The 10-year landscape of United States-registered Parkinson disease clinical trials: 2007-2016

Running title: *PD and clinicaltrials.gov*

Authors:
Kara J. Wyant, MD[1], Erika Yasuda[1], Vikas Kotagal, MD, MS[1,2]

Veterans Affairs Ann Arbor Health System (VAAAHS) & VAAAHS GeriatriResearch Education and Clinical Center (GRECC), Ann Arbor, Michigan

Corresponding Author:
Vikas Kotagal
Building 14, North Campus Research Complex
University of Michigan
2800 Plymouth Road
Ann Arbor MI, 48109
vikaskot@med.umich.edu
Phone: 734-936-9010
Fax: 734-615-4991

Keywords: Parkinson disease, clinical trials, gait, funding, publication

Title character count: 94
Running title character count: 25
Abstract word count: 250
Introduction word count: 494
Discussion word count: 1385
Manuscript word count: 3107
References: 33
Figures: 3
Tables: 1

Funding sources and Conflicts of Interest: No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work

Financial Disclosures for the previous 12 months:
Dr. Wyant receives funding from the Eli Lilly & Co. Foundation for her role as a site-investigator on a clinical trial. She anticipates future funding from the Michael J Fox Foundation (MJFF) for an upcoming site investigator role on an MJFF-funded multicenter trial.

Ms. Yasuda has no other sources of funding to disclose.

Dr. Kotagal receives funding from the NIH (NIA P30AG024824 KL2, NINDS R56NS082941), and the VA Health System (IK2CX001186 and VAAAHS GRECC).

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 clincialtrials.gov between 2007-2016 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 1/1/2007-12/31/2016. 766 trials met 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.[1] 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 prepared to not only donate their time and effort but also willing take on the prospect of intervention-associated risks,[2] all done for the small prospect of hypothetical future benefits conferred to many people affected by PD, including hopefully themselves.[3] This contribution by trial participants and their

caregivers is one that justifies their role as stakeholders in the development, design, and conduction of relevant clinical trials.[4]

Many feel that engaging relevant clinical populations in priority-setting decisions about the relative merits of different trials is an important basic principle of ethical clinical research.[5-7] Collaborative partnerships between disease-focused community groups and trial funders and investigators also yield a practical benefit— better recruitment, improved projected adherence, and higher rates of subject retention all are favorable signs for a trial's chances of success.[8, 9] Perhaps more importantly, collaborative partnerships between 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.[10] 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".[4, 11]

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 website beginning in 2007.[12] The FDAAA also legally required study teams to update clincialtrials.gov with certain data related to a trial's ongoing conduct including enrollment, adverse events, and results as they become available. These rules have been revisited by international clinical trial oversight bodies[13] and the FDAAA itself was revised in 2016 to further clarify reporting rules.[14] Despite variable reporting of data related to ongoing study conduct,[15] 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 clinicaltrials.gov over a ten-year period between 2007 and 2016 to explore how well trial primary 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,[16, 17] 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 1/1/2006 and 12/31/2016,

we identified a total of 1297 studies. Datasets were downloaded from clincialtrials.gov between 8/17/16 and 2/15/17. After study team review (Figure 1) 531 studies were excluded: 195 because they began either prior to 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 clincaltrials.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.[4] 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 1-3) as a primary outcome reference group. For studies reporting multiple primary outcome markers, we restricted our categorization of primary outcomes to no more than 2 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 of 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 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(s) from the title of the trial registered on 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 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 clincialtrials.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

766 PD therapeutic trials were 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 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) (Figure 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) vs. all others (n=65). No significant trend was seen for an increasing frequency of physiotherapy/exercise trials over the 2007-2016 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 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 (χ^2=5.31, p=0.021). 375 trials (49.0%) were double blinded. Industry sponsored trials were more likely to be double-blinded (χ^2=38.33, p<0.0001) and trials funded by individual US Medical Centers/Universities/Research Institutes were less likely to be double blinded (χ^2=5.51, p =0.019). A total of 350 (45.7%) of trials were placebo controlled. Trials receiving Industry funding (χ^2=28.94, p<0.0001) or a medical foundation funding (χ^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 as

unpublished (Figure 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 (χ^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, χ^2=0.007, p=0.933), individual US Medical Centers/Universities/Research Institutes (n=61, χ^2=0.301, p=0.583), or US Federal organizations (n=22, χ^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 (χ^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 favored by individuals with PD and PD researchers as well.[4, 18] This is a good sign. Our findings, however, do not

suggest any 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 is a concerning finding. 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.[19, 20] 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.[21-23] 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 2 ranked clinical research priorities along with understanding prodromal disease progression.[18] A limitation of clincaltrials.gov is that trials of interventions other than drugs or devices—i.e. those that are not FDA regulated—such

as exercise or physical therapy may not always be registered and subsequently may not be captured. For example, a recent review of PD fall-prevention clinical trials with >100 participants since 2011 revealed 2 drug trials and 5 exercise-related trials.[23] 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 clinicaltrials.gov, may be one reason why the percentage of drug or device interventions remain static.[24, 25] The lack of change in the dyskinesia trial proportion may reflect increasing utilization of deep brain stimulation for management of PD motor fluctuations including dyskinesias.[26] Alternatively, the ability to successfully recruit for anti-dyskinesia trials may be challenging given their temporally-limited prevalence among people with PD.[27, 28] Mood disorders in PD include depression, apathy, and anxiety. Each are commonly seen as early features in the natural history of PD.[29] It is possible that non-motor mood symptoms remain under-recognized by patients and providers, contributing to an under-prioritization of their treatment as a primary objective of trials.[30] 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 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.[31] 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 afterwards--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 important to also 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 is an encouraging finding that 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 include a tighter and more transparent bond between stakeholders who fund a given foundation and their expectation of a return on investment. This 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 US federally funded studies. The US National Institutes of Health recognized this issue related to non-publication of trial findings[32] and in 2017 revised its policies to better "exercise proper stewardship of precious public resources".[33] Industry sponsored trials, though they are characterized by rigorous scientific planning and well-coordinated execution, may be initiated for reasons that differ from non-Industry trials. Understanding the factors 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 clinicaltrials.gov website. It is possible that inaccurate trial registration details may have led us to over- or under-

estimate the true prevalence of certain primary outcomes. Given the heterogeneity of reporting quality seen in more complex elements of study registration data—such as blinding, phase of trial, secondary outcome measures, etc.—we did not utilize these more advanced data to answer other impactful questions about changes in PD trial design over the 2007-2016 time period. Registration in clincialtrials.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 clincialtrials.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 2007-2016 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 clincialtrials.gov website. We also note that we excluded studies that recruited participants without synucleinopathies (e.g. recruitment cohorts that included both Parkinson disease and Alzheimer's disease subjects). These exclusion criteria allowed us to more specifically assess PD-focused trials but may also have impacted our findings.

