Palliative Care for Persons with Late-stage Alzheimer's and Related Dementias and their Caregivers: A Randomized Clinical Trial

PROTOCOL

National Clinical Trial (NCT) Identified Number: NCT04948866

Principal Investigator: Laura C. Hanson, MD, MPH

Sponsor: University of North Carolina at Chapel Hill

Grant Brief Title: ADRD-PC Study

Grant Number: R01AG065394

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20 March 2023

STATEMENT OF CONFIDENTIALITY

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonization Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator:

Signed:  Date: 20 March 2023

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1 PROTOCOL SUMMARY

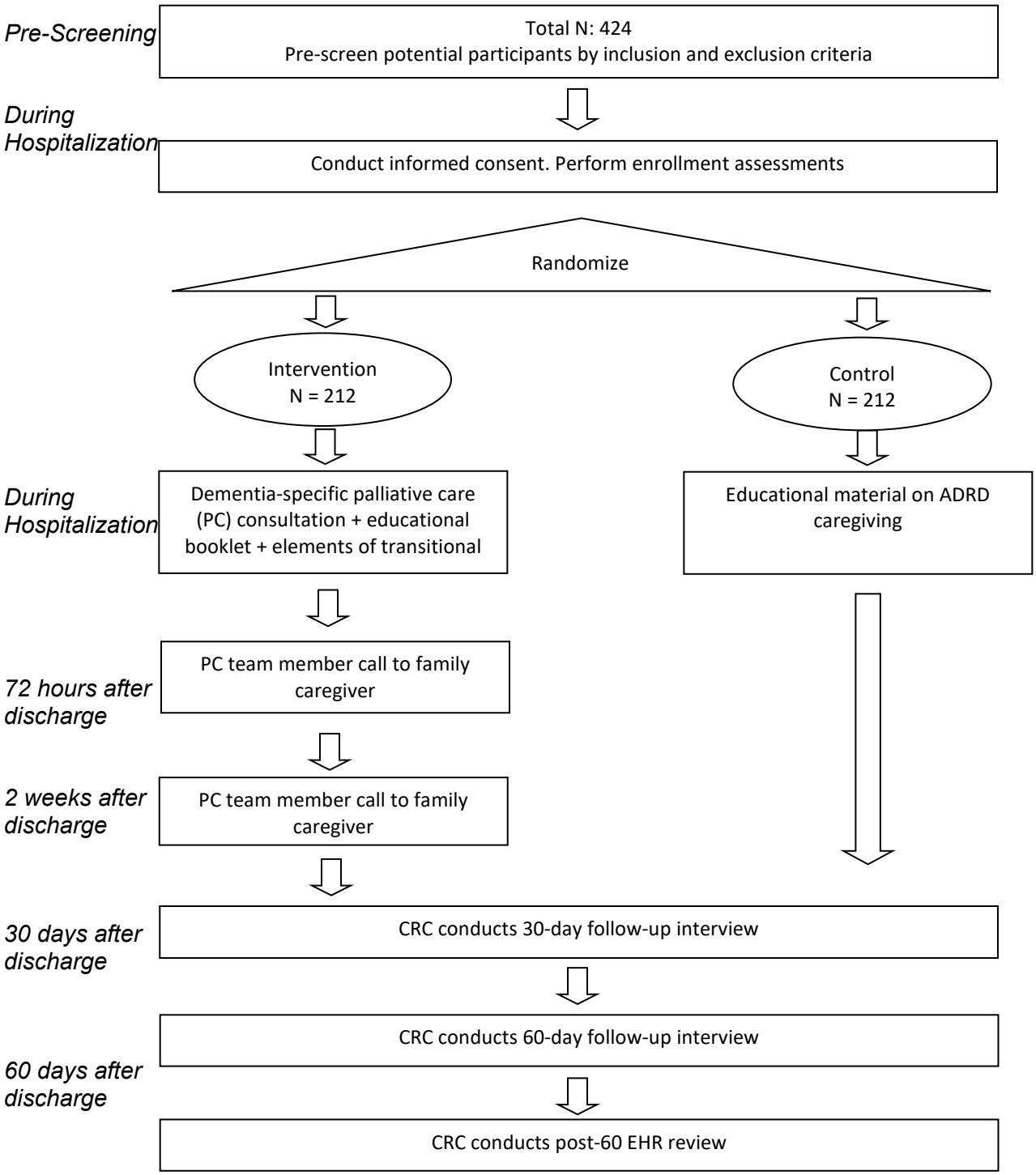
1.1 SYNOPSIS

Title:	Palliative Care for Persons with Late-stage Alzheimer's and Related Dementias and their Caregivers: A Randomized Clinical Trial
Grant Number:	R01AG065394
Study Description:	This study is a multi-site RCT of the ADRD-PC program of dementia-specific palliative and transitional care for people with late-stage ADRD and their caregivers.
Objectives:	**Aim 1**: To conduct a multi-site RCT of the ADRD-PC program (intervention arm) vs publicly available educational material for dementia caregivers (control arm) to compare 60-day hospital transfers (hospitalization and emergency room visits) for persons with late-stage ADRD (primary outcome). **Aim 2**: To compare patient-centered secondary outcomes between intervention and control arms: a) symptom treatment; b) symptom control; c) post-acute use of community palliative care or hospice; and d) new nursing home transitions. **Aim 3**: To compare caregiver-centered secondary outcomes between intervention and control arms: a) communication about prognosis and goals of care; b) shared decision-making; and c) caregiver distress.
Endpoint/ Outcomes:	60-day hospital transfers (Aim 1, primary outcome). Patient-centered secondary outcomes (Aim 2); a) symptom treatment (Palliative Care Domain index); b) symptom control (Symptom Management at the End of Life in Dementia scale, Neuropsychiatric Inventory Questionnaire); c) post-acute use of community palliative care or hospice; and d) new nursing home transitions. Caregiver-centered secondary outcomes (Aim 3); a) communication about prognosis and goals of care; b) shared decision-making; and c) caregiver distress (Family Distress in Advanced Dementia scale, Zarit Burden short form).
Study Population:	424 dyads of hospitalized patients with late-stage ADRD and their family caregivers and 50 dyads of hospitalized patients with late-stage ADRD and their family caregivers who identify as Hispanic/Latino
Phase or Stage:	NIA Behavioral Intervention Efficacy trial (Stage II)

Description of Sites/Facilities Enrolling Participants:	5 medical centers with interdisciplinary specialty palliative care teams - University of North Carolina (UNC), University of Indiana (IU), University of Colorado (UC), Massachusetts General Hospital (MGH), Emory University (EU)
Description of Study Intervention:	The ADRD-PC program includes 3 main components: dementia-specific palliative care consultation, standardized caregiver education, elements of evidence-based transitional care.
Study Duration:	60 months
Participant Duration:	60 days post hospitalization

SCHEMA

Flow Diagram



1.2 SCHEDULE OF ACTIVITIES

	Visit 1: During Hospitalization	Visit 2: During Hospitalization (Intervention)	Visit 3: PC Call 72 hours after discharge (Intervention)	Visit 4: PC Call 2 weeks after discharge (Intervention)	Visit 5 CRC interview 30 days post Hospitalization	Visit 6 CRC interview 60 days post hospitalization	CRC EHR Review post-60-day Hospitalization
STUDY ENROLLMENT ACTIVITIES							
EHR Eligibility Screen	X						
Informed Consent	X						
Enrollment Baseline Assessment	X						
Randomization	X						
Control arm	X				X	X	X
ADRD-PC intervention arm	X	X	X	X	X	X	X
DATA COLLECTION ACTIVITIES							
Hospital / ED transfers					X	X	X
Palliative Care Domain Index							X
Symptom Management at the End of Life in Dementia (SM-EOLD)					X	X	
Neuropsychiatric Inventory Questionnaire (NPI-Q)					X	X	
Post-acute use of palliative care, hospice					X	X	
New NH transition							X
Documented discussion of dementia prognosis							X
Documented decision-making for goals of care							X
Shared decision-making about hospitalization & burdensome treatments					X	X	
Family Distress in Advanced Dementia scale					X	X	
Zarit Burden scale					X	X	

2 INTRODUCTION

2.1 STUDY RATIONALE

Alzheimer's disease and related dementias (ADRD) are progressive and incurable. ADRD affects 5.6 million Americans at an annual cost of $157 billion. Approximately 3 million Americans are living with late-stage, or moderately severe to advanced dementia. They suffer with progressive dependency, loss of awareness of self and family, and escalating physical and neuropsychiatric symptoms. ADRD also adversely affects families; caregivers for late-stage ADRD experience marked physical, emotional, and financial strain.

