SPECIFIC AIMS

Parkinson's disease (PD) is the second most common neurodegenerative illness affecting 1-2% of adults over age 65.[1] This incurable and relentlessly progressive disease affects approximately 1.5 million Americans and is the 14th leading cause of death in the United States.[2] PD is traditionally described as a movement disorder with characteristic motor symptoms such as tremor, rigidity, bradykinesia (slowness) and postural instability. However, more recent research demonstrates the extremely high prevalence and impact of nonmotor symptoms such as pain, depression, fatigue and dementia.[3] Both motor and nonmotor symptoms impact mortality, patient quality of life (QOL), disability, nursing home placement and caregiver distress with most studies suggesting that nonmotor symptoms have a greater impact than motor symptoms in these domains.[4, 5] Regarding PD care models, evidence suggests that care including a neurologist results in lower mortality, hip fractures and nursing home placement than care solely from a primary care physician (PCP).[6] Unfortunately, there is also significant evidence that many of the needs most important to PD patients and their caregivers (e.g. depression, advance care planning) are poorly addressed under current models of care.[7, 8] We also plan to include the closely related neurodegenerative conditions of multiple systems atrophy (MSA), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and Lewy Body Dementia (LBD). These disorders are collectively referred to as Parkinson-plus syndromes or atypical parkinsonian disorders (APD) and are closely related to PD in terms of both clinical manifestations and pathology.[9]

Palliative care is an approach to caring for individuals with life-threatening illnesses that addresses potential causes of suffering including physical symptoms such as pain, psychiatric symptoms such as depression, psychosocial issues and spiritual needs. Palliative care approaches have been successfully applied to improve patient-centered outcomes in cancer as well as several chronic progressive illnesses including heart failure and pulmonary disease.[10, 11] To date there have been minimal attempts to apply these principles to PD although preliminary evidence suggests that PD patients have significant unmet needs under current models of care which may be amenable through a palliative care model.[12] Notably, there is a small but growing cadre of centers now providing outpatient interdisciplinary palliative care for PD patients and caregivers with some evidence of effectiveness. This proposal will provide critical information to forward this field including data on the comparative effectiveness of outpatient palliative care for PD versus current standards of care; effects of this intervention on cost and service utilization; and the characteristics of patients most likely to benefit from such an approach and the specific services most needed by PD patients and their caregivers.

Our long-term goal is to improve outcomes for persons living with PD and their family caregivers. We hypothesize that outpatient interdisciplinary palliative care will improve patient-centered outcomes for PD patients at high-risk for poor outcomes. By targeting these at-risk individuals with a focused intervention we intend to provide a care model that efficiently deploys resources to those who need it most,

Aim 1: Determine whether interdisciplinary outpatient palliative care for PD and APD improves patient quality of life (QOL) and caregiver burden as compared to usual care including a neurologist. We will randomize 300 PD and APD patients from 3 sites who are at high risk for poor outcomes in a 1:1 ratio to either: a) Usual care or b) Usual care augmented by an outpatient interdisciplinary palliative care team. Data regarding patient symptoms, QOL and caregiver burden will be measured at baseline, 3, 6, 9 and 12 months. Our primary outcomes will be differences between groups in patient QOL and caregiver burden at 6 months. We will also examine patient symptom burden, spiritual wellbeing and mood as planned secondary outcomes. We *predict* that patient QOL and caregiver burden will be significantly improved in the palliative care group versus usual care at 6 months and that this difference will persist and widen by 12 months.

Aim 2: Describe the effects of an interdisciplinary outpatient palliative care intervention on patient and caregiver costs and service utilization. Data regarding health-related costs, including informal caregiver time, and the use of health and social services for the three months prior to each study visit will be assessed for all participants from Aim 1 using a standard schedule. Our primary outcome will be the difference between groups in total patients and caregiver costs from month 0 to month 6 of the study. Secondary analyses will

examine changes in healthcare utilization and cost from a systems perspective. We *predict* patient/caregiver costs will be lower for the palliative care group versus usual care at 6 months and that service utilization will shift towards home services and away from acute care such as emergency room visits and hospitalizations.

Aim 3: Identify opportunities to optimize palliative care for this population by: a) describing patient and caregiver characteristics associated with intervention benefits; and b) through direct patient and caregiver interviews. For Aim 3a, interactions in linear regression models using data from Aim 1 will be used to identify patient/caregiver features that modify treatment effects. For Aim 3b, we will augment quantitative data through qualitative interviews of a subset of study participants. Standard qualitative and mixed methods techniques will be used to better understand patient and caregiver satisfaction with the intervention and to identify opportunities for optimizing this intervention as well as develop future interventions. We *predict* nonmotor symptoms, caregiver burden and psychosocial factors will predict benefit from palliative services.

RESEARCH STRATEGY

SIGNIFICANCE

Parkinson's disease (PD) is the second most common neurodegenerative illness after Alzheimer's disease affecting 1-2% of people over age 65, representing over 1 million Americans.[1] Although PD is traditionally viewed as a movement disorder with characteristic motor symptoms which affects quality of life (QOL) but not mortality our understanding of this illness has shifted markedly over the past 20 years. Over the course of the illness nonmotor symptoms have a greater impact on patient suffering, nursing home placement, and caregiver burden despite being under-recognized.[13] These symptoms include pain, fatigue, psychosis, depression, anxiety, and dementia. In patients with PD surviving 20 years or longer, three fourths ultimately develop dementia making it the leading cause of nursing home placement in PD.[5] There is also increasing recognition of the impact of PD on mortality with recent CDC statistics ranking PD as the 14th leading cause of death with a clearly rising trend and potential for this statistic to be an underestimate.[2, 14] Finally, pathological studies reveal the effects of PD involve not only dopamine, but nearly every ascending neurotransmitter system, and include effects outside of the central nervous system.[15, 16] *Thus PD should be viewed as a multi-system chronic illness associated with impaired QOL, pain, disability, dementia and increased mortality.* Despite these advances in our understanding of PD, clinical care and research continues to be driven by a chronic illness model.[17] Features of this model relevant to this proposal include an intense focus on managing and monitoring motor symptoms with care driven by a patient-physician dyad. Notable gaps in this model include care for caregivers, management of non-motor symptoms, advance care planning, and use of interdisciplinary services.[17]

Palliative care is an approach to improving the QOL of patients and their families that focuses on the relief of suffering through the assessment and treatment of physical, psychosocial and spiritual issues.[18] While traditionally associated with cancer, palliative approaches have been successfully applied to several chronic illnesses including congestive heart failure, chronic pulmonary disease and multiple sclerosis.[10,11, 19] Several lines of research, many driven by collaborators on this proposal, suggest that PD patients and their families have many unmet needs that may be effectively addressed through palliative models. First, PD patients are more likely than age-matched controls to die in hospitals supporting contentions that advance care planning and timely identification of patients appropriate for hospice are lacking.[8] Second, studies of PD caregivers demonstrate high levels of strain and distress and a large proportion who feel unprepared for their role.[20] Third, symptom burden in advanced PD is similar to patients with metastatic cancer and may be significantly improved through an outpatient palliative clinic.[12] Notably, nonmotor symptoms, such as depression, fatigue, pain, and nutritional status are frequently not identified or treated in current models of care but are the focus of the medical component of palliative interventions.[21-23] Finally, while there is a recognition by experts in the field, including the American Academy of Neurology, that "optimal care of such patients requires that neurologists understand and apply the principles of palliative medicine" there are virtually no data to guide clinicians in this charge with striking gaps in assessing spiritual and psychosocial needs, identifying patients in need of palliative services, use of advance care planning and appropriate management strategies.[24, 25] *Given these documented needs a fundamental next step in moving this field forward and developing PD-specific palliative services will be clinical trials of palliative care interventions for PD patients and their family caregivers.*

Figure 1 provides a conceptual model of current care practices and a proposal for addressing currently unmet needs. Care including a neurologist reduces mortality, hip fractures and nursing home placement compared to care solely from a primary care physician (PCP), likely through improved medication and motor symptom management.[6] However, as shown in Figure 1A, some medical needs, such as nonmotor symptoms and nutrition, are poorly met while other needs such as advance care planning, caregiver support and

psychosocial issues are left to patients and caregivers to arrange.[13, 17, 26] Figure 1B depicts an alternate model of care which incorporates an interdisciplinary outpatient palliative care team to address unmet needs, improve coordination of care and relieve patients and caregivers of the responsibility of securing resources. Notably, there is a small but growing cadre of centers worldwide, including this proposal's 3 study sites, who are beginning to offer these types of services with some signs of efficacy.[27, 28] However, as noted in recent reviews, *there are significant gaps in the evidence needed to support widespread adoption of this care model.*[29] *Gaps which will be addressed in this proposal include*:

1) The first randomized controlled comparative effectiveness trial of palliative care for PD to determine whether such care does in fact improve patient-centered outcomes versus current standards of care.
2) Data to guide referral and selection of appropriate patients for this time and resource intensive intervention.
3) Data to standardize and optimize which services are provided and how they are delivered, optimally with direct input from PD patients and their caregivers.

