


BMJ Open Protocol for an observational cohort study identifying factors predicting accurately end of life in dementia with Lewy bodies and promoting quality end-of-life experiences: the PACE-DLB study

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ABSTRACT

Introduction Dementia with Lewy bodies (DLB) is one of the most common degenerative dementias. Despite the fact that most individuals with DLB die from complications of the disease, little is known regarding what factors predict impending end of life or are associated with a quality end of life.

Methods and analysis This is a multisite longitudinal cohort study. Participants are being recruited from five academic centres providing subspecialty DLB care and volunteers through the Lewy Body Dementia Association (not receiving specialty care). Dyads must be US residents, include individuals with a clinical diagnosis of DLB and at least moderate-to-severe dementia and include the primary caregiver, who must pass a brief cognitive screen. The first dyad was enrolled 25 February 2021; recruitment is ongoing. Dyads will attend study visits every 6 months through the end of life or 3 years. Study visits will occur in-person or virtually. Measures include demographics, DLB characteristics, caregiver considerations, quality of life and satisfaction with end-of-life experiences. For dyads where the individual with DLB dies, the caregiver will complete a final study visit 3 months after the death to assess grief, recovery and quality of the end-of-life experience. Terminal trend models will be employed to identify significant predictors of approaching end of life (death in the next 6 months). Similar models will assess caregiver factors (eg, grief, satisfaction with end-of-life experience) after the death of the individual with DLB. A qualitative descriptive analysis approach will evaluate interview transcripts regarding end-of-life experiences.

Ethics and dissemination This study was approved by the University of Florida institutional review board (IRB202001438) and is listed on clinicaltrials.gov (NCT04829656). Data sharing follows National Institutes of Health policies. Study results will be disseminated via traditional scientific strategies (conferences, publications) and through collaborating with the Lewy Body Dementia Association, National Institute on Aging and other partnerships.

Strengths and limitations of this study

- The Identifying Factors Predicting Accurately End-of-Life in Dementia with Lewy Bodies and Promoting Quality End-of-Life Experiences (PACE-DLB) study is a multisite longitudinal observational cohort study that will follow individuals with at least moderately advanced DLB and their caregivers for 3 years or until 3 months after the death of the person with DLB, providing important insight into patient and caregiver predictors of the final months of life in DLB.
- The PACE-DLB study will also investigate factors associated with a quality end of life in DLB and caregiver experiences after the death of the person with DLB, resulting in identification of opportunities for improving end-of-life care.
- The use of both virtual and in-person visits has strengths and limitations; this approach allows for recruitment of dyads who do or do not receive subspecialty care and recruitment of individuals with DLB too disabled to attend in-person study visits, but results in some differences in administration of study measures (though all measures will be verbally administered by study staff).
- The PACE-DLB study is US based, so issues relating to palliative and hospice care—or other aspects of healthcare—may not fully generalise to international locations.

INTRODUCTION

Context and unmet needs

Dementia with Lewy bodies (DLB) is one of the most common degenerative dementias after Alzheimer disease (AD) dementia. Despite DLB prevalence, evidence regarding prognosis and natural history is scarce—particularly when considering later stages—and represents a major unmet need.¹ Known

barriers to quality end-of-life care in dementia include lack of physician knowledge, prognostic uncertainty, difficulty assessing symptoms, and lack of physician recognition of terminal dementia stages and dementia as a cause of death.² In DLB, fewer than half of caregivers reported discussions with a physician about what to expect at the end of life (40% had discussions, only 22% to a helpful degree).³ Lack of knowledge regarding what to expect about the end of life in DLB—particularly the fact that DLB is terminal—was also a contributor to poor end-of-life experiences described in caregiver interviews.⁴

