# A PRAGMATIC TRIAL OF THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DEMENTIA CARE/COMPARATIVE EFFECTIVENESS OF HEALTH SYSTEM-BASED VERSUS COMMUNITY-BASED DEMENTIA CARE

## STUDY PROTOCOL

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| **TITLE:** | **COMPARATIVE EFFECTIVENESS OF HEALTH SYSTEM-BASED VERSUS COMMUNITY-BASED DEMENTIA CARE/ A PRAGMATIC TRIAL OF THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DEMENTIA CARE** |
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| Title | COMPARATIVE EFFECTIVENESS OF HEALTH SYSTEM-BASED VERSUS COMMUNITY-BASED DEMENTIA CARE/ A PRAGMATIC TRIAL OF THE EFFECTIVENESS AND COST-EFFECTIVENESS OF DEMENTIA CARE |
| Study Design | The design is a pragmatic randomized 3-arm superiority trial. The unit of randomization is the patient/caregiver dyad. |
| Study Duration | 6 years |
| Trial Sites | 4 trial sites: Baylor, Scott, & White Health; Geisinger Health; University of Texas Medical Branch Health Care System; Wake Forest University |
| Objective | Conduct a pragmatic randomized trial to determine the comparative effectiveness and cost-effectiveness of two evidence-based models of comprehensive dementia care as well as the effectiveness and cost-effectiveness of both arms versus usual care. |
| Number of Subjects<br><br>(Target) | 2150: 1000 in each intervention arm and 150 in the usual care group |
| Main Inclusion Criteria | Community-living, including Assisted Living Facilities (cannot reside in a nursing home at the time of recruitment), persons with diagnosis of dementia established by a physician or other primary care provider (PCP), have family or friend caregiver(s) who speak English or Spanish, and have a PCP who is willing to partner with the program |

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| Interventions | Health systems-based dementia care (based on the UCLA Alzheimer's and Dementia Care program) provided by a nurse practitioner or physician's assistant Dementia Care Specialist who works within the heath system.<br><br>Community-based dementia care (using the BRI Benjamin Rose Institute Care Consultation model) provided by a social worker or nurse Care Consultant who works at a community-based organization (CBO).<br><br>Both arms include structured assessments and creation of care or action plans, care coordination, and caregiver education and support, but they differ in key areas including the frequency and mode of communication with persons with dementia and caregivers, the degree of integration into the health system, including order-writing capability and use of the electronic health record.<br><br>Usual care with consistent referral to Alzheimer's Association Helpline (1-800-272-3900) to speak to master's level consultants for decision-making support, crisis assistance, and caregiver education, and referral to local programs and services. |
| Duration of Intervention and Follow-up | 18 months |
| Primary Outcome | Behavioral symptoms and resulting caregiver distress as measured by the NPI-Q Severity and Modified Caregiver Strain Index scales. |
| Primary Analysis | All analyses will be according to intent-to-treat. The analysis of the two primary outcomes – NPI-Q Severity and Modified Caregiver Strain Index scores – will be done using a longitudinal repeated measures analysis based on maximum likelihood methods adjusted for the stratified randomization by site. Treatment differences will be summarized by least square means and multiplicity corrected confidence intervals. |
| Secondary Outcomes | NPI-Q Distress, caregiver unmet needs and confidence, and caregiver depressive symptoms. |
| Tertiary Outcomes | Patient long-term nursing home placement, functional status, cognition, goal attainment scaling (GAS), "days spent at home", Dementia Burden Scale-Caregiver, a composite measure of clinical benefit, Quality of Life of persons with dementia, Positive Aspects of Caregiving |

| | |
|---|---|
| Cost-effectiveness Analysis | Ratio of incremental net Medicare costs to incremental effects of the two primary outcomes, costs to Medicaid and consumers, changes in utilization by type of use, caregiver costs for spouses who have fee-for-service Medicare |
| Interim Analysis | Because this is a minimal risk trial with a relatively short follow-up period (18 months), no monitoring for efficacy or futility is proposed; only monitoring for safety will be done. |