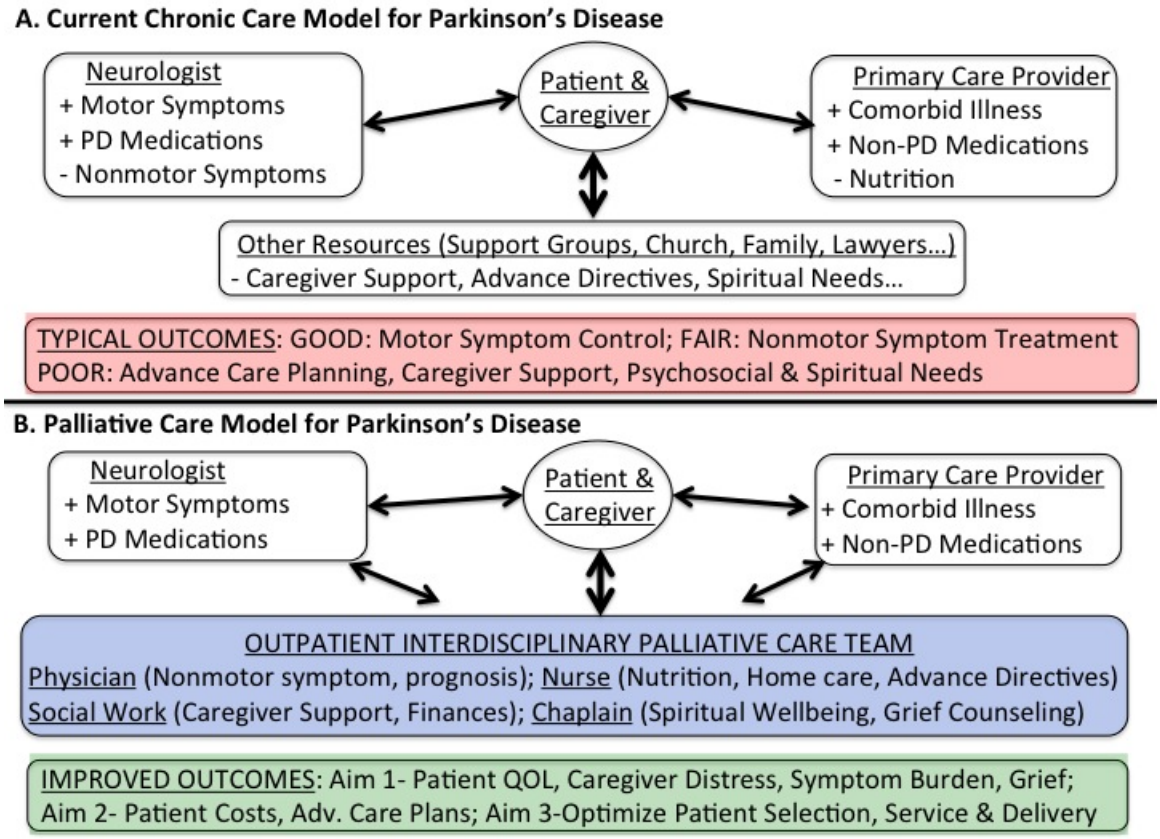

Figure 1. Conceptual model of current (A) and palliative (B) care for PD emphasizing where needs are met,; coordination of care; quality of care (areas well-met = '+' or variably met = '-'); and relation to Specific Aims.

We were approved by PCORI to modify of our research protocol to expand our inclusion criteria from Parkinson's disease (PD) to also include the closely related neurodegenerative conditions of multiple systems atrophy (MSA), corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and Lewy Body Dementia (LBD). These disorders are collectively referred to as Parkinson-plus syndromes or atypical parkinsonian disorders (APD) and are related to PD in terms of both clinical manifestations and pathology.[9] Current standards of care for APD patients are very similar to PD patients, and include care from a neurologist and PCP as well as trials of the same medications used to treat PD. These patients suffer from many of the same complications as PD patients (e.g. falls, dysphagia, dementia, depression) and tend to have less response to motor treatments (e.g. levodopa) and faster progression. Although these conditions are individually rare, collectively they account for approximately 15% of all parkinsonism and, because they are largely untreatable and more rapidly progressive than PD, may have a higher proportion of patients and caregivers with high palliative care needs.[30, 31] All of the palliative care clinics involved in this study see APD patients which makes the question of clinical effectiveness equally important for APD patients, caregivers and clinicians as it is for PD.

From a practical standpoint, recruitment has been more challenging than initially anticipated. We have had higher than expected rates of refusal due to time commitment and logistical challenges among patients. We have also had many potential participants refuse to agree to be randomized as they feel they have high needs and do not want to take the 50% chance of being randomized to usual care. Although this is the first trial of a palliative care intervention in Parkinson's disease (PD), similar issues have been described in palliative care trials for other conditions.[32, 33] Expansion of our recruitment criteria to include APD patients is anticipated to improve our recruitment numbers and may account for one-third of our final sample. We have already had several potential participants excluded because of having an undiagnosed APD and have had requests from referring clinicians to see their APD patients in the study.

From a theoretical standpoint there are several reasons why the inclusion of APD patients is attractive. First, regarding palliative care services there are no significant differences in the care our palliative care clinics provide to APD versus PD patients in terms of symptomatic needs (e.g. dementia, depression, dysphagia), goals of care, caregiver support, psychosocial issues or spiritual care.[31] Second, there is a paucity of clinical therapeutic research to guide care for patients with APD and this study will help fill this gap and encourage other investigators to include this patient population.[34] Finally, the inclusion of APD patients is consistent with PCORI and palliative care principles to move towards patient-centered care based on symptoms or other shared challenges (e.g. elderly multiple comorbidities) as opposed to specific diagnoses and there are other clinical researchers in neurology and palliative care moving in this direction.[35]

INNOVATION

Although growing evidence supports palliative models for several chronic illnesses there is scant evidence and no randomized trials supporting this approach in PD.[12, 19, 36, 37] This proposal will conduct the first randomized trial of outpatient palliative care for PD. While this trial builds on prior palliative trials our approach is innovative in its application of these methods to the specific needs of PD. *Specifically, our Aims will be the first studies to*:

1) Test the impact of outpatient palliative care in PD on patient QOL and caregiver burden in a randomized controlled trial. The intervention is based on our collective experience in providing palliative care for PD. Our study sites represent the first clinics and longest experience with this work in North America. Clinical trial results for other illnesses do not directly translate to PD due to unique aspects of PD such as the long duration of illness (10-20 years) and variable combination of motor and nonmotor symptoms.

2) Use the recently developed Needs Assessment Tool - Parkinson's Disease to provide standard and reproducible screening of high-risk patients. This instrument was modified for PD by Drs. Miriam Johnson and Edward Richfield with input from Dr. Kluger (PI) from the Palliative Care Needs Assessment Tool.[38]

3) Describe the impact of outpatient palliative care on cost and service utilization from a patient and caregiver perspective. As opposed to traditional cost-effectiveness analyses, these analyses do not depend on assumptions valuing quality of life years or other complex modeling. Rather they are designed to provide practical data directly relevant to patients, caregivers and PD advocacy groups.

4) Include patients with and without PD-related dementia (PDD) in a randomized clinical trial. One of the challenges of building a palliative care model for PD is the wide variability of clinical phenotypes, including a wide range of cognitive abilities and impairment. Our goal is to strive for inclusivity, specifically including PDD patients who are often excluded from clinical research but represent a very high-risk population for palliative care needs. We have specifically chosen primary outcome measures not dependent on cognitive status.

5) Use the Quality of Life: Alzheimer's Disease (QOL-AD)[39] and recently developed Edmonton Symptom Assessment Scale – Parkinson's Disease (ESAS-PD)[12] to measure of QOL and symptom burden respectively. We chose these scales for their applicability to patients with advanced disease, ease of use with cognitive impairment, brevity and caregiver proxy reporting. More commonly used PD quality of life outcomes (e.g. the Parkinson's Disease Questionnaire 39[40]) are less relevant to the needs of the population we are serving as they focus primarily on functional activities, many of which are beyond the abilities of our patients.

PRELIMINARY DATA AND FEASIBILITY

1) Effectiveness of Outpatient Palliative Care for PD: Dr. Janis Miyasaki (University of Alberta site PI) and colleagues published a case series of 109 PD patients who had received outpatient palliative care from her team.[27] This study showed a significant improvement in symptom burden as measured by the Edmonton Symptom Assessment Scale PD (ESAS-PD) between their baseline (mean $\pm$ STD = 56 $\pm$ 19) and first follow-up visit (40 $\pm$ 17; paired t-test $p < 0.0001$). Significant improvements were seen in many individual symptoms including pain, anxiety, drowsiness and dysphagia. Although there was no control group, these patients were largely referred by their treating neurologist because of limited success with usual care. Further findings from an article in press by Dr. Miyasaki and Dr. Benzi Kluger (PI) showed that over 80% of PD patients participating

in outpatient palliative clinics died at home and less than 10% died in a hospital.[41] While there was no control group, historical data shows over 50% of PD patients typically die in hospitals and less than 10% die at home.[8]

2) Patient and Caregiver-Centeredness of Intervention: Dr. Kluger (PI) obtained a Clinical Effectiveness and Patient Safety Grant through the University of Colorado Hospital in July 2013 to optimize our outpatient palliative care clinic with the non-negotiable goal of achieving high quality, patient-centered care. We collected data through surveys and phone interviews with patients and caregivers and made ongoing adjustments in our clinic based on feedback received. Specifically, we revised clinic processes by: 1) Providing written information about palliative care and our clinic to patients prior to their first visit; 2) Clarifying team member roles to reduce redundancy and ensure coverage of key issues; 3) Providing written instructions to patients in real time from each team member; and 4) Following up on visit recommendations with phone calls within 2 weeks. We tracked patient and caregiver satisfaction through the course of this project and obtained mean scores of at least 9 (on a 10 point scale) on all items by the end of our 1-year improvement period including overall satisfaction, answering their questions and likelihood of referring other patients to our program.