A PD clinical trial is often the end 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 end 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.[10] 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: A. Writing of the first draft, B. Review and Critique.

KJW: 1ABC, 2C, 3B
EY: 1BC, 3B
VK: 1ABC, 2AB, 3A

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.

References

1. Cohen PD, Herman L, Jedlinski S, Willocks P, Wittekind P. Ethical issues in clinical neuroscience research: a patient's perspective. Neurotherapeutics 2007;4(3):537-544.

2. Mathur S, DeWitte S, Robledo I, Isaacs T, Stamford J. Rising to the Challenges of Clinical Trial Improvement in Parkinson's Disease. J Parkinsons Dis 2015;5(2):263-268.

3. Wendler D, Krohmal B, Emanuel EJ, Grady C. Why patients continue to participate in clinical research. Arch Intern Med 2008;168(12):1294-1299.

4. Deane KH, Flaherty H, Daley DJ, et al. Priority setting partnership to identify the top 10 research priorities for the management of Parkinson's disease. BMJ Open 2014;4(12):e006434.

5. Weijer C, Emanuel EJ. Ethics. Protecting communities in biomedical research. Science 2000;289(5482):1142-1144.

6. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? The benchmarks of ethical research. J Infect Dis 2004;189(5):930-937.

7. Nurmi SM, Halkoaho A, Kangasniemi M, Pietila AM. Collaborative partnership and the social value of clinical research: a qualitative secondary analysis. BMC Med Ethics 2017;18(1):57.

8. Alexander W. The uphill path to successful clinical trials: keeping patients enrolled. P t 2013;38(4):225-227.

9. Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance, compliance, and compliance. Mol Interv 2011;11(2):107-110.

10. Crowe S, Fenton M, Hall M, Cowan K, Chalmers I. Patients', clinicians' and the research communities' priorities for treatment research: there is an important mismatch. Research involvement and engagement 2015;1:2.

11. Partridge N, Scadding J. The James Lind Alliance: patients and clinicians should jointly identify their priorities for clinical trials. Lancet (London, England) 2004;364(9449):1923-1924.

12. Zarin DA, Tse T. Medicine. Moving toward transparency of clinical trials. Science 2008;319(5868):1340-1342.

13. De Angelis CD, Drazen JM, Frizelle FA, et al. Is this clinical trial fully registered?--A statement from the International Committee of Medical Journal Editors. The New England journal of medicine 2005;352(23):2436-2438.

14. Zarin DA, Tse T, Williams RJ, Carr S. Trial Reporting in ClinicalTrials.gov - The Final Rule. The New England journal of medicine 2016;375(20):1998-2004.

15. Cahan A, Anand V. Second thoughts on the final rule: An analysis of baseline participant characteristics reports on ClinicalTrials.gov. PLoS One 2017;12(11):e0185886.

16. Dorsey ER, Wagner JD, Bull MT, et al. Feasibility of Virtual Research Visits in Fox Trial Finder. J Parkinsons Dis 2015;5(3):505-515.

17. Sherer TB. Money without collaboration won't bring cures. Nat Med 2013;19(2):127.

18. Sieber BA, Landis S, Koroshetz W, et al. Prioritized research recommendations from the National Institute of Neurological Disorders and Stroke Parkinson's Disease 2014 conference. Annals of neurology 2014;76(4):469-472.

19. Anang JB, Gagnon JF, Bertrand JA, et al. Predictors of dementia in Parkinson disease: a prospective cohort study. Neurology 2014;83(14):1253-1260.

20. Pinter B, Diem-Zangerl A, Wenning GK, et al. Mortality in Parkinson's disease: a 38-year follow-up study. Movement disorders : official journal of the Movement Disorder Society 2015;30(2):266-269.

21. Allen NE, Sherrington C, Paul SS, Canning CG. Balance and falls in Parkinson's disease: a meta-analysis of the effect of exercise and motor training. Movement disorders : official journal of the Movement Disorder Society 2011;26(9):1605-1615.

22. Shen X, Wong-Yu IS, Mak MK. Effects of Exercise on Falls, Balance, and Gait Ability in Parkinson's Disease: A Meta-analysis. Neurorehabilitation and neural repair 2016;30(6):512-527.

23. Fasano A, Canning CG, Hausdorff JM, Lord S, Rochester L. Falls in Parkinson's disease: A complex and evolving picture. Movement disorders : official journal of the Movement Disorder Society 2017;32(11):1524-1536.

24. Davis AA, Racette B. Parkinson disease and cognitive impairment: Five new things. Neurology Clinical practice 2016;6(5):452-458.

25. Leung IH, Walton CC, Hallock H, Lewis SJ, Valenzuela M, Lampit A. Cognitive training in Parkinson disease: A systematic review and meta-analysis. Neurology 2015;85(21):1843-1851.

26. Youngerman BE, Chan AK, Mikell CB, McKhann GM, Sheth SA. A decade of emerging indications: deep brain stimulation in the United States. Journal of neurosurgery 2016;125(2):461-471.

27. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Movement disorders : official journal of the Movement Disorder Society 2001;16(3):448-458.

