Contemporary Clinical Trials 79 (2019) 28–36

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Does outpatient palliative care improve patient-centered outcomes in Parkinson's disease: Rationale, design, and implementation of a pragmatic comparative effectiveness trial

Benzi M. Kluger[a,*], Maya Katz[b], Nicholas Galifianakis[b], Steven Z. Pantilat[c], Jean S. Kutner[d], Stefan Sillau[a], Mark Gritz[e], Jacqueline Jones[f], Diane Fairclough[g], Malenna Sumrall[a], Kirk Hall[a], Janis Miyasaki[h]

[a] Department of Neurology, University of Colorado School of Medicine, 12631 E 17th Ave, MS-B185, Aurora, CO 80045, USA
[b] Movement Disorders and Neuromodulation Center, University of California, San Francisco 1635 Divisadero Street, Suite 520, San Francisco, CA 94118, USA
[c] Division of Palliative Medicine, Department of Medicine, University of California, San Francisco 533 Parnassus Ave., Suite U-109, Box 0131, San Francisco, CA 94143, USA
[d] Division of General Internal Medicine, Department of Medicine, University of Colorado School of Medicine, 12631 E 17th Ave, MS-B180, Aurora, CO, USA
[e] Division of Healthcare Policy and Research, Department of Medicine, University of Colorado, 13199 East Montview Boulevard, MS-F480, Aurora, CO 80045, USA
[f] College of Nursing, University of Colorado, 13120 East 19th Avenue, MS-C288, Aurora, CO 80045, USA
[g] School of Public Health, Department of Biostatistics and Informatics, University of Colorado, 13199 East Montview Boulevard, MS-F443, Aurora, CO 80045, USA
[h] Division of Neurology, University of Alberta, 11350-83 Avenue, 7-112 Clinical Sciences Building, Edmonton, AB T6G 2G3, Canada

ARTICLE INFO

Keywords:
Palliative care
Randomized clinical trial
Quality of life
Parkinson's disease
Atypical parkinsonian disorders
Comparative effectiveness

ABSTRACT

Patients with Parkinson's disease and related disorders (PDRD) and their families have considerable unmet needs including non-motor symptom management, caregiver support, spiritual wellbeing, advance care planning, and end-of-life care. There is increasing interest in applying palliative care (PC) models to better meet these needs. While PC has been shown to improve care and quality of life (QOL) for people with cancer and heart failure, few studies have evaluated the role of PC for people with PDRD. Well-designed clinical trials are needed to optimize the PC approach for PDRD and to influence policy and implementation efforts. We initiated a randomized multicenter comparative effectiveness trial of team-based outpatient PC versus usual care for people with PDRD and their caregivers. The primary aims of this study are to determine the effects of PC on patient QOL and caregiver burden. Qualitative interviews will be utilized to gain additional insights into the impact of PC on participants, the outcomes that matter most to this population, and to find opportunities to refine future interventions and trials. As a novel application of PC, challenges involved in the design of this study include choosing appropriate inclusion criteria, standardizing the intervention, defining usual care, and choosing outcome measures suitable to our research questions. Challenges involved in implementation include participant recruitment, retention, and management of participant burden. We anticipate the results of this trial will have relevance for both clinical care and future clinical research trial design in evaluating models of PC for people with PDRD and other serious illnesses.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative illness affecting 1–2% of adults over age 65 [1]. While PD is traditionally defined by its motor symptoms, non-motor symptoms including pain, depression, and dementia are common and contribute significantly to quality of life (QOL) and disability [2,3]. PD is currently ranked as the 14th leading cause of death in the US and this may be an underestimate as PD contributes to other causes of death such as pneumonia and falls [4,5]. People living with PD are five times more likely to be placed in a nursing home and die in hospitals significantly more often than age-matched peers [6,7]. PD is also associated with

* Corresponding author at: University of Colorado School of Medicine, Department of Neurology, 12631 E 17th Ave, MS-B185, Aurora, Colorado 80045, United States.
E-mail addresses: Benzi.Kluger@ucdenver.edu (B.M. Kluger), Maya.Katz@ucsf.edu (M. Katz), Nicholas.Galifianakis@ucsf.edu (N. Galifianakis), Steve.Pantilat@ucsf.edu (S.Z. Pantilat), Jean.Kutner@ucdenver.edu (J.S. Kutner), Stefan.Sillau@ucdenver.edu (S. Sillau), Mark.Gritz@ucdenver.edu (M. Gritz), Jacqueline.Jones@ucdenver.edu (J. Jones), Diane.Fairclough@ucdenver.edu (D. Fairclough), miyasaki@ualberta.ca (J. Miyasaki).

https://doi.org/10.1016/j.cct.2019.02.005
Received 10 August 2018; Received in revised form 24 January 2019; Accepted 13 February 2019
Available online 16 February 2019

significant effects on family caregivers including high rates of stress, depression, and increased mortality [8,9]. Multiple systems atrophy, corticobasal degeneration, progressive supranuclear palsy, and Lewy Body Dementia are collectively referred to as Parkinson-plus syndromes or atypical parkinsonian disorders and are often referred to as PD and related disorders (PDRD) [10]. These disorders share many of the same symptoms and complications as PD but have less response to medical treatments and faster progression. Although individually rare, collectively they account for approximately 15% of all parkinsonism and are associated with high palliative care needs [11–13].

Despite advances in our understanding of the burden of PDRD on patients and caregivers, clinical care continues to be driven by a chronic illness model focused on managing motor symptoms through a patient-physician dyad [14]. Potential gaps in this model include a failure to address psychosocial and spiritual concerns; under-recognition and under-treatment of non-motor symptoms; low rates of advance care planning and supportive end-of-life care including hospice; and under-recognition of caregiver needs [14,15].