3) Experience and Standardization of Intervention: Dr. Miyasaki created the first outpatient palliative care program in the world dedicated to PD patients and their families at the University of Toronto in 2008. From the time of its inception this program became a model for other centers including the University of Colorado Denver (UCD) and University of California San Francisco (UCSF) and an integral part of care for patients with advanced PD in Toronto addressing goals of care, refractory nonmotor symptoms, caregiver support, advance care planning and spiritual wellbeing. Dr. Nicholas Galifianakis (UCSF Co-I) and colleagues presented findings from the development of their PD palliative clinic and first 25 patients at the 2012 International Congress of Parkinson's Disease and Movement Disorders.[42] Relevant findings from this presentation include a description of their intervention and the most common referral reasons including goals of care, management of non-motor symptoms and caregiver support. Although our programs have always been similar, we have shared experiences, forms and other materials in the planning of this proposal to ensure standardization across sites.

4) Palliative Care Needs of PD Patients and Caregivers – Quantitative Data: Dr. Kluger (PI) obtained a pilot grant in June 2013 from the Veterans Affairs Medical Center (VAMC) to perform a cross-sectional study of 90 patients with PD and 45 patients with advanced cancer (inoperable or metastatic) to determine whether palliative issues contributed to QOL in PD and compare palliative needs in PD to those with cancer. Key findings of this study (manuscripts under review) relevant to this proposal include: 1) PD patients across all stages of the disease had similar or higher levels of symptom burden, grief, depression, QOL impairments, and caregiver burden as advanced cancer patients; 2) Palliative specific issues (e.g. grief, spiritual wellbeing) were associated with QOL even when controlled for motor severity and depression; 3) The majority (80%) of PD patients felt advance care planning should begin early in the disease process; 4) Caregiver burden was driven largely by factors not well addressed in current models of care including financial concerns, grief, depression and patient functional status; 5) Higher medication use was associated with high caregiver burden and reduced patient QOL even when controlling for disease stage; and 6) Components of symptom burden differed significantly between cancer and PD patients (e.g. higher psychiatric symptoms in PD population).

5) Palliative Care Needs of PD Caregivers: Drs. Kluger and Jones (co-I) obtained a grant in September 2013 through the University of Colorado's National Institute on Aging funded Palliative Care Program (1 K07 AG030337-01A2: PI - Kutner) to perform qualitative interviews and focus groups with PD patients and their caregivers with the goal of creating a patient-centered model of palliative care for PD. Key findings from over 60 hours of interviews from 45 patients, caregivers and support groups (manuscript under review) relevant to this proposal include: 1) Both patients and caregivers expressed significant concerns about their future ranging from what symptoms to expect to finances; 2) PD challenged many patients' sense of roles and identity; 3) Spirituality was a significant source of strength for many patients; 4) PD patients and caregivers identified many needs not met with current models of care including greater education, particularly regarding what to expect in the future; 5) Patients often under-reported symptoms to their physicians for fear of having their medications increased; and 6) Patients and caregivers expressed significant openness to team-based outpatient approaches to addressing currently unmet needs; and 7) Both patients and caregivers felt that key components of palliative care (e.g. spiritual counseling, frank discussions about future needs) would be a welcome addition to current models of care.

6) Clinical Research Experience in PD: Dr. Kluger has experience as PI in PD trials including serving as co-PI in a 3-site investigator-initiated study of rasagaline for fatigue[43] and PI for a single site study of acupuncture for fatigue recruiting 95 participants in 2.5 years (manuscript in preparation). Dr. Katz (UCSF site

PI) has experience in PD clinical trials and will work closely with Dr. Jill Ostrem (co-I) an experienced clinical trialist. Dr. Miyasaki (UA site PI) similarly has a long history of serving as a site PI in multisite clinical trials.

Of note, palliative care as prescribed in the "intervention arm" of this trial is already available to and being utilized with PD patients at UCH. The "comparator arm" is meant to reflect the current standard of care in the community at large. At UCH, this trial represents a comparison of effectiveness of 2 currently-available standards of care.

APPROACH (see Appendix 1 for schedule of procedures in table format)

Aim 1: Determine whether interdisciplinary outpatient palliative care for PD improves patient quality of life (QOL) and/or caregiver burden versus usual care including a neurologist.

Rationale and Design: The objective of this Aim is to provide the first comparative effectiveness data on whether augmenting usual care with interdisciplinary outpatient palliative care improves patient QOL and/or caregiver burden in patients at high risk for poor outcomes. Given the unmet needs facing this population there are great potential benefits from incorporation of this approach. Although it may seem obvious that more care would be better than less, several multidisciplinary interventions in PD and palliative care have failed to meet their primary endpoints in randomized trials and thus could present an additional burden to patients and caregivers in terms of time, cost and emotional investment.[44, 45] We will randomize 300 PD patients from 3 sites who are at high risk for poor outcomes in a 1:1 ratio to either: a) Usual care including a neurologist or b) Usual care augmented by an outpatient interdisciplinary palliative care team. Data regarding patient quality of life, symptom burden and caregiver distress will be measured at baseline, 3, 6, 9 and 12 months. Our primary outcomes will be differences between groups in patient symptom burden and caregiver burden at 6 months. This time point was chosen to capture both early effects of the intervention as well as probable measurable decline in control arm. We will examine symptom burden, spiritual wellbeing and mood as planned secondary outcomes. We *predict* that patient QOL and caregiver burden will be significantly improved in the palliative care group versus usual care at 6 months and that this difference will persist at 12 months.

Study Settings/Recruitment: Participants will be *identified and recruited* for this study through three institutions: 1) The University of Colorado Denver (UCD); 2) The University of California San Francisco (UCSF); and 3) The University of Alberta. The institutions represent the 3 first outpatient palliative care clinics for PD in North America and were chosen based on their collective experience. Recruitment at each institution will occur through three main venues: 1) Referral from investigators' clinics or their colleagues at primary study sites (tertiary care academic clinics and community health clinics); 2) Referral from community physicians with ongoing working relationships with site institutions and investigators; and 3) Self-referral by patients who learn of the study through community organizations, talks, advertisements or websites (e.g. clinicaltrials.gov; foxtrialfinder). To ensure inclusion of community and rural participants, each study site has partnered with community neurologists and regional patient organizations which provide services to rural patients. Study sites also provide services through inner city clinics serving indigent populations and the two US sites are partnered with Veterans Affairs Medical Centers. Efforts made to *retain* participants will include: reimbursement for travel and expenses; providing baseline and/or follow-up study visits at participant homes or by telehealth for patients and/or caregivers with health, mobility, or transportation issues; incorporation of telemedicine approaches as needed for rural and other locations; mailed updates of study progress to participants; incorporation of feedback from participants regarding study procedures; and a welcome letter referring to participants as important members of the study team. A caregiver will be consented/enrolled for each participant who has one available. In some cases, the consent process will occur in a telehealth (phone or video) meeting with the participant and will be performed by study personnel. The patient/caregiver/LAR will have a copy of the consent form and the UCD study coordinator will go through the consent process with them via phone or video, just as they would in person. Patient/caregiver/LAR will give verbal consent.

Participants: *Inclusion Criteria*: Patients must be fluent English Speakers, over age 40 and meet UK Brain Bank criteria for a diagnosis of probable PD[46] or standard criteria for progressive supranuclear palsy (PSP),[47] corticobasal degeneration (CBD),[48] multiple systems atrophy (MSA),[49] or Lewy Body Dementia (LBD).[50] Although PD may be seen in individuals under age 40, it is more frequently related to specific genes and may display different clinical features than typical idiopathic PD. Patients must be at high risk for poor outcomes as identified by the Palliative Care Needs Assessment Tool (PC-NAT)[38] modified for PD which screens patients on the basis of social factors (e.g. presence of caregiver), disease severity, and symptom burden. Every effort

will be made to allow inclusion of patients with dementia and cognitive impairment per NIH guidelines[51] (see **Human Subjects** section for details on consenting process).