Hospitalizations present a unique opportunity for dementia-specific palliative care, since 72% of hospitals have interdisciplinary palliative care teams. Palliative care improves symptom control and quality of life in serious illnesses, but has never been adapted and tested for the unique needs of late-stage ADRD.

We have therefore designed the **ADRD Palliative Care (ADRD-PC)** program of dementia-specific palliative and transitional care, and demonstrated its feasibility and potential efficacy. We now propose a rigorous multi-site efficacy clinical trial of ADRD-PC.

2.2 BACKGROUND

Alzheimer's disease and related dementias (ADRD) have unprecedented public health impact. ADRD affects 5.6 million Americans and their family caregivers; 3 million live with late-stage ADRD. The prevalence and incidence of ADRD is increased for under-represented minority populations, who are in turn a growing proportion of the US population. Annual dementia care costs exceed $157 billion. ADRD contributes to 1 in 3 deaths over age 65, and is the only major cause of death with no clinically relevant treatment to prevent, cure or slow disease progression.

Current care demonstrates unmet needs for palliative care. People with late-stage ADRD suffer progressive dependency and distressing symptoms, and their family caregivers experience physical, emotional, and financial strain. Healthcare disparities magnify symptoms and suffering associated with late-stage ADRD, and Hispanic / Latino families provide more intensive caregiving compared to White Americans. Clinical care is highly fragmented, with frequent transitions between home, emergency department, hospital, and nursing facilities. Persons with late-stage ADRD become "healthcare nomads," experiencing frequent burdensome transitions between hospitals and home or facility care. Acute illness hospitalizations for infections, injurious falls, or dehydration worsen physical and neuropsychiatric symptoms, and trigger decisions about goals of care and intensive treatments. Acute illness hospitalizations are burdensome, yet 23-47% are potentially avoidable.

Palliative care is rare for ADRD, and no major RCT tests dementia-specific palliative care. Persons with ADRD and their caregivers have unique palliative care needs that do not match standard models of palliative care. Culturally adapted ADRD care is needed, but interventions are rarely designed or adapted. Palliative care clinicians lack training in dementia-specific skills, and rarely see persons with ADRD. Our research team completed two pilot trials demonstrating feasibility and potential efficacy of the ADRD-PC program. Thus, the necessary next step to advance the science of dementia-specific palliative care is an adequately powered efficacy RCT of the ADRD-PC program to improve patient and caregiver outcomes. Research responds to the National Alzheimer's Project Act, Alzheimer's Association guidelines, and NIA priorities for

geriatric palliative care (PA-18-502) and research to improve quality of care and quality of life for persons with ADRD (PAS-18-030).

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

There are minimal risks associated with participation in this study. All components of the ADRD-PC program – palliative care consultation, transitional care procedures – have been previously established as evidence-based clinical interventions that improve outcomes for other serious illness populations. This risk is no greater than a similar risk encountered in all current healthcare involving hospital care for persons with late-stage ADRD and the varied treatment choices confronting their family caregivers.

The primary risk to people with ADRD is potential loss of confidentiality, as personal protected health information (PHI) will be collected.

- To protect against this risk, all collected data, including PHI, will be defined by the research protocol, and limited to research purposes. We will protect confidential medical information from EHR reviews by abstracting data directly into a secure database or onto coded paper forms separated from personal identifiers. Data will be entered in a password protected secure database, and all paper documentation will be maintained in locked files. The Sheps Information Technology group enables standard operating procedures required to secure the network and databases, including operational and technical controls. All servers are located within a hardened data center. Modes of communication between the study coordinating center at the University of North Carolina, and between Site-CRC, Site-PI and hospital attending physicians will be restricted to encrypted e-mail, secure text messages, or secure verbal communication to protect confidential health information.

The primary risk for family caregivers is potential emotional distress related to learning more about dementia prognosis and participation in goals of care decisions. Participation in the study, particularly in the intervention group, may draw family members' attention to ADRD as a serious and progressive illness, and ask them to consider the pros and cons of different treatment options. This risk is no greater than a similar risk encountered in all current healthcare involving hospital care for persons with late-stage ADRD and the varied treatment choices confronting their family caregivers. However, given the vulnerable characteristics of persons with ADRD and the level of strain documented for ADRD caregivers, training of site-based research staff and investigators will explicitly address this potential risk.

- To protect against emotional distress for the family caregiver, we will inform them of their right to skip interview items, pause during participation, or withdraw from the study at any time. During the course of data collection, the CRC may identify clinical concerns or extreme emotional distress expressed by the family caregivers. The Principal Investigator, Site-PI or other senior investigator will be available to provide timely guidance for response to these concerns.

  All CRCs will be trained to notify Site-PIs for any caregiver who expresses extreme emotional distress in response to study participation activities such as consent or interview items, or scores > 4.1 points average / 37 points summed score (one standard deviation above the mean) on the Emotional Distress Subscale of the Family Distress in Advanced Dementia scale. The instrument has construct validity established with correlation to depression scoring instruments. CRCs will follow-up with caregivers with a script asking about their access to current emotional support, and desire for additional access to mental health resources. If the caregiver expresses need for additional mental

health resources, the CRC will contact the Site-PI, who will assist the CRC in exploring level of need and identification of appropriate referral resources, which may include the family caregiver's primary care provider, the current hospital attending physician and social worker, or local mental health services.

2.3.2 KNOWN POTENTIAL BENEFITS

Potential individual benefits: Study participants in the intervention arm may benefit from the palliative care and transitional care services provided in ADRD-PC. Participants in both arms will report on their lived experience during study interviews and will receive high quality educational material on dementia caregiving. Thus, all participants may benefit from the increased opportunity to communicate about the experience of family caregiving for people with late-stage ADRD, and from educational materials provided.

Potential societal benefits: This study is the first RCT of a hospital-based dementia-specific palliative and transitional care intervention. For people with late-stage ADRD and their caregivers, there is an urgent need to improve outcomes of burdensome hospital transfers, symptom distress, shared decision-making, and caregiver distress. The study is responsive to the National Alzheimer's Project Act call for enhancements in quality of care for people with ADRD and their caregivers, and to NIA / NIH research priorities. Thus, potential benefits include enhanced understanding of interventions to improve the quality of palliative care and outcomes for people with late-stage dementia and their caregivers. If efficacious, ADRD-PC has potential to reduce suffering for millions of people living with ADRD and their caregivers.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The benefit to risk ratio is highly favorable in this study. First, the ADRD-PC intervention has low risk of harms, as it is composed of evidence-based and minimal-risk interventions which are shown to improve outcomes for other serious illness populations. Second, there are significant potential benefits to participants in both study arms.