Improved end-of-life care and research are needed across dementias,⁵ but existing research focused largely on individuals with advanced dementia living in facilities and enrolled individuals with various dementias, particularly AD and mixed dementia.^{6–9} Individuals with Lewy body dementia—an umbrella diagnosis including DLB and Parkinson disease dementia—accounted for fewer than 3% of participants in these studies.^{7–9} Experiences for patients and family

caregivers are likely to be different between AD and DLB. Individuals with DLB have shorter survival and die at a younger age than those with AD dementia.^{10 11} Individuals with Lewy body dementia also have more than double the likelihood of respiratory death as those with AD dementia.¹² Most individuals with DLB die of the dementia itself/failure to thrive (72%) or pneumonia/ aspiration (23%), which is commonly DLB related.³ Terminal dementia symptoms (eg, stopping speaking, inability to mobilise independently, requiring help with activities of daily living, dysphagia or stopping eating) likely overlap between dementias, but DLB-specific symptoms¹³ such as worsening hallucinations, parkinsonism, and daytime sleepiness were identified in caregiver interviews as additional end-of-life features in DLB.⁴ These symptoms are missing from current tools predicting end of life in dementia (table 1).^{14 15} Additionally, current tools have limitations even in dementia more generally. Medicare dementia hospice guidelines, which incorporate

Table 1 Predictors of end of life in dementia

	US medicare hospice benefit Guidelines ¹⁵	ADEPT Score ¹⁴	Interviews with DLB caregivers ⁴
Population included	Dementia	Nursing home residents with advanced dementia	DLB
Increasing age		✓	
Male sex		✓	
Functional dependence	✓	✓	
Unable to ambulate	✓		✓
Increased falls			✓
Bedfast most of day		✓	✓
Generalised weakness			✓
Increased rigidity			✓
Limited speech	✓		✓
Increased hallucinations			✓
Worsened daytime somnolence			✓
Incontinence	✓	✓	
Shortness of breath		✓	
Insufficient oral intake	✓	✓	✓
Weight loss/low BMI		✓	✓
Hospitalisation or procedure			✓
Pressure ulcers	✓	✓	
Swallowing difficulties, aspiration pneumonia	✓		✓
Pyelonephritis, upper urinary tract infection	✓		
Sepsis	✓		
Congestive heart failure		✓	

ADEPT, Advanced Dementia Prognostic Tool; BMI, body mass index; DLB, dementia with Lewy bodies.

Functional Assessment Staging (FAST), had a sensitivity of only 0.20 for 6-month mortality when applied to a nursing home population with advanced dementia (area under the curve (AUC) 0.55; specificity 0.89).¹⁴ The Advanced Dementia Prognostic Tool (ADEPT), developed in a nursing home setting, performed only marginally better (AUC 0.58; sensitivity 0.27; specificity 0.89).¹⁴ These knowledge gaps limit the ability of individuals with DLB and their families to anticipate and adequately plan for care transitions and needs.

Study aims

The current study aims to investigate end-of-life experiences for patient/caregiver dyads living with DLB with or without subspecialty care. The study aims to determine patient and caregiver predictors of end of life in DLB (defined as death within 6 months, based on the window for US Medicare coverage for hospice services). Additionally, the study will identify the impact of demographics, healthcare factors, DLB symptoms and caregiver factors on patient quality of life (QoL) and caregiver experiences at the end of life of the person living with DLB.

The primary outcome for aims 1 and 2 is death within 6 months. We hypothesise that predictors of death within 6 months for individuals with DLB will include symptoms (eg, worsening hallucinations, fluctuations) not captured in existing dementia end-of-life prediction tools. We also hypothesise that there will be worsening caregiver burden, depression, grief and QoL preceding the last 6 months of life, controlling for variables such as resilience, support, and living situation. Finally, we hypothesise that location (rural, urban, suburban), provider experience (eg, specialist vs not), patient residence (eg, home, skilled nursing), degree of behavioural symptoms, caregiver type and caregiver characteristics (self-efficacy, perceived social support, resilience and coping) will affect patient

and caregiver experiences at the patient's end of life, including patient and caregiver QoL and caregiver burden (primary outcome for predeath analysis), well-being, depression, grief and satisfaction with end-of-life care (primary outcome for postdeath analysis).