Palliative care (PC) seeks to improve the quality of life (QOL) of people affected by serious illness by relieving suffering through the assessment and treatment of physical, psychosocial, and spiritual issues [16]. While traditionally associated with cancer, palliative approaches have been successfully applied to several chronic illnesses including heart failure and pulmonary disease [17,18]. Recent review articles and case series suggest PC may be beneficial for PDRD and a small but growing number of academic centers now offer outpatient PC for PDRD [19–21]. However, there are significant gaps in the evidence needed to support widespread adoption of this care model including:

1) A need for randomized controlled comparative effectiveness trials in PDRD to determine whether PC improves outcomes compared to usual care.
2) Data to guide referral of appropriate patients for this time and resource intensive intervention.
3) Data to standardize which services are provided and how they are delivered.
4) Development of care models that account for limitations in current healthcare delivery (e.g. work force shortage of PC physicians) [22].

This manuscript describes the rationale and challenges involved in the design and implementation of a clinical trial of outpatient PC for PDRD embedded within a neurology clinic. We also describe efforts made to collect data beyond the primary aims of the study to address methodological issues important for facilitating future trials in this field.

2. Specific aims

Aim 1: Determine whether interdisciplinary outpatient palliative care improves patient QOL or caregiver burden in PDRD compared to usual care provided by a neurologist.
Aim 2: Identify characteristics of PDRD patients most likely to benefit from a palliative care approach.
Aim 3: Interview PDRD patients and caregivers to elicit their direct input on what PC services are most helpful, what additional services may be needed, and preferences for service delivery.
Exploratory Aim: Characterize differences in patterns of healthcare utilization (e.g. emergency room visits, hospitalizations, use of home health care) between the PC and usual care groups.

3. Study design

3.1. Overview

210 people with PDRD and moderate PC needs will be randomized to either: a) continue their current care (usual care); or b) receive additional team-based PC embedded within a neurology clinic. Caregivers, when present, will be randomized along with their respective patients as a dyad. As a pragmatic comparative effectiveness trial, our goals are to understand whether there are differences in patient or caregiver outcomes between current standards of practice versus those receiving additional outpatient PC as currently practiced in academic neurology centers offering these services.

Following randomization, participants will be followed for 12 months, with data collection and intervention visits scheduled at 3, 6, 9, and 12 months. To minimize recall bias, we will collect data on healthcare utilization every 6 weeks. The primary outcomes for this trial are change in patient QOL (measured with the Quality of Life Alzheimer's Disease; QOL-AD) and caregiver burden (measured with the Zarit Burden Inventory; ZBI) at 6 months [23,24].

The study will be conducted at three sites with longstanding experience in PC for PDRD: the University of Colorado, the University of Alberta, and the University of California San Francisco. Clinical care for patients in the usual care arm include patients from regional community practices as well as patients receiving their care from other providers at these academic institutions. The study was approved by the institutional review boards of all participating institutions. The University of Colorado, as the coordinating site, will serve the additional roles of hosting a central database, data monitoring, and biostatistical analysis. The trial was registered with clinicaltrials.gov (NCT 02533921) prior to participant enrollment.

A summary of innovations of the current trial include:

1) Our PC intervention is administered by a clinical team led by a neurologist with PC experience and informal training with a board-certified palliative medicine specialist serving primarily in a coaching and advisory role. If effective, this model may be more readily implemented and avoids limitations due to potential workforce shortages of palliative medicine specialists [22].
2) Use of the recently developed Needs Assessment Tool – Parkinson's Disease (NAT-PD) to provide standard and reproducible screening of patients with moderate palliative care needs (see Appendix 1) [25].
3) Use of checklists for all intervention team clinical roles to improve fidelity and reproducibility while still allowing clinicians the flexibility to meet the unique needs and care goals of patients and families (see Appendix 2).
4) Inclusion of patients with and without PD-related dementia (PDD). One of the challenges of building a PC model for PDRD is the wide variability of clinical phenotypes, including a wide range of cognitive function. We specifically want to include patients with dementia who are often excluded from clinical research but represent a very high-risk population for PC needs.
5) Use of the Quality of Life: Alzheimer's Disease (QOL-AD) and recently developed Edmonton Symptom Assessment Scale – Parkinson's Disease (ESAS-PD) to capture QOL and symptom burden respectively [23,26]. More commonly used PD QOL outcomes such as the Parkinson's Disease Questionnaire [27] were not developed for PC applications and focus heavily on functional activities that may be beyond the abilities of persons with advanced disease.
6) Use of mixed methods to evaluate the effectiveness and appropriateness of the inclusion criteria, outcome measures, and intervention.

3.2. Role of PD patient and caregivers advisory council

In alignment with the requirements of the Patient Centered Outcomes Research Institute (PCORI) and the PCORI engagement rubric we engaged a group PD patients and caregivers to be involved in study planning, conduct, and dissemination [28]. Our patient advisory council was led and formed by a patient (KH) who had previously completed the Patient Advocacy In Research (PAIR) [29] training through the Parkinson Foundation (formerly Parkinson's disease

Foundation) and was actively involved with several support group leaders through the Parkinson's Association of the Rockies. The advisory council's roles included:

1) Planning: Patient involvement was present from the inception of the study and grew from conversations of the PI (BMK) and advisory council leader (KH) in their PAIR work. The council is involved in reviewing study protocols, testing, and timing study protocols for participant acceptability, providing input on wording for all patient materials (including advertisements and consent form), going through intervention checklists, providing input into qualitative interview guides, and helping to choose outcome measures. Some specific contributions from this process include anticipation of patient barriers to participation, such as concerns for out-of-pocket costs for the intervention, validation of the patient and caregiver-centeredness of our outcomes, and vetting decisions that could impact participants such as when to include participants with high PC needs or dementia. These contributions will improve the study design and conduct, substantiate our claims of patient-centeredness, and mitigate concerns of regulatory boards for participant burden and acceptability.
2) Conduct: The council will play an instrumental role in developing recruitment and retention strategies including giving peer perspectives on the study in community informational and recruitment talks and contributing to our study newsletter.
3) Dissemination: The council will assist us with our qualitative analyses and will help in reviewing quantitative papers and providing summaries of our findings through patient venues ranging from support groups to national organizations. As research partners, we welcome suggestions for novel analyses which have already led to at least one unique paper.

3.3. Ethics

In designing this trial, we were faced with the ethical challenge of whether to randomize patients with urgent and significant PC needs. On the one hand, our clinical experience strongly suggests that the benefits of this intervention would be greatest for those with high and urgent needs and that excluding such patients could reduce our chances of finding a statistically and clinically significant effect. On the other hand, we strongly questioned the ethics of randomization that could deny patients access to care already available to them outside of the research study, particularly given evidence that in uncontrolled studies that PC would benefit these patients and that studies of PC in other populations have not shown any harm [21,26,30].