3 OBJECTIVES AND ENDPOINT / OUTCOMES

OBJECTIVES	ENDPOINT / OUTCOMES	JUSTIFICATION
Primary		
To conduct a multi-site RCT of the ADRD Palliative Care (ADRD-PC) program of dementia-specific palliative and transitional care (**intervention arm**) vs publicly available educational material for dementia caregivers (**control arm**) to compare 60-day hospital transfers (hospitalization and	Number of emergency room visits + hospital admissions within 60 days after discharge from index hospitalization	Hospital transfers are common for persons with late-stage ADRD, and are burdensome and stressful for the person and their family caregivers. Evidence shows that some hospital transfers are avoidable because acute illness can be treated in lower intensity settings, OR because goals of care are more comfort-focused.

OBJECTIVES	ENDPOINT / OUTCOMES	JUSTIFICATION
emergency room visits) for persons with late-stage ADRD (**primary outcome**).		
Secondary		
To compare patient-centered secondary outcomes between intervention and control arms	a) Palliative Care Domain Index b) Symptom Management at End of Life in Dementia c) Neuropsychiatric Inventory Questionnaire d) Post-acute use of palliative care, hospice e) NH transitions	Physical and neuropsychiatric symptom distress is common in late-stage ADRD, and worsens toward death. Post-acute access to palliative services can improve outcomes, while new nursing home transitions may be avoidable with added community-based services and supports.
To compare caregiver-centered secondary outcomes between intervention and control arms	a) documented communication about prognosis and goal of care b) shared-decision making about hospitalization and other major treatment decisions c) Family Distress in Advanced Dementia scale d) Zarit Burden scale	Family caregivers serve as surrogate decision-makers in late-stage ADRD. They experience poor quality communication in usual care. In addition, caregivers experience significant emotional strain relative to caregiving role.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Study design is an RCT conforming to SPIRIT and CONSORT statements for trial methods and protocol. Our approach uses NIA standards for a multi-site efficacy trial (Stage II) of a protocolized behavioral intervention, while incorporating pragmatic features to support sustainability and future dissemination. We will use 1:1 randomization of patient-caregiver dyads with concealed allocation until study assignment. Research will occur at 5 geographically diverse sites of the Palliative Care Research Cooperative (PCRC) network, with study leadership and centralized IRB at UNC. Sites will enroll N=424 dyads of hospitalized patients with late-stage ADRD (GDS 6-7 or GDS 5 with significant co-morbidity) with their family caregivers. Sites will additionally enroll N=50 dyads that identify as Hispanic/Latino. Intervention dyads will receive the ADRD-PC program of i) dementia-specific palliative care, ii) standardized caregiver education, and iii) transitional care. Control dyads will receive publicly available educational material on dementia caregiving. Outcomes will be measured at 30 days (interim) and 60 days post-discharge. The primary outcome will be 60-day hospital transfers, defined as visits to an emergency department or hospitalization (**Aim 1**). Secondary patient-centered outcomes will be symptom treatment, symptom control, use of community palliative care or hospice, and new nursing home transitions (**Aim 2**). Secondary caregiver-centered outcomes will be communication about prognosis and goals of care, shared decision-making about hospitalization and other treatments, and caregiver distress (**Aim 3**). The Principal Investigator

and outcome assessors will be masked; as in most behavioral interventions clinicians and participants cannot be masked to study arm. Analyses will use intention-to-treat, and pre-specified exploratory analyses will examine effects of sex as a biologic variable, race / ethnicity, and GDS stage.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

We conducted a pilot RCT, randomizing 62 dyads of hospitalized patients with GDS 5-7 ADRD and their family caregivers to the ADRD-PC program vs usual care with publicly available education material. While underpowered to show a difference in 60-day hospital transfers, we found marked differences in intermediate outcomes. Intervention dyads were more likely to have an active POLST advance directive (79% vs 30%, p<0.001) and to make a decision to avoid future hospitalization (13% vs 0%, p=0.033). With ADRD-PC, persons with late-stage ADRD had more palliative care domains addressed in their treatment plan (Palliative Care Domain index score 7.6 vs 2.7, p<0.001, range 0-10), and symptom management for dyspnea (77% vs 34%, p<0.001), constipation (93% vs 25%, p<0.001), depression (83% vs 25%, p<0.001) and delirium (80% vs 19%, p<0.001). Caregivers were more likely to discuss prognosis (90% vs 3%, p<0.001) and goals of care (90% vs 25%, p<0.001). Intervention dyads also increased use of post-discharge palliative care (21% vs 7%, p=0.124) and hospice (25% vs 3%, p<0.019). Results indicate the potential for ADRD-PC to improve patient and caregiver-centered outcomes, including hospital transfers.

4.3 JUSTIFICATION FOR INTERVENTION

Our preliminary studies justify the proposed RCT. First, we have created novel and effective methods to find and recruit dyads in hospital. Second, ADRD-PC is feasible and acceptable to people with ADRD, caregivers and clinicians. Third, palliative care clinicians deliver the ADRD-PC program with high fidelity, ranging from 77% (two follow-up calls) to 93% (dementia-specific palliative care, standardized education). Fourth, we used best practices to optimize enrollment and retention. Fifth, pilot data support relevance of ADRD-PC to persons with GDS 5-7, as in our pilot trial all stages enrolled equally, had similar death rate, and all 60-day hospital transfers affected GDS 5-6. Sixth, results show ADRD-PC improves intermediate outcomes strongly linked to hospital transfers. Thus, the necessary next step to advance the science of dementia-specific palliative care is an adequately powered RCT of the ADRD-PC program to test efficacy to improve patient and caregiver centered outcomes.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as completion of the 60-day EHR chart review for all dyads.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

Target enrollment is N=424 dyads of people with late-stage dementia and their family caregiver, and N=50 dyads that identify as Hispanic/Latino.

People with ADRD will be eligible if they are: (1) aged 55 or older, (2) hospitalized, (3) have a physician-confirmed diagnosis of ADRD, and (4) staged GDS 6 or 7; or GDS 5 with additional

co-morbidity defined by Charlson Comorbidity Index scored 5 or higher. As in the pilot, ADRD stage will be confirmed by the attending physician and caregiver.

Caregivers will be eligible if they are: (1) the adult (aged 18 or older) legally authorized representative (LAR) for healthcare and have capacity to serve in this role, (2) support the person with ADRD, and (3) can complete interviews in English or Spanish. As in our prior ADRD research, other family caregivers may be present per primary caregiver request, but only the primary caregiver is a participant.

5.2 EXCLUSION CRITERIA

Dyads will be excluded if (1) the LAR is not a family caregiver, (2) the patient currently receives palliative care or hospice, (3) patient or caregiver would be unduly stressed, or (4) dyad is not successfully randomized.

5.3 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment and retention of seriously ill patients with stressed caregivers is challenging, and can threaten validity. We will train all sites in the Palliative Care Research Collaborative best practices to assure compliance with research ethics standards, complete and timely case-finding, compassionate approach and messaging, and flexibility to accommodate caregivers.

Participant screening: Site-CRCs will use an EHR algorithm for rapid case-finding. This method, developed during the pilot research, generates daily automated EHR lists of newly hospitalized patients with ADRD. Site-CRCs will conduct brief chart reviews under a HIPAA waiver to confirm eligibility criteria and forward patients with probable late-stage ADRD to the Site-PI for review. After brief EHR reviews by Site-CRCs and Site-PIs to confirm eligibility, Site-PIs will contact the inpatient attending physicians. They will confirm GDS stage as 5 ,6 or 7, and seek permission to approach caregivers.