METHODS AND ANALYSIS

Study design

Identifying Factors Predicting ACcurately End-of-Life in Dementia withLewy Bodies and Promoting Quality End-of-Life Experiences (PACE-DLB) is an observational longitudinal cohort study involving five Lewy Body Dementia Association Research (LBDA) Research Centers of Excellence in the USA (University of Florida, University of Michigan, Mayo Clinic Rochester, University of Virginia, University of Miami) and recruitment of a virtual cohort (not receiving subspecialty care) through the LBDA. There are two cohort types: (1) cohorts with or without subspecialty care and (2) division of the overall cohort into a group where the individual with DLB lives 6 months after the study visit vs the group where the individual with DLB dies during the 6 months between study visits (**figure 1**). The cohort where the individual with DLB lives with continued disease progression versus the end-of-life cohort will change throughout the study based on the timing of death. The statistical approaches account for this. Study visits occur every 6 months and are completed either in-person or virtually (via phone or videoconferencing). After the individual with DLB dies, the caregiver will complete a virtual end-of-study visit 3 months after the patient's death to assess grief and recovery. A 3-month postdeath follow-up was chosen based on research showing that caregiver depression declines significantly in the 13 weeks after the death of an individual with dementia¹⁶ and bereaved family member survey responses were stable between 3 and 9 months after

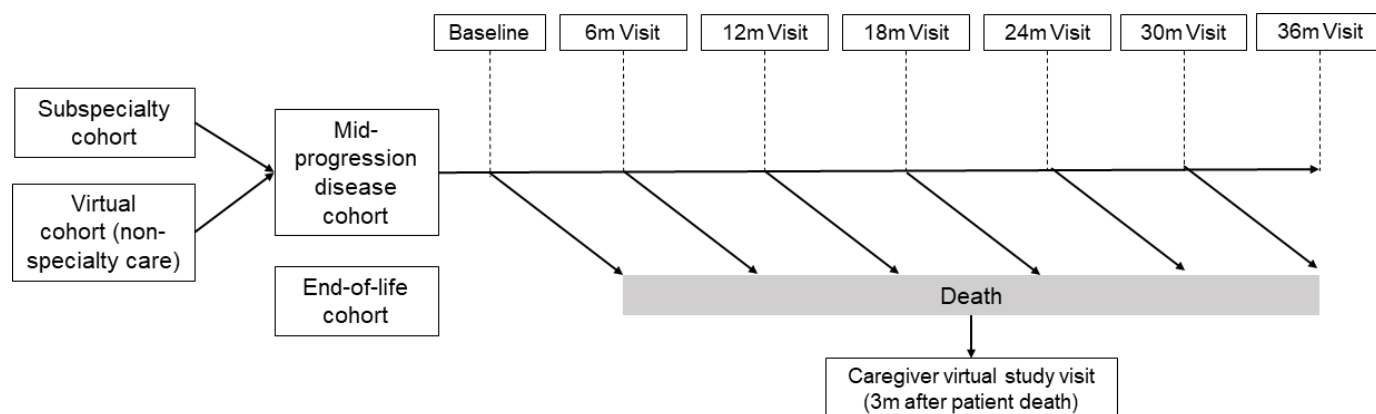


Figure 1 Identifying Factors Predicting ACcurately End-of-Life in Dementia withLewy Bodies and Promoting Quality End-of-Life Experiences (PACE-DLB) study design: the PACE-DLB study will recruit 75 dyads (individuals with DLB and their primary informal caregiver) from subspecialty clinics and 75 dyads not receiving subspecialty care. After meeting inclusion criteria, dyads will have a baseline study visit and then return for follow-up study visits every 6 months for 3 years or until the death of the individual with DLB. Caregivers of individuals with DLB who die during the study will complete a final study visit 3 months after the death of the person with DLB. DLB, dementia with Lewy bodies.

the death of individuals on hospice.¹⁷ The first dyad was enrolled 25 February 2021 and recruitment is ongoing.

Study participants

Inclusion criteria include: (1) patient and caregiver willing to participate as a dyad, (2) US residents, (3) patient with a clinical diagnosis of DLB, (4) patient with at least moderate severity dementia as assessed by the Quick Dementia Rating System (QDRS, score of >12 suggestive of moderate dementia),¹⁸ (5) patient expected to live at least 6 months and (6) caregiver Telephone Interview for Cognitive Status score of >31 to ensure that the caregiver is able to reliably complete study visits.¹⁹ Diagnosis of DLB will be supported using the Lewy Body Composite Risk Score (LBCRS, score ≥ 3 consistent with DLB).²⁰

The participating caregiver must be the person providing the majority of the patient's informal care (whether the individual with DLB is living at home or in a facility) and attending the majority of the patient's clinical visits. The caregiver can represent any relationship with the individual with DLB (eg, spouse, child). The type of relationship will be captured to assess the impact of this relationship/role. The participating caregiver must remain the same throughout the study. If the primary caregiver changes (eg, due to caregiver death), that dyad will drop out of the study. The location of the person with DLB (eg, home, facility) will be tracked for its influence on outcomes and its relationship with informal caregiver responsibilities.

