

# The 10-year Landscape of United States-Registered Parkinson Disease Clinical Trials: 2007–2016

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**Abstract:** Background: We know little about how well the goals and results of clinical trials in Parkinson disease (PD) reflect the priorities of patients and the broader PD community.

Objectives: We conducted a review of registered trials on clinicaltrials.gov from 2007 to 2016 to explore whether PD trials have moved closer to the therapeutic priority goals articulated by the PD community.

Methods: Using the search terms: Parkinson, interventional trials, phase “0-4,” we categorized therapeutic PD studies from clinicaltrials.gov between January 1, 2007 and December 31, 2016. Seven hundred and sixty-six trials met the criteria for analysis. We explored temporal trends in the utilization of balance problems and falls; mood symptoms, including stress and anxiety; cognitive dysfunction, including dementia; and dyskinesias as primary outcomes. We analyzed trials where recruitment was listed as “completed” (n = 391) to explore publication rates.

Results: Balance problems and falls were listed as primary outcome measures in 125 studies (16.3%), cognitive measures in 48 (6.3%), mood features in 37 (4.8%), and dyskinesias in 30 (3.9%). Trials using balance problems and falls as a primary outcome increased in frequency per year between 2007 and 2016 ( $Z = -2.128, p = 0.033$ ) unlike the proportion of trials evaluating cognitive dysfunction including dementia ( $Z = -0.380, p = 0.704$ ), mood symptoms including stress and anxiety ( $Z = 0.345, p = 0.730$ ), or dyskinesias ( $Z = 0.340, p = 0.734$ ), which did not show temporal changes. 231 (59.1%) completed trials had results published in manuscript form as of 5/1/2017, leaving 40.9% of trials unpublished.

Conclusions: PD trials focusing on balance problems and falls are becoming more common. About 40% of completed PD trials are unpublished, reflecting suboptimal utilization of participant efforts.

## Introduction

The successful conduct of clinical trials in Parkinson disease (PD) relies on a covenant of shared priorities between investigators and the PD community.<sup>1</sup> The design and execution of PD clinical trials is nearly always contingent upon the successful recruitment & retention—often with the added complexity of blinding and randomization—of interested participants. These individuals are prepared to not only donate their time and effort but also willing take on the prospect of intervention-associated risks,<sup>2</sup> all done for the small prospect of hypothetical future benefits conferred to many people affected by PD, including

hopefully themselves.<sup>3</sup> This contribution by trial participants and their caregivers is one that justifies their role as stakeholders in the development, design, and execution of relevant clinical trials.<sup>4</sup>

Many feel that priority-setting decisions about the relative merits of different trials in relevant clinical populations are an important basic principle of ethical clinical research.<sup>5–7</sup> Collaborative partnerships between disease-focused groups, trial funders, and investigators also yield a practical benefit—better recruitment, improved projected adherence, and higher rates of subject retention are all favorable signs for a trial’s chances of success.<sup>8,9</sup> Perhaps more importantly, collaborative partnerships between

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researchers and research subjects offer the potential to shift a research field's objectives towards the priorities of patients and their caregivers, which may differ from those of researchers.<sup>10</sup> Efforts by previous groups have worked towards this goal by trying to understand patient and community priorities for therapeutic development in variety of different disease states including PD, where top PD-community priority goals related to new treatment development were identified in 2014: treatments for "balance problems and falls," "stress and anxiety," "dyskinesias," and "dementia."<sup>4,11</sup>

In a separate effort to improve both the access to clinical trials & trial results as well as improve the coordination of sponsors and the output delivered to the American public, the United States (US) Congress passed the Food and Drug Administration (FDA) Amendments Act (FDAAA) of 2007 that required all applicable clinical trials of drugs or devices to be registered on the publically-accessible [clinicaltrials.gov](http://www.clinicaltrials.gov) website beginning in 2007.<sup>12</sup> The FDAAA also legally required study teams to update [clinicaltrials.gov](http://www.clinicaltrials.gov) with certain data related to a trial's ongoing conduct including enrollment, adverse events, and results as they become available. International clinical trial oversight bodies have revisited these rules,<sup>13</sup> and the FDAAA itself was revised in 2016

to clarify reporting rules further.<sup>14</sup> Despite variable reporting of data related to ongoing study conduct,<sup>15</sup> <http://www.clinicaltrials.gov> serves as an indexed registry of all applicable PD therapeutic clinical trials since 2007.