Recruitment and informed consent: Recruitment will utilize diverse communication approaches with family caregivers; these approaches are identical to clinical communication used with family caregivers for people with dementia who lack decisional capacity. Since family caregivers may be present in hospital, or may be barred from visitation due to COVID-19 restrictions and safety concerns, or may live at a great distance from the hospital, recruitment and enrollment procedures will include both in-person and telephone / virtual communication methods. Further, flexibility of communication is essential for the enrollment of the project number of participants, because study enrollment and participation in the ADRD-PC intervention must both occur during acute illness hospitalization.

Site-CRCs will introduce the study to eligible family caregivers using scripted telephone calls or in-person visits. When the Site-CRC conducts recruitment and enrollment via telephone, the Site-CRC will ask if the individual is in a private location, and feels comfortable talking about the study at that time; they will schedule an alternative time if necessary. The Site-CRC will explain the study over the phone using a telephone script. Spanish-speaking CRCs will introduce and explain the study to any Spanish-speaking participants using translated recruitment scripts and study materials.

If the family caregiver is interested and wants to participate, the Site-CRC will conduct the informed consent with them verbally in person or over the phone. If the family caregiver agrees to consent, study informational materials and the informed consent form will be sent to them by mail or secure e-mail.

Due to the low risk of study participation and the restrictions on immediate written consent described above, verbal consent will be accepted for participation in the enrollment caregiver interview, and for randomization with initiation of the ADRD-PC or control conditions.

Site-CRCs will introduce the study in scripted introductory phone calls or in-person visits. After informed consent, the caregiver will complete the enrollment interview.

Retention: Retention is supported first and foremost by respectful, flexible, and compassionate interpersonal encounters with site-based research staff which will be consistently emphasized in training and coaching communication. Secondly, retention is supported by setting appointments for follow-up interviews with recognizable Site-CRC names and contact information. Third, retention is supported by obtaining multiple contact information for family caregivers. And fourth, retention is promoted by small payments for completion of study visits. Family caregivers will receive a $25 gift card for completing each of the three interviews (enrollment, 30-day, and 60-day follow-up), for a total of $75.

6 STUDY INTERVENTION AND CONTROL CONDITIONS

6.1 STUDY INTERVENTION

Intervention Condition: Patient-caregiver dyads randomized to the intervention will receive the ADRD-PC program, described below and in Table 1.

Delivering the ADRD-PC Program

Elements	Content	Method of Delivery
Dementia-specific Palliative Care	1) Prognosis – exploration and communication of stage, trajectory and prognostic awareness 2) Symptoms – assessment and treatment for physical and neuropsychiatric symptoms 3) Shared decision-making – exploration of values and goals of care; discussion of treatment decisions 4) Transitional care – assessment of needs, care planning and recommendation for support services	* Interdisciplinary palliative care clinicians meet with the person with ADRD and family caregiver. * ADRD-PC Note Template used to record encounters addressing these 4 domains
Standardized Caregiver Education	1) Dementia and its stages 2) Determining the primary goal of care 3) Approach to decision-making 4) Approach to eating problems 5) Approach to decisions about hospitalization 6) Approach to decisions for infections 7) How dementia affects the family 8) What is hospice and palliative care?	* Clinicians share booklet Advanced Dementia: A Guide for Families and individualize content during counseling for prognostic awareness and decision-making
Transitional Care	1) Palliative Care Plan – written summary of dementia stage and prognosis, recommendations for symptom	* Palliative Care Plan addressing 4 domains provided to the

	treatment, goals of care and treatment decisions, and for support services. 2) New referrals to support services – examples include community palliative care, hospice, home health, geriatric clinic, dementia clinic, caregiver support group, adult day care, support group. 3) Contact information for the palliative care team	outpatient clinician AND caregiver * Referrals to community support services * Post-discharge supportive calls at 72 hours and 2 weeks

1) Dementia-specific palliative care will be delivered by hospital-based specialty interdisciplinary palliative care teams. Encounters will include a physician or advanced practice provider and at least one additional discipline (nurse, social worker, chaplain). Visits will continue until hospital discharge, and will be documented in the EHR with the ADRD-PC Note Template.Palliative care clinicians will address four domains. First, the palliative care team will promote caregivers' **prognostic understanding** of dementia stage and its trajectory, contextualizing the acute illness with information about ADRD. Second, the palliative care team will conduct ADRD-specific **symptom management** of pain, other physical and neuropsychiatric symptoms, and recommend treatment consistent with best practices for ADRD. Third, the palliative care team will facilitate **shared decision-making** with the caregiver. Discussions may include exploration of overall goals of care, and decision-making about potentially burdensome treatments of resuscitation, ventilator use, feeding tubes, antibiotics, or future hospitalizations. When clinically appropriate, consultation will also include completion of new advance directives such as a Physician Orders for Life Sustaining Treatment (POLST) or comparable portable order set to document decisions for current care plans. POLST or similar documentation is in all study states and enhances treatment matched to patient preferences across healthcare transitions. Fourth, the palliative care team will assess **transitional care needs for community support services**. They will support dyads with post-discharge follow-up calls and referral to community services. (see Transitional care).

2) Standardized caregiver education will be provided by the palliative care team. Clinicians will share and discuss the booklet Advanced Dementia: A Guide for Families, which addresses common concerns and treatment decisions. Clinicians will individualize its content, highlighting key content and providing counseling about its relevance for current or future caregiving and treatment decision-making.

3) Transitional care will be provided by the palliative care team. Pre-discharge, the palliative care team will explore **adequacy of patient and caregiver support for practical, emotional and spiritual needs**. Based on needs, they will recommend **community-based support services**. Examples could include community palliative care, hospice, home health, specialty geriatric or dementia clinics, adult day care or Alzheimer caregiver support groups. Near discharge, a member of the palliative care team will create a templated Palliative Care Plan and provide copies to the primary or post-acute care provider (PACP) AND the family caregiver. This document will summarize recommendations in the four domains and provide contact information for the palliative care team for follow-up questions. Post-discharge, a designated palliative care team member – usually a social worker or nurse coordinator – will call the family caregiver within 72 hours and again within 2 weeks after discharge. These calls may also be facilitated by a site CRC. The purpose of these calls will be to support implementation of the Palliative Care Plan and access to post-acute

supportive services. Calls will also be used to solicit concerns, offer emotional support, and make recommendations to help the caregiver overcome barriers to services.

Control condition: Patient-family caregiver dyads randomized to the control arm will receive educational materials from the Alzheimer's Association, specifically designed for late-stage ADRD caregivers. The patient will receive usual hospital and post-acute care.

6.1.1 ADMINISTRATION AND/OR DOSING

N/A

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

Ensuring fidelity to the ADRD-PC will be the responsibility of all site-based investigators. Our approach is based on NIH Behavior Change Consortium standards, with elements relevant to study design, interventionist training and standard operating procedures, and tools to support delivery of the ADRD-PC intervention.

Types of Fidelity	Procedures to Ensure Fidelity	Fidelity Monitoring
Study Design	• Intervention based on a well-defined protocol • Standardized tools and templates	• Protocol review and version control supported by Palliative Care Research Cooperative group
Standardized Training and Delivery	• Training of Site-PIs on study protocol and SOPs • Training of Site-CRCs on study protocol and SOPs • Training of PC clinicians to deliver ADRD-PC • Audio-recorded training modules for consistent re-training or for new personnel • ADRD-tools and templates	• Training material review by Palliative Care Research Cooperative group • Completed training • Post-training evaluation for PC clinicians (threshold score 80%) • Delivery of tools and templates to all study sites
ADRD-PC Intervention Enactment	• Monthly conference calls (led by Dr. Hanson) with site PC clinicians • Monthly conference calls (led by UNC Project Manager) with site CRCs and site PIs=Utilization of ADRD-PC Program with standardized content areas • Documentation of clinical encounters in site medical record	• Site-CRC tracking of completion of 4 ADRD-PC components: a) PC encounter, b) caregiver education, c) delivery of PC Plan to caregiver and primary or post-acute care provider (PACP) , and d) completion of 2 transitional care calls. • Threshold score 80% of dyads with completion of 4 ADRD-PC components. • Site specific feedback when fidelity drops below threshold. • Review 10% random of deidentified ADRD-PC encounter notes to ensure adherence,

		scored for quality of content across 4 clinical domains

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND MASKING

Randomization will occur following the enrollment interview, with the dyad as the unit of randomization and analysis. Allocation will be concealed prior to randomization. Randomization will be generated within REDCap software, and transmitted by the Site-CRC to the PC team to initiate ADRD-PC (intervention) or to deliver dementia caregiver educational material (control).