By including individuals with DLB with at least moderate dementia severity, it is anticipated that a majority of participants will reach end of life over the 3 years of the study. Median duration from diagnosis to death in DLB is 3–4 years.^{3 11 21} Thus, even if enrolling individuals early in their disease course, half would likely approach end of life during a 3-year study. By focusing on individuals already in at least moderate dementia stages, the proportion of individuals progressing to end of life during the study will be higher. The study does not require that all participants progress to death during the 3-year period.

Recruitment

Study sites will recruit from patient-caregiver dyads presenting to their LBDA Research Centre of Excellence clinics (subspecialty cohort). For the virtual cohort without subspecialty care, participants will be recruited through the LBDA website, emails to individuals subscribed to the LBDA's mailing list and social media posts. The study is also listed on clinicaltrials.gov (NCT04829656).

Study measures

We prioritised measures used by existing DLB cohorts in the USA (DLB Consortium, National Alzheimer's Coordinating Center (NACC) cohorts) so that data can be combined with other cohorts to answer future research questions. For PACE-DLB, measures are identical for in-person and virtual visits except that the Unified Parkinson Disease Rating Scale (UPDRS) motor subscale²²

will only be completed at in-person visits. All measures are caregiver-completed except the motor UPDRS and QoL-AD, which is completed by both the patient (if able) and the caregiver.

Demographics include patient and caregiver gender, sex, age, racial/ethnic background, education, disease duration, hours spent caregiving and the relationship of the caregiver to the patient. Collected background will also include details regarding the medical team caring for the person with DLB, such as clinician types (eg, primary care physician, geriatrician, general/specialty neurologist) and ancillary services used (eg, therapy, social work/care coordination, palliative care). Transitions will be noted, including home to hospital, home to hospice, home to nursing home, etc.²³

Formal scales assess patient and caregiver experiences (table 2). The LBCRS will measure the breadth of DLB symptoms present.²⁰ While designed as a screening instrument rather than a measure of disease severity, this interview-based scale will provide a way to assess disease scope using an instrument that can be completed verbally. Cognitive function will be assessed via the QDRS, which can be converted to a CDR Dementia Staging Instrument score but takes substantially less time (~3–5 min) to complete.¹⁸ The Neuropsychiatric Inventory Questionnaire^{24 25} is the most commonly used measure for assessing behavioural and psychological symptoms of dementia in people with DLB. The Mayo Fluctuations Scale²⁶ and Clinician Assessment of Fluctuations²⁷ will measure fluctuations. The Mayo Sleep Questionnaire²⁸ and Epworth Sleepiness Scale²⁹ will assess aspects of sleep relevant to DLB (eg, symptoms consistent with REM sleep behaviour disorder, daytime sleepiness). The Autonomic Systems Checklist from the NACC Lewy body dementia module will identify the presence of autonomic symptoms. QoL of the individual with DLB will be assessed using participant and caregiver-completed versions of the QoL-AD scale, validated for individuals with dementia.³⁰ This scale is not AD-specific and was used previously with individuals with DLB.³¹

To investigate clinical factors potentially contributing to quality end-of-life care in dementia, we will assess medication prescribing by collecting concomitant medications and applying the Anticholinergic Cognitive Burden scale^{32 33} and STOPP criteria for potentially inappropriate prescribing.³⁴ Caregiver-reported medication use will help inform whether use of certain 'hospice pack' medications, such as haloperidol or lorazepam, is associated with different end-of-life experiences. To assess estimates of approaching end of life, we will use the FAST scale used in Medicare dementia hospice guidelines¹⁵ and the ADEPT score.¹⁴