We conducted a review of registered PD clinical therapeutic trials on <http://www.clinicaltrials.gov> over a ten-year period between 2007 and 2016 to explore how well primary trial outcomes aligned with the goals of the PD community at large. Given that PD-specific foundations have increasingly helped to empower and advocate for the broader PD community in the arena of clinical trials,<sup>16,17</sup> we hypothesized that PD clinical trial outcome measures would increasingly reflect the top priorities of the PD community.

## Methods

Using the search terms "Parkinson" and advanced filters "interventional studies," "phase '0-4,'" and a date range of studies first posted between January 1, 2006 and December 31, 2016, we identified a total of 1297 studies. Datasets were downloaded from [clinicaltrials.gov](http://www.clinicaltrials.gov) between August 17, 2016 and February

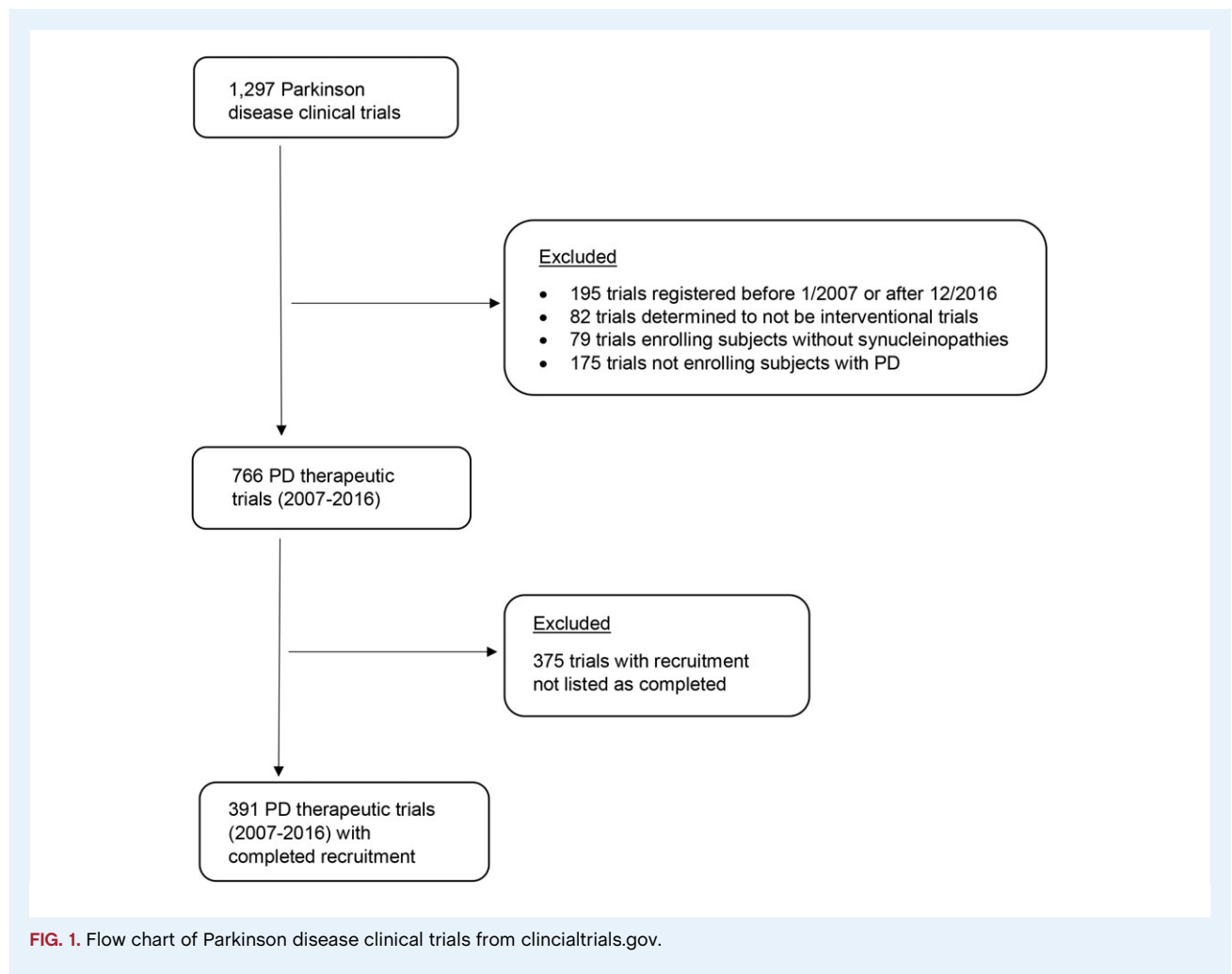


FIG. 1. Flow chart of Parkinson disease clinical trials from [clinicaltrials.gov](http://www.clinicaltrials.gov).