We decided that persons with urgent PC needs would be excluded from randomization and fast-tracked into university PC clinics given our primary ethical responsibility of beneficence despite the potential risk of reducing our effect size and increasing the chances of having a negative trial for an effective therapy. From a pragmatic perspective, we felt this decision could be further justified by focusing our trial on the question of whether palliative care applied early or to more moderate needs results in changes in clinical outcomes. As there is greater clinical equipoise about early, proactive palliative care for patients with moderate needs, the results of this trial may have a greater chance of influencing current clinical practice.

We practically define urgent PC needs as any PC issue for which the patient or caregiver were unwilling to wait 6 months (time of primary outcome) or that the site principal investigator (PI) felt would cause undue distress to the patient or caregiver if PC care was delayed. For persons in the usual care arm, we also have chosen to allow patients to cross-over to the intervention if they developed urgent needs as determined by their regular treating physician, the patient or caregiver, or the assessment of the study team.

3.4. Eligibility

3.4.1. Inclusion criteria

Patients must be fluent English speakers, over the age of 40, and meet UK Brain Bank criteria for a diagnosis of probable PD or standard criteria for progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), multiple system atrophy (MSA), or dementia with Lewy bodies (DLB) [31–35]. Caregivers, 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 the clinic?” For patients with severe dementia, family caregivers could be self-identified and could be included in the study even if the patient had cognitive or communication limitations in order to obtain data relevant to these highly vulnerable and under-represented patients. Included patients (and/or caregivers when present) demonstrated moderate to high palliative care needs assessed using the Palliative Care Needs Assessment Tool [25] modified for PD (NAT-PD, see Appendix 2) which screens patients on the basis of social factors (e.g. presence of caregiver), disease severity, and symptom burden and caregivers on the basis of psychological distress, caregiver burden, and relationship issues. In anticipation of the recruitment of persons with dementia we purposefully included primary outcome measures validated in dementia and for proxy reporting and planned to allow an option for a reduced survey battery for persons or dyads with severe communication issues, time burden or fatigue.

3.4.2. 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 directly referred to appropriate services); 2) Unable or unwilling to commit to study procedures including randomization and study visits; 3) Presence of additional medical illnesses which may require PC (e.g. metastatic cancer); or 4) Already receiving PC including hospice. We will keep our inclusion/exclusion criteria broad to allow for greater generalizability of results and to ensure inclusion of potentially under-represented subgroups (e.g. persons with dementia).

3.5. Participant recruitment and retention

Recruitment strategies included: 1) Referrals from colleagues within academic practices; 2) Referrals from community physicians notified about the study through personal connections, solicitations through email and letters, and continuing medical education (CME) events; 3) Community talks given to patients by investigators or patient/caregiver advisors sponsored by support groups or local PD organizations; 4) Advertisements through local PD organizations (e.g. newsletters); and 5) Postings on clinical research websites (clinicaltrials.gov and foxtrialfinder.michaeljfox.org).

Efforts will be made to retain participants including: 1) Reimbursement for time and travel-related expenses; 2) Option for telemedicine approaches for data collection and clinical intervention for persons with transportation or mobility issues; 3) Option for reduced data collection of prioritized outcome measures (only primary and key secondary outcomes); 4) Newsletter for participants reinforcing purpose of the study and including updates of study progress; and 5) Offer to fast-track patients in usual care arm into the PC clinic at study completion.

3.6. Randomization

Participants will be randomized in a 1:1 ratio to either the palliative or usual care group through a randomized block design stratified by site, presence of dementia (using standard criteria for PD-related dementia [36]), and disease stage (dichotomized as mild to moderate or severe using the Hoehn and Yahr scale [37]). This randomization strategy was chosen to minimize potential confounding effects in this

relatively small sample based on time of study entry, site differences, and clinical characteristics expected to influence study outcomes.

3.7. Usual care arm

Usual care consists of care from the patient's primary care provider (PCP) and a neurologist. We consider this the current standard of care given evidence that PD care with a neurologist results in better outcomes (e.g. falls, mortality) than care with a PCP alone [38]. Patients not seeing a neurologist at study entry will have appointments with a neurologist covered by their insurance arranged by the study team. As a pragmatic trial, we recorded but did not prescribe how frequently patients saw their neurologist or PCP. Notably, we anticipate that a significant fraction of neurologic care in this arm will be provided by movement disorders specialists at our academic centers as recruitment from colleagues is one of our primary sources of participants. The majority of care at each academic center is not based on the PC model and only physicians not directly involved in PC can serve as neurologists in the usual care arm.

3.8. Intervention arm

Our intervention consists of usual care plus the addition of an outpatient interdisciplinary PC team embedded within an academic neurology clinic, a service currently available at these centers and covered by most insurances including US and Canadian Medicare. PC visits will be performed in person or via telemedicine every 3 months. These visits may 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. Over the first year of the study, we found that these calls were not always needed and could be redundant although most patients appreciated them – we thus made them optional rather than required at the discretion of the clinical team and captured whether and when they were completed. Summaries of visits will be sent to the patient, caregiver, PCP, and neurologist and suggestions for care outside of PC issues deferred to the patients' usual care team.

The interdisciplinary PC team was led by a movement disorders neurologist with informal PC training. This training generally consisted of workshops (e.g. at national meetings), reading and clinical practice with guidance from a palliative medicine specialists but did not include fellowship training. The nurse and social worker on the team were part of the movement group and acquired additional PC experience through reading, workshops and communication with clinicians at the institutions' primary PC team. The chaplain was part of the hospital PC team. A board-certified palliative medicine physician is available at each site for team guidance, periodic chart review, and in-person patient consultations. The palliative medicine physician's primary role is one of coaching and guidance. This involves reviewing the checklists, procedures and documentation at each site at study outset and providing ongoing coaching at the discretion of the team, including through co-management of complex patients, during the course of the study. As the core team becomes more experienced, including through real-time coaching of the palliative medicine specialist, the involvement of the palliative medicine specialist will decrease to infrequent consultations for specific issues or patients. This model is reflective of current practices in neurology centers offering these services and allows for potentially greater impact from a limited pool of palliative medicine specialists in the outpatient arena [21]. Visits will be standardized through the use of checklists as summarized in Table 1 (full Checklists available in Appendix 1). All staff except the palliative medicine physician will be present for all visits and summary meetings at the end of each clinic to ensure interdisciplinary care.