28. Fabbrini G, Brotchie JM, Grandas F, Nomoto M, Goetz CG. Levodopa-induced dyskinesias. Movement disorders : official journal of the Movement Disorder Society 2007;22(10):1379-1389; quiz 1523.

29. Tan LC. Mood disorders in Parkinson's disease. Parkinsonism & related disorders 2012;18 Suppl 1:S74-76.

30. Bhidayasiri R, Truong DD. Therapeutic strategies for nonmotor symptoms in early Parkinson's disease: the case for a higher priority and stronger evidence. Parkinsonism & related disorders 2012;18 Suppl 1:S110-113.

31. Hakala AK, Fergusson D, Kimmelman J. Nonpublication of trial results for new neurological drugs: A systematic review. Annals of neurology 2017;81(6):782-789.

32. Hudson KL, Lauer MS, Collins FS. Toward a New Era of Trust and Transparency in Clinical Trials. Jama 2016;316(13):1353-1354.

33. National Institutes of Health https://grantsnihgov/policy/clinical-trials/why-changeshtm.

Figure 1: Flow chart of Parkinson disease clinical trials from clincialtrials.gov

Figure 2: Trends in four categories of primary outcomes in registered Parkinson disease clinical trials (2007-2016)

Figure 3: Peer-reviewed published manuscripts among completed Parkinson disease clinical trials (2007-2016)

COPYRIGHT TRANSFER AGREEMENT

Date: 3/13/2018

Contributor name: Kara J Wyatt

Contributor address: 1324 Taubman Center, Reception C, 1500 E Medical Center Dr. SPC 5322, Ann Arbor, MI 48109

Manuscript number:

Re: Manuscript entitled: The 10-year landscape of registered Parkinson disease clinical trials: 2007-2016 (the "Contribution")

for publication in: Movement Disorders (the "Journal")

Published by Wiley on behalf of The International Parkinson and Movement Disorder Society (the "Owner")

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void. **Publication cannot proceed without a signed copy of this Agreement.**

A. COPYRIGHT

The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to reproduce, publish, republish, transmit, sell, transfer, distribute, and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution. This reservation of rights does not affect or limit the rights assigned to Owner in Section A.

C. PERMITTED USES BY CONTRIBUTOR

1. License. The Owner grants to Contributor a non-exclusive, non-transferable and limited license to reproduce and distribute copies of the print or electronic "preprints" of the unpublished Contribution, in the original form submitted to the Journal prior to the peer review process, solely to colleagues within the Contributor's nonprofit organization or educational institution. The Contributor shall make no more than 100 printed copies of the preprints in any calendar year. Such preprints may be posted as electronic files on the Contributor's own personal website, on the Contributor's internal intranet at Contributor's nonprofit organization or educational institution, or on a secure external website at the Contributor's nonprofit organization or educational institution, provided that access is limited to employees and/or students at Contributor's non-profit organization or educational institution. Contributor shall not charge a fee for any

preprints, and Contributor's use under this Section C shall not be for any commercial purpose, or for any systematic external distribution (e.g., posting on a listserve, public website, database connected to a public access server, or automated delivery system). The license grant in this Section does not apply to for-profit corporations, and any proposed use outside of the scope of this Section C must be pre-approved in writing by the Owner. The rights granted to Contributor under this Section C do not include reproduction, distribution or any other use of rating scales, videos or other audiovisual materials associated with the Contribution.

2. Required Citation. Prior to publication, the Contributor must provide full credit and acknowledgement of the Journal in all preprints in the following format: This is a preprint of an article accepted for publication in [Journal Title], Copyright © [year] The International Parkinson and Movement Disorder Society. After publication, the Contributor must provide a citation to the Journal in all preprints in the following format: This is a preprint of an article that was published in [Journal title]: (Title of Article, Contributor, Journal Title and Volume/ Issue, Copyright © [year] The International Parkinson and Movement Disorder Society). An electronic link must be provided to the Journal's website, located at http://www.interscience.Wiley.com. The Contributor agrees not to update the preprint or replace it with the published version of the Contribution.

3. Accepted Version. Re-use of the accepted and peer-reviewed (but not the final typeset published) version of the Contribution (the "Accepted Version") is not permitted under this Agreement. There are separate arrangements with certain funding agencies governing reuse of the Accepted Version. Additional terms apply if the Contributor receives or received funding from these agencies. The details of those relationships, and other offerings allowing open web use, are set forth at the following website: http://www.wiley.com/go/ funderstatement.

4. Additional Terms for Certain Funders. Certain funders, including the NIH, members of the Research Councils UK (RCUK) and Wellcome Trust require deposit of the Accepted Version in a public repository after an embargo period. Details of funding arrangements are set out at the following website: http://www.wiley.com/go/funderstatement. Additional terms may be applicable. Please contact the production editor for the journal at MDSprod@wiley.com if you have additional funding requirements.

If any Contributor receiving funds from applicable sources does not choose the Owner's OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in a public repository after the following applicable embargo period has expired, subject to further conditions imposed by the RCUK:

a. 12 months from first publication online of the final published version of the Contribution for research funded by members of the Research Councils UK (RCUK) other than The Economic and Social Research Council (ESRC) and the Arts and Humanities Research Council (AHRC); or
b. 24 months from first publication online of the final published version of the Contribution for research funded by ESRC or AHRC.

5. Additional Terms for Certain Institutions. Wiley has arrangements with certain educational institutions to permit the deposit of the Accepted Version in the institutional repository after an embargo period. Details of such arrangements are set out at the following website: http://olabout.wiley.com/WileyCDA/Section/id-406074.html . Additional terms may be applicable.

If any Contributor affiliated with these applicable educational institutions does not choose the Owner's OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in the educational institution's repository after the following applicable embargo period has expired. See the following website for details: http://olabout.wiley.com/WileyCDA/Section/id-817011.html.

D. CONTRIBUTIONS OWNED BY EMPLOYER

If the Contribution was written by the Contributor in the course of the Contributor's employment (as a "work-made-for-hire" in the course of employment), the Contribution is owned by the company/institution which must execute this Agreement (in addition to the Contributor's signature). In such case, the company/institution hereby assigns to the Owner, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in Section A above.