## ABBREVIATIONS

**ADC**=Alzheimer's and Dementia Care

**BRI**=Benjamin Rose Institute

**CPM**=central project management

**CTS**=clinical trial sites

**CBDC**=Community-based dementia care

**CBO**=community-based organization

**DCC**=data coordinating center

**DCM**=Dementia Care Manager (now changed to Dementia Care Specialist [DCS])

**DCS**=Dementia Care Specialist (formerly Dementia Care Manager)

**DQCQ**=Data Quality Control Query

**DSMB**=data safety monitoring board

**EDC**=Electronic Data Capture

**EHR**=Electronic Health Record

**HSDC**=Health system-based dementia care

**HTE**=Heterogeneity of Treatment Effects

**IRB**=Institutional Review Board

**LPSC**=local Patient and Stakeholder Committee

**MAR**=missing at random

**MCID**=minimal clinically important difference

**MCSI**=modified caregiver strain Index

**MMSE**=Mini-Mental State Exam

**MOCA**=Montreal Cognitive Assessment

**MOP**=manual of procedures

**NP**=nurse practitioner

**NPI-Q**=Neuropsychiatric Inventory

**NPSC**=national Patient and Stakeholder Committee

**PA**=physician's assistant

**PCORI**=Patient-Centered Outcomes Research Institute

**PCP** =primary care provider

**PHQ-8**=Patient Health Questionnaire-8

**QOL-AD**=Quality of Life Alzheimer's Disease

**SAC**=Study Advisory Committee

**SAE**=Serious Adverse Events

**SNF**=skilled nursing facility

**SOP**= standard operating procedures

**STRIDE**=Strategies to Reduce Injuries and Develop confidence in Elders

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## 1. INTRODUCTION

This document is a protocol for a human research study to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations, and institutional research policies and procedures.

## 2. STUDY OBJECTIVES

This pragmatic randomized clinical trial of 2150 participants at four diverse clinical trial sites will compare the effectiveness and cost-effectiveness of 18 months of health systems-based dementia care (based on the UCLA Alzheimer's and Dementia Care program) provided by a nurse practitioner Dementia Care Specialist who works within the heath system versus community-based dementia care (using the BRI Benjamin Rose Institute Care Consultation model) provided by a social worker or nurse Care Consultant who works at a CBO and will compare both dementia care interventions to usual care. Caregivers and patients bring their unique personal perspectives of how dementia affects their lives, what outcomes are important to them, and what attributes of the interventions render them feasible, scalable, and sustainable. The clinical sites bring participants, clinical environments, and expertise in patient-centered research and implementation. The investigators, patients, and other stakeholders planned and prepared this protocol jointly; these partners will continue to be collaboratively engaged in all aspects of the trial's implementation.

The study's Specific Aims are:

1. To engage 4 sets of health systems and community-based organizations, patients, families, and other stakeholders in a pragmatic clinical trial
2. To adapt and implement 2 dementia care interventions at each CTS, including training of DCS' and Care Consultants and pilot testing of the interventions, assessments, and outcomes
3. To recruit 2150 participants and randomize them to receiving HSDC (N=1000), CBDC (N=1000), or usual care (N=150)
4. To administer the interventions for 18 months for all participants
5. To collect self/caregiver-reported outcomes and use claims data to evaluate other secondary and tertiary outcomes
6. To compare the effectiveness of the 2 dementia care interventions versus each other and versus usual care
7. To conduct a cost-effectiveness analysis of the two intervention arms versus each other and versus usual care
8. To conduct analyses of tertiary outcomes of both interventions versus usual care including mortality, time spent at home, long-term nursing home placement, patient/caregiver satisfaction, goal attainment scaling (in the 2 active intervention groups), and comparing all three groups on several types of utilization and out-of-pocket expenses. We will assess physician satisfaction with dementia care provided by the 3 treatment groups.

## 3. BACKGROUND

In the United States, an estimated 5.7 million persons are affected by Alzheimer's disease, the most common type of dementia.[1] The total number with dementia is higher because Alzheimer's disease is responsible for only 60-80% of dementias and is expected to grow to 7.7 million in 2030. The clinical manifestations of dementia are devastating including cognitive impairment, immobility and falls, swallowing disorders and aspiration pneumonia, and behavioral disturbances. These sequelae often lead to caregiver stress, burnout, and medical illnesses. Thus, dementia can be considered the prototype for a disorder with complex needs that

span both the patient and caregiver, medical and social domains, and health system and community-based organizations (CBOs).