3.9. Primary and secondary outcome measures

Our primary outcomes are change in patient QOL, as measured by the Quality of Life: Alzheimer's Disease (QOL-AD), and caregiver burden, as measured by the Zarit Caregiver Burden Interview short form (ZBI) [23,24]. The QOL-AD was chosen for this study for several reasons including its brevity, insensitivity to cognitive impairment, validated proxy reporting, responsiveness, and coverage of issues identified to be relevant to PD patients and caregivers in prior studies and through our advisory council [39,40]. Although there is currently no QOL instrument specifically validated for PDRD patients with dementia, the QOL-AD is validated in mixed dementia and covers issues relevant to all dementias [41]. The ZBI is the most commonly used self-report measure of caregiver distress, including in PD. [8,42] 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 [43]. It is also sensitive to change with interventions, including palliative care [44].

Table 2 summarizes primary and secondary outcome measures. Patient advisors actively participated in identification of outcome domains and selection of study instruments. We tracked patterns of healthcare utilization (e.g. hospitalization, nursing home placement) and financial impact of illness on patients and caregivers through loss of work or time spent in caregiving activities using questions drawn or modified from the Ambulatory and Home Care Record (AHCR) with the goal of obtaining outcomes relevant to healthcare providers and insurers in addition to patients and families (Appendix 3) [45]. We included several commonly used measures of patient QOL in PD and PC to address the clinimetric validity of these outcomes for this population and appropriateness for future trials, including using global impression scores to assess responsiveness.

A subset of patients and caregivers in both intervention and usual care arms will additionally participate in semi-structured qualitative interviews to gain additional insights into the impact of PC on participants, the outcomes that matter most to this population, and to find opportunities to refine future interventions and trials (Table 3). These questions were drawn from prior qualitative studies as well as domains of interest based on prior work in this field [19,39,40]. Patients and caregivers will be interviewed individually to avoid allow both groups to speak openly on issues they may be afraid to speak on with their partner present.

3.10. Data collection

Data regarding patient QOL, symptom burden and caregiver distress will be measured at baseline, 3, 6, 9, and 12 months. Primary outcomes are differences between treatment arms in patient QOL and caregiver burden at 6 months. Symptom burden, spiritual wellbeing, and mood will be assessed as secondary outcomes. To reduce loss of events due to prolonged recall, we will assess healthcare utilization every 6 weeks.

3.11. Statistical analysis

The main objective of the study (Aim 1) is to determine the comparative effectiveness of interdisciplinary outpatient PC versus usual care with a neurologist for PD on patient QOL and caregiver burden. Secondary outcomes (see Table 2) include symptom burden, mood, and spiritual wellbeing as well as occurrence of key events including hospitalization and nursing home placement. Controlling covariates include gender, age, disease severity (Unified Parkinson's disease Rating Scale [48]), cognitive dysfunction (Montreal Cognitive Assessment [49]), and depressive symptoms (HADS Depression Subscale [50]). The explanatory variables will be checked for randomization and multicolinearity. Successful randomization should minimize covariate imbalances between treatment groups, but including them in the model adjusts for lingering confounding effects and accounts for variance in the outcome variable.

The outcomes will be modeled with mixed regression model

Table 1
Interdisciplinary palliative care visit checklist.

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 - PDRD education relevant to disease stage including prognosis - Goals of Care
Social Worker (for both patient and caregiver if present)	- Caregiver distress - Need for help at home/community resources - Financial issues and concerns - Long-term care needs
Chaplain (for both patient and caregiver if present)	- Spiritual wellbeing - Sources of support and stress - Fear, anger and guilt - Grief and demoralization
Nurse	- Advance care planning documentation - Healthcare proxy designation and documentation - Wound care/skin integrity - Nutritional status and diet
Palliative Medicine Physician	- Coaching and guidance for primary team - In-person or phone consultation for advanced symptom management or complex goals of care at discretion of primary team - Periodic review of charts from palliative perspective

Table 2
Outcomes of interest to patients, caregivers, and other stakeholders assessed in this proposal.

Measure	Domain of interest
Quality of Life: Alzheimer's Disease (QOL-AD) [23]	Patient Quality of Life (QOL; Primary Outcome)
Zarit Burden Interview (ZBI) [34]	Caregiver Distress (co-Primary Outcome)
Parkinson's disease Questionnaire (PDQ-39) [30]	Patient Functional Status and secondary QOL
McGill Quality of Life Questionnaire [46]	Secondary Patient QOL
Patient-Reported Outcomes Measurement Information System (PROMIS) 29-item short form [47]	Secondary patient QOL
Edmonton Symptom Assessment Scale (ESAS-PD) [26]	Patient symptom burden
Hospital Anxiety and Depression Scale (HADS) [37]	Patient and Caregiver Mood
Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing (FACIT-SW) [39]	Patient and Caregiver Spiritual Wellbeing
Prolonged Grief Questionnaire (PG-12) [23]	Patient and Caregiver Grief
Unified Parkinson's disease Rating Scale [41]	Patient Motor symptom Severity (motor exam only)
Montreal Cognitive Assessment (MOCA) [46,56]	Patient Cognitive Status (baseline visit only)
Hoehn and Yahr Scale [44]	Patient Disease Stage (baseline visit only)
Charlson Comorbidity Index [61,66]	Medical Comorbidities (baseline visit only)

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, 6, 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.

Table 3
Interview domains and sample questions.

Interview domain	Sample questions
Needs Assessment	What aspects of your illness are most difficult for you to deal with?
Meaningful Outcomes	If there was one thing we could improve about your current situation what would it be?
Satisfaction with Services Provided	What services provided by your care team did you find helpful? Were there any services provided you did not need?
Optimization of Services	Were there any services which you did not receive from your care team or others that you think would be helpful?
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?