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official U.S. Government purposes only, if the U.S. Government contract or grant so requires. (U.S. Government, U.K. Government, and other government employees: see notes at end.)

F. CONTRIBUTOR'S REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor's original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. The Contribution is submitted only to this Journal and has not been published before. (If excerpts from copyrighted works owned by third parties are included, the Contributor will obtain written permission from the copyright owners for all uses as set forth in the Journal's Instructions for Contributors, and show credit to the sources in the Contribution.) The Contributor also warrants that the Contribution contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury. Upon request, Contributor will provide the data or will cooperating fully in obtaining and providing the data on which the Contribution is based for examination by the editors or their assignees.

G. FINANCIAL DISCLOSURES

The Contributor certifies that his/her financial and material support for this research and work, regardless of date, is clearly identified on Exhibit A to this Agreement. The Contributor has also identified on Exhibit A, all other support unrelated to this research, covering the past year from the date of submission (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields).

H. VIDEO AND PHOTOGRAPHY CONSENT

In the event that the Contribution includes, discloses or incorporates any content (including, without limitation, any video clip or photograph) which identifies any individual patient(s) ("patient identifiable content"), the Contributor obtained from such patient(s) written consent to such inclusion, disclosure or incorporation and that this consent fully complies with all legal requirements, including without limitation, all of the requirements of the laws of the jurisdiction(s) to which the patient(s) and the patient(s)' physician are subject, including the United States Health Insurance Portability and Accountability Act of 1996 ("HIPAA") if applicable. The Contributor hereby certifies that, if the patient consent form is in a language other than English, such consent form meets all of the requirements set forth in the Instructions to Authors. In addition, the Contributor hereby confirms that he/she obtained from patient(s) written consent to use the patient identifiable content in both print and online (i.e., internet/web-based) publication formats. The Contributor further certifies that the person executing any such patient consent form, to the best of his/her knowledge, had legal capacity under applicable law to execute the form on behalf of the patient.

I. ACKNOWLEDGEMENTS

The Contributor should obtain written permission from all individuals named in the acknowledgement since readers may infer their endorsement of data and conclusions. The Contributor certifies that all individuals named in the acknowledgement section have provided written permission to be named.

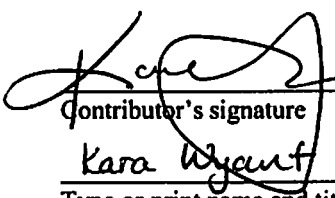
J. MISCELLANEOUS

This Agreement may be amended or modified only in a writing executed by both parties. The waiver or failure of any party to exercise any rights under this Agreement shall not be deemed a waiver or other limitation of any other right or any future right. This Agreement shall inure to the benefit of, and shall be binding upon, the parties, their respective successors and permitted assigns. This Agreement may be executed in two (2) or more counterparts, each of which shall be an original and all of which taken together shall constitute one and the same agreement. Executed copies of this Agreement may be delivered by facsimile transmission, pdf/email or other comparable electronic means. If for any reason any provision of this Agreement shall be deemed by a court of competent jurisdiction to be legally invalid or unenforceable, the validity, legality and enforceability of the remainder of this Agreement shall not be affected and such provision shall be deemed modified to the minimum extent necessary to make such provision consistent with applicable law and, in its modified form, such provision shall then be enforceable and enforced. The parties agree to do such further acts and to execute and deliver such additional agreements and instruments from time to time as either may at any time reasonably request in order to assure and confirm unto such requesting party the rights, powers and remedies conferred in the Agreement. This Agreement, including any exhibits attached hereto, contains the entire agreement and understanding of the parties with respect to the subject matter hereof, and supersedes all prior agreements, negotiations, representations and proposals, written and oral, relating thereto.

All Contributors must sign below. Contributors must check one box except that NIH grantees should check both Contributor-owned work and the NIH grantee box. If your Contribution was written during the course of employment, your employer must also sign where indicated.

Please send your original completed and signed forms by fax or email a scanned copy to the Journal production editor. For production editor contact details please visit the Journal's online author guidelines. **Do not send in hard copies of these forms.**

[_____] Contributor-owned work



Contributor's signature — Date: 3/13/2018

Kara Wyant

Type or print name and title

Co-Contributor's signature — Date

Type or print name and title

[_____] Company/Institution-owned Work (made-for-hire in the Course of employment)

_____ Company or Institution (Employer-for-Hire) _____ Date

_____ Authorized signature of Employer _____ Date

_____ Contributor's signature _____ Date

_____ Type or print name and title

ATTACH ADDITIONAL SIGNATURE PAGES AS NECESSARY

[_____] U.S. Government work

Note to U.S. Government Employees

A contribution prepared by a U.S. federal government employee as part of the employee's official duties, or which is an official U.S. Government publication, is called a "U.S. Government work", and is in the public domain in the United States. In such case, Paragraph A.1 will not apply but the Contributor must type his/her name (in the Contributor's signature line) above. Contributor acknowledges that the Contribution will be published in the United States and other countries. If the Contribution was not prepared as part of the employee's duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[_____] U.K. Government work (Crown Copyright)

Note to U.K. Government Employees

The rights in a contribution prepared by an employee of a UK government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown. Contributors must ensure they comply with departmental regulations and submit the appropriate authorisation to publish. If your status as a government employee legally prevents you from signing this Agreement, please contact the Journal production editor.

[_____] Other

Including Other Government work or Non-Governmental Organisation work

Note to Non-U.S., Non-U.K. Government Employees or Non-Governmental Organisation Employees

If your status as a government or non-governmental organisation employee legally prevents you from signing this Agreement, please contact the Journal production editor.

Kara J. Wyant MD.

Exhibit A

Financial Disclosure

The Contributor has received financial and material support for this research and work regardless of date from the following sources: NA

Name: _____

Address: _____

Type of support: _____

This material will be printed with the published article.