Caregivers, when present, will be identified by asking the patient: "Could you please tell us the one person who helps you the most with your PD outside of clinic?" For patients with severe dementia, family caregivers may be self-identified and may be included even if the patient has communication limitations in order to obtain data relevant to these highly vulnerable and underrepresented patients. We anticipate 90% of patients will have caregivers present based on our clinical experience and have performed separate power calculations for caregiver outcomes, including with lower percentages of complete dyads. Notably, our primary patient outcome measure has been validated in patients with dementia and with proxy caregiver reporting.[52]

Exclusion Criteria: Patients will be excluded if any of the following are present: 1) Immediate and urgent palliative care needs (these patients will not be randomized and will be offered appropriate services immediately); 2) Unable or unwilling to commit to study procedures including randomization, study visits or the addition of a neurologist to their care team if in the usual care arm and not currently seeing a neurologist; 3) Presence of additional chronic medical illnesses which may require palliative services (e.g. metastatic cancer); or 4) Already receiving palliative care and/or hospice services. We have purposefully kept our inclusion/exclusion criteria broad to allow for greater generalizability of results and to ensure inclusion of potentially underrepresented and understudied subgroups.

Randomization: Individual patients and patient-caregiver dyads will be randomized in a 1:1 fashion to either: 1) Usual care defined as including both a PCP and neurologist; or 2) Usual care augmented by an outpatient interdisciplinary palliative care team. Randomization will be stratified by site, presence of caregiver, presence of dementia using Movement Disorders Society Guidelines for PD-related dementia and the Montreal Cognitive Assessment,[53, 54] and performed in balanced blocks to minimize potential biases.

Description of the Intervention and Comparator Arms: *Comparator*: Usual care will consist of care from the patient's primary care physician (PCP) and a neurologist. We consider this the current standard on the basis of evidence showing that care with a neurologist results in better outcomes (e.g. falls, mortality) than care with a PCP alone.[6] For patients without a neurologist, we will arrange appointments with a neurologist covered by their insurance or a patient assistance program. Patients will be asked to see their neurologist at least every 3 months to match the frequency of visits in the intervention arm and may see their PCP at their typical frequency. Data collection for those in the Usual care arm could occur in person, over the phone, using mailed or electronic survey distribution, or via telemedicine. To ensure treatment fidelity, investigators will not serve as neurologists in the comparator arm.

Intervention Arm: Out intervention will consist of Usual Care plus the addition of an outpatient interdisciplinary palliative care team. Palliative care visits will be performed in person (or telemedicine if needed for rural areas and/or limited transportation) every 3 months and will include consultation with all team members. In addition, visits will be supplemented by optional phone calls one week after each visit to confirm understanding of team recommendations and at 6 weeks to check-in with patient and caregiver. Data collection for those in the Intervention arm could occur in person, over the phone, using mailed or electronic survey distribution, or via telemedicine. Patients and caregivers may also contact the team as needed. Summaries of visits will be sent to the patient, caregiver, PCP and neurologist. The palliative team will enact changes related to core palliative care issues (Table 1) and make suggestions for care outside of palliative care issues to be sent to the patients' Usual Care team.

The interdisciplinary team will consist of a neurologist, a nurse, a social worker, and a chaplain. A board-certified palliative care physician will also be available at each site for phone consultations and monthly review of charts. Visits will be standardized through checklists of topics covered by each team member to ensure consistency across sites as summarized in Table 1. These issues were developed on the basis of our collective experience and studies of palliative care needs contributing to patient QOL and caregiver burden (see **Preliminary Data**). All staff except the palliative care physician will be present for in person visits and will participate in summary meetings at the end of each clinic to ensure interdisciplinary feedback, integrated care, appropriate follow-up and completion of any needed referrals or medication changes.

Table 1. Standardized Interdisciplinary Palliative Care Team Membership and Roles

Team Member	Issues to Address
Palliative Neurologist	- Medical history, medications and physical examination - Cognitive status and testing - Psychiatric symptoms (e.g. depression, hallucinations) - Pain, sleep, fatigue and other nonmotor symptoms

	- Swallowing, sialorrhea and falls - Recent hospitalizations, infections or other medical issues - PD education relevant to disease stage including prognosis - Goals of Care
Nurse	- Advance care planning and documentation - Healthcare proxy designation and documentation - Nutritional status and diet - Home safety for both patient and caregiver - Wound care/skin integrity
Social Worker	- Caregiver distress - Need for help at home/community resources - Financial issues and concerns - Long-term care needs
Chaplain	- Spiritual wellbeing - Sources of support and stress - Fear, anger and guilt - Grief and demoralization
Palliative Care Physician	- Phone consultation for advanced symptom management issues - Monthly review of charts from palliative perspective

Primary Outcome Measures: Our primary outcomes for this proposal are the Quality of Life: Alzheimer's Disease (QOL-AD) and the Zarit Caregiver Burden Interview short form (ZBI).[39, 55] The QOL-AD was chosen for this study for several reasons including its brevity, insensitivity to cognitive impairment, validated proxy reporting, sensitivity to change and coverage of issues identified to be relevant to PD patients and caregivers in our qualitative interviews (see **Preliminary Data** above for these issues).[56, 57] Although there is currently no QOL instrument specifically validated for PD patients with dementia the QOL-AD has been validated in mixed dementia and issues relevant to all dementias.[58] The ZBI is the most commonly used self-report measure of caregiver distress, including in PD.[59, 60] The ZBI is well validated in terms of psychometric properties and is notably insensitive to variations in age, gender, socioeconomic status or locale indicating that it is appropriate for use in diverse and mixed populations.[61] It is also sensitive to change with interventions, including palliative care.[19]

Secondary Outcome Measures: Table 2 summarizes outcomes and other relevant data collected from patients and caregivers. To assess patient functional status and provide an alternate QOL measure we will administer the PDQ-39, the most commonly used measure of health-related QOL in PD. It was developed in 1995 on the basis of in-depth interviews of PD patients and has excellent psychometric properties and construct validity.[40, 62] The PDQ-39 also provides validated subscores regarding mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication and pain. The PDQ-39 is sensitive to change over time with disease progression and improvement with interventions and minimally clinically important differences have been reported for the overall scale and subscores.[63] To assess symptom burden we will administer the ESAS-PD, a modified version of the Edmonton Symptom Assessment Scale.[12] The ESAS-PD was developed by Dr. Miyasaki to incorporate common PD symptoms not in the original scale (e.g. confusion) and demonstrates adequate psychometric properties, including proxy reporting and sensitivity to change.[12] Other patient related outcomes will include: the Hospital Anxiety and Depression Scale (HADS)[64], the Prolonged Grief Questionnaire (PG-12; anticipatory grief)[65], and the Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing (FACIT-SW)[66] Other caregiver outcomes will include the HADS. Total time for all assessments is estimated to be 60-90 minutes and may actually be faster for more impaired patients due to reliance on proxy responses.

Table 2. Data Collected from Patients and Caregivers for Aim 1

Measure	**Domain of Interest**
Quality of Life: Alzheimer's Disease (QOL-AD)[39]	Patient Quality of Life (QOL)
Zarit Burden Interview (ZBI)[34]	Caregiver Distress
Parkinson Disease Questionnaire (PDQ-39)[30]	Patient Functional Status and secondary QOL
Edmonton Symptom Assessment Scale (ESAS-PD)[12]	Patient symptom burden
Hospital Anxiety and Depression Scale (HADS)[37]	Patient and Caregiver Mood
Functional Assessment of Chronic Illness Therapy-	Patient and Caregiver Spiritual Wellbeing

Spiritual Wellbeing (FACIT-SP)[39]	
Patient Reported Outcome Measurement Information System (PROMIS-29)	Patient QOL (Validation of NIH Common Data Element)
Clinical Global Impression of Change	Patient, Caregiver and Clinician's global impressions of change
Prolonged Grief Questionnaire (PG-12)[40]	Patient and Caregiver Grief
Unified Parkinson Disease Rating Scale[41]	Patient Motor symptom Severity (motor exam only)
Montreal Cognitive Assessment (MOCA)[46, 56]	Patient Cognitive Status
Hoehn and Yahr Scale[44]	Patient Disease Stage (baseline visit only)
Charlson Comorbidity Index[61, 66]	Medical Comorbidities (baseline visit only)

Statistical Analysis: The main objective of the study is to determine the comparative effectiveness of interdisciplinary outpatient palliative care versus usual care with a neurologist for PD regarding effects on patient QOL and caregiver burden. The primary outcome variables will be the QOL-AD and the ZBI.[40, 55] Secondary outcomes (see **Table** 2) include scales for symptom burden, mood, and spiritual wellbeing. Controlling covariates will include gender, age, disease severity (measured continuously using the Unified Parkinson Disease Rating Scale[67]), cognitive dysfunction (measured continuously using the Montreal Cognitive Assessment[68]), and baseline depression (measured continuously using the HADS Depression Subscale[64]). The explanatory variables will be checked for randomization and multicollinearity. Successful randomization should minimize covariate imbalances between groups, but including them in the model can adjust for lingering confounding effects and account for variance in the outcome variable.