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.

A secondary objective (Aim 2) of this proposal is to explore factors modifying the effect of PC compared with standard treatment. This will specifically include the following patient characteristics: age, gender, medical comorbidities (Charlson Comorbidity Index [51]), presence of caregiver, cognitive status, depression, caregiver distress, income, race/ethnicity, and home environment (e.g. rural, inner city, nursing home). We will also examine whether there are differences between academic sites or between persons receiving care at academic centers versus community practices for their primary neurologic care. 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 [52]), 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. Since the study lacks the power to investigate effect heterogeneities with precision, Aim 2 will be largely exploratory and descriptive unless very large effect sizes are detected.

3.12. Power considerations

3.12.1. Aim 1

Allowing for up to 15 dropouts per group by the 6-month time point, a two sample *t*-test with 90 samples per treatment group (180 total) would detect a difference in our patient continuous outcomes equal to half 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 [53]. For caregivers, assuming 80% of patients have caregivers and a similar drop-out rate, we would have 72 samples per treatment (144 total) and could detect a difference of equal to half the standard deviation with 85% power and an alpha of 0.05. 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 [54]. Notably, prior studies of palliative interventions have found effect sizes of 0.5 SD/mean and greater [44]. 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.

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, 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 90 per treatment group (180 total) would be virtually certain to detect a difference of 50% of standard deviation at 6 months (6 sd*months of area, 0.5 sd on average) for very small alpha levels, and so a Bonferroni correction could be applied to handle multiple comparisons. A sample size of 90 per treatment group (180 total) would achieve more than 90% power with an alpha level of 0.05 and an effect size equivalent to 30% of the standard deviation at 6 months (3.6 sd*months area, 0.3 sd on average). For a test of mean difference in change from baseline at 6 months in caregivers, 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 90 per group (180 total) would achieve 97% power. The test would have more than 90% power even after a Bonferroni adjustment for four tests. Alternatively, 90 samples per group (180 total) 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 [55].

3.12.2. Aim 2

Regarding power, 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 44 samples in each combination (176 total) would require a difference in treatment effect equal to 85% of the standard deviation. Alternatively, a sample of 180 total would be able to detect an increase in the r^2 statistic of the regression model of 0.04 with 80% power and an alpha level of 0.05. A test for the treatment effect within a subgroup of half the sample (90 out of 180, 45 palliative care and 45 standard care patients), with an alpha level of 0.05, would require an effect sizes of 60% and 70% 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 situation where the treatment effect interacted with a binary variable and sample was evenly distributed among the four combinations of treatment and the interaction binary variable, a sample size of 45 in each combination (180) total could achieve 90% power with an alpha level of 0.05 and a difference in treatment effect equal to 40% of the standard deviation. 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 30% of the standard deviation. 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. Adjusting for multiple comparisons would make the individual tests more conservative. However, the linear model eliminates the need for multiple tests across time points.

3.13. Qualitative interviews and mixed methods analysis

For Aim 3 we plan to recruit a total of 30 patients and 30 caregivers based on prior studies in this population but may interview more or less patients if needed to obtain thematic saturation in our domains of interest. Recruitment will initially be a convenience sample but will shift to maximum variance sampling as interviews progress to ensure representation of the spectrum of patients (e.g. across age and disease severity), important subgroups (dementia, no caregiver), study group assignment and insights into any key issues emerging as interviews proceed.

To meet the primary goal of optimizing and evaluating outpatient PC in PDRD we will utilize an iterative, inductive, and deductive toolkit of analytical strategies drawing on field notes and memoing, qualitative content methods of analysis, consultative and reflexive team analysis, and audit and member checking as performed by members of the research and clinical teams and patient advisory council [56–58]. ATLAS.ti will be used for data organization and 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 a PRA with qualitative experience and a qualitative expert (JJ) who will discuss codes, establish inter-code reliability, and create an initial master code list. The code list will be revisited and revised with continued data collection and with input from the multidisciplinary study team including patient advisors. 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 caregivers and patients. Secondary analyses will develop similar tables to determine whether there are potential differences in needs based on age, gender, race, disease stage, or cognitive status. Through this process we will develop figures of themes which will be modified based on feedback from our multidisciplinary team of advisors and potentially through feedback at presentations prior to publication. Observer triangulation (using interdisciplinary team, stakeholders, and patient advisors), participant triangulation (comparing caregiver and patient perspectives), member checking (eliciting feedback on themes from subsamples of participants), and comparison to quantitative results will be employed to increase validity.

4. Lessons and challenges from implementation and early study conduct

4.1. Challenges in participant recruitment

Our initial expectations regarding enrollment rates were overly optimistic as the population in which we were interested differed in key ways from participants in other clinical trials. Our population tended to be excluded from prior studies and thus less likely to be engaged in research; were less likely to be a part of support groups; and were more sensitive to potential demands on their time or need to travel (even if it involved additional care). To overcome our initial under-enrollment we expanded our inclusion criteria to include related disorders (PSP, CBD, DLB) as the palliative needs of these populations are similar and these patients routinely received PC care in our academic centers [13,59]. This population made up 11.9% (25/210) of our final enrollment numbers. We also redoubled efforts to give community talks and provide consistent reminders to colleagues at our institutions which were the two primary sources of referrals for this trial.

4.2. Challenges in participant retention

Our dropout rate was lower than anticipated (12.9% as of June 30, 2018), likely due to the excellent connections our coordinators established with participants in both groups. We believe this connection was fostered through passionate coordinators who believed in the study purpose, were genuinely concerned about participants, and were available to participants in both groups for PC questions. In fact, our coordinators were often the first person participants in both groups contacted if they were struggling with PC issues. Other measures to retain participants included reimbursement for time and travel; availability of telemedicine and online forms to minimize data collection burden; options for reduced data collection (e.g. dropping additional QOL measures and utilization questions); providing a biannual study newsletter including articles on study progress, study purpose, and motivation from our patient advisory council; and option for persons in the usual care group to receive PC upon study completion.