CRCs who collect outcome data will be masked to study arm in family caregiver interviews. Since the EHR will have ADRD-PC palliative care encounters, Site-CRCs will complete follow-up EHR reviews only after 60-day follow-up interviews. Dr. Hanson (PI) will remain masked to study arm assignments to minimize bias in study procedures and analysis.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Due to the low risk of harm to study participants anticipated for this intervention, no interim analyses for efficacy or a priori stopping rules are planned. During the first DSMB meeting, in coordination with the NIA Program Official, the DSMB members will be asked to consider and recommend possible a priori stopping rules, if any, based on adverse event reporting.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. An investigator may discontinue a participant from the study for the following reasons:

- Significant study intervention non-adherence
- Lost-to-follow up; unable to contact subject (see **Section 7.3, Lost to Follow-Up**)
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not initiate either the intervention or control procedures may be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to be reached for follow-up surveys and study staff are unable to contact the participant after at least 5 attempts.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

Data collection will be identical for both arms. Data will be obtained from caregiver enrollment interviews and 30- and 60-day interviews post-discharge, and from electronic health record (EHR) reviews encompassing the 60-day period post-hospitalization. Based on the pilot RCT, we estimate 10% of persons with late-stage ADRD will die during follow-up; caregiver interview data collection will proceed using a Bereavement Interview adaptation. Outcome measures will focus on 60-day interviews; 30-day interim interviews are necessary to support retention, ensure data capture for persons with ADRD who die, and for valid recall of hospital transfers (primary outcome) and secondary outcomes.

Family Caregiver Interviews:

1. Emergency room visits + hospital admissions after discharge from index hospitalization
2. Use of hospice or community palliative care services
3. Patient symptom distress
    a. Instrument: Symptom Management at the End of Life in Dementia (SM-EOLD)
    b. Instrument: Neuropsychiatric Inventory Questionnaire (NPI-Q)
4. Shared decision-making about hospitalization
5. Shared decision-making about other burdensome treatments
6. Caregiver distress
    a. Instrument: Family Distress in Advanced Dementia Scale
    b. Zarit Burden scale, short form

Electronic Health Record Review:

1. Symptom assessment and management plans during hospitalization-
    a. Palliative Care Domain Index Items
2. Documented discussion of dementia prognosis
3. Documented discussion decision-making for goals of care
4. New nursing home transfers
5. Return to acute care – ED or Hospital readmissions within 60 days and up to 3 reasons for return

8.2 SAFETY ASSESSMENTS

The Principal Investigator and research team will comply with the University of North Carolina Office of Human Research Ethics (OHRE) requirements and consistent with DHHS 45 CFR part 46 and NIA guidelines for defining, collecting and reporting any unanticipated problems, adverse events or serious adverse events during the conduct of research.

This study uses a single IRB (University of North Carolina-Chapel Hill) to conduct ethical review required for the protection of human subjects. The study is a multi-site clinical trial, and the participating sites will utilize a single protocol and have agreed to the single IRB oversight structure.

All study procedures, informed consent forms, and recruitment procedures will undergo review by the Institutional Review Board at the University of North Carolina-Chapel Hill prior to initiating research, and will be subject to annual and other required reviews. Enrolled participants will be dyads of persons with late-stage ADRD and their family caregivers; caregivers will provide written informed consent for dyad participation. Investigators will work with NIA to convene a

Data Safety and Monitoring Board to oversee the human subjects' safety and adverse event reporting for this multi-site clinical trial.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

Adverse events (AE) are defined as

- Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal exam or laboratory finding), symptom or disease temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.
- *In the ADRD-PC study tracked AEs will include major emotional distress for family caregivers, and confidentiality risk events for the person with ADRD.*

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse events (SAE) are defined as

- Death
- Life-threatening health events
- Acute illness causing hospitalization
- Health event causing persistent new disability or incapacity, or
- Similar significant hazardous events
- *In the ADRD-PC study these events will be tracked for all participants. These events are expected health outcomes for people with ADRD and may also occur for family caregivers. SAEs will be included in study data collection but will not be included in AE reporting; see explanation below.*

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used to describe severity.

- **Mild** – limited in intensity and duration, without sustained effect on participant
- **Moderate** – limited in intensity or in duration, with some sustained effect on participant
- **Severe** – significant intensity and duration of event, with significant sustained effect on participant

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study procedures administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study procedures should be clinically plausible. The event must be pharmacologically or phenomenologically definitive.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study procedures, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of study procedures). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study procedures administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study procedures) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study procedures administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.]

8.3.3.3 EXPECTEDNESS

An investigator team member with expertise in advanced dementia and palliative care will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. Any medical or psychiatric condition that is present at the time that the participant is enrolled will be considered as baseline and not reported as an AE.

All AEs, not otherwise precluded per the protocol, will be captured on the appropriate case report form (CRF). All AEs occurring while on study will be documented appropriately regardless of relationship. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

Adverse event reporting will be refined with input from the DSMB during its initial meeting, to address any specific concerns related to this study protocol.

Site-based PIs will report any Unanticipated Problem Involving Risk to Subjects or Others (UPIRSO)s or AEs to the overall PI and Project Manager in a timely manner.
When a UPIRSO or AE is present, the overall PI and Project Manager will submit a report to the UNC IRB within 3 working days of receipt of this information. Generally, the report should contain the following:

- Detailed information about the event or issue, including relevant dates. The report should identify the affected subjects by their study codes and not by their names or other personal identifiers.
- An assessment of whether any subjects or others were placed at risk or suffered any harm (e.g., physical, social, financial, legal or psychological) as a result of the event.
- If the event involves noncompliance, describe the result of the root cause analysis.
- Any corrective and preventative actions, planned or already taken.
- Any other information requested by OHRE, if applicable.
- If the report cannot be completed in its entirety within the required time period, the report should describe what information is still needed and when the investigator anticipates that a follow-up report will be submitted.

Information previously unknown to the IRB that suggests new or increased risk to subjects or others (hereinafter referred to as New Safety Information) is promptly reportable to OHRE within 7 calendar days of the investigator becoming aware of the information.

- Information for which the sponsor requires reporting to the IRB, may be summarized and submitted to the IRB at continuing review.
- Protocol deviations that did not harm subject(s) or others or place subject(s) or others at increased risk must be summarized and reported to the IRB at continuing review.
- Researchers may consult with the OHRE Compliance Manager if they are uncertain about what information is reportable.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

The reporting of any AE / SAE will be based on NIA and UNC IRB standards, on the severity of the AE, its level of attribution to the intervention, and whether or not it is anticipated.