Caregiver QoL will be measured using the Carer Well-being and Support Questionnaire, recently identified as the most appropriate QoL instrument for informal caregivers for individuals with dementia.³⁵ Caregiver depression will be measured with the Centre for Epidemiologic Studies Depression Scale, also used in prior end-of-life

Table 2 Measures for the PACE-DLB study

Category	Measure
DLB symptoms	Lewy Body Composite Risk Score
Global cognitive rating	Quick Dementia Rating System
Motor function	Unified Parkinson's Disease Rating Scale Part III (motor subscale)*
Neuropsychiatric	Neuropsychiatric Inventory—Questionnaire*
Fluctuations	Mayo Fluctuations Scale* Clinician Assessment of Fluctuations
Sleep (including RSD, daytime sleepiness)	Mayo Sleep Questionnaire (caregiver-reported)* Epworth Sleepiness Scale
Autonomic function	Autonomic symptoms checklist*
Appropriate drug prescribing	Concomitant medications Anticholinergic Cognitive Burden scale STOPP criteria
Measures of approaching end-of-life	Functional Assessment Staging US Medicare dementia hospice guidelines Advanced Dementia Prognostic Tool Score
Patient quality of life	Quality of Life in Alzheimer's disease (individual with DLB, caregiver)
Caregiver quality of life	Carer Well-Being and Support Questionnaire
Caregiver depression	Centre for Epidemiologic Studies Depression Scale
Caregiver self-efficacy	Revised Scale for Caregiving Self-Efficacy
Caregiver resilience	The Resilience Scale
Caregiver social support	Multidimensional Scale of Perceived Social Support
Caregiver coping	Brief Coping Orientation to Problems Experienced
Caregiver burden	Short Zarit Revised Burden Interview
Caregiver anticipatory grief	Meuser-Marwit Caregiver Grief Inventory-Short Form
Caregiver bereavement	Texas Revised Inventory of Grief
End-of-life care experiences	National Health and Ageing Trends Study last month of life survey

*Used by DLB Consortium and/or National Alzheimer's Coordinating Center (Unified Data Set or Lewy body dementia module V.3). DLB, dementia with Lewy bodies; LBCRS, Lewy Body Composite Risk Score.

dementia bereavement research.^{16 36} The Revised Scale for Caregiving Self-Efficacy covers topics relating to confidence obtaining respite, responding to disruptive behaviours, and controlling upsetting thoughts about caregiving.^{37 38} The Multidimensional Scale of Perceived Social Support is a social support scale^{39 40} recommended by the National Alzheimer's Disease Resource Center.⁴¹ Coping strategies will be measured by the Brief Coping Orientation to Problems Experienced,⁴² also recommended by the National Alzheimer's Disease Resource Center⁴¹ and used in prior studies with caregivers of individuals with dementia at the end of life.⁴³ Caregivers will complete the shortened Zarit Revised Burden interview (sZBI),⁴⁴ used in prior studies with caregivers of individuals with DLB.⁴⁵ Caregiver anticipatory grief will be measured with the Meuser-Marwit Caregiver Grief Inventory-Short Form, specifically developed for caregivers of individuals with dementia.⁴⁶ Postdeath grief (bereavement) will be measured using the Texas Revised Inventory of Grief, used previously to measure postdeath grief of informal caregivers of individuals with dementia.³⁶ Caregiver resilience will be measured using the Resilience Scale, the original

resilience measure and one used previously in dementia caregiver studies.^{47 48} At the 3-month postdeath visit, caregivers will receive the National Health and Aging Trends Study last month of life interview,⁴⁹ which queries end-of-life experiences relating to pain, dyspnoea, anxiety/sadness, decision making, needs, respect and communication, and which solicits an overall rating of end-of-life care. As with a prior study,⁵⁰ we will supplement the last month of life questionnaire-based interview with semi-structured interview questions to further investigate end-of-life experiences.

Study visits

Measures will be administered verbally to minimise differences in conduct between the virtual and in-person groups. Verbal administration will be used across measures because some older caregivers would be uncomfortable with self-administered electronic form completion. Visits are expected to last 2–3 hours. Multiple approaches will be used to limit survey fatigue and burden. For in-person visits, breaks and snacks will be provided to limit fatigue. For virtual participants who may have difficulty being

on the phone or videoconference for 2–3 hours continuously, we will encourage breaks and if needed, provide the option of completing the scales over two sessions, one focusing on the patient experience and one focusing on the caregiver experience.