15, 2017. After study team review (Fig. 1) 531 studies were excluded: 195 because they began either before 2007 or after 2016, 82 were not trials of therapeutic interventions, 175 did not include PD participants in their enrollment, and 79 enrolled participants without synuclein-related disorders. The remaining 766 studies were registered trials of therapeutic interventions that limited enrollment to either only PD participants or to participants with PD and other synucleinopathies.

We extracted data about the intended primary therapeutic outcome marker for eligible PD clinical trials from their postings on clinicaltrials.gov. We specifically sought to categorize trials that employed markers of balance problems and falls; cognitive features, including dementia; dyskinesias; and mood features, including stress and anxiety as primary outcome measures. These four outcome measures, along with a fifth clinical research priority focused on understanding disease heterogeneity in PD, were selected on the basis of a PD patient and community survey conducted by Deane et al. as the final top 5 prioritized and ranked uncertainties for the management of Parkinson disease, with an overarching research aspiration being the goal of finding an effective cure for Parkinson disease.<sup>4</sup> We conducted an exploratory analysis to determine whether trials focusing on motor fluctuations (including both dyskinesia treatment and/or increase in on-time/reduction in off-time as outcome markers) had changed in frequency over this time frame. We also tracked the use of the Unified Parkinson's Disease Rating Scale (UPDRS) or the Movement Disorders Society revised UPDRS (MDS-UPDRS) motor exam and total (parts 1 to 3) as a primary outcome reference group. For studies reporting multiple primary outcome markers, we restricted our categorization of primary outcomes to no more than two outcome measures per study. Study team members (K.W., V.K.) reviewed outcome measures and trial characteristics to determine whether the primary objective of a given trial matched one of the four pre-specified categories identified by Deane et al.

## Publication Analysis in Completed Trials

We conducted a literature search to explore publications related to clinical trials whose recruitment was complete ( $n = 391$ ) in May 2017. We searched Pubmed, Google Scholar, Medline, and ISI Web of Science. We used an initial search term of the trial NCT number registered on <http://www.clinicaltrials.gov>. When no

publications were found, we then used additional search terms in an advanced search using linkage term “and” including last name and first initial of the principal investigator, “Parkinson\*,” and a key word or key words from the title of the trial registered on <http://www.clinicaltrials.gov>. We coded studies as either published or not published based on these factors. Abstracts and abstract summaries drawn from meetings were coded as not published since they generally lacked salient details on study design, primary outcome measures, efficacy of randomization, and study conduct.

Funding sources for published relevant clinical trials were determined through a review of a study's posting on <http://www.clinicaltrials.gov>. Organizations listed as either the “Sponsor” or, when relevant, as “Collaborator” were identified as study funders. Eligible funding agencies were categorized as one of five categories: industry organizations, United States (US) federal organizations, US medical centers/universities/research institutes, and other US medical foundations, or “Other” for any remaining funding organizations.

## Statistical Analysis

Descriptive statistics, including means, proportions, and percentages, were used to categorize eligible PD trials over the 10-year period. The Cochran-Armitage test of trend was used to explore temporal changes in the use of balance problems and falls; dyskinesias; cognitive symptoms, including dementia; and mood symptoms, including stress and anxiety as primary outcomes. Clinical trials were categorized according to the year they began. We hypothesized that PD trials would show an increasing trend towards utilization of these primary outcomes over time. In the subset of trials whose recruitment was listed as “completed” on clinicaltrials.gov, we used chi-square testing to explore whether funding source category associated with peer-reviewed publication status of trial results. This retrospective study was granted not regulated status by the University of Michigan IRBMED.