5. Discussion

This study is a pragmatic multicenter randomized comparative effectiveness trial that is designed to determine whether interdisciplinary outpatient PC for PDRD embedded within a neurology clinic improves patient QOL or caregiver burden compared to current standards of care. This trial involved patient and caregiver stakeholders at every step to ensure that the intervention, issues addressed, and outcomes are important, relevant, and meaningful to those with this condition and their loved ones. The study is also designed to investigate what patient and caregiver characteristics are most predictive of benefit and to utilize qualitative interviews to identify ways of optimizing our intervention as well as other aspects of our clinical research such as what outcomes patients and caregivers feel we should be measuring. We anticipate a positive result will lead to future implementation trials and, as a pragmatic intervention currently supported in several academic centers, influence other academic movement disorders centers to implement similar services. Negative results will also be explored further to determine whether future efforts may need to redesign the intervention, recruitment criteria, or outcome measures.

Our intervention bridges two areas of interest for integrating PC approaches in the outpatient setting, namely embedded PC and training non-palliative medicine specialists to deliver PC as PCPs or as specialists (e.g. oncologists, neurologists) [60–63]. Interest in these approaches stems from a desire to find models that will not be limited by palliative medicine work force shortages [22], build on specialist knowledge, and acknowledge the essential role specialists and PCPs must play in any functional system of PC, even if that role is only to refer [64]. To our knowledge, this is the first study utilizing neurologists as the primary physician providing PC services to patients. If successful, this is a model that could be rapidly implemented in other PDRD centers with multidisciplinary resources.

In a 1996 review, the American Academy of Neurology Ethics and Humanities Subcommittee stated: “Many patients with neurologic disease die after long illnesses during which a neurologist acts as the principal or consulting physician. Therefore, it is imperative that neurologists understand, and learn to apply, the principles of palliative medicine.” [65] Similarly, the Accreditation Council for Graduate Medical Education (ACGME) requires neurology residents receive instruction in end-of-life and palliative care and recent quality metric guidelines for PD include advance care planning [66,67]. However, there are major gaps in the education of neurology resident physicians in these topics and evidence that PC needs in PDRD are generally underrecognized and managed by neurologists [20,68,69]. This trial may serve several roles in meeting the charge of the AAN to begin to develop an evidence base for how to provide PC to PDRD and other neurologic conditions and encourage research and educational efforts in this area.

As a relatively new application of PC, we would encourage other investigators designing trials in this area to consider trials as an opportunity not only to evaluate clinical interventions but also as opportunities to forward methodological research. Challenges in the design of this trial included lack of standards in inclusion criteria, intervention components, control condition, and outcome measures. While we are comfortable with the rationale behind our design choices, we are intentionally collecting data to address methodology for future trials including: 1) Collecting reasons for inclusion and exclusion, including qualitative input from site investigators, to evaluate the NAT-PD; 2) Planning analysis of heterogeneity of treatment effects to further optimize screening and eligibility criteria for future clinical and research efforts; 3) Assessing the fidelity of our intervention using checklists and patient/caregiver-perceptions of the most important aspects of this intervention using qualitative interviews; 4) Including multiple secondary outcome measures including alternative means of assessing patient QOL; and 5) Supplementing quantitative outcomes with qualitative interviews.

This trial is innovative in its pragmatic design, allowance of telemedicine, focus on providing PC to community-dwelling patients in an outpatient setting, and application of outcome measures to a mixed PDRD population including persons with dementia to evaluate the impact of PC. There are also several notable limitations to our trial. We are not randomizing patients/caregivers with high and urgent PC needs and thus may miss an opportunity to evaluate this intervention in persons with potentially highest benefit. We are prohibited by PCORI from evaluating economic outcomes or cost-effectiveness. While our

utilization measures may provide some insight on this point, there are better and more direct methods to answer these questions of importance to healthcare payors and policy makers. This is a multidimensional intervention and we do not have direct means of assessing which components are most essential or effective to which patients. Regarding our intervention phone calls, it could be argued that we should have let patients to decide to opt out rather than leave it to the discretion of our clinical team. Although not formally part of our care team, some patients and families reached out to our study coordinators with questions or to help arrange care and this additional layer of support was not specifically captured but could influence satisfaction and efficacy of care. Lastly, our intervention is based in academic centers and may not translate to community practices where many patients receive their care.

6. Conclusions

The summary conclusions of a recent international PD and Palliative Care Working Group meeting funded by the Parkinson's disease Foundation identified many areas where further research is needed to forward this field [19]. Chief among these was comparative effectiveness trials to determine whether this model of care results in improved outcomes compared to current standards of care. Other items that are at least partially addressed in this trial include clinimetric assessment of potential outcome measures in PD, development of standardized checklists for team-based care, assessment of a needs assessment tools, and determination of patient and caregiver characteristics associated with benefits of this model of care.

As a burgeoning field we would encourage others interested in applying palliative care approaches in neurology to consider clinical research methodology outcomes in addition to their primary clinical endpoints.

Acknowledgments

Research reported in this publication was funded through a Patient-Centered Outcomes Research Institute (PCORI) Award (IHS-1408-20134).

The statements presented in this publication are solely the responsibility of the authors(s) and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute (PCORI), its Board of Governors or Methodology Committee.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2019.02.005.