In response, several dementia care programs have been developed to comprehensively meet the needs of patients and their families including providing care coordination, high quality dementia care, and caregiver support. Some have been based within health care systems and reach out to the communities whereas others are based in the community and reach in to the health care system. Although both approaches have demonstrated effectiveness on quality and clinical outcomes, the comparative effectiveness of these two models is unknown.

## 4. STUDY DESIGN

The study is a pragmatic randomized clinical trial of 2150 participants at four diverse clinical trial sites to compare the effectiveness of 18 months of health systems-based dementia care (based on the UCLA Alzheimer's and Dementia Care program) provided by a nurse practitioner Dementia Care Specialist (DCS) who works within the heath system versus community-based dementia care (using the BRI Benjamin Rose Institute Care Consultation model) provided by a social worker or nurse Care Consultant who works at a CBO versus usual care.

### 4.1 Number of Subjects

The study will enroll 2150 dyads of participants and their caregivers. Note, throughout this protocol, families and caregivers are used interchangeably. The vast majority of caregivers are expected to be family members but, occasionally, a friend may be the primary or sole caregiver and would be eligible for participation.

### 4.2 Subject Selection and Withdrawal

#### 4.2.1 Inclusion and Exclusion Criteria

Table 1 lists the inclusion and exclusion criteria for participation in the trial

| Table 1: Inclusion and Exclusion Criteria |
|---|
| Inclusion Criteria<br>i. The participant must have a diagnosis of dementia established by a physician or other primary care provider<br>ii. The participant must have a caregiver who speaks English or Spanish and has a phone<br>iii. The participant must have a PCP who is willing to partner with the program<br>iv. Persons living with dementia in assisted living facilities will be eligible if they do not meet any exclusion criteria (however, no more than 25% of participants can be living in assisted living facilities at the time of enrollment. This will be monitored when the first 25% of the sample has been enrolled.) |
| Exclusion Criteria<br>i. The participant resides in a nursing home at the time of recruitment.<br>ii. The participant is enrolled in hospice (at the time of screen)<br>iii. The participant plans to move out of the area within the coming year |

iv. The participant's caregiver is unwilling or anticipates being incapable of providing self-reported outcome measures for 18 months
v. Baseline measures refused or not completed
vi. The caregiver is paid and is not a relative or close friend of the participant
vii. At telephone or in-person screener, the caregiver has cognitive impairment
viii. The patient or caregiver is participating in another dementia intervention study
ix. Patients and caregivers who are members of a sites' Local Patient & Stakeholder Committee
x. There is already a member of the same household participating in the study.

Because many of the outcomes have not been translated into other languages, it is not feasible to enroll participants who do not speak English or Spanish.

### 4.3 Screening, Recruitment, and Enrollment

#### 4.3.1 Screening

To facilitate recruitment, each site will generate a list of patients at participating practices site who have a diagnosis of dementia established by charge diagnosis (ICD 9/10) or on problem list and/or past medical history codes. Lists will be forwarded to the PCPs, practice nurses, or likely partnering physicians (determined by the sites) to review and obtain permission to contact patient/caregiver and confirm willingness to partner.

#### 4.3.2 Recruitment and Enrollment

Participants will be recruited through physician referral. PCPs will be made aware of the trial through e-mail, fliers, and other traditional marketing techniques. In addition, clinical trial site staff will make presentations at meetings of participating medical practices, support groups, council meetings, senior centers, and health fairs. Local Patient and Stakeholder Committees (LPSC) will also provide advice about local strategies to promote recruitment (e.g., wording of documents, incentives). Some physicians or practices may opt to provide a "blanket" referral for all their patients with dementia and, if so, study team members may reach out directly to recruit participants. Alternatively, PCPs may choose to review their lists of persons with dementia and delete any patients who should not be contacted about the study or for whom they would not be willing to fill the role of the partnering physician.