- All **adverse events that are both serious** (SAE) **and unexpected** would be reported to IRB, DSMB / SO, and NIA PO **within 48 hours** of the study's knowledge of SAE.
- Summary of SAEs would be reported to NIA PO and to the DSMB / PO **quarterly**, unless otherwise requested by the DSMB or a Safety Officer.
- Summary of all AEs regardless of classification would be presented for each DSMB meeting at 6-month intervals

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the UNC Office of Human Research Ethics (OHRE).
Unanticipated Problems are defined as

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review

Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized
- UPIRSO - Unanticipated Problem Involving Risk to Subjects or Others is any incident, experience, or outcome that:
    - is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
    - is related or possibly related to a participant's participation in the research; and
    - is serious or suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Aim 1: To conduct a multi-site RCT of the ADRD-PC program (**intervention arm**) vs publicly available educational material for dementia caregivers (**control arm**) to compare 60-day hospital transfers (hospitalization and emergency room visits) for persons with late-stage ADRD (**primary outcome**). ***H1****: 60-day hospital transfers will be lower in the intervention vs. control arm.*

Aim 2: To compare patient-centered secondary outcomes between intervention and control arms: a) symptom treatment (Palliative Care Domain index); b) symptom control (Symptom Management at the End of Life in Dementia scale, Neuropsychiatric Inventory Questionnaire); c) post-acute use of community palliative care or hospice; and d) new nursing home transitions. *Patients in intervention vs. control arms will have better symptom treatment (**H2a**) and symptom control (**H2b**); increased use of community palliative care or hospice (**H2c**); and fewer new nursing home transitions at 60 days post-discharge (**H2d**).*

Aim 3: To compare caregiver-centered secondary outcomes between intervention and control arms: a) communication about prognosis and goals of care; b) shared decision-making; and c) caregiver distress (Family Distress in Advanced Dementia scale and Zarit scale). *Caregivers in intervention vs control arms will more often have documented communication about prognosis and goals of care (**H3a**); report more shared decision-making about hospitalization and treatments (**H3b**); and report less caregiver distress at 60-days post-discharge (**H3c**).*

9.2 SAMPLE SIZE DETERMINATION

Based on prior ADRD research, we project 15% dropouts (death, withdrawal) equally distributed between groups; caregiver data collection is completed after deaths as in our prior ADRD

research. Total sample size for analysis of 60-day follow-up outcomes is thus n=360. All statistical tests will be 2-tailed with an overall 0.05 significance level for pre-specified analyses. Statistical power is based on a 2-sided alpha of 0.05 significant tests and using standard deviation estimates from our pilot study (**Table 3**).

Power calculations assume a "best guess" 15% dropout (death, withdrawal) rate based on prior ADRD research (n=180 per group at 60-day follow-up) and a "worst case" 25% dropout rate (n=159 per group). These rates consider 9% patient mortality and 92% caregiver retention rate in the pilot. In our pilot data, 0.52 is the lower bound of the 95% CI for the IRR comparing

Table 3: Power for Comparing Intervention and Control Arms Based upon the Study Design

Aim	Measure	Control	SD	Difference	Power, 15% dropout	Power, 25% dropout
1	60-day hospital transfers (Poisson rate)	0.53	--	0.25, 0.2	0.96, 0.82	0.95, 0.79
60-day hospital transfers (overdispersed)		0.53	--	0.25, 0.2	0.81, 0.60	0.76, 0.55
2a	PC Domain Index (0-10)	2.7	1.7	5, 0.5	>0.99, 0.80	>0.99, 0.75
2b	60-day hospice use (%)	3%	--	22%,8%	>0.99, 0.85	>0.99,0.80
2c	Symptom distress (SM-EOLD)	36.4	7.8	4, 2.3	>0.99, 0.80	>0.99, 0.75
2d	Transition to nursing home care (%)	33%	--	30%,15%	>0.99, 0.82	>0.99, 0.78
3a	Discussion of dementia prognosis	3%	--	87%, 8%	>0.99, 0.85	>0.99, 0.80
3a	Discussion of goals of care (%)	25%	--	65%,14%	>0.99, 0.82	>0.99, 0.77
3b	Decision-making about hospitalization	0%	--	13%, 4%	>0.99, 0.78	>0.99, 0.73
3b	Decision-making about treatments	6%	--	47%, 9%	>0.99, 0.80	>0.99, 0.75
3c	Family Distress in Advanced Dementia	2.4	0.5	0.15, 0.1	0.81, 0.47	0.76, 0.43

Administrative Supplement Power Estimation:

Given the early-stage nature of the proposed supplementary research, we do not anticipate adequate power to detect clinically meaningful differences for our primary and several secondary outcomes for Hispanic / Latino dyads alone. However, it is possible to detect promising trends in some secondary outcomes that had a large effect size in our pilot study.

We anticipate using this supplementary grant to collect the pilot data for effectiveness of our intervention in the key outcomes of our interest in this particular population.

9.3 POPULATIONS FOR ANALYSES

N/A

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

Analysis: Descriptive analyses of variables will examine distributions, influential data points, and missing data. Means (standard deviations) will be reported for continuous variables and frequencies (percentages) for categorical variables. Continuous variables (e.g., PC Domain Index, etc) that are poorly distributed may be transformed or analyzed using non-parametric

tests. We anticipate missing data on independent variables will be minimal. We will use simple mean and mode imputation for those variables included in regression models if less than 5% of patients have missing data; else, conditional (i.e., regression) imputation will be used. Available case analysis will be conducted for 30-day outcomes. Missing 60-day dichotomous outcomes will be multiply imputed if missingness exceeds 10%. Caregiver data collection is completed after deaths as in our prior ADRD research. Primary analysis will use intention-to-treat analysis. We will evaluate the effectiveness of randomization by comparing intervention and control participants on baseline measures. Variables that are not equally distributed between arms could potentially bias results. We will include these variables in each initial model and use a change-in-effect method for determining whether they are confounders. If removing any of these variables from the model does not appreciably change the regression coefficient estimate of the intervention group variable, we will not need to include them in the final model. Given our randomized design, we anticipate little confounding. A priori exploratory analyses will examine effects by sex as a biological variable, race / ethnicity, and GDS stage.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

Aim 1: *To conduct a multi-site RCT of the ADRD-PC program of dementia-specific palliative and transitional care (**intervention arm**) vs publicly available educational material for dementia caregivers (**control arm**) to compare 60-day hospital transfers (hospitalization and emergency room visits) for persons with late-stage ADRD (**primary outcome**).*
Analysis to Meet Aim 1: We will compare control and intervention arms on hospital transfers (primary outcome) during 60 days post-discharge. This count outcome is defined as the total number of emergency room visits plus hospital admissions per at-risk patient-days. We will use Poisson regression with empirical 'robust' standard errors allowing for overdispersion to compare the transfer rates between groups. We will use the length of follow-up as the offset variable, which means that patients who have data only from the 30-day interview will be included. The primary analysis will be based on the model with main effects for treatment group, study site, GDS Stage and patient and caregiver sex as biological variables. Evaluation of the treatment effect will be based on a Wald test. The covariate-adjusted treatment effect will be quantified as an incidence rate ratio (IRR) with a 95% confidence interval. Considering that over 60% of patients in the pilot study did not have any hospital transfers, we will conduct a sensitivity analysis for the treatment effect on 60-day hospital transfers with a marginalized zero-inflated Poisson (MZIP) model, which may modestly increase power. Secondary Poisson and MZIP analyses will compare study arms for 30-day hospital transfer rates. An exploratory analysis will be conducted to examine interactions of treatment group with study site, sex, race / ethnicity and GDS Stage, respectively, on 60-day hospital transfers. While the proposed study is powered to detect whether or not ADRD-PC is effective, a much larger study would be needed to have adequate power to detect differences by sex or GDS Stage and would be justifiable only after the completion of this initial trial. An interaction model will be used if an omnibus test for interactions is statistically significant at the 0.05 level. A second exploratory analysis will evaluate a dose-response effect of the intervention on the hospital transfer rate. A dose for patients receiving the intervention is defined as the number of key intervention components used in fidelity monitoring (range 0 to 4 with 0 for controls). The dose effect is the incremental benefit of adding a single component; its rescaling gives the per-protocol effect of the full intervention.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

Aim 2: *To compare patient-centered secondary outcomes between intervention and control arms: a) symptom treatment (Palliative Care Domain index); b) symptom control (Symptom Management at the End of Life in Dementia scale, Neuropsychiatric Inventory Questionnaire); c) post-acute use of palliative care or hospice; and d) transition to nursing home care.*
Analysis to Meet Aim 2: We will compare study arms during 60 days post-discharge on the following outcomes:

2.a. Symptom treatment: This ordinal outcome is the summation of presence (=1) or absence (=0) of 10 domains of palliative care. We will treat it as a continuous variable due to a high variation observed in the pilot data. We will use Student's t-test to compare the mean difference between study arms unless violation of assumptions warrants the Mann-Whitney test. We will use a multiple linear regression model with main effects for treatment group, study site, GDS Stage and patient and caregiver sex as a biological variable.