The outcomes will be modeled with mixed regression model analysis, with correlation for repeated measures, at baseline and at 3, 6, 9, and 12 months. The empirical covariance estimator may be used to safeguard against model misspecification. The models will control for time, interaction between treatment and time, and potential baseline confounders, including gender, age, depression, and disease severity. The default model will have linear time trajectories for each treatment group, and linear functions for baseline controlling covariates. The linearity assumptions will be checked. Non-linear functions could be approximated with piece-wise linear functions or transforms. The main contrasts will be the difference in areas under the fixed effect change from baseline curves for the palliative and treatment control groups, and the mean difference in change between 6 months and baseline between the groups. Secondary tests will be conducted for the mean difference in change from baseline between the groups at the 3, 9, and 12-month time points. The contrasts, controlled for all covariates, will be tested for significance using T-tests and F-tests, with an alpha level of 0.05. The effect estimates, 95% confidence intervals, and p values will be reported. In the process, the interaction between time and treatment will be tested. If the time trajectories are linear, then all tests are stochastically equivalent to the time by treatment interaction test with one parameter. Binary outcomes and count outcomes will be analyzed with logistic regression and Poisson regression respectively. Generalized mixed models will account for repeated measures. We plan to perform subgroup analyses for patients with dementia, severe disease, and depression and may perform exploratory subgroup analyses depending on primary results.

Item non-response for the scales will be dealt with using the half rule, or specific scale instructions when available (e.g. QOL-AD[57]). The half rule is the standard method for completing validated scales with missing items when the items are not hierarchical and generally has better performance than more complex imputation methods.[69] Descriptive statistics will be compiled for missing scales and assessed for patterns. Logistic regression for missingness will be used to demonstrate its dependency on variables. The initial analysis will use the maximum likelihood for all available data for a response variable when data exists for all explanatory variables. In mixed models correlation on repeated outcomes provides some information on the times with missing outcome values. The data will be assumed missing at random. As a sensitivity analysis, joint models will combine the longitudinal outcomes of patient and caregiver proxy reports on the QOL-AD and use their correlations to provide additional values if a subset of the outcomes are missing. Finally, joint models for the longitudinal QOL scale outcomes and the time to drop out will be fit to incorporate drop out information. Even if outcomes for one scale are not missing at random conditional on the observed data, measurements on other scales at the time, or time to drop out, can serve as proxies. Models for different outcomes and time to drop out will be joined through shared covariance structures and/or shared random effects.

The functions in the regression model will be checked for linearity. Piecewise linear functions or transforms can be used to approximate non-linearities. Crossover of group assignment will be treated in different ways and the results will be compared. The primary analysis will use intent-to-treat, but analysis according to actual treatment, with time varying covariates, and adherers only will also be considered. Results

from models using all available data for a response variable will be compared to the models with missing data methods. The random effects linking together the joint models will be tested. The missing data methods assume missing at random (MAR). Randomization will be checked for baseline variables with summary statistics and two-way tables. Covariates can partially control for deviations from ideal randomization. Homoskedascity and approximate normality for the outcomes will be checked with standard methods. Homoskedascity can be remedied with heterogeneous variance structures or weights. Non-normality should not be much of an issue, unless severe, and can be dealt with using standard methods such as logarithmic transformations. With our sample size the parameter estimates should be consistent and asymptotically normal because of the Central Limit Theorem. All variables will be checked for outliers, and influential outliers will be considered for removal using standard tests (e.g. Cook's D).

Sample Size and Power Considerations: Allowing for up to 25 dropouts per group by the 6-month time point, a two sample T-test with 125 samples per treatment group (250 total) will detect a difference in our continuous outcomes equal to 42% of the standard deviation with 90% power and an alpha level 0.05. This is greater than the suggested minimal clinically significant change for the QOL-AD of 3 points.[70] For our secondary measure of QOL the difference of half the standard deviation for the PDQ-39 has been suggested in prior studies to be clinically important and detectable with change over time or with outpatient interventions.[63, 71, 72] For the ZBI, assuming 110 complete dyads per group would diminish our effect size to 44% of the standard deviation with 90% power and an alpha level 0.05. Even a sample of 90 complete dyads would provide an effect size of 0.5 SD/mean. Minimal clinically important differences have not been established for the ZBI but will be estimated in this study using caregiver global impression of improvement and an anchor based approach.[73] Notably, prior studies of palliative interventions have found effect sizes of 0.5 SD/mean and greater for the ZBI.[19] The sample size will also enable us to fit models with a large number of parameters and as described below, the longitudinal mixed models and linear time functions will increase our efficiency. Caregivers will be enrolled for each part

For a longitudinal model with non-linear time trajectories, the difference in area under the change from baseline curve can summarize treatment effect across all times. If the true time trajectory is linear, and we model it as a piece-wise linear function, with a common intercept and knots at each time point, and the outcome is difference in area under the change from baseline curve, then a sample size of 25 per treatment group (50 total) would achieve 90% power with an alpha level of 0.05 and an effect size equivalent to 50% of the standard deviation at 6 months (6 sd*months of area, 0.5 sd on average). A sample size of 125 per treatment group (250 total) would be virtual certain to detect the effect, even for very small alpha levels, and so a Bonferroni correction could be applied to handle multiple comparisons. A sample size of 125 per treatment group (250 total) would achieve more than 90% power with an alpha level of 0.05 and an effect size equivalent to 22.5% of the standard deviation at 6 months (2.7 sd*months area, 0.225 sd on average). For a test of mean difference in change from baseline at 6 months, a sample size 64 per treatment group (128 total) would achieve 90% power with an alpha level of 0.05 and an effect size equal to 50% of the standard deviation. A sample size of 125 per group (250 total) would almost certainly detect the effect. The test would have more than 90% power even after a Bonferroni adjustment for almost 50 tests. Alternatively, 125 samples per group (250 total) could detect an effect equal to 36% of the standard deviation with 90% power and an alpha level of 0.05. Alternatively, for our minimal dyad size of90 samples per group (180 total) we could detect an effect equal to 42% of the standard deviation with 90% power and an alpha level of 0.05.All sample size calculations for longitudinal data models assume a compound symmetric covariance structure and a correlation of 0.5 for repeated measures on a participant which is relatively conservative for QOL measures.[69]

Aim 2: Describe the effects of an interdisciplinary outpatient palliative care intervention on patient and caregiver costs and service utilization.

Rationale and Design: There is a growing interest in the economics of healthcare delivery and palliative care.[74] While there are clear motivations for examining this from a payer and systems perspective, there is also an emerging interest in understanding this from patient and caregiver perspectives.[75] This also agrees with our qualitative interviews of PD patients and caregivers where one of the most frequent concerns regarding their present situation and the future was finances. The types of services provided for a given cost are also clearly important. For example, one of the services our palliative care clinics provide patients is setting up home care for physical therapy which benefits both patients and caregivers. Our objectives for this Aim are therefore to describe how the addition of outpatient palliative care may alter costs and services for patients and caregivers and also to assess whether recommendations of the palliative care team are implemented and maintained.

Participants: Participants will be identical to Aim 1. Data will be collected from patient-caregiver dyads through interviews and rater-administered questionnaires using items drawn from existing instruments modified to account for PD and the cognitive functioning of dyads. These may be performed by phone within a week of scheduled visits depending on patient/caregiver preferences to minimize fatigue and burden or in person visits.

Economic Outcomes: From the patient and caregiver perspective there are two key economic outcomes that affect their financial health: out-of-pocket costs for healthcare and non-medical costs resulting from changes in work behaviors and earnings. From a payer and systems perspective the total cost of care is the economic outcome of interest. These economic outcomes will be assessed at baseline and every 6 weeks during the course of the study via modified versions of items drawn from existing questionnaires that have been used with similar populations which may be administered in person or by telephone. Out-of-pocket health-related costs will be assessed using questions drawn from the *Ambulatory and Home Care Record (AHCR)* and the *Medical Expenditure Panel Survey (MEPS)*. Measures of total cost of care will be derived from comprehensive service utilization questions described below including both public and private costs.[76] Costs will be assigned uniformly for purchased services regardless of patients' underlying insurance status or location using Medicare reimbursement rates for the Denver Metropolitan Area. For services not covered by Medicare (e.g. unskilled home care) we will use average rates for the Denver Metropolitan Area. Measures of work behaviors and earnings will be obtained from questionnaire items adapted from the *Work Productivity and Activity Impairment Questionnaire (WPAI)* and the *World Health Organization Health and Work Performance Questionnaire (HPQ)*. Measures at baseline and follow up will include work activities in the week prior to the assessment, absences from work due to health issues or caregiving and, for caregivers only, the number of hours spent providing care. At baseline we will obtain detailed information on the patient's and caregiver's current or most recent job including usual weekly hours worked, earnings, industry, and occupation. This baseline information will be used to value work absences due to caregiving activities and caregiver's health, time providing care for caregivers, and any patient absences from work. Time losses from work will be assigned a monetary value using the human capital approach with adjustments made by year for inflation (will use dollar value of final year of data collection), vacations and benefits.[77] Caregiver time spent providing care will be valued using the human capital approach for caregivers that are employed at baseline and for those not employed at baseline we will value their time using local market wage rates for paid home health aides.

Service Utilization: Health care utilization data will be collected at baseline, and every 6 weeks along with the economic outcome assessments including information on caregiver and patient use of healthcare services (i.e. emergency room services, hospitalizations, hospice and palliative care services, respite care and other stays in long-term care facilities, home health services, and caregivers' use of psychological health services) as well as outpatient visits to physicians or other services. We will also record place of service (e.g. home, community, tertiary center) and number of medications taken. Utilization measures will use items from the AHCR, MEPS and HPQ.