## Results

There were 766 PD therapeutic trials registered between 2007 and 2016 (Table 1). Balance problems and falls as a primary outcome measure were listed in 125 studies (16.3%), cognitive measures

**TABLE 1** Primary Outcomes in applicable Parkinson disease clinical trials 2007-2016 registered on <http://www.clinicaltrials.gov>

		All therapeutic trials (n=766)	Published therapeutic trials (n=391)
<b>High priority outcome measures</b>	<b>Primary outcomes</b>	<i>N (%)</i>	<i>N (%)</i>
	Gait/Balance	125 (16.3%)	50 (12.8%)
	Cognitive	48 (6.3%)	24 (6.1%)
	Mood	37 (4.8%)	16 (4.1%)
<b>Other common outcome measures</b>	Dyskinesia	30 (3.9%)	15 (3.8%)
	Safety/tolerability outcomes	88 (11.5%)	75 (19.2%)
	UPDRS/MDS-UPDRS Motor exam	75 (9.8%)	38 (9.7%)
	Biomarker primary outcomes	62 (8.1%)	26 (6.6%)
	Optimizing on/off-time	61 (8.0%)	39 (10.0%)
	UPDRS/MDS-UPDRS total exam	38 (5.0%)	19 (4.9%)

Abbreviations: MDS-UPDRS, Movement Disorders Society revised Unified Parkinson's Disease Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

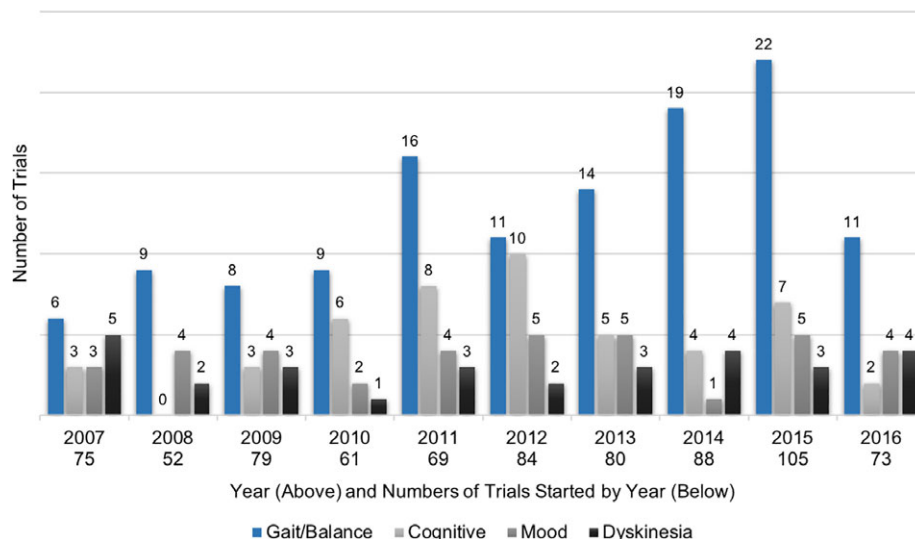


FIG. 2. Trends in four categories of primary outcomes in registered Parkinson disease clinical trials (2007–2016).

including dementia in 48 (6.3%), dyskinesias in 30 (3.9%), and mood features, including stress and anxiety in 37 (4.8%). Trials using balance problems and falls as a primary outcome measure increased in frequency/year over the study period (Cochran-Armitage test of trend  $Z = -2.128$ ,  $p = 0.033$ ; Fig. 2). To determine whether this increase was due to an increasing trend of physiotherapy or exercise trials focused on gait and balance, we categorized interventions among the 125 balance studies as ones involving any element of physiotherapy/exercise ( $n = 60$ ) versus all others ( $n = 65$ ). No significant trend was seen for an increasing frequency of physiotherapy/exercise trials over the 2007 to 2016 timeframe ( $Z = -0.935$ ,  $p = 0.351$ ). Trials employing cognitive measures including dementia ( $Z = -0.380$ ,  $p = 0.704$ ), dyskinesias ( $Z = 0.340$ ,  $p = 0.734$ ), or mood features including stress and anxiety ( $Z = 0.345$ ,  $p = 0.730$ ) as primary outcomes did not show any change in proportion-per-year over the 10-year study period. There were no changes in the proportion of trials focusing on motor fluctuations, including either dyskinesias and/or optimization of on/off-time as a primary outcome marker, but rather a non-significant trend towards a decrease in the proportion of these trials ( $Z = 1.854$ ,  $p = 0.064$ ) over this 10-year period. Trials using either part III (motor exam summative score) or a total score of either the UPDRS or MDS-UPDRS as a primary outcome were listed in 75 (9.8%) and 38 (5.0%) studies respectively. Neither UPDRS/MDS-UPDRS motor exam nor total scores showed a relative increase in use over this 10-year period (motor exam: [ $Z = 0.873$ ,  $p = 0.383$ ]; total exam: [ $Z = 0.038$ ,  $p = 0.969$ ]).