In the past year from the date of submission, the Contributor has also received the following support unrelated to this research (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields):

Name: Michael J Fox Foundation for Parkinson's Research

Address: Grand Central Station, P.O. Box 4777, New York, NY 10163

Type of support: Grant

This material will be posted on the journal website and may be printed at the Editors' discretion.

ATTACH ADDITIONAL INFORMATION AS NECESSARY

Eli Lilly + Co. Foundation
Lilly Corporate Ctr, D.C. 1627, Indianapolis, IN 46285-0001
Site-Investigator on Industry Sponsored protocol

COPYRIGHT TRANSFER AGREEMENT

Date: 3/8/18

Contributor name: Erika Yasuda

Contributor address: 406 Packard St. Ann Arbor, MI 48104 (Apt. 206)

Manuscript number: _____

Re: Manuscript entitled: The 10-year landscape of registered Parkinson disease clinical trials: 2007-2016 (the "Contribution")

for publication in: Movement Disorders (the "Journal")

Published by Wiley on behalf of The International Parkinson and Movement Disorder Society (the "Owner")

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void. **Publication cannot proceed without a signed copy of this Agreement.**

A. COPYRIGHT

The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to reproduce, publish, republish, transmit, sell, transfer, distribute, and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution. This reservation of rights does not affect or limit the rights assigned to Owner in Section A.

C. PERMITTED USES BY CONTRIBUTOR

1. License. The Owner grants to Contributor a non-exclusive, non-transferable and limited license to reproduce and distribute copies of the print or electronic "preprints" of the unpublished Contribution, in the original form submitted to the Journal prior to the peer review process, solely to colleagues within the Contributor's nonprofit organization or educational institution. The Contributor shall make no more than 100 printed copies of the preprints in any calendar year. Such preprints may be posted as electronic files on the Contributor's own personal website, on the Contributor's internal intranet at Contributor's nonprofit organization or educational institution, or on a secure external website at the Contributor's nonprofit organization or educational institution, provided that access is limited to employees and/or students at Contributor's non-profit organization or educational institution. Contributor shall not charge a fee for any

I. ACKNOWLEDGEMENTS

The Contributor should obtain written permission from all individuals named in the acknowledgement since readers may infer their endorsement of data and conclusions. The Contributor certifies that all individuals named in the acknowledgement section have provided written permission to be named.

J. MISCELLANEOUS

This Agreement may be amended or modified only in a writing executed by both parties. The waiver or failure of any party to exercise any rights under this Agreement shall not be deemed a waiver or other limitation of any other right or any future right. This Agreement shall inure to the benefit of, and shall be binding upon, the parties, their respective successors and permitted assigns. This Agreement may be executed in two (2) or more counterparts, each of which shall be an original and all of which taken together shall constitute one and the same agreement. Executed copies of this Agreement may be delivered by facsimile transmission, pdf/email or other comparable electronic means. If for any reason any provision of this Agreement shall be deemed by a court of competent jurisdiction to be legally invalid or unenforceable, the validity, legality and enforceability of the remainder of this Agreement shall not be affected and such provision shall be deemed modified to the minimum extent necessary to make such provision consistent with applicable law and, in its modified form, such provision shall then be enforceable and enforced. The parties agree to do such further acts and to execute and deliver such additional agreements and instruments from time to time as either may at any time reasonably request in order to assure and confirm unto such requesting party the rights, powers and remedies conferred in the Agreement. This Agreement, including any exhibits attached hereto, contains the entire agreement and understanding of the parties with respect to the subject matter hereof, and supersedes all prior agreements, negotiations, representations and proposals, written and oral, relating thereto.

All Contributors must sign below. Contributors must check one box except that NIH grantees should check both Contributor-owned work and the NIH grantee box. If your Contribution was written during the course of employment, your employer must also sign where indicated.

Please send your original completed and signed forms by fax or email a scanned copy to the Journal production editor. For production editor contact details please visit the Journal's online author guidelines. **Do not send in hard copies of these forms.**

[✓] Contributor-owned work

Erika Yasuda
Contributor's signature

3/18/18
Date

Erika Yasuda
Type or print name and title

Co-Contributor's signature

Date

Type or print name and title

COPYRIGHT TRANSFER AGREEMENT

Date: 3/13/18

Contributor name: Vikas Kotagal

Contributor address: 2800 Plymouth Rd, NCRC - Building 14, Ann Arbor, MI 48109

Manuscript number:

Re: Manuscript entitled: The 10-year landscape of registered Parkinson disease clinical trials: 2007-2016 (the "Contribution")

for publication in: Movement Disorders (the "Journal")

Published by Wiley on behalf of The International Parkinson and Movement Disorder Society (the "Owner")

Dear Contributor(s):

Thank you for submitting your Contribution for publication. In order to expedite the editing and publishing process and enable the Owner to disseminate your Contribution to the fullest extent, we need to have this Copyright Transfer Agreement executed. If the Contribution is not accepted for publication, or if the Contribution is subsequently rejected, this Agreement shall be null and void. **Publication cannot proceed without a signed copy of this Agreement.**

A. COPYRIGHT

The Contributor assigns to the Owner, during the full term of copyright and any extensions or renewals, all copyright in and to the Contribution, and all rights therein, including but not limited to the right to reproduce, publish, republish, transmit, sell, transfer, distribute, and otherwise use the Contribution in whole or in part in electronic and print editions of the Journal and in derivative works throughout the world, in all languages and in all media of expression now known or later developed, and to license or permit others to do so.

B. RETAINED RIGHTS

Notwithstanding the above, the Contributor or, if applicable, the Contributor's employer, retains all proprietary rights other than copyright, such as patent rights, in any process, procedure or article of manufacture described in the Contribution. This reservation of rights does not affect or limit the rights assigned to Owner in Section A.