Statistical Analyses: To estimate economic outcomes, all costs will be aggregated for each 6 week period and expressed as a rate per 30 days (monthly costs). Our primary economic comparison will be for total care costs plus non-medical costs in the period preceding the 6-month visit using a mixed regression model with adjustments made for site, baseline costs and work behaviors of the caregiver. Secondary economic models will examine differences by specific source of cost (e.g. missed work, informal caregiving, direct healthcare costs) and will use linear regression analyses to determine whether patient or caregiver variables (e.g. gender, age, cognitive status) are predictive of costs under either interventions. We will also conduct sensitivity analyses of these cost measures (e.g., measuring cost of missed work and informal caregiving time using both a human capital approach and local wages of home health aides for caregivers not employed at baseline).

Our primary service utilization analysis will compare number of hospitalizations, emergency room visits and nursing home placement between groups. T-tests and regression analyses will be used for continuous outcomes, Poisson regression will be used for count outcomes, and chi-square association tests, Fisher's exact association tests, and logistic regression will be used for binary outcomes. Secondary analyses will examine utilization and place of service for ancillary therapies (e.g. physical, occupational and speech therapy). We will use regression models to determine if total number of medications is associated with QOL and ZBI (as it was in our Preliminary data) and whether palliative intervention influences medication use.

Sample Size and Power Calculations: A two sample T-test with a sample size 125 subjects per group (250 total) could detect an effect equal to 42% of the standard deviation with 90% power and an alpha level of 0.05. For the cost per month model with longitudinal data, if the contrast is the difference in mean total cost between treatment groups after 6 months of follow up, then a sample size of 125 per group (250 total) would achieve

90% power for an effect of 1.75 sd*months (0.29 sd on average) and an alpha level of 0.05. Here sd is in cost per month. If the contrast is the difference in mean total cost between treatment groups after 12 months of follow-up time, then an effect size of 3 sd*months (0.25 sd on average). The power calculations assume a compound symmetric covariance structure with a correlation of 0.5 for repeated measures on a patient.

For a binary outcomes, the following arrangements achieve 90% power with an alpha level of 0.05 and a sample size of 125 per group (250 total): 26% for the control group and 10% for the treatment group, a difference of 0.16 and an odds ratio of 0.316; 50% for the control group and 30% for the treatment group, a difference of 0.2 and an odds ratio of 0.429. For a Poisson count outcome, if the control rate is 0.5 per person year, and the exposure time is one year, then a sample size of 125 per group (250 total) would achieve 90% power with a rate ratio of 0.53 and an alpha level of 0.05.

Aim 3: Identify opportunities to optimize outpatient palliative care by: a) describing PD patient and caregiver characteristics associated with intervention benefits; and b) through direct patient and caregiver interviews.

Rationale and Design: As the first randomized controlled trial of a palliative care intervention we have based our trial on our collective experience providing services to PD patients and their caregivers as well as literature from other illnesses. The objectives of this Aim are too optimize this intervention and plan for future implementation and dissemination efforts by answering two critical questions. First, given the expense and potential inconvenience of this intervention it is critical to identify patients and caregivers who are most likely to benefit from these additional services. This data may be used to further revise the PC-NAT for PD. Aim 3A will use regression models to determine whether patient or caregiver factors predict benefit from the palliative care intervention in terms of QOL-AD or ZBI. Second, is to capture patient and caregiver input regarding what services are most beneficial, what additional services may be needed and preferences for delivery methods. Aim 3b will engage patients and caregivers through semistructured interviews. As palliative care in neurology is relatively new, it is imperative that we elicit patient and caregiver input for process evaluation, particularly as Preliminary data presented above suggests that these persons have unique needs not reflected in palliative approaches to cancer or other diseases. Regarding delivery methods, this is particularly relevant as telemedicine, group clinics and other novel approaches have begun to show efficacy for other applications and may offer advantages to patients and caregivers regarding access, social support, efficiency and cost.[78, 79]

Participants: Participants for Aim 3a will be identical to Aim 1. For Aim 3b (qualitative interviews), we will select a subgroup of participants and caregivers using purposive sampling to complete an additional interview following the final study visit to assess patient/caregiver satisfaction and suggestions of optimization of services and delivery. We will initially use a convenience sample, however as the study progresses we will use maximum variance sampling to ensure heterogeneity in terms of study site, gender, age, PD severity, and cognitive status. We may also use contextual information brought up in interviews or through Aim 3A to inform recruitment. We will interview patients assigned to both the intervention and usual care group as patients in the usual care arm may have less biases related to our service model or personal interactions with our team.

Primary Outcomes: Our primary outcome variables will be change at 6 months in the QOL-AD and ZBI. We will also look at symptom burden, mood, grief and spiritual wellbeing in secondary models.

Predictor Variables: Patient features will include: age, gender, medical comorbidities, presence of a caregiver, depression and disease severity (Hoehn and Yahr score). Caregiver features will include age, gender, depression, and socioeconomic status. Other variables including educational attainment, living situation (independent, assisted living, nursing home), location (rural, suburban, urban) and race/ethnicity will also be examined if sufficient variability in data permits.

Statistical Analyses Aim 3a: Starting from the models in Aim 1, the effect modifiers will introduced as interaction terms, so the time function for each treatment of group can be different for different levels of the interacting variable. The model with the interaction will be tested against the no interaction model. Interaction effects at individual time points may also be tested. The treatment effects for different levels of the interacting variable will be reported. For categorical interacting variables, the treatment effect will be reported at all levels of the interacting variable. For continuous interacting variables, the treatment effect will be reported at pre-specified values of the interacting variable (e.g. dementia and mild cognitive impairment cut-points for the Montreal Cognitive Assessment[54]), natural boundaries (e.g. decades for age), or quartiles (e.g. for baseline caregiver burden). Categories will be collapsed when necessary and justified to prevent sparsely populated cells. An overall test for treatment effect across the different levels of the interacting variable will be performed as a multiple comparisons safe guard. Each interaction effects will be considered in separate models.

Qualitative Interview: For Aim 3B we will perform semi-structured interviews with patients and caregivers to determine patient and caregiver perspectives on what services are most helpful, what services may be needed, delivery of services and timing of services (see Table 3). Additionally, after consenting, we will assess providers' perspectives as to the effectiveness, satisfaction and quality of delivering palliative care services using telemedicine. While the quantitative assessments will occur after each telemedicine visit with a patient, qualitative interviews with the providers will occur late in year 2 of the project, after the majority of participants complete their 12-month visits. We will also validate and build upon prior qualitative data from our group (see **Preliminary Data**) regarding needs to ensure adequate coverage by our intervention. These interviews will be performed by an investigator not part of the primary intervention team who will ask patients and caregivers for their honest opinions to avoid potential biases related to pleasing clinicians. Interviews will be performed in clinic or at patient's home following the final study visit. We will also attempt to interview participants who discontinue the study to avoid potential selection bias in our final dataset. Finally, for patients who are receiving care via telemedicine we will administer a brief survey to get their feedback on how well this type of visit worked in meeting their needs.

Table 3. Interview Domains and Sample Questions

Interview Domain	Sample Questions
Satisfaction with Services Provided	What services provided by the palliative care team did you find helpful? Were there any services provided you did not need? Providers' questions: Satisfaction with technical quality, convenience, and/or care that was able to be provided?
Optimization of Services	Were there any services which you did not receive from the palliative care team or others that you think would be helpful? Providers' questions: Did the use of telemedicine have an impact on your ability to engage or treat the patient and/or caregiver?
Care Delivery	How would you prefer (service discussed earlier) to be provided? For example, in person visits versus phone call.
Other Services	What additional services could be provided to improve you quality of life?
Timing of Services	When in the course of PD do you think palliative services should be started?
Who to Refer	Thinking of yourself and other people you know with PD, who do you think would benefit most from these services?

Mixed Method Analyses Aim 3b: To meet the goal of understanding patient and caregiver preferences for services and delivery methods we will utilize an iterative, inductive and deductive toolkit of analytical strategies drawing on field notes, qualitative content methods of analysis, consultative and reflexive team analysis, and member checking.[80] ATLAS.ti will be used for data management. Analysis will commence with the first participant and proceed alongside data collection, informing and modifying our interview guide and recruitment. Initial coding will be done independently by the PI and PRA who will then discuss codes, establish inter-code reliability, and create an initial master code list. Dr. Jones will be available for adjudication if coding differences persist. The code list will be revisited and revised with continued data collection and with input from the multidisciplinary team. Text within and between codes will be compared to develop themes. Tables will be developed displaying counts of codes to search for patterns, similarities and differences between patients. Through this process we will develop figures of themes which will be modified based on feedback from our multidisciplinary team of advisors. Observer triangulation (using multidisciplinary team) and member checking (eliciting feedback on themes from subsamples of participants) will be employed to increase validity.