Patients and/or caregivers may also self-refer. Self-referrals may originate from a variety of ways. For instance, an individual may see a poster in a clinic waiting room, or they may be informed about the study by an existing participant, or from an employee of a community-based organization. If potential participants would like to know more about the study, they must contact the site's staff directly (i.e., self-refer). Then the site coordinator will provide further information about the study (and answer any of their questions), and if the patient and/or caregiver is interested in participating, the site coordinator should assess whether the dyad meets the study's eligibility criteria (i.e., conduct an eligibility screening). If eligible, the potential participant's PCP will be notified and will be asked about her or his willingness to partner. If the potential participant meets

eligibility criteria and does not meet exclusion criteria and if the PCP is willing to partner, an enrollment/ baseline interview will be scheduled.

At the time of enrollment, study staff at each site will identify the primary and a back-up caregiver (in the event that the primary caregiver is no longer able to participate), review inclusion and exclusion criteria, discuss the study with the caregiver over the telephone, and schedule the baseline assessment.

Upon successful completion of baseline assessment, caregivers and patients who are able to consent (see informed consent section **11.2**) will be consented and enrolled into the study.

### 4.3.3 Early Withdrawal of Participants

Because this trial is based on the principle of "intent-to-treat", all participants will be analyzed in the group to which the participant was randomly assigned, regardless of whether they complete the intervention or not. This preserves the effect of randomization. Because the intervention will be integrated into the work flow of the practice and community-based care, we expect relatively few withdrawals from the interventions. We will have four levels of study withdrawal:

- Withdrawal from study interventions but willing to provide study outcomes by questionnaire/interview and allow analysis of medical records and CMS claims data. Subsequent Information on health care utilization outcomes will be obtained from CMS claims data and medical records.

- Withdrawal from study interventions and willing to provide study outcomes by questionnaire/interview but unwilling to allow analysis of medical records and CMS claims data.

- Withdrawal from study interventions and unwilling to provide study outcomes by questionnaire/interview but willing to allow analysis of medical records and CMS claims data. Subsequent Information on health care utilization outcomes will be obtained from CMS claims data and medical records.

- Withdrawal from study interventions and unwilling to provide study outcomes by questionnaire/interview or allow analysis of medical records and CMS claims data. If the participant elects full withdrawal from the study, this will be recorded on the Participant Final Disposition Form and no further information will be obtained about the participant.

For participants who are lost to follow-up but who have not withdrawn from the study, we will be able to obtain information from the electronic health record or from the utilization or claims data on secondary and tertiary outcomes.

Each of the interventions will be administered until the final 18-month assessment is completed unless any of the following occur:

- Patient or caregiver withdraw and there is not a willing replacement caregiver (see 4.3.3)
- Patient Death
- Moves out of the catchment area and unable to continue to receive the intervention

## 5. STUDY INTERVENTIONS

There are three arms to the study:

1. Health systems-based dementia care (HSDC) – Comprehensive dementia care delivered by a nurse practitioner or physician's assistant Dementia Care Specialist who works within the heath system, and reaches out to the community for additional services;

2. Community-based dementia care (CBDC) – Comprehensive dementia care delivered by a social worker, nurse or licensed therapist within a community-based organization who reaches out to the health system by coaching persons with dementia and their caregivers to more effectively interact with their doctors;

3. Usual care with consistent referral to Alzheimer's Association Helpline (1-800-272-3900) to speak to master's level consultants for decision-making support, crisis assistance and education on issues families face every day and referral to local programs and services

Table 2 highlights the differences and similarities of the three arms.