C. PERMITTED USES BY CONTRIBUTOR

1. License. The Owner grants to Contributor a non-exclusive, non-transferable and limited license to reproduce and distribute copies of the print or electronic "preprints" of the unpublished Contribution, in the original form submitted to the Journal prior to the peer review process, solely to colleagues within the Contributor's nonprofit organization or educational institution. The Contributor shall make no more than 100 printed copies of the preprints in any calendar year. Such preprints may be posted as electronic files on the Contributor's own personal website, on the Contributor's internal intranet at Contributor's nonprofit organization or educational institution, or on a secure external website at the Contributor's nonprofit organization or educational institution, provided that access is limited to employees and/or students at Contributor's non-profit organization or educational institution. Contributor shall not charge a fee for any

preprints, and Contributor's use under this Section C shall not be for any commercial purpose, or for any systematic external distribution (e.g., posting on a listserve, public website, database connected to a public access server, or automated delivery system). The license grant in this Section does not apply to for-profit corporations, and any proposed use outside of the scope of this Section C must be pre-approved in writing by the Owner. The rights granted to Contributor under this Section C do not include reproduction, distribution or any other use of rating scales, videos or other audiovisual materials associated with the Contribution.

2. Required Citation. Prior to publication, the Contributor must provide full credit and acknowledgement of the Journal in all preprints in the following format: This is a preprint of an article accepted for publication in [Journal Title], Copyright © [year] The International Parkinson and Movement Disorder Society. After publication, the Contributor must provide a citation to the Journal in all preprints in the following format: This is a preprint of an article that was published in [Journal title]: (Title of Article, Contributor, Journal Title and Volume/ Issue, Copyright © [year] The International Parkinson and Movement Disorder Society). An electronic link must be provided to the Journal's website, located at http://www.interscience.Wiley.com. The Contributor agrees not to update the preprint or replace it with the published version of the Contribution.

3. Accepted Version. Re-use of the accepted and peer-reviewed (but not the final typeset published) version of the Contribution (the "Accepted Version") is not permitted under this Agreement. There are separate arrangements with certain funding agencies governing reuse of the Accepted Version. Additional terms apply if the Contributor receives or received funding from these agencies. The details of those relationships, and other offerings allowing open web use, are set forth at the following website: http://www.wiley.com/go/ funderstatement.

4. Additional Terms for Certain Funders. Certain funders, including the NIH, members of the Research Councils UK (RCUK) and Wellcome Trust require deposit of the Accepted Version in a public repository after an embargo period. Details of funding arrangements are set out at the following website: http://www.wiley.com/go/funderstatement. Additional terms may be applicable. Please contact the production editor for the journal at MDSprod@wiley.com if you have additional funding requirements.

If any Contributor receiving funds from applicable sources does not choose the Owner's OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in a public repository after the following applicable embargo period has expired, subject to further conditions imposed by the RCUK:

a. 12 months from first publication online of the final published version of the Contribution for research funded by members of the Research Councils UK (RCUK) other than The Economic and Social Research Council (ESRC) and the Arts and Humanities Research Council (AHRC); or
b. 24 months from first publication online of the final published version of the Contribution for research funded by ESRC or AHRC.

5. Additional Terms for Certain Institutions. Wiley has arrangements with certain educational institutions to permit the deposit of the Accepted Version in the institutional repository after an embargo period. Details of such arrangements are set out at the following website: http://olabout.wiley.com/WileyCDA/Section/id-406074.html . Additional terms may be applicable.

If any Contributor affiliated with these applicable educational institutions does not choose the Owner's OnlineOpen option, the Contributor will be allowed to self-archive by depositing the Accepted Version in the educational institution's repository after the following applicable embargo period has expired. See the following website for details: http://olabout.wiley.com/WileyCDA/Section/id-817011.html.

D. CONTRIBUTIONS OWNED BY EMPLOYER

If the Contribution was written by the Contributor in the course of the Contributor's employment (as a "work-made-for-hire" in the course of employment), the Contribution is owned by the company/institution which must execute this Agreement (in addition to the Contributor's signature). In such case, the company/institution hereby assigns to the Owner, during the full term of copyright, all copyright in and to the Contribution for the full term of copyright throughout the world as specified in Section A above.

E. GOVERNMENT CONTRACTS

In the case of a Contribution prepared under U.S. Government contract or grant, the U.S. Government may reproduce, without charge, all or portions of the Contribution and may authorize others to do so, for official U.S. Government purposes only, if the U.S. Government contract or grant so requires. (U.S. Government, U.K. Government, and other government employees: see notes at end.)

F. CONTRIBUTOR'S REPRESENTATIONS

The Contributor represents that the Contribution is the Contributor's original work, all individuals identified as Contributors actually contributed to the Contribution, and all individuals who contributed are included. The Contribution is submitted only to this Journal and has not been published before. (If excerpts from copyrighted works owned by third parties are included, the Contributor will obtain written permission from the copyright owners for all uses as set forth in the Journal's Instructions for Contributors, and show credit to the sources in the Contribution.) The Contributor also warrants that the Contribution contains no libelous or unlawful statements, does not infringe upon the rights (including without limitation the copyright, patent or trademark rights) or the privacy of others, or contain material or instructions that might cause harm or injury. Upon request, Contributor will provide the data or will cooperating fully in obtaining and providing the data on which the Contribution is based for examination by the editors or their assignees.

G. FINANCIAL DISCLOSURES

The Contributor certifies that his/her financial and material support for this research and work, regardless of date, is clearly identified on Exhibit A to this Agreement. The Contributor has also identified on Exhibit A, all other support unrelated to this research, covering the past year from the date of submission (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields).

H. VIDEO AND PHOTOGRAPHY CONSENT

In the event that the Contribution includes, discloses or incorporates any content (including, without limitation, any video clip or photograph) which identifies any individual patient(s) ("patient identifiable content"), the Contributor obtained from such patient(s) written consent to such inclusion, disclosure or incorporation and that this consent fully complies with all legal requirements, including without limitation, all of the requirements of the laws of the jurisdiction(s) to which the patient(s) and the patient(s)' physician are subject, including the United States Health Insurance Portability and Accountability Act of 1996 ("HIPAA") if applicable. The Contributor hereby certifies that, if the patient consent form is in a language other than English, such consent form meets all of the requirements set forth in the Instructions to Authors. In addition, the Contributor hereby confirms that he/she obtained from patient(s) written consent to use the patient identifiable content in both print and online (i.e., internet/web-based) publication formats. The Contributor further certifies that the person executing any such patient consent form, to the best of his/her knowledge, had legal capacity under applicable law to execute the form on behalf of the patient.