Participants will complete study visits every 6 months either in person or virtually for the 3 years of the study or until the death of the person with DLB. If the person with DLB dies, the caregiver will complete one final study visit 3 months after the death of the individual with DLB (figure 1). The postdeath study visit will include the Center for Epidemiologic Studies Depression Scale, Resilience Scale, Texas Revised Inventory of Grief, National Health and Aging Trends Study last month of life interview (questionnaire based), and a semistructured interview about end-of-life experiences.

Data collection

Coordinators will enter data directly into electronic case report forms. Study data will be collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the University of Florida.^{51 52} REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages and (4) procedures for data integration and interoperability with external sources. The postdeath caregiver interviews will be audio-recorded and professionally transcribed.

Analysis

Sample size

Target sample size for the overall cohort was based on a pairwise comparison of the sZBI score before and after entering the last 6 months of life. If recruiting 128 dyads and using an sZBI SD reported previously in DLB (8.8) and assuming the within-participant correlation of the outcome ranges from 0.2 to 0.8, the minimum detectable pairwise difference ranges from 1.4 to 2.7 with 80% power and two-sided type I error rate of 0.05. This standardised minimum detectable difference range is from 0.16 SD to 0.31 SD which gives sufficient power for the study. To account for a~15% drop-out, 150 total dyads will be enrolled. Target enrollment will be split evenly between in-person and virtual cohorts, with a target of 75 dyads recruited from the five LBDA Research Center of Excellence sites and 75 virtual dyads recruited through the LBDA.

Overall analysis

Descriptive statistical measures including mean, median, SD, minimum and maximum values of continuous variables and frequency of categorical variables will be generated. Appropriate transformations (eg, natural-log) will be applied as needed to comply with normality. Data visualisation such as scatter plots will be implemented.

Analysis of predictors of end of life

A variable that predicts the end of life will be defined as a variable changing substantially (eg, quick drop of QoL) once the patient enters last 6 months of life. Statistical models will estimate the longitudinal trajectories of potential candidate variables to identify those with significantly different trajectory patterns in the last 6 months of life. A preliminary analysis will evaluate candidate variables in the decedents subsample and compare scores before and after entering the last 6 months of life to identify variables that have substantial changes. Subsequently, a terminal trend model (TTM)^{53 54} will estimate the terminal trends of the candidate variables to test the difference of longitudinal pattern before and after entering last 6 months of life to select the variables that are significant predictors of end of life. TTM can include participants who drop out or do not die. By modelling the longitudinal and survival data simultaneously, TTM addresses the cohort effect of analysing a subsample (eg, decedents only) of the entire study because every patient contributes to the joint analysis. TTM can also alleviate the burden of missing data due to censoring. A dynamic prediction model will identify variables that might predict conditional survival probability, which could be helpful for identifying variables predicting the last 6 months of life. All these analyses will be adjusted for potential confounders such as resilience, support, living situation and DLB severity. The cohorts will be combined for the analyses but we will also conduct the analyses in cohorts with and without subspecialty care to check cohort-specific effects. Stratified analyses will examine potential differences relating to sex or gender.

Analysis of factors associated with quality end-of-life experiences

The outcome measures assessing end-of-life experiences include the QoL of the person with DLB (at the last predeath visit) and caregiver-reported measures obtained at the last predeath visit and the 3 months postdeath visit including caregiver burden, well-being and support, depression, grief and satisfaction (as captured by the last month of life survey). Independent variables of interest include patient demographics (eg, age, gender, sex, race/ethnicity, disease duration, level of education), caregiver demographics (eg, age, gender, sex, race/ethnicity, relationship to patient, level of education), disease characteristics (eg, overall symptom burden, cognition, motor function, neuropsychiatric symptoms, functional status, fluctuations, sleep-related symptoms, autonomic symptoms, medications), elements of care (rural/urban, type of healthcare provider, patient residence) and caregiver measures (self-efficacy, social support, coping skills). Associations/correlations of independent variables and the dependent variables/outcomes will be assessed using nonparametric methods such as Wilcoxon rank sum test for binary demographic variables, Kruskal-Wallis test for categorical demographic variables and Spearman correlation for continuous demographic variables.