**Table 2:** Comparison of HSDC, CBDC and Usual Care

| | HSDC | CBDC | Usual Care |
|---|---|---|---|
| Key personnel | Dementia Care Specialist (Nurse practitioner or physician's assistant) | Care Consultant (Social worker, nurse, or therapist) | Care Consultant (masters-level) |
| Key personnel base | Health system | CBO | Alzheimer's Association |
| Face-to-face or telemedicine visits | At least annually | None | None |
| Structured assessments | √ | √ | None |
| Creation of individualized care plans | Care Plan | Action Plan | None |
| Monitoring and revising care plans | √ | √ | None |
| Access 24/7 365 days/year | √ | No or Alzheimer's Association helpline | Alzheimer's Association helpline |
| Identification and prioritization of goals | √ | √ | No |
| Communication with physicians | Electronic health record/phone | Mail or fax | None |
| Order writing | √ | No | No |
| Caregivers support and education | √ | √ | Existing local resources |
| Helping caregivers access community services | √ | √ | Existing local resources |
| Geri's List (online directory of local resources) | √ | √ | √ |
| Coaching on physicians' visits | No | √ | No |

## 5.1 HSDC

This intervention will be based on the model originally developed at Indiana University and subsequently modified in the UCLA Alzheimer's and Dementia Care (ADC) program[8], a 2012 Center for Medicare and Medicaid Services Healthcare Innovations Challenge Awardee. The UCLA ADC program is based at an academic health care system and partners with CBOs to provide comprehensive, coordinated, patient-centered care for patients with dementia. The goals of the program are to optimize patient function, independence and dignity, minimize caregiver strain and burnout and reduce unnecessary costs through improved care.

HSDC utilizes a nurse practitioner (NP) or physician assistant (PA) Dementia Care Specialist (DCS) supervised by a physician dementia specialist to tailor and facilitate dementia care delivery in collaboration with the primary care physician (co-management). Based on input from stakeholders who will be key to disseminating this intervention if it is successful, the name of this professional has been changed from Dementia Care Manager, which was used in the original UCLA Alzheimer's and Dementia Care program, to Dementia Care Specialist. NPs and Pas can write orders, communicate directly through the EHR, and facilitate clinical care. Dementia care is based in the health care system, which partners with CBOs to provide comprehensive, coordinated, patient-centered care for persons with dementia. Key components include:

- Structured needs assessments of patients and their caregivers. HSDC begins with an in-person visit or via telemedicine, with a Dementia Care Specialist (DCS) including the patient and at least one family member or primary caregiver. To prepare for the visit and make it most efficient, patients (if early stage) and/or caregiver are asked to complete a structured pre-visit instrument (http://dementia.uclahealth.org/workfiles/for-physicians/Intake-Form-2017.pdf ) that includes information about the patient and caregivers. The assessment is scheduled as a 90-minute in-person or via telemedicine session during which additional information is obtained by structured interview and examination. In this manner, the DCS assesses the patient and caregiver's needs and their resources.

- Creation and implementation of individualized dementia care plans based on needs assessments. Based on these initial assessments, the DCS works with the patient and family to draft a personal care plan, which is sent to the referring PCP for approval or modification. This interaction with the PCP is aimed at ensuring continuity of care. To be efficient and succinct, this EHR-delivered information is divided into medical recommendations that the primary care physician is asked to address (and respond back through the EHR) and social and behavioral recommendations that the DCS implements independently. When the DCS has received a response from the referring physician, the assessment note is finalized and uploaded to the EHR. The patient/caregiver then receives a phone call from the DCS to discuss the final recommendations.

  All patients and their families receive ongoing dementia care management by a DCS supervised by a physician dementia specialist, which may include:
  - In-person or telemedicine sessions at which patient and family members' specific questions about problems, resources, and implementing care plans are answered
  - Telephone follow-up to monitor implementation of dementia care plans
  - Facilitation of appointments with consultants when needed
  - Teaching dementia management skills to caregivers through individual counseling including information on: legal and financial planning with referral to community services, behavioral techniques to avoid/manage behavioral problems, and coping strategies for caregivers.

  Other components of the care plan are tailored to the individual and can include the following components:
  - Consultation with neurology, geriatric psychiatry, psychology, or geriatrics for additional diagnostic evaluation (e.g., if there are unusual symptoms) or management of refractory complications
  - Caregiver support groups, either community-based or provided by the health system

- Caregiver education through a community lecture series. These monthly webinars are archived on program's website, http://dementia.uclahealth.org/aces-webinars .
- Referral to community-based organizations for services such as delivered meals, adult day care, care/case management, financial and legal counseling, and transportation assistance as well as caregiver training.