Per NIH Mixed Methods Best Practice Guidelines[81], we will be using a sequential quantitative-to-qualitative design for the purposes of *Triangulation* (use of qualitative data to increase confidence in survey results and trial outcomes), *Complementarity* (use of qualitative data to increase depth of understanding), and *Expansion* (use of qualitative data to identify novel issues not measured in surveys). *Integration of Data* will occur at the levels of: 1) Participant Selection through the use of survey results and interim analyses to guide maximum variance sampling; 2) Analysis through the use of survey data to enrich qualitative interviews and the use of qualitative responses to evaluate accuracy and adequacy of surveys; and 3) Interpretation through the combination of qualitative and quantitative data in evaluating and optimizing our current intervention and developing novel care delivery strategies.

Sample Size and Power Calculations: In a situation where the treatment effect interacted with a binary variable, and the sample was evenly distributed among the four combination of treatment and the interacting binary variable, achieving 80% power with an alpha level of 0.05 and 63 samples in each combination (252 total) would require a difference in treatment effect equal to 71% of the standard deviation. Alternatively, a

sample of 252 total would be able to detect an increase in the R^2 statistic of the regression model of 0.031 with 80% power and an alpha level of 0.05. A test for the treatment effect within a subgroup of half the sample (126 out of 252, 63 palliative care and 63 standard care patients), with an alpha level of 0.05, would require effect sizes of 51% and 59% of the standard deviation to achieve 80% and 90% power respectively.

Longitudinal mixed models and linear time functions however would increase this efficiency. For a model with piece-wise linear functions for the time trajectories, with knots at each time point, and in a situation where the true time trajectories are linear, the treatment effect interacts with a binary variable, and the sample was evenly distributed among the four combinations of treatment and the interaction binary variable, a sample size of 63 in each combination (252 total) could achieve 90% power with an alpha level of 0.05 and a difference in treatment effect equal to 44% of the standard deviation at 6 months (5.3 sd*months area, 0.44 sd on average) . A test for a treatment effect within a subgroup of half the sample could achieve 90% power with an alpha level of 0.05 and a treatment effect equal to 32% of the standard deviation at 6 months (3.8 sd*months area, 0.32 sd on average). If the time functions are linear, and linear slopes are used for the model, then 252 samples, equally partitioned among the combinations, could detect, with 90% power, a difference in treatment effect of 32%, and a within group treatment effect of 23%, of the standard deviation at 6 months. The sample size calculations for longitudinal data models assume a compound symmetric covariance structure and a correlation of 0.5 for repeated measures on a participant. Adjusting for multiple comparisons would make the individual tests more conservative. A model with linear time functions eliminates the need for comparisons at different time points.

For Aim 3b, based on our prior work we will aim for 30 patients and up to 30 caregivers taking into account that not all patients will have a caregiver. Rather than controlling the dyad experience we will allow for a more naturalistic occurrence of living with PD, i.e. with or without a caregiver. Based on our iterative analysis of these qualitative data we will determine the need to increase or stop data collection. We aim to reach a point where no new context variation is evident or dominant. To ensure we have explored the experiences to optimal potential we will use maximum variation sampling in later patient identification based on our analysis. We will apply this logic to both intervention and usual care participant groups.

Study Management across Sites

Laura Palmer will act as project coordinator across sites and will handle issues relating to budget, regulatory concerns and conduct of the study in coordination with the PI, Dr. Kluger. This will include annual site visits to review study related procedures and documentation. All data will be entered into a central electronic HIPAA compliant database (REDCAP) housed and managed at the University of Colorado and maintained by our UCD biostatisticians Drs. Stefan Sillau and Diane Fairclough. Sr. Sillau will routinely check database for accuracy and completeness and notify local PI's and coordinators for any issues. Hard copies of all study related documents will be housed at local sites and kept in locked filing cabinets in locked research offices and kept for a minimum of 5 years following completion of the study. Ongoing and frequent coordination and communication between all three sites will occur with ad hoc, as well as regularly scheduled monthly calls and emails. This will allow for quick response to concerns if/as they arise during the study.

Potential Problems and Alternative Strategies

1) *As the intervention is enacted by 3 experienced teams at tertiary care centers will it be replicable or relevant for typical clinical practice?* We have taken several measures to ensure that our intervention is replicable across study sites and other centers. Our first planned manuscript will include our study protocol and a detailed description of our intervention and clinic related forms to allow dissemination to interested sites. Our study neurologists have not completed formal palliative training; rather the clinic structure itself is the key to providing the time and interdisciplinary skills needed to address patient and caregiver needs.

2) *What if the intervention is not successful in meeting primary or secondary outcomes?* This will be an important, if undesired, result that would still contribute to this field and suggest a need for alternate approaches. The value of Aim 3 will be heightened in this scenario by examining benefits to subgroups (suggesting a need for better screening) and eliciting patient and caregiver input on services and delivery.

3) *What if recruitment is slow or retention below expected?* Our recruitment goals are modest and similar goals have been achieved by investigators at all study sites. If needed, further recruitment efforts may include adding additional local sites through community partners and/or more aggressive advertising strategies. A high

drop-out rate would also be an important data point suggesting a need to revise delivery method.

4) *This population is heterogenous and it is possible that outcomes may not apply to all subgroups or that important outcomes for particular subgroups are missed.* This is a significant challenge facing palliative care for PD which may be one factor hampering palliative research for this disease versus more homogenous illnesses such as amyotrophic lateral sclerosis and Alzheimer's disease.[82] As this heterogeneity is a naturally occurring feature of PD we have made every effort to include the full spectrum of PD in our screening forms and intervention. Aim 3 will provide subgroup analyses to inform future interventions and screening efforts.

5) *Will results be biased without blinding?* It is impossible to truly blind an intervention of this nature. We have used patient-reported outcomes to increase the relevance of results as there are no objective biomarkers relevant to our research questions. Despite this, prior multidisciplinary and palliative intervention trials have reported negative results suggesting that blinding biases do not overwhelm clinical effects.[44]

Future Directions

If this intervention is successful in improving patient QOL and/or caregiver distress we would plan to explore alternate delivery methods to improve the efficiency and dissemination of this approach including telemedicine, group visits, smaller teams and mixed approaches (e.g. in person physician visit and telehealth counseling). Cost-effectiveness studies would also be an important follow-up question to influence system level decisions for this model of care. Lastly, application to other progressive neurological illnesses, including mixed populations, may be warranted as patients with advanced chronic neurological illness tend to be similar in terms of symptoms and needs.

If this intervention is not successful, future studies would be guided by the results of Aim 3. Benefits found in specific subgroups would suggest a need for the development of better screening instruments, while poor responses across the sample would suggest a need for a different model. High drop-out rates or noncompliance with the intervention would suggest a need for alternate delivery methods.

HUMAN SUBJECTS

1. Risks to Human Subjects

1.a. Human Subjects Involvement, Characteristics and Design

Due to the nature of our research questions regarding clinical, psychosocial and spiritual needs in PD patients and their family caregivers we feel that involvement of human research subjects is necessary and justified. As we will discuss below, the risks of this research to human subjects are minimal and the potential for benefit for the involved human subjects, other people and family members living with PD, and society is significant.

We will recruit PD patients over age 40 diagnosed with probable PD using UK Brain Bank Criteria[46] or atypical parkinsonian disorders (APD) who are identified to have high potential for palliative care needs using the Palliative Care Needs Assessment Tool.[38] When present their family caregivers will also be included. We plan to recruit a total of 300 PD patients and project that at least 80% will have family caregivers who will also be included in this study.

We will *select* participants using the following inclusion and exclusion criteria described above.

PD patients with dementia (PDD) may be considered a vulnerable population but are necessary to answering our research questions. For all patients with cognitive impairment we will formally assess capacity to consent using the University of California Brief Assessment of Capacity to Consent (UBACC) modified for our specific study design where needed.[83] For patients who fail this screen or if investigators have additional concerns we will require that their guardian participate in the consenting process and sign an informed consent. We will also require that PDD subjects give consent, or at minimum assent if fully informed consent is not possible. Our protocol and consent forms will be approved by our local IRBs before approaching any potential subjects.

Caregivers will be consented and enrolled using a caregiver-specific consent form.

After enrollment, screening and consent, patients will be randomized in a 1:1 ratio to either usual care or an usual care supplemented by an outpatient interdisciplinary clinic. The interdisciplinary team will consist of a neurologist with palliative care experience, a nurse, social worker, and a chaplain. For the usual care arm, patients not currently seeing a neurologist randomized to this arm have appointments with a neurologist

covered by their insurance or patient assistance programs arranged by the study team. Patients will be asked to see their neurologist at least every 3 months to match the frequency of visits in the intervention arm and may see their PCP at their typical frequency. In the intervention arm, palliative care visits will be performed in person (or telemedicine if needed for rural areas and/or limited transportation or health issues) every 3 months. In addition, visits will be supplemented by phone calls one week after each visit to confirm understanding of team recommendations and at 6 weeks to check-in with patient and caregiver. Patients and caregivers may also contact the team as needed. Summaries of visits will be sent to the patient, caregiver, PCP and neurologist and suggestions for care outside of palliative care issues will be left to the patients' Usual Care team.

1.b. Sources of Materials

Data will be obtained from subjects non-invasively via interviews, questionnaires, cognitive testing, and neurological examination as described above.