2.b. Symptom control: We will use Symptom Management (SM-EOLD) scale to measure caregiver report of patients' uncontrolled symptom distress and Neuropsychiatric Inventory Questionnaire (NPI-Q) to measure caregiver report of patients' neuropsychiatric symptom distress. Linear mixed models with random intercepts for patients will be used with a time indicator (30 vs 60 days follow-up) with the above main effects.

2.c. Use of post-acute palliative care or hospice: This outcome will be defined by whether patients ever use hospice or outpatient palliative care during the time from discharge to 60 days follow-up. We will compare the proportions using Pearson's chi-square test. Logistic regression will be used for multivariable modeling with the same main effects as in Aim 2.a. Final estimates will be reported as covariate-adjusted odds ratios.

2.d. Transition to nursing home care: This outcome will be defined by whether patients transition to nursing home care during the time from discharge to 60 days follow-up. We will compare proportions using Pearson's chi-square test. Logistic regression will be used for multivariable modeling with the same main effects as in Aim 1. Final estimates will be reported as covariate-adjusted odds ratios.

Aim 3: *To compare caregiver-centered secondary outcomes between intervention and control arms: a) communication about prognosis and goals of care; b) shared decision-making; and c) caregiver distress (Family Distress in Advanced Dementia scale, Zarit Burden interview).*
Analysis to Meet Aim 3: For the dichotomous outcome variables pertaining to communication (hypothesis 3a) and shared decision-making (hypothesis 3b), Pearson's chi-square test will test for differences in proportions between study arms. We will use logistic regression for the multivariable modeling. Treatment effect estimates will be reported as adjusted odds ratios. To test hypothesis 3c, we will use Student's t-test for mean difference since the outcome, Family Distress in Advanced Dementia (FDAD), is continuous. Linear mixed models as described for Aim 2.b. above will be used to test treatment effects for 30-day and 60-day outcomes jointly.

Administrative Supplement Analysis:

Supplement Aim 2: To determine the feasibility, acceptability and preliminary efficacy of the ADRD-PC intervention for n= 50 Hispanic / Latino dyads living with late-stage dementia in a pilot randomized clinical trial: Descriptive analyses of variables will examine distributions, influential data points, and missing data. Means (standard deviations) will be reported for continuous variables and frequencies with percentages for categorical variables. Continuous variables (e.g., PC Domain Index, etc) that are poorly distributed may be transformed, or analyzed using non-parametric tests. We anticipate that missing data on independent variables will be minimal. We will use simple mean and mode imputation for those variables included in regression models if less than 5% of patients have missing data; else, conditional (i.e., regression) imputation will be used. Available case analyses will be conducted for 30-day outcomes. Missing 60-day dichotomous outcomes will be multiply imputed if

missingness exceeds 10%. Caregiver data collection is completed after deaths as in our prior ADRD research.

Analysis of feasibility outcomes: Simple descriptive statistics will be used to assess feasibility. We will report frequencies for rates of screening, eligible vs. ineligible, and consented vs. refused dyads. We will report on de-identified demographic and clinical characteristics of those who are eligible and consent vs refuse participation. We will use similar descriptive comparisons to report on dyads who enroll and complete all study procedures compared to those who are not retained for complete outcome assessments. ADRD-PC will be feasible for Hispanic / Latino dyads if we successfully achieve target enrollment (n=50 dyads), and study retention (80%) within 20% these goals.

Analysis of acceptability outcomes: Acceptability will be evaluated using qualitative methods to analyze results of open-ended questions in family caregiver interviews. Interview transcripts will be entered into ATLAS.ti software to facilitate qualitative content analysis and coding. Dr. Fischer will oversee the qualitative coding process, and two Spanish-speaking CRCs will conduct paired coding of all transcripts.

Analysis of preliminary efficacy outcomes data: Primary analysis will use intention-to-treat analysis. We will evaluate the effectiveness of randomization by comparing intervention and control participants on baseline measures. Variables that are not equally distributed between arms could potentially bias results. We will include these variables in each initial model and use a change-in-effect method for determining whether they are confounders. If removing any of these variables from the model does not appreciably change the regression coefficient estimate associated with the intervention group variable, we will not need to include them in the final model. Given our randomized design, we anticipate little confounding. A priori exploratory analyses will examine the effects stratified by sex as a biologic variable, and GDS stage.

As in the parent ADRD-PC randomized trial, we will compare control and intervention arms on hospital transfers (primary outcome) during 60 days post-discharge. This count outcome is defined as total number of emergency room visits plus hospital admissions per at-risk patient-days. We will use Poisson regression with empirical ‘robust’ standard errors allowing for overdispersion to compare the transfer rates between groups. We will use length of follow-up as the offset variable, which means that patients who have data only from the 30-day interview will be included. The primary analysis will be based on the model with main effects for treatment group, study site, GDS Stage and patient and caregiver sex as biological variables. Evaluation of the treatment effect will be based on a Wald test. The covariate-adjusted treatment effect will be quantified as an incidence rate ratio (IRR) with 95% confidence interval. We will conduct a sensitivity analysis for the treatment effect on 60-day hospital transfers with a marginalized zero-inflated Poisson (MZIP) model, that may modestly increase power. Secondary Poisson and MZIP analyses will compare study arms for 30-day hospital transfer rates. An exploratory analysis will be conducted to examine interactions of treatment group with study site, sex and GDS Stage, respectively, on 60-day hospital transfers. An interaction model will be used if an omnibus test for interactions is statistically significant at the 0.05 level.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATION

10.1.1 INFORMED CONSENT PROCESS

SEE STATEMENT OF COMPLIANCE

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks will be provided to the family caregiver, who provides consent for their participation and that of the person with late-stage dementia. As described below, verbal consent will be accepted and documented for study enrollment. Written documentation, including consent forms for review will be provided during in-person visits, or sent by mail or secure electronic communication when visits are conducted virtually.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Since family caregivers may be present in hospital or may be barred from visitation due to COVID-19 restrictions and safety concerns or may live at a great distance from the hospital, recruitment and enrollment procedures will include both in-person and telephone / virtual communication methods. These approaches are comparable to routine clinical communication used with family caregivers for people with dementia who lack decisional capacity. Further, flexibility of communication is essential, because study enrollment and participation in the ADRD-PC intervention must both occur during acute illness hospitalization.