Of the 766 total trials, 554 (72.3%) involved some element of randomization. Trials involving US Federal funding were more likely to be randomized ( $\chi^2 = 5.31$ ,  $p = 0.021$ ). 375 trials (49.0%) were double-blinded. Industry-sponsored trials were more likely to be double-blinded ( $\chi^2 = 38.33$ ,  $p < 0.0001$ ) and trials funded by individual US Medical Centers/Universities/

Research Institutes were less likely to be double-blinded ( $\chi^2 = 5.51$ ,  $p = 0.019$ ). A total of 350 (45.7%) of trials were placebo-controlled. Trials receiving Industry funding ( $\chi^2 = 28.94$ ,  $p < 0.0001$ ) or a medical foundation funding ( $\chi^2 = 4.31$ ,  $p = 0.038$ ) were more likely to use a placebo.

Of the 391 studies with completed recruitment, 231 (59.1%) had results published in manuscript form, leaving 40.9% of trials with complete recruitment unpublished (Fig. 3). Among studies that began in the first half of our study window (between 2007 and 2011 [ $n = 234$ ]), 29.5% were unpublished. Of studies with complete recruitment that began between 2012 and 2016 ( $n = 157$ ), 57.96% were unpublished. Among the 391 completed-recruitment studies, receiving funding from a medical foundation ( $n = 29$ ) associated with a higher likelihood of a trial being published ( $\chi^2 = 4.80$ ,  $p = 0.029$ ). The Michael J. Fox Foundation ( $n = 20$ ) and the National Parkinson Foundation ( $n = 4$ ) were the two most common foundation-funding agencies. There were no significant associations between publication status and receiving funding from an Industry source ( $n = 184$ ,  $\chi^2 = 0.007$ ,  $p = 0.933$ ), individual US Medical Centers/Universities/Research Institutes ( $n = 61$ ,  $\chi^2 = 0.301$ ,  $p = 0.583$ ), or US Federal organizations ( $n = 22$ ,  $\chi^2 = 1.334$ ,  $p = 0.248$ ). Of the 766 registered PD therapeutic trials, 338 (44.1%) had performance sites in the US. Of the 391 completed trials, studies with performance sites in the US ( $n = 176$  of 391; 45%) showed a similar rate of publication compared to those without US performance sites ( $\chi^2 = 0.691$ ,  $p = 0.406$ ).

## Discussion

Parkinson disease clinical trials are increasingly focusing on treatments of balance problems and falls as primary outcomes, a trend