Non-parametric scatter plots with splines will be used to visualise possibly non-linear relationships.

For multivariate analyses, TTM will test the (possibly time-varying) effects of demographic variables on the longitudinal trajectories of end-of-life measures. Demographic variables will be modelled as independent variables simultaneously in the TTM approach to control for potential confounding effects between the demographics and the end-of-life measures will be dependent outcomes. Demographics that have significant effects on the trajectories of end-of-life outcomes will be selected based on effect size and significance level (indicated by p values). When necessary (eg, many demographic variables), regularisation approaches including least absolute shrinkage and selection operator (LASSO),⁵⁵ minimax concave penalty (MCP)⁵⁶ and knockoff filter⁵⁷ will be incorporated into the TTM approach to select independent variables that have larger impact on the outcomes. False discovery rate will be controlled by selecting tuning parameters with permutation approaches. Cross-validation such as 10-fold cross-validation will be used in the regularisation approaches to validate the model by randomly splitting the data into partitions where the model is trained and tested in difference partitions. Unsupervised learning approaches⁵⁸ will also be used to identify clusters that might be associated with specific outcomes. Latent class models⁵⁹ will be applied to identify latent clusters that might be associated with the trajectory of the outcomes. Potential confounders will be adjusted in all the analyses. Subsample analyses will assess for cohort and sex/gender effects.

Investigators will use a qualitative descriptive approach to analyse transcripts of the post-death caregiver interviews. The qualitative descriptive approach reports experiences without intending to generate or use theory.⁶⁰

Patient and public involvement

The research questions for this study were informed by a survey and interviews with individuals whose loved ones died of DLB. Caregivers indicated that they did not know what to expect at the end of life in DLB and that this negatively impacted end-of-life experiences.^{3 4} Staff associated with the LBDA—a US-based advocacy organisation for individuals with DLB and their families—participated in study design and grant development. There was no community advisory board.

Data monitoring

Due to the minimal risk nature of this observational study, there is no external data and safety monitoring board. The principal investigator, coinvestigators and study staff will monitor study conduct internally. Consistency across sites will be achieved through study protocol training, regular study teleconferences with representatives from all sites, and site evaluations by the coordinating site. Each site will maintain participant screening and enrolment logs with contact information and other identifiable data. Data entered into the electronic case report

forms will be deidentified apart from visit and death dates (required for the time-based analyses). Reports detailing study progress will be submitted to the National Institutes on Aging annually.

Ethics and dissemination

Ethics approval

This study is managed by a single Institutional Review Board at the University of Florida (IRB202001438) consistent with requirements from the National Institutes of Health.

Informed consent

Caregivers will consent for their own participation. Legally authorised representatives (who may or may not be the caregiver) will provide consent on behalf of the person with dementia. Each site will follow local (state) laws for determining the legally authorised representative. Individuals with DLB will be asked to provide assent if able. If a potential participant resists participating, he or she will not be enrolled. Informed consent will be obtained in manners following good clinical practice.

Data sharing

Consistent with data sharing regulations from the National Institutes of Health, investigators will make the final data and associated documentation available to users under a data-sharing agreement that provides for a commitment to: (1) use the data for research purposes only; (2) not identify any individual participant (the final dataset will be deidentified prior to release, but there remains the possibility of deductive disclosure of participants with specific characteristics); (3) use appropriate data security and (4) destroy the data after analyses are completed. PACE-DLB measures were chosen to facilitate combining DLB data sets to answer future research questions.

Dissemination

The results of this study are important to disseminate to individuals with DLB, caregivers, advocacy organisations and healthcare professionals. Traditional strategies for scientific dissemination will be utilised, including conference presentations and peer-reviewed publications. Results relevant for individuals living with DLB and caregivers will be disseminated through the Lewy Body Dementia Association, already a study partner, and through the National Institutes on Aging, which has educational webpages dedicated to end of life in DLB. The LBDA has existing strategies for communicating with populations living with DLB including webpages highlighting research results, webinars and social media use. Results will also be shared with the general population through mechanisms like the website 'The Conversation,' which partners with academic organisations to educate the public.