References

[1] E.R. Dorsey, R. Constantinescu, J.P. Thompson, et al., Projected number of people with Parkinson disease in the most populous nations, 2005 through 2030, Neurology 68 (2007) 384–386.
[2] O. Bernal-Pacheco, N. Limotai, C.L. Go, H.H. Fernandez, Nonmotor manifestations in Parkinson disease, Neurologist 18 (2012) 1–16.
[3] M.A. Hely, W.G. Reid, M.A. Adena, G.M. Halliday, J.G. Morris, The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years, Mov. Disord. 23 (2008) 837–844.
[4] M.K. Beyer, K. Herlofson, D. Arsland, J.P. Larsen, Causes of death in a community-based study of Parkinson's disease, Acta Neurol. Scand. 103 (2001) 7–11.
[5] S.X.J. Murphy, K. Kochanek, Deaths: preliminary data for 2010, Nat. Vital Stat. Rep. 60 (2012) 1–52.
[6] C. Vossius, O.B. Nilsen, J.P. Larsen, Parkinson's disease and nursing home placement: the economic impact of the need for care, Eur. J. Neurol. 16 (2009) 194–200.
[7] K. Snell, S. Pennington, M. Lee, R. Walker, The place of death in Parkinson's disease, Age Ageing 38 (2009) 617–619.
[8] P. Martinez-Martin, S. Arroyo, J.M. Rojo-Abuin, C. Rodriguez-Blazquez, B. Frades, J. de Pedro Cuesta, Burden, perceived health status, and mood among caregivers of Parkinson's disease patients, Mov. Disord. 23 (2008) 1673–1680.
[9] M. Nielsen, J. Hansen, B. Ritz, et al., Cause-specific mortality among spouses of Parkinson disease patients, Epidemiology 25 (2014) 225–232.
[10] A.G. Facca, W.C. Koller, Differential diagnosis of parkinsonism, Adv. Neurol. 91 (2003) 383–396.
[11] G.K. Wenning, F. Krismer, W. Poewe, New insights into atypical parkinsonism, Curr. Opin. Neurol. 24 (2011) 331–338.
[12] T.Z. Saleem, I.J. Higginson, K.R. Chaudhuri, A. Martin, R. Burman, P.N. Leigh, Symptom prevalence, severity and palliative care needs assessment using the Palliative Outcome Scale: a cross-sectional study of patients with Parkinson's disease and related neurological conditions, Palliat. Med. 27 (2013) 722–731.
[13] L. Wiblin, M. Lee, D. Burn, Palliative care and its emerging role in Multiple System Atrophy and Progressive Supranuclear Palsy, Parkinsonism Relat. Disord. 34 (2017) 7–14.
[14] M. Lanoix, Palliative care and Parkinson's disease: managing the chronic-palliative interface, Chronic. Illn. 5 (2009) 46–55.
[15] M. Hu, J. Cooper, R. Beamish, et al., How well do we recognise non-motor symptoms in a British Parkinson's disease population? J. Neurol. 258 (2011) 1513–1517.
[16] L.K. Bunting-Perry, Palliative care in Parkinson's disease: implications for neuroscience nursing, J. Neurosci. Nurs. 38 (2006) 106–113.
[17] J.G. Howlett, Palliative care in heart failure: addressing the largest care gap, Curr. Opin. Cardiol. 26 (2011) 144–148.
[18] D.F. Heigener, K.F. Rabe, Palliative care concepts in respiratory disease, Respiration 82 (2011) 483–491.
[19] B.M. Kluger, S. Fox, S. Timmons, et al., Palliative care and Parkinson's disease: Meeting summary and recommendations for clinical research, Parkinsonism Relat. Disord. 37 (2017) 19–26.
[20] J.M. Miyasaki, B. Kluger, Palliative care for Parkinson's disease: has the time come? Curr. Neurol. Neurosci. Rep. 15 (2015) 26.
[21] B.M. Kluger, M.J. Persenaire, S.K. Holden, et al., Implementation issues relevant to outpatient neurology palliative care, Ann. Palliat. Med. 7 (3) (2017 Nov 29) 339–348.
[22] D. Lupu, American Academy of H, Palliative Medicine Workforce Task F. Estimate of current hospice and palliative medicine physician workforce shortage, J. Pain Symptom Manag. 40 (2010) 899–911.
[23] L. Thorgrimsen, A. Selwood, A. Spector, et al., Whose quality of life is it anyway? The validity and reliability of the Quality of Life-Alzheimer's Disease (QoL-AD) scale, Alzheimer Dis. Assoc. Disord. 17 (2003) 201–208.
[24] M. Bedard, D.W. Molloy, L. Squire, S. Dubois, J.A. Lever, M. O'Donnell, The Zarit Burden Interview: a new short version and screening version, Gerontologist 41 (2001) 652–657.
[25] A. Waller, A. Girgis, D. Currow, C. Lecathelinais, Development of the palliative care needs assessment tool (PC-NAT) for use by multi-disciplinary health professionals, Palliat. Med. 22 (2008) 956–964.
[26] J.M. Miyasaki, J. Long, D. Mancini, et al., Palliative care for advanced Parkinson disease: an interdisciplinary clinic and new scale, the ESAS-PD, Parkinsonism Relat. Disord. 18 (Suppl. 3) (2012) S6–S9.
[27] V. Peto, C. Jenkinson, R. Fitzpatrick, R. Greenhall, The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease, Qual. Life Res. 4 (1995) 241–248.
[28] PCORI, Engagement Rubric [online], Available at: https://www.pcori.org/sites/default/files/Engagement-Rubric.pdf , Accessed date: 14 March 2018.
[29] Parkinson's Foundation, [online]. Available at http://parkinson.org/research/Patient-Engagement/Advocate-for-Research (Accessed June 28, 2018).
[30] T.J. Smith, S. Temin, E.R. Alesi, et al., American Society of Clinical Oncology provisional clinical opinion: the integration of palliative care into standard oncology care, J. Clin. Oncol. 30 (2012) 880–887.
[31] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184.
[32] S. Gilman, G.K. Wenning, P.A. Low, et al., Second consensus statement on the diagnosis of multiple system atrophy, Neurology 71 (2008) 670–676.
[33] M.J. Armstrong, I. Litvan, A.E. Lang, et al., Criteria for the diagnosis of corticobasal degeneration, Neurology 80 (2013) 496–503.
[34] I.G. McKeith, Consensus guidelines for the clinical and pathologic diagnosis of dementia with Lewy bodies (DLB): report of the Consortium on DLB International Workshop, J. Alzheimers Dis. 9 (2006) 417–423.
[35] I. Litvan, Y. Agid, D. Calne, et al., Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop, Neurology 47 (1996) 1–9.
[36] M. Emre, D. Aarsland, R. Brown, et al., Clinical diagnostic criteria for dementia associated with Parkinson's disease, Mov. Disord. 22 (2007) 1689–1707 quiz 1837.
[37] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology 17 (1967) 427–442.
[38] A.W. Willis, M. Schootman, B.A. Evanoff, J.S. Perlmutter, B.A. Racette, Neurologist care in Parkinson disease: a utilization, outcomes, and survival study, Neurology 77 (2011) 851–857.
[39] I. Boersma, J. Jones, J. Carter, et al., Parkinson disease patients' perspectives on palliative care needs: What are they telling us? Neurol. Clin. Pract. 6 (2016) 209–219.
[40] I. Boersma, J. Jones, C. Coughlan, et al., Palliative care and Parkinson's disease: caregiver perspectives, J. Palliat. Med. 20 (2017) 930–938.
[41] S.K. Holden, W.E. Jones, K.A. Baker, I.M. Boersma, B.M. Kluger, Outcome measures for Parkinson's disease dementia: a systematic review, Mov. Disord. Clin. Pract. 3 (2016) 9–18.
[42] S.H. Zarit, K.E. Reever, J. Bach-Peterson, Relatives of the impaired elderly: correlates of feelings of burden, Gerontologist 20 (1980) 649–655.
[43] R. Hebert, G. Bravo, M. Preville, Reliability, validity and reference values of the