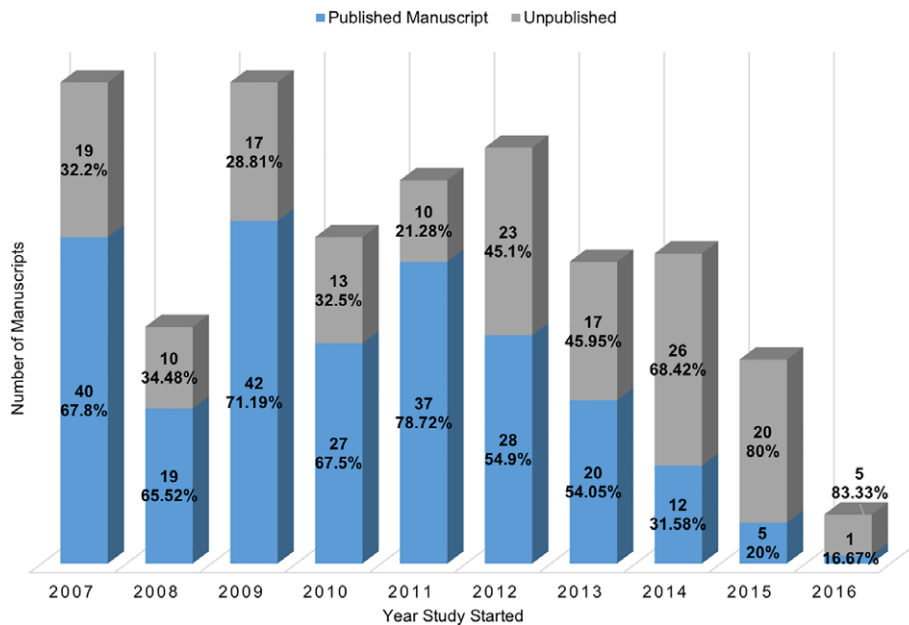


FIG. 3. Peer-reviewed published manuscripts among completed Parkinson disease clinical trials (2007–2016).

avored by individuals with PD and PD researchers as well.<sup>4,18</sup> This is a good sign. Our findings, however, do not suggest an increase in the proportion of trials focusing on other key PD community research goals such as cognitive impairment including dementia, mood features including stress and anxiety symptoms, or dyskinesias. Only about 60% of all registered PD trials with complete recruitment between 2007 and 2016 have published their results in manuscript form; this finding is concerning. Completed trials funded by extramural medical foundations were more likely to be published in contrast to studies funded by industry, US federal agencies, or US single-center medical centers. Collectively, these findings are both a sign of optimism and point to future directions for targeted improvement in PD clinical trials planning and execution.

Balance problems and falls are significant determinants of disability in PD and strong risk factors for subsequent cognitive decline and mortality.<sup>19,20</sup> PD balance impairments commonly have multifactorial etiologies, varied early clinical manifestations, and no well-validated set of outcome parameters with which to track either disability or the efficacy of therapeutic interventions, making the design and conduct of clinical trials more challenging.<sup>21–23</sup> Parkinson's researchers in a panel commissioned by the US National Institute of Neurological Disorders and Stroke (NINDS) recognized the goal of developing treatments for gait and balance impairments as one of their top two ranked clinical research priorities along with understanding prodromal disease progression.<sup>18</sup> A limitation of clinicaltrials.gov is that trials of interventions other than drugs or devices (ie, those that are not FDA-regulated) such as exercise or physical therapy may not always be registered and subsequently may not be captured. The

may be particularly relevant for trials focused on improving balance impairments in PD. For example, a recent review of PD fall-prevention clinical trials with > 100 participants since 2011 revealed two drug trials and five exercise-related trials.<sup>23</sup> Trends towards increasing emphasis on gait and balance markers in PD trials are encouraging and suggest an increasing alignment between patient and researcher priorities in PD therapeutic development.

Registered clinical trials focusing on cognitive impairment, including dementia; mood symptoms, including stress and anxiety; and dyskinesia burden as primary outcomes remain a relatively small fraction of the body of PD trials and are not becoming more common. The growth of non-pharmacological cognitive training interventions, with variable registration on <http://www.clinicaltrials.gov>, may be one reason why the percentage of drug or device interventions remain static.<sup>24,25</sup> The lack of change in the dyskinesia trial proportion may reflect increasing utilization of deep brain stimulation for managing PD motor fluctuations, including dyskinesias.<sup>26</sup> Alternatively, the ability to successfully recruit for anti-dyskinesia trials may be challenging given their temporally-limited prevalence among people with PD.<sup>27,28</sup> Mood disorders in PD include depression, apathy, and anxiety. Each can occur as early features in the natural history of PD.<sup>29</sup> It is possible that non-motor mood symptoms remain under-recognized by patients and providers, contributing to an under-prioritization of these symptoms as a primary objective of trials.<sup>30</sup> It is also possible that patients with symptoms of anxiety or depression are, by virtue of the severity of their affective disease burden, more reluctant to participate in clinical trials in general, limiting the enthusiasm for such primary

outcome targets on the part of funding agencies. It should be noted that the Deane et al. study enrolled a cohort of PD community members in the United Kingdom (UK). It is possible that their ranked priorities may not mirror those of PD community members in other countries including the US.