DISCUSSION

This protocol outlines the methodology for the PACE-DLB study, a multicentre observational cohort study investigating patient-related and caregiver-related predictors of end of life in DLB and factors associated with a quality end of life. The study makes use of a classic longitudinal cohort model, but focuses on collecting data pertinent to the end of life rather than biomarker and natural history data, the focus of most longitudinal DLB cohorts. To overcome the limitation in many natural history studies in which participants are only enrolled at specialty centres (with negative implications for generalisability) and where consent to autopsy is sometimes required (further biasing enrolment), PACE-DLB uses a subspecialty care cohort and a virtual cohort without DLB subspecialty care to obtain a broad representation of experiences. In addition to improving generalisability, this approach allows an assessment of whether certain care settings (eg, primary care vs general neurology vs subspecialty care) impact end-of-life experiences. Designing visits to be compatible with phone-based or teleconference-based administration also facilitates following participants in the subspecialty cohort even if they are unable to come to clinic. Enrolling participants in dyads enables assessment of patient-related outcomes but also caregiver outcomes relating to burden, resilience, and grief, before and after the death of the individual with DLB. Through this longitudinal study following dyads through the end-of-life period, the death of the person with DLB, and initial bereavement for the caregiver, PACE-DLB will identify predictors and experiences of end of life in DLB with various care experiences. This will improve prognostic and end-of-life counselling for individuals and families living with DLB and also identify areas that can be targeted to improve end-of-life experiences.

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Contributors MJA conceived and designed the study, serves as the principal investigator for the grant, drafted the protocol, and serves as the guarantor of the work. HLP, SMM, JAF, AML, BFB and CM provided feedback on study design, revised the protocol critically for important intellectual conduct, and serve as coinvestigators on the grant. JEG and AT provided feedback on study design, revised the protocol critically for important intellectual conduct and serve as consultants on the grant. ZL provided feedback on study design, designed the statistical analysis, revised the protocol critically for important intellectual conduct and serves as a coinvestigator on the grant. All authors provided approval for the protocol to be published.

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Competing interests MJA receives research support from the NIA (P30AG047266, R01AG068128) and the Florida Department of Health (grant 20A08). She is the local PI of a Lewy Body Dementia Association Research Center of Excellence. She serves on the Scientific Advisory Board of the Lewy Body Dementia Association. HLP receives funding from the NIA (1P30AG053760) and is the local PI of a Lewy Body Dementia Association Research Center of Excellence. SMM has no competing interests. JAF receives research support from the NIA (U01NS100620, R01AG068128, R43AG65088). AML receives research support from the NIA (P30AG62677, R43AG65088). She is a Program Coordinator for the local a Lewy Body Dementia Association Coordinating Center Research Center of Excellence. BFB has served as an investigator for clinical trials sponsored by Biogen, Alector and EIP Pharma. He serves on the Scientific Advisory Board of the Lewy Body Dementia Association, Association for Frontotemporal Degeneration and Tau Consortium. He is the site PI of a Lewy Body Dementia Association Research Center of Excellence program, as well as coordinating center PI of the program. He receives research support from the NIH, the Mayo Clinic Dorothy and Harry T. Mangurian Jr. Lewy Body Dementia Programme, and the Little Family Foundation. CM receives research support from ACL/DHHS (90ALGG0014-01-00), NIA/NIH (2SB1AG037357-04A1, R01-AG-054435), HRSA (U1QHP287440400) and DoD (AZ190036). She is the local PI of a Lewy Body Dementia Association Research Center of Excellence. JEG is the creator of the QDRS and the LBCRS. He is supported by grants from the National Institutes of Health (R01 AG069765, R01 AG057681, R01 NS101483, P30 AG059295, U54 AG06354, R01 AG056531, U01 NS100610, R01 AG056610, R01 AG054425, R01 AG068128) and the Leo and Anne Albert Charitable Trust. He is the local PI of the Lewy Body Dementia Association Research Center of Excellence at the University of Miami and serves on the Scientific Advisory Board of the Lewy Body Dementia Association. AT is an employee of the Lewy Body Dementia Association. ZL has no competing interests.

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