Zarit Burden Interview for assessing informal caregivers of community-dwelling older persons with dementia, Can. J. Aging 19 (2000) 494–507.
[44] I.J. Higginson, P. McCrone, S.R. Hart, R. Burman, E. Silber, P.M. Edmonds, Is short-term palliative care cost-effective in multiple sclerosis? A randomized phase II trial, J. Pain Symptom Manag. 38 (2009) 816–826.
[45] D.N. Guerriere, P.C. Coyte, The ambulatory and home care record: a methodological framework for economic analyses in end-of-life care, J. Aging Res. 2011 (2011) 374237.
[46] S.R. Cohen, B.M. Mount, E. Bruera, M. Provost, J. Rowe, K. Tong, Validity of the McGill Quality of Life Questionnaire in the palliative care setting: a multi-centre Canadian study demonstrating the importance of the existential domain, Palliat. Med. 11 (1997) 3–20.
[47] Working Group on Health Outcomes for Older Persons with Multiple Chronic C, Universal health outcome measures for older persons with multiple chronic conditions, J. Am. Geriatr. Soc. 60 (2012) 2333–2341.
[48] MotUDC S Fahn, Unified Parkinson's Disease Rating Scale, Macmillan, New York, 1987.
[49] Z.S. Nasreddine, N.A. Phillips, V. Bedirian, et al., The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment, J. Am. Geriatr. Soc. 53 (2005) 695–699.
[50] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (1983) 361–370.
[51] M.E. Charlson, P. Pompei, K.L. Ales, C.R. MacKenzie, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation, J. Chronic Dis. 40 (1987) 373–383.
[52] J.C. Dalrymple-Alford, M.R. MacAskill, C.T. Nakas, et al., The MoCA: well-suited screen for cognitive impairment in Parkinson disease, Neurology 75 (2010) 1717–1725.
[53] J. Hoe, G. Hancock, G. Livingston, B. Woods, D. Challis, M. Orrell, Changes in the quality of life of people with dementia living in care homes, Alzheimer Dis. Assoc. Disord. 23 (2009) 285–290.
[54] R.D. Crosby, R.L. Kolotkin, G.R. Williams, Defining clinically meaningful change in health-related quality of life, J. Clin. Epidemiol. 56 (2003) 395–407.
[55] D.L. Fairclough, Design and analysis of quality of life studies in clinical trials. 2nd ed, Tarlor and Francis Group, LLC, Boca Raton, Fl, 2010.
[56] B.F.M.W. Crabtree, Doing Qualitative Research, 2 ed., Sage Publications, Thousand Oaks, CA, 1999.
[57] D.B. Bekelman, C.T. Nowels, J.H. Retrum, et al., Giving voice to patients' and family caregivers' needs in chronic heart failure: implications for palliative care programs, J. Palliat. Med. 14 (2011) 1317–1324.
[58] J. Jones, C.M. McDermott, C.T. Nowels, D.D. Matlock, D.B. Bekelman, The experience of fatigue as a distressing symptom of heart failure, Heart Lung 41 (2012) 484–491.
[59] I.J. Higginson, W. Gao, T.Z. Saleem, et al., Symptoms and quality of life in late stage Parkinson syndromes: a longitudinal community study of predictive factors, PLoS One 7 (2012) e46327.
[60] C.J. Creutzfeldt, M.T. Robinson, R.G. Holloway, Neurologists as primary palliative care providers: Communication and practice approaches, Neurol. Clin. Pract. 6 (2016) 40–48.
[61] J.C. Muir, F. Daly, M.S. Davis, et al., Integrating palliative care into the outpatient, private practice oncology setting, J. Pain Symptom Manag. 40 (2010) 126–135.
[62] B. Gandesbery, K. Dobbie, E.Z. Gorodeski, Outpatient Palliative Cardiology Service Embedded Within a Heart Failure Clinic: Experiences With an Emerging Model of Care, Am. J. Hosp. Palliat. Care 35 (4) (2018 Apr) 635–639 1049909117729478.
[63] D. Hui, E. Bruera, Models of integration of oncology and palliative care, Ann. Palliat. Med. 4 (2015) 89–98.
[64] K. Hall, M. Sumrall, G. Thelen, B.M. Kluger, Parkinson's Disease Foundation sponsored "Palliative C, Parkinson's Disease" Patient Advisory C. Palliative care for Parkinson's disease: suggestions from a council of patient and carepartners, NPJ Parkinsons Dis. 3 (2017) 16.
[65] Palliative care in neurology, The American Academy of Neurology Ethics and Humanities Subcommittee, Neurology 46 (1996) 870–872.
[66] Education ACfGM, Neurology Program Requirements [online], Available at: www.acgme.org , Accessed date: 11 December 2013.
[67] S.A. Factor, A. Bennett, A.D. Hohler, D. Wang, J.M. Miyasaki, Quality improvement in neurology: Parkinson disease update quality measurement set: Executive summary, Neurology 86 (2016) 2278–2283.
[68] C.J. Creutzfeldt, T. Gooley, M. Walker, Are neurology residents prepared to deal with dying patients? Arch. Neurol. 66 (2009) 1427–1428.
[69] L.M. Chahine, B. Malik, M. Davis, Palliative care needs of patients with neurologic or neurosurgical conditions, Eur. J. Neurol. 15 (2008) 1265–1272.