Due to the low risk of study participation and the restrictions on immediate written consent described above, verbal consent will be accepted for participation in the enrollment caregiver interview, and for randomization with initiation of the ADRD-PC or control conditions. To ensure informed consent, the Site-CRC will provide verbal information about the study, indicate the participation is voluntary and he/she has the right to stop at any time. They will enumerate benefits and risks verbally during the consent process, reading from the consent form. Additionally, the informed consent verbal communication and written documents will include a specific statement relating to posting of deidentified clinical trial information at ClinicalTrials.gov.

Site-CRCs will introduce the study to eligible family caregivers using in-person visits in hospital or scripted telephone calls when being present in hospital is not possible. When recruitment and enrollment is in-person, the Site-CRC will provide written and verbal study information (in either English or Spanish), review the informed consent form, obtain verbal consent, and complete the enrollment interview in-person. When the Site-CRC conducts recruitment and enrollment via telephone, the Site-CRC will ask if the individual is in a private location and feels comfortable talking about the study at that time; they will schedule an alternative time if necessary. The Site-CRC will explain the study over the phone using a telephone script. If the family caregiver is interested and wants to participate, the Site-CRC will review and complete informed consent with them verbally over the phone. If the family caregiver consents to participate, study informational materials and the informed consent form will be sent to them by mail or secure e-mail for later review.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

The study will be closed after completion of target enrollment, and study procedures discontinued after follow-up data collection, and planned data analyses with appropriate presentation, publication and data sharing.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, the safety and oversight monitor(s), and the sponsor(s) and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific study participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in a private setting. The study participant's contact information will be securely stored at each clinical site for internal use during the study. All collected data, including PHI, will be defined by the research protocol and limited to research purposes. We will protect confidential medical information from EHR reviews by abstracting data directly into a secure database or onto coded paper forms separated from personal identifiers. Data will be entered in a password protected secure database, and all paper documentation will be maintained in locked files. The Sheps Information Technology group enables standard operating procedures required to secure the network and databases, including operational and technical controls. All servers are located within a hardened data center. Modes of communication between the study coordinating center at the University of North Carolina, and between Site-CRC, Site-PI and hospital attending physicians will be restricted to encrypted e-mail, secure text messages, or secure verbal communication to protect confidential health information.

The study monitor, other authorized representatives of the sponsor or funding agency, representatives of the Institutional Review Board (IRB), regulatory agencies or representatives from companies or organizations supplying the product, may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

At the end of the study, all records will be deidentified and then shared with the Palliative Care Research Collaborative Group, which will store deidentifed data and continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

The research team will be led by Dr. Laura Hanson (PI) and managed by Project Manager reporting to Dr. Hanson. Dr. Hanson and the Project Manager will provide administrative leadership and study coordination, to ensure timely completion of research tasks and consistency with protocol standards. The University of North Carolina's Cecil G. Sheps Health Services Research Center will be the administrative home for the UNC research investigators and staff, and will function as the data coordinating site to receive, house, clean and support all data analyses. Ms. Wessell (UNC research staff) will facilitate data management, and data analysis will be led by the study biostatistician Feng-Chang Lin. Staff from the Palliative Care Research Cooperative group's Project Coordinating Center housed at the University of Denver (Dr. Kutner, Site-PI) will provide technical assistance to ensure good clinical practice, protocol version control and central coordination of IRB tasks necessary for a large-scale multi-site clinical trial.

Research enrollment sites will be the University of North Carolina (Drs. Hanson, Kistler), Indiana University (Dr. Sachs, Site-PI), Massachusetts General Hospital affiliated with Harvard Medical School (Dr. Ritchie, Site-PI), the University of Colorado-Denver (Dr. Lum, Site-PI), and Emory University (Drs. Lowers and Kavalieratos, Site-PIs).

10.1.6 SAFETY OVERSIGHT

This multi-site RCT will utilize a single IRB and a unified protocol for all study sites. All study protocols and amendments, informed consent forms, and other study materials will undergo review by the Institutional Review Board at the University of North Carolina-Chapel Hill prior to initiating research, and will be subject to annual and other required reviews.

In addition to study monitoring and oversight by Dr. Hanson (PI) and the Project Manager, we will work with the NIA Program Official to select a Data and Safety Monitoring Board (DSMB) with expertise relevant to the proposed multi-site clinical trial. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet at least twice per year to assess safety and efficacy data from each arm of the study. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the National Institute on Aging.

10.1.7 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data collection, documentation and completion. All sites will follow a common quality management plan.

Quality control (QC) procedures will be implemented as follows:
Informed consent --- Study staff will review both the documentation of the consenting process as well as a percentage of the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source documents and the electronic data --- Data will be initially captured on source documents and will ultimately be entered into the study database. To ensure accuracy site staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity — Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in **Section 6.2.1, Interventionist Training and Tracking**.

Protocol Deviations – The study team will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

Should independent monitoring become necessary, the PI will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor/funding agency, and inspection by local and regulatory authorities.

10.1.8 DATA HANDLING AND RECORD KEEPING

10.1.8.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The Principal Investigator (PI) will be responsible for ensuring participants' safety on a daily basis. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to the NIA Director to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Data collection will be the responsibility of the site-based CRCs under the supervision of the site-based PI, with overall supervision from Dr. Hanson (PI) and the Project Manager. The Site-PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data. Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents will be consistent with the data recorded on the source documents.

All identifying information will be stored in a separate, locked file cabinet from data collected during the interview. All identifying information will be destroyed once all analysis and reporting is complete. At no time will personal identifying information be stored on portable laptop computer devices.

All research data will be entered into REDCap, a 21 CFR Part 11-compliant data capture system provided by the University of North Carolina at Chapel Hill. REDCap includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.8.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 3 years after will comply with all NIH and NIA data retention standards.

10.1.9 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol, International Council on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- Section 4.5 Compliance with Protocol, subsections 4.5.1, 4.5.2, and 4.5.3
- Section 5.1 Quality Assurance and Quality Control, subsection 5.1.1
- Section 5.20 Noncompliance, subsections 5.20.1, and 5.20.2.

It will be the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations will be addressed in study source documents, reported to National Institute on Aging Program Official and University of North Carolina at Chapel Hill IRB. Protocol deviations will be sent to the reviewing Institutional Review Board (IRB) per their policies. Laura Hanson, MD (PI) and other site investigator will be responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

10.1.10 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:
National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 2 years after the completion of the primary endpoint by contacting the Palliative Care Research Collaborative Group. Considerations for ensuring confidentiality of these shared data are described in Section 10.1.3.

10.1.11 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed

and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the National Institute on Aging has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ABBREVIATIONS AND SPECIAL TERMS

ADRD	Alzheimer's disease and related dementias
AE	Adverse Event
CFR	Code of Federal Regulations
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRC	Clinical Research Coordinator
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
EHR	Electronic Health Record
GCP	Good Clinical Practice
GDS	Global Deterioration Scale
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
ITT	Intention-To-Treat
LAR	Legally authorized representative
MOP	Manual of Procedures
NIA	National Institute on Aging
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
RCT	Randomized Clinical Trial
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SPIRIT	Standard Protocol Items Recommendations for Interventional Trials
UP	Unanticipated Problem
UPIRSO	Unanticipated Problem Involving Risk to Subjects or Others

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.0	16 February 2020	Initial protocol	
1.1	09 July 2021	Removal of secondary written consent and authorization of verbal consent for all participants	Verbal consent approval for low risk study by UNC IRB
1.2	02 September 2021	Revision of emotional distress screen threshold and response procedures to appropriately identify unusual or severe levels of emotional distress thresholds.	Initial threshold was incorrectly set below the mean scoring range for the FDAD subscale, causing usual caregiver distress levels to trigger. Threshold is now adjusted to one std dev above the mean and further clarifies response procedures.
2.0		Adding Spanish supplement information and added Emory University as a 5th site	

11 REFERENCES

N/A