I. ACKNOWLEDGEMENTS

The Contributor should obtain written permission from all individuals named in the acknowledgement since readers may infer their endorsement of data and conclusions. The Contributor certifies that all individuals named in the acknowledgement section have provided written permission to be named.

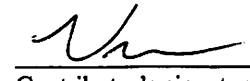
J. MISCELLANEOUS

This Agreement may be amended or modified only in a writing executed by both parties. The waiver or failure of any party to exercise any rights under this Agreement shall not be deemed a waiver or other limitation of any other right or any future right. This Agreement shall inure to the benefit of, and shall be binding upon, the parties, their respective successors and permitted assigns. This Agreement may be executed in two (2) or more counterparts, each of which shall be an original and all of which taken together shall constitute one and the same agreement. Executed copies of this Agreement may be delivered by facsimile transmission, pdf/email or other comparable electronic means. If for any reason any provision of this Agreement shall be deemed by a court of competent jurisdiction to be legally invalid or unenforceable, the validity, legality and enforceability of the remainder of this Agreement shall not be affected and such provision shall be deemed modified to the minimum extent necessary to make such provision consistent with applicable law and, in its modified form, such provision shall then be enforceable and enforced. The parties agree to do such further acts and to execute and deliver such additional agreements and instruments from time to time as either may at any time reasonably request in order to assure and confirm unto such requesting party the rights, powers and remedies conferred in the Agreement. This Agreement, including any exhibits attached hereto, contains the entire agreement and understanding of the parties with respect to the subject matter hereof, and supersedes all prior agreements, negotiations, representations and proposals, written and oral, relating thereto.

All Contributors must sign below. Contributors must check one box except that NIH grantees should check both Contributor-owned work and the NIH grantee box. If your Contribution was written during the course of employment, your employer must also sign where indicated.

Please send your original completed and signed forms by fax or email a scanned copy to the Journal production editor. For production editor contact details please visit the Journal's online author guidelines. **Do not send in hard copies of these forms.**

[✓] Contributor-owned work



Contributor's signature

3/13/18

Date

Vikas Kotagal MD, Assistant Professor of Neurology

Type or print name and title

Co-Contributor's signature

Date

Type or print name and title

[_____] Company/Institution-owned Work (made-for-hire in the Course of employment)

_____ Company or Institution (Employer-for-Hire) _____ Date

_____ Authorized signature of Employer _____ Date

_____ Contributor's signature _____ Date

_____ Type or print name and title

ATTACH ADDITIONAL SIGNATURE PAGES AS NECESSARY

[_____] U.S. Government work

Note to U.S. Government Employees

A contribution prepared by a U.S. federal government employee as part of the employee's official duties, or which is an official U.S. Government publication, is called a "U.S. Government work", and is in the public domain in the United States. In such case, Paragraph A.1 will not apply but the Contributor must type his/her name (in the Contributor's signature line) above. Contributor acknowledges that the Contribution will be published in the United States and other countries. If the Contribution was not prepared as part of the employee's duties or is not an official U.S. Government publication, it is not a U.S. Government work.

[_____] U.K. Government work (Crown Copyright)

Note to U.K. Government Employees

The rights in a contribution prepared by an employee of a UK government department, agency or other Crown body as part of his/her official duties, or which is an official government publication, belong to the Crown. Contributors must ensure they comply with departmental regulations and submit the appropriate authorisation to publish. If your status as a government employee legally prevents you from signing this Agreement, please contact the Journal production editor.

[_____] Other

Including Other Government work or Non-Governmental Organisation work

Note to Non-U.S., Non-U.K. Government Employees or Non-Governmental Organisation Employees

If your status as a government or non-governmental organisation employee legally prevents you from signing this Agreement, please contact the Journal production editor.

Exhibit A

Financial Disclosure

The Contributor has received financial and material support for this research and work regardless of date from the following sources:

Name: NONE

Address: _____

Type of support: _____

This material will be printed with the published article.

In the past year from the date of submission, the Contributor has also received the following support unrelated to this research (e.g., grants, advisory boards, employment, consultancies, contracts, honoraria, royalties, expert testimony, partnerships, or stock ownership in medically-related fields):

Name: VA Grant (IK2CX001186), NIH grants (NIA P30AG024824) (NINDS R56NS082941)

Address: _____

Type of support: Grant support -

This material will be posted on the journal website and may be printed at the Editors' discretion.