Approximately 40% of completed PD clinical trials were not published in manuscript form in peer-reviewed journals. This percentage is a high number that points to inefficiencies and wasted participant effort in the PD trials enterprise. Similar concerning trends have been seen in other neurological disorders as well.<sup>31</sup> We found it was not uncommon for large, completed trials to be presented in abstract form at national or international meetings, only to be shrouded from public view afterward—searchable in some cases through an aggregate list of hundreds of published abstracts using only a subset of scientific literature search engines. Given the lack of details about study design, planned primary outcomes, blinding, randomization, and recruitment targets, these abstracts are not able to sufficiently inform a reader about whether a hypothesized treatment intervention was successful or not. It is also important to note that published data for recently completed trials may be forthcoming and in general and should be viewed differently from trials that completed enrollment many years ago. Interestingly, trials receiving funding from PD foundations were more likely to be published than those receiving funding from other sources. This finding is encouraging because it suggests US medical foundations such as the Michael J Fox Foundation among others may currently be identifying successful elements of trial execution in the peer review stage. Our data are of limited granularity, but overall, they give us no reason to believe that non-foundation trials are more poorly designed than foundation-sponsored trials. One of several possible reasons foundation-sponsored trials may be more likely to be published includes a tighter and more transparent bond between stakeholders who fund a given foundation and their expectation of a return on investment. This bond may lead to a more explicit directive for foundations and their staff to be involved in the public dissemination of foundation-funded trials. One would imagine that this is less true in the US federally funded studies. The US National Institutes of Health recognized this issue related to non-publication of trial findings<sup>32</sup> and in 2017 revised its policies to better “exercise proper stewardship of precious public resources.”<sup>33</sup> Although industry-sponsored trials are characterized by rigorous scientific planning, they may be initiated for reasons that differ from non-industry trials. These factors may also affect publication rates. Understanding the reasons for non-publication of clinical trials is an issue with emerging public health relevance.

Our presented analyses have several limitations. First, they rely on accurate reporting of trial parameters by the study team through the <http://www.clinicaltrials.gov> website. It is possible that inaccurate trial registration details may have led us to over- or underestimate the true prevalence of certain primary outcomes. Given the heterogeneity of reporting quality seen in more complex elements of study registration data, including blinding, the phase of the trial, and secondary outcome measures, we did not utilize these more advanced data to answer other impactful questions about changes

in PD trial design from 2007 to 2016. Registration in <http://www.clinicaltrials.gov> is legally mandated for US FDA-regulated studies and is typically encouraged, though not required, for other clinical trials aiming to publish results in US-affiliated journals. By relying only on [clinicaltrials.gov](http://www.clinicaltrials.gov), we did not capture a broad cohort of studies from other websites in use across Asia, Europe, South America, Africa, and other regions of the world where PD is common and where trial registration requirements differ. It is also possible that some of the 2007 to 2016 longitudinal temporal trends seen in our study do not reflect the true distribution of all PD therapeutic clinical trials, but instead more closely reflect an increasing familiarity among study teams with the use of the <http://www.clinicaltrials.gov> website. We also note that we excluded studies that recruited participants without synucleinopathies (eg, recruitment cohorts that included both Parkinson disease and Alzheimer’s disease subjects). These exclusion criteria allowed us to assess PD-focused trials more specifically, but may also have impacted our findings.

A PD clinical trial is often the result of years of preclinical and translational research. Developing systematic ways to give PD patients and community members a greater say in research goals and priorities is likely to yield a body of trials that more efficiently use finite human resources and whose results better suit the needs of intended consumers. Clear first steps towards this goal might include reaching out to PD community members to serve on scientific review panels, a practice already being conducted by a number of PD funding agencies. Others have favored using a measure of “relevance” as pre-funding review criteria.<sup>10</sup> Equally important may be giving PD community members an identified forum—perhaps via social media or through Parkinson-related meetings—to influence the ideas of PD scientists. Either way, a more common vision of shared priorities between researchers and PD community members is likely to improve the long-term fruits of PD clinical research.

## Author Roles

1. Research Project: A. Conception, B. Organization, C. Execution; 2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique; 3. Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

K.J.W.: 1ABC, 2C, 3B

E.Y.: 1BC, 3B

V.K.: 1ABC, 2AB, 3A

## Disclosures

**Ethical Compliance Statement:** The authors confirm that this retrospective study was granted not regulated status by the University of Michigan IRBMED. Further approval of an institutional review board was not required for this work. We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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