- Monitoring and revising care plans, as needed, including active monitoring and support of the caregiver's emotional and physical health. Adjustments to the care plan are made as deemed appropriate by the DCS and communicated to the referring physician. All patients are re-evaluated for disease progression and adequacy of resources every 3-4 months by phone and at no greater than 1-year intervals in person or via telemedicine.

- Access 24/7, 365 days a year for assistance and advice. Daytime calls are handled by the DCS, and nights and weekend calls are managed by on-call physicians who are aware of the program.

Participants in this arm will also have access to Geri's List, an on-line program that lists community-based services, customized to fit local resources, that caregivers or persons with dementia can access.

HSDC will be guided by custom-designed dementia care management software created for the UCLA ADC and subsequently adapted for the STRIDE Falls study to include electronic data capture using REDCap. The software will be further modified to use STRIDE-developed software innovations.

Fidelity Documentation of care will be site-specific using common instruments customized to local and will include:

i. Initial and annual visits
ii. Calls/emails to patient/caregiver with frequency per acuity protocol
    a) Red ≤ 1 month
    b) Yellow ≤ 2 months
    c) Green 3-4 months
iii. DCS added as part of the care team on EHR (all sites are using EPIC) to receive Admission/Discharge/Transfer (ADT) alerts
iv. DCS contacts inpatient team within 48 hours of admission to offer assistance with dementia-related issues, care transitions and/or goals of care, if hospitalized

**5.2 CBDC**

BRI Care Consultation is a care coaching program for patients with dementia and/or other chronic illnesses and for their family or friend caregivers. Grounded in the Stress Process Conceptual Framework[2,3], BRI Care Consultation is consumer-driven, with a focus on problems or concerns that are important to patients and caregivers.

Care Consultants deliver the program. They have bachelor's or master's degrees in social work, nursing, or other helping professionals and work in community-based organizations. BRI Care Consultation gives equal attention to the patients and their primary family or friend caregivers. Despite their dementia, patients are engaged in the program, whenever possible.[4] Caregivers can be the sole program participant when patients are too impaired. The program establishes a long-term relationship between Care Consultants and families. The exact content of assistance provided is tailored to the preferences of individual patients and caregivers and is holistic in the range of potential concerns of problems addressed. General areas of assistance include:

- Increasing access to and monitoring the use of community services and resources,

- Mobilizing support from the informal network of family and friends,
- Providing and helping families use care- and caregiving-related information and consumer-ready educational materials about medical and non-medical issues,
- Offering emotional support to both patients and caregivers, and
- Facilitating communication and coordination of assistance among patients/caregivers, health care providers, and community service providers.

BRI Care Consultation is low-cost and convenient to use because it is delivered by telephone, computer, and mail; no in-person contacts are required. It has a standardized protocol that requires at least monthly contacts between Care Consultants and patients and/or caregivers during the first four months. Required contacts decrease to every three months thereafter, although more frequent contacts can be made as part of the Action Plan (described below). Contacts often increase when there are changes in patients' symptoms, caregivers' availability or capacity, when new problems arise, or when there are transitions in care settings (e.g., after a hospital admission, nursing home placement).

BRI Care Consultation has 3 main components: 1) Action Plan, 2) Initial- and Re-assessment, and 3) Ongoing monitoring.

- Action Plan*:* The first priority, when patients and caregivers begin the program, is creating and implementing the Action Plan to address concerns identified by patients and/or caregivers as most important to them. With coaching from Care Consultants, the action plan is populated with simple, achievable Action Steps, each with an expected completion date and responsible person. Action steps should be feasible to accomplish by whoever is the responsible person; most are assigned to caregivers, patients, and Care Consultants. Care Consultants provide guidance on action-step content and new action steps are added to deal with changes in the illness, caregiving, and preferences of patients and caregivers. Needed adjustments and modifications to Action Steps are regarded as opportunities for learning and reformulation. As Action Steps cumulate, patients and caregivers move toward informing and/or finding solutions to identified problems.

  The initial action plan is mailed or emailed to patients and/or caregivers by the end of week three in the program. Updates are sent as action steps are added. The action plan is also sent to the PCP to be integrated into the larger medical or service records of the organization implementing the program.