ATTACH ADDITIONAL INFORMATION AS NECESSARY

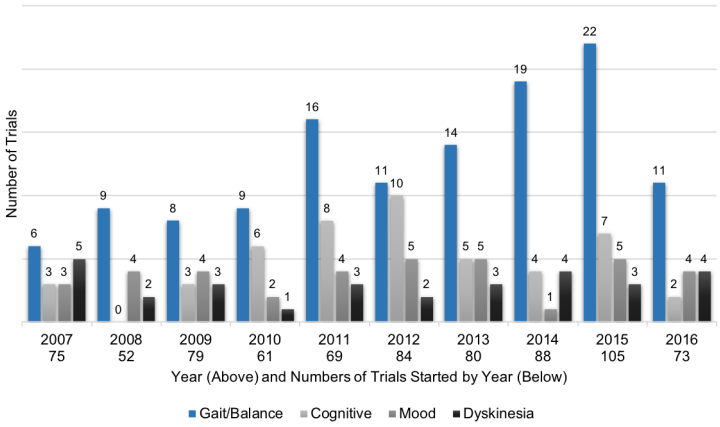


Figure2_new.tif

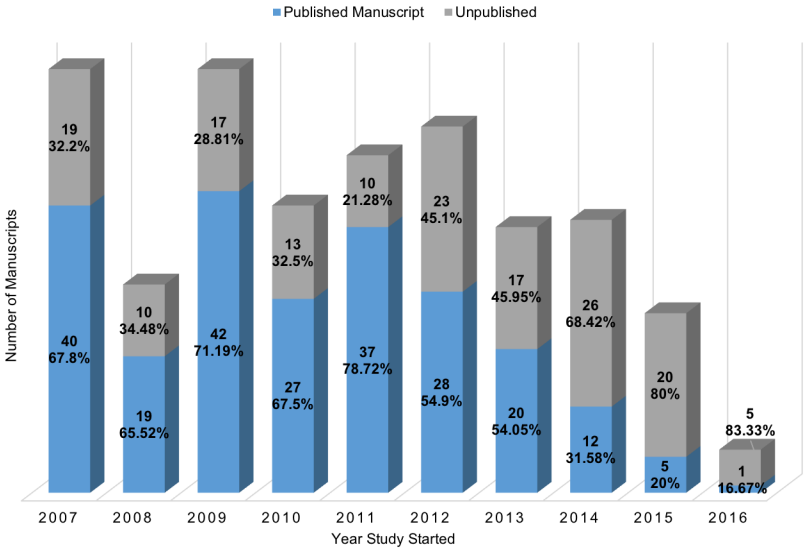


Figure3_new.tif

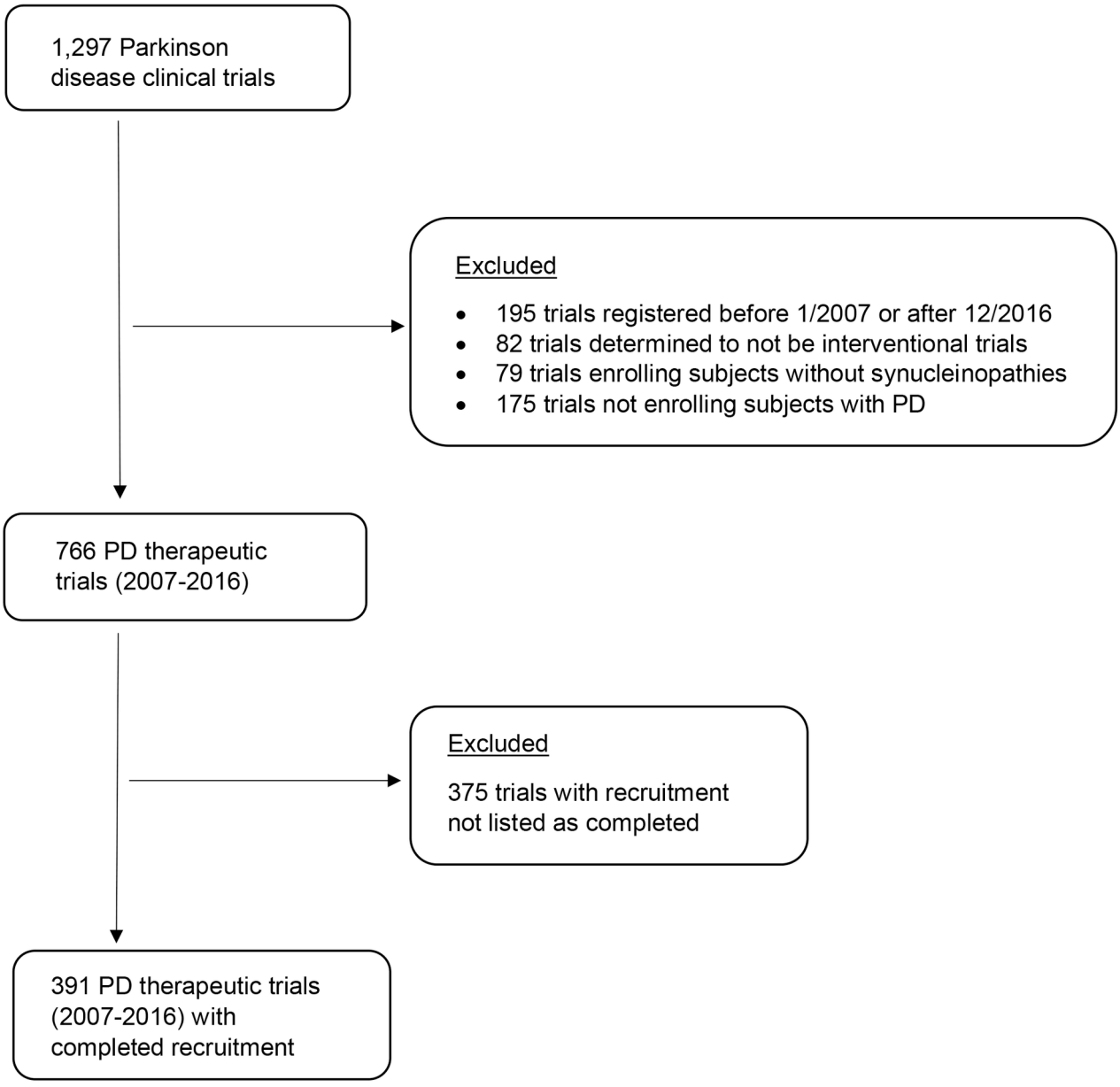


Figure 1_new.tif

Table 1: Primary Outcomes in applicable Parkinson disease clinical trials 2007-2016 registered on clinicaltrials.gov

		All Therapeutic Trials (n=766)	Published Therapeutic Trials (n=391)
High Priority Outcome Measures	***Primary Outcomes***	*N (%)*	*N (%)*
	Gait/Balance	125 (16.3%)	50 (12.8%)
	Cognitive	48 (6.3%)	24 (6.1%)
	Mood	37 (4.8%)	16 (4.1%)
	Dyskinesia	30 (3.9%)	15 (3.8%)
Other Common Outcome Measures	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%)

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