination in other interventional studies[12,13] and meta-analyses.[19] Interestingly, we found that trials funded by either multiple sources or the NIH were associated with increased trial success, while those supported by non-NIH, non-industry sources were associated with decreased trial success. Interestingly, this is in contrast to a similar study that identified industry funding as associated with spinal procedure trial failure.[12] It is possible that such discrepancies are due to differences in primary study aims, as DBS research commonly implements imaging and computational means (such as tractography for elucidating functional neural networks) that are less driven by device companies and industry funding. This often is different from research in, for example, spine neurosurgery, where additional emphasis is placed on improvement of available tools and techniques.[12]

There are several possible explanations as to why NIH-funded DBS clinical trials are less likely to be terminated. First, NIH funding is predicated upon a peer review process that includes a standardized, multifaceted assessment.[20] Continuous improvements to the review process have aimed to further enhance scientific rigor and transparency.[21] Trials that are eventually funded by the NIH are required to complete these review processes, which may serve to ensure that such trials are more scientifically rigorous, transparent, and utilize methods that are more likely to result in trial success (for example, in DBS studies, sample size analysis or advanced randomization techniques). This process may not be as common for non-NIH funding sources. Second, the NIH provides several funding mechanisms with varying funding durations whereby investigators may better align the study timeline with the specific trial of interest. Third, funding from the NIH does not depend on business or external interests that may impede or infringe upon study progress.[22] This may promote scientific investigations that serve to advance novel scientific and medical theory[23] rather than trials that are closer to the translational relevance that may be more prevalent among non-NIH funded trials. Finally, a recent review of NIH-funded studies has revealed a strong bias towards providing funding to larger, more reputable institutions with a record of prior funding.[24] As DBS trials require substantial institutional and clinical commitment, such institutions may be more likely to have existing resources and infrastructure that promote trial success. As the NIH changes the peer review process to de-emphasize such biased metrics in 2025,[25] we anticipate some impact on DBS clinical trials.

Movement disorders have been the longest running FDA-approved indication for DBS with approval for essential tremor in 1997,

Parkinson's Disease in 2002, dystonia in 2003, and refractory epilepsy in 2018, constituting the largest proportion of identified DBS-related clinical trials.[26–29] However, we also identified a significant number of trials that recruited patients for a variety of experimental conditions including obsessive-compulsive disorder and depression, showing a trend towards utilization of interventional treatment of psychiatric conditions rather than medication use alone. This reinforces previous results that showed how current research is focused more on expanding use for experimental conditions rather than optimizing DBS to improve efficacy for previously approved conditions.[14] We identified a total of 64 trials for experimental (non-FDA approved) conditions, of which 52 trials were successful and 12 were unsuccessful. Of these unsuccessful trials for experimental conditions, most were for treatment-resistant depression (TRD) with a few studies that were aborted due to concern for futility.[30,31] More recent studies have shown promise by utilizing a network-based approach that implement stereoelectroencephalography (SEEG) electrodes or DBS leads with chronic local field potential-sensing capabilities to identify and map the dysfunctional network prior to implementing DBS,[32–36] but increased understanding of these networks will be required to optimize utilization of DBS for TRD.

DBS exerts its effect by applying direct electrical stimulation to specific targets, thereby modulating neural circuitry. Due to the design and focal function of the electrodes, including with directional DBS electrodes, only specific and precise areas can be stimulated rather than diffuse circuits.[14,37] This may explain the success in Parkinson's Disease and other movement disorders where dysfunction in a single subcortical structure or network leads to clinical symptoms such as tremor. Although the concept of minimally invasive, non-pharmaceutical, adjustable, and reversibly ablative treatment is appealing, the lack of a defined, precise target will limit the applicability of DBS in these conditions characterized by circuit dysfunction.[4] Since movement disorders have gained FDA approval for DBS, trials have shifted from identifying targets or establishing safety and efficacy to investigating quality of life, patient outcomes, economic benefit, novel techniques, and treatment parameters. With this shift in focus has come a change in publication trends; there was an increase in DBS publications between 1991 and 2014 but a decrease over the recent years, likely reflecting the FDA acceptance of DBS and the transition to more experimental applications.[4]

Our study found that failures of patient recruitment and sponsorship were associated with trial termination. Unlike other trials that struggle with recruitment due to the relative rarity of the treating condition, movement disorders are rather prevalent, with an estimated 1 million Americans having Parkinson's Disease.[38,39] In this case, patient recruitment for movement disorders may be related to the treatment algorithm or associated cost of DBS. Medications are the first line treatment for all DBS-treated conditions, both neurologic and psychiatric, and DBS is considered only when symptoms are refractory. Therefore, opportunities for patient enrollment in trials will not come with diagnosis and will instead occur after years of treatment. Therefore, if DBS is not an FDA-approved standard of care, enrollment in clinical trials will rely on provider initiative and institutional infrastructure for experimental or invasive options. When considering DBS trials for neuropsychiatric conditions, the heterogeneity of these populations and lack of standardized consensus for refractory disease will make enrolling patients, generalizing results, and finding significant or non-futile results difficult. It is also possible that investigators leading DBS clinical trials overestimate the population of patients who fulfill the inclusion criteria, similar to the vast clinical trial landscape.[40]

There is no single solution for optimizing patient recruitment in clinical trials,[41–44] but there are several strategies that may improve enrollment for DBS trials. We will highlight some key considerations here:

1. It is imperative to increase societal and community awareness of clinical trials, including targeted outreach to trial-specific patient-, institution-, and organization-run support groups.[45] Partnership with these organizations will optimize transfer of trial-related information to more interested individuals, including information from patients to the clinical trial team. Importantly, as the indications and active clinical investigation of DBS continues to expand, especially with regards to highly-prevalent neuropsychiatric conditions, this will necessitate interaction with a wider array of support groups.
2. It is critical to deliver trial-related information in a clear, concise manner. Recent studies have highlighted the inadequacies of our current practices in delivering information to neurosurgical patients.[46] It is recommended that documents relating to a clinical study, such as consent forms, be prepared for an age level of 11–12 years.[47] This standard should extend to any other forms of communication, including any trial-related advertising or communication in other venues (for example, at presentations to support groups). Communication and comprehension will optimize understanding by both the participant and clinical trial team, and will promote discussion of expectations and barriers to participation that may exist. As DBS patients may more readily rely on personal support networks, including family members and caretakers, these communication standards should extend to these individuals as well. Ideally, these discussions should highlight components of the trial that are common causes of participant dropout, including the need for additional follow-up appointments for research study and the possibility of current/future alternative treatment options.
3. Communication with the participants should place emphasis on understanding and solving patient-specific concerns and barriers. It is critical for the clinical trial team to adhere to the same standard of care as clinical teams, including consideration of a participants' logistical, social, and financial needs. For clinical care, patients closely interact with a multidisciplinary care team that includes social workers, financial advisors, and patient advocates. The clinical trial team should have the same (or greater) level of expertise to accommodate for barriers that patients may face. Patient-reported outcomes (PROs) may be utilized as a mechanism to initiate targeted communication about patient concerns and feedback.[48]
4. Clinical trials should carefully select inclusion and exclusion criteria to find balance between scientific rigor and recruiting from a larger patient population. It is critical to maintain the non-negotiable aspects of clinical trials, including optimizing the benefit to participants while minimizing risk. Beyond this, there are several criteria that may be modified, including age, specifying disease subtype, and inclusion or exclusion of medical comorbidities.
5. Finally, patient recruitment exists on a continuum between passive recruiting (for example, advertising on a centrally-located display) to active recruiting (for example, delivering a presentation to a support group or contacting patients in a registry).[43] There are trial-specific considerations to be made regarding which modalities to utilize, but it is important to cater to patients with the primary condition of interest. For example, in studies investigating DBS for TRD, self-referral rates are higher than professional-guided referrals, but these patients do not often meet inclusion criteria.[44]

Clinical trials are a large financial investment and trial termination is a huge loss for those involved. The cost of DBS is not well or consistently reported, but estimated costs can range from tens to hundreds of thousands of dollars. Therefore, trials and studies for DBS often come from high-income countries.[4,49] Even if a trial receives funding, the financial burden taken on by patients (and the influence of insurance coverage, especially in experimental conditions) may dissuade patients from enrolling. Industry sponsorship is related to company interest in advancing DBS research. For years the lack of diversity and competition in the DBS device market led to little motivation for industry sponsorship. A recent increase in industrial "players" may lead to a greater number of DBS trials.[4] As shown in our analysis, NIH-backed or multi-source funding is of increased importance for successful

completion of DBS trials (but not necessarily for the publication of meaningful results).

There are several limitations to the present study. First, although ClinicalTrials.gov is considered a relatively comprehensive dataset, it may be incomplete, especially for studies that were not labelled as a clinical trial. Of note, once a trial is registered, it may not be removed from the database. This mitigates sampling bias for unsuccessful trials. This database is also likely to be biased towards United States-based trials, as only trials conducted within the US are mandated to register with ClinicalTrials.gov.[50] Clinical trials conducted outside of the US may differ in success rates and it is likely that the barriers to trial completion differ.[51] To this end, focused study on the characteristics of international clinical trials is needed, as the globalization of DBS clinical trials will support the drive to make this therapy more accessible to the global community and ensure that study findings are generalizable beyond the US. Hence, it is imperative that we continue to strive towards multinational cooperative clinical trials,[52] including finding novel solutions to accommodate for variations in institutional frameworks and cultural attitudes that may impact clinical trial success. It is also possible that there is some delay or failure to update trials in this database by the investigators or institutions. Furthermore, the "Why Study Stopped" data element was introduced in February 2007, and such trials may have diminished data quality and presence. There are several limitations of multinomial logistic regression models. We utilized the assumption that data entries are completely independent from each other. However, it is possible that clinical trials were developed from results from other clinical trials. This may hold especially true for institutions or research teams with more extensive clinical trial experience and ongoing study.

5. Conclusion

DBS is utilized for a wide, expanding range of indications, and clinical trials are necessary to evaluate its efficacy. One out of five clinical trials for DBS were found to be unsuccessful, most commonly due to patient recruitment difficulties. Source of funding appears to be associated with trial success. Those with multiple sponsors or funding from the NIH were found to be more successful than trials without such support. As the DBS research footprint continues to expand, such analysis can provide insight into the current and future state of ongoing clinical study.

Statement of ethics

An ethics statement was not required for this study type, no human or animal subjects or materials were implemented.

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Data availability statement

All study data and analytic scripts may be made available upon reasonable request by contacting the corresponding author.

CRediT authorship contribution statement

Akash Mishra: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Sabrina L. Begley:** Writing – review & editing, Data curation. **Harshal A. Shah:** Methodology, Data curation, Conceptualization. **Brandon A. Santhumayor:** Writing – review & editing. **Ritesh A. Ramdhani:** Writing – review & editing, Supervision. **Albert J. Fenoy:** Writing – review & editing, Supervision. **Michael Schulder:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

CI: Confidence Interval
DBS: Deep Brain Stimulation
ET: Essential Tremor
FDA: Food and Drug Administration
MDD: Major Depressive Disorder
NIH: National Institutes of Health
OCD: Obsessive-Compulsive Disorder
OR: Odds Ratio
PD: Parkinson's Disease
SEEG: Stereoelectroencephalography
TRD: Treatment-resistant Depression