This data will be accessible only to the research team and, if requested, by appropriate regulatory bodies such as the IRB and FDA. All documents generated by this study, including consent, will be stored in a locked filing cabinet in the locked office of the Principal Investigator (PI). Electronic data will be de-identified with the exception of a correlational spreadsheet including demographic information and study IDs for scheduling and safety contact purposes. This, and all other data, will be stored on a password protected network drive and backed-up on the hard-drive of the PI, also password protected, and kept in the PI's locked office. Identifying information will not be shared outside of the research team or regulatory bodies (e.g. IRB).

1.c. Potential Risks

There are minimal risks involved in the proposed research. There are no known significant risks from the intervention, interviews or surveys proposed for this study. Experiences from collaborators on this study suggest that most patients and caregivers welcome the opportunity to talk about their experiences, even on these potentially delicate subjects. Our interviewers will be cognizant of signs of emotional distress in participants and will suggest breaks and remind them that participation is voluntary. Cognitive testing and surveys as proposed in this study may induce boredom or restlessness. Any new diagnoses detected during screening (e.g. depression or dementia) will be referred for appropriate treatment, including emergent treatment if indicated. There are no known significant risks to the proposed team-based intervention for addressing palliative care needs. Participants will be reminded of the voluntary nature of this research and informed that we can follow them outside of the intervention or they can completely discontinue the study if they find it excessively burdensome or otherwise troubling.

2. Adequacy of Protection Against Risks

2.a. Recruitment and Informed Consent

Participants will be recruited from the academic medical centers (University of Colorado, University of California San Francisco, University of Alberta), associated clinics, community neurologists, and direct advertisements and contact with patients (e.g. clinicaltrials.gov, community seminars). Protocols will be approved by the relevant regulatory body at each institution before any contact is made with potential participants. We will obtain informed consent before any study related activities are performed. Potential subjects will be specifically told that their participation or lack of participation will not affect the clinical care they receive. For PD Dementia subjects, special procedures will be in place to involve both guardians and patients in the informed consent process, and both guardians and subjects will be required to give consent in person or by phone if performing visit by telehealth (or assent for PDD subjects unable to give full informed consent). The consenting process will use standard IRB terminology and will include a full description of expected subject involvement, procedures, risks, rights, and benefits. Capacity will be formally assessed in any patients with cognitive impairments and guardian consent and patient assent will be required in these cases.[83]

2.b. Protections Against Risks

All subjects will be reminded that they can take breaks or discontinue the study at any time if they find it upsetting. PD dementia subjects will be required to give consent (if they have capacity) or assent with caregiver consent to avoid potential manipulation of a vulnerable population. Regarding patient privacy, all research procedures will be performed in a confidential setting. All documents generated by this study, including consent, will be stored in a locked filing cabinet in the locked office of the PI. Electronic data will be de-identified with the exception of a correlational spreadsheet including demographic information and study IDs for scheduling and safety contact purposes. This, and all other data, will be stored on a password protected

network drive and backed-up on the hard-drive of the PI, also password protected, and kept in the PI's locked office. Identifying information will not be shared outside of the research team or regulatory bodies (e.g. IRB).

3. Potential Benefits of the Proposed Research to Human Subjects and Others

All subjects participating will receive a free neurological examination and history from a movement disorder trained specialist, and screening for dementia and depression. These results will be reviewed by a study neurologist and referred for appropriate care if abnormalities are identified. Participants randomized to the usual care arm will have care with a neurologist arranged if they do not already have this in place. Participants randomized to the palliative intervention will have access and care from an interdisciplinary team. This proposal has the potential to further our knowledge of care models in PD and has the potential to influence our ability to address many currently unmet needs for patients and caregivers. As discussed below, the knowledge gained by this proposal has a significant potential to advance our knowledge of palliative needs in PD which has large positive implications for PD patients, the scientific community and society.

4. Importance of Knowledge to be Gained

Parkinson's disease (PD) affects 1-2% of adults over age 65 representing approximately 1.5 million Americans. Although PD is traditionally characterized by motor symptoms such as tremor and slowed movement more recent research shows that PD patients also commonly experience non-motor symptoms such as pain, fatigue, depression and dementia. PD interferes with patients' quality of life, leads to disability, decreases length of life and causes significant distress for caregivers. Unfortunately, many of the needs most important to patients and their caregivers (e.g. depression, planning for the future) are poorly addressed under current models of care. The goal of this proposal is to take a patient-centered approach to answering these questions. Our specific objectives are to: 1) Determine whether an outpatient palliative care team improves patient quality of life and caregiver distress compared to usual care with a neurologist; 2) Determine what patient and caregiver characteristics best predict benefit from palliative care services; and 3) Interview patients and caregivers to optimize service delivery and selection. This project is important to patients and their family caregivers because it assesses a new approach to PD care that has the potential to improve quality of life, caregiver burden and other important outcomes (e.g. nursing home placement). By testing the effectiveness of this approach and determining who benefits most we hope to provide a new option to assist those PD patients at highest risk for poor outcomes. Information generated by this proposal will also be important for other stakeholders interested in PD including hospitals, insurers and patient advocacy organizations.

5. Data and Safety Monitoring Plan

We will not assemble a Data and Safety Monitoring Board (DSMB) as this is a minimal risk study comparing the effectiveness of two currently available approaches to the care of PD and APD patients. The site PI will be notified of any adverse events occurring at all sites and will notify the study's central IRB (COMIRB) of all adverse events and any change in our appraisal of the risks and benefits of this study from our data or other published literature.

6. ClinicalTrials.gov Requirements

We will register this trial with clinicaltrials.gov prior to enrollment of the first participant at any site.

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Study Procedures	Baseline	6 wk assessment	3 mos. visit	6 wk assessment after 3 mos. visit	6 mos. visit	6 wk assessment after 6 mos. visit	9 mos. visit	6 wk assessment after 9 mos. visit	12 mos. visit	Optional post study interview & Telemedicine Surveys
Consent ΩΩ	P, C, Poviders (for telemed)									
University of California Brief Assessment of Capacity to Consent (UBACC)ΩΩ	P									
Medications ΩΩ			P		P		P		P	
Need Assessment Tool – PD (NAT – PD)*	P									
History *	P									
Charlson Comorbidity Index *	P									
Hoehn and Yahr Staging *	P									
UK Brain Bank Clinical Diagnostic Criteria*	P									
MDS UPDRS Motor Subscale*	P				P				P	
MOCA*	P				P				P	
Patient Performance Scale*	P				P				P	
Inclusion/Exclusion*	P									
QOL – AD ΩΩ	P, C		P, C		P, C		P, C		P, C	
Zarit Burden of Care Instrument (ZBI) **β**	C		C		C		C		C	
Advance Directives	Pt				Pt				Pt	
Edmonton Symptom Assessment Scale (ESAS –PD)ü	P		P		P		P		P	
Functional Assessment Of Chronic Illness – SP (FACIT – SP)ü	P,C		P,C		P,C		P,C		P,C	
Hospital Anxiety and Depression Scale (HADS) ΩΩ	P, C		P, C		P, C		P, C		P, C	
Parkinson's Disease Questionnaire – 39 (PDQ – 39) ü	P		P		P		P		P	
Prolonged Grief Questionnaire – 12 (PG – 12)ü	P		P		P		P		P	
PROMIS – 29 ü	P		P		P		P		P	
Demographics ΩΩ	P, C									
Health Utilization Questionnaire ΩΩ	P, C	P, C	P	P, C	P	P, C	P	P, C	P, C	
Strata Adherence ΩΩ			P		P		P		P	
Randomization	P									

Qualitative Interview										P, C, Providers

APPENDIX 1

* administered by clinician – inclusion/exclusion form, NAT – PD, MOCA, MDS UPDRS Motor Subscale, Hoehn and Yahr Staging, History, UK Brain Bank Clinical Staging, Patient Performance Scale and Charlson Comorbidity Index

ΩΩ administered by coordinator – consent, UBACC, QOL – AD, PROMIS – 29, Medications, Demographics and Health Utilization

ϋ self-administered (patient) - PDQ – 39, ESAS –PD, FACIT – SF, PG -12 and PROMIS -29

β self- administered (caregiver) - Zarit Burden of Care Instrument, EQ-5D

After review of consent with subject, UBACC then should be administered next by the coordinator to see if subject has the capacity to consent prior to signing consent.

No study procedures should be completed prior to the consent process.

QOL – AD and Zarit Burden of Care Instrument (ZBI) [care giver] if applicable, should be administered first prior to any other study procedures.

Please note, CGI will be administered by coordinator at 3 and 9 month visit (omit questions 2C at 3 and 9 month visits) and at 6 and 12 month visit it will be administered by the clinician.

6 week assessment after every scheduled visit will be done by phone.

3, 6, 9 and 12 month visit, only capture medication changes.

Data collection for all study visits can be done by phone, online survey, via telehealth, or in person.

Time windows for study visits and data collections are as follows:

- The 3, 6, 9, and 12-month visits should occur within +/- 4 weeks of scheduled date.
- The one week follow-up phone call should occur within 1 week of scheduled date.
- The six week follow-up phone call should occur within 2 weeks of scheduled date.
- The six-week health care utilization survey call should occur within 2 weeks of scheduled date.