- Initial- and Re-assessment*:* Although patient- and caregiver-identified needs drive BRI Care Consultation, the initial- and re-assessments act as a safety net to ensure that Care Consultants discuss with patients and/or caregivers 39 common problems related to dementia. There are 23 potential problems for patients (e.g., coordinating and accessing services, medication management, getting and understanding the diagnosis), and 16 for caregivers (e.g., finding and accessing community services, care-related strains and depression). Single-item trigger questions are provided to Care Consultants and can be used to prompt discussion. The 39 potential problem areas must be at least touched upon in discussions with patients and/or caregivers sometime during the first four months of enrollment and re-assessed at least every six months. More frequent re-assessment is recommended for persistent problems.

- Ongoing Monitoring*:* A key feature that facilitates development of the long-term relationship between Care Consultants and patients/caregivers is monitoring activities, including scheduled follow-up contacts by Care Consultants to check whether Action Steps were accomplished by their due dates. Depending on experiences with assigned Action Steps, follow-up contacts often are used to set new Action Steps representing next steps in the process of moving toward solutions. When there are no active Action Steps, ongoing monitoring is done by Care Consultants completing pre-scheduled check-in calls. The timing of these check-ins is set at the time of enrollment according to the program's protocol. Check-in contacts can be brief when there are no new issues that patients and/or caregivers want to bring up. These contacts

also provide opportunities to complete required re-assessments and assure patients and caregivers that Care Consultants are still available whenever they are needed.

Participants in this arm will also have access to Geri's List, customized to fit local resources.

Fidelity Documentation of care will be site-specific and will include:

i. all contacts
ii. initial and every 6-month action steps
iii. initial and every 6-month assessment domains for patients and caregivers
iv. consumer-ready educational resources from the Educational Resources Library
v. direct and indirect time associated with providing the intervention

Data will be available through the Care Consultant Software being used for the study.

### 5.3 USUAL CARE

After enrollment, participants in the UC arm will receive standardized educational materials (hard copies and internet-based resources); referral to the national Alzheimer's Association helpline (1-800-272-3900) to speak to master's level consultants for decision-making support, crisis assistance and education on issues families face every day, and referral to local programs and services; and access to Geri's List, an online directory of local resources.

## 6. OUTCOME MEASURES AND OTHER DATA TO BE COLLECTED

### 6.1 Definition and Ascertainment of Outcomes

**Primary, secondary, and tertiary outcomes are summarized in** Table 3. Most of these outcomes are patient-reported and all are clinically meaningful to patients and caregivers as well as payers.

**Table 3. Outcome Domains, Instruments and Timing**

| Measure | Administration | Month | | | | |
|---|---|---|---|---|---|---|
| | | Baseline (in-person)* | 3 (phone) | 6 (phone) | 12 (phone) | 18 (phone) |
| **Sociodemographic characteristics** | | X | | | | |
| | | | | | | |
| **Primary outcomes** | | | | | | |
| NPI-Q Severity (patient behaviors) | Questionnaire | X | X | X | X | X |
| Caregiver strain (MCSI) | Questionnaire | X | X | X | X | X |
| | | | | | | |
| **Secondary Outcomes** | | | | | | |
| NPI-Q Distress (caregiver) | Questionnaire | X | X | X | X | X |
| Caregiver depression (PHQ-8) | Questionnaire | X | X | X | X | X |
| Caregiver self-efficacy | Questionnaire | X | | X | | X |
| | | | | | | |
| **Tertiary Outcomes** | | | | | | |
| Cognition (MOCA) | Interview | X | | | | X |
| Functional status (FAQ) | Interview | X | | | | X |
| Functional Status (Katz ADL) | Interview | X | | | X | |
| Goal attainment scaling *** | Interview | | | X | | X |
| Mortality | CMS | | | | | X |
| | Interview | | X | X | X | X |
| Time spent at home | CMS | | | | | X |
| Inpatient hospital use** | CMS | | | | | X |
| Acute inpatient rehabilitation use** | CMS | | | | | X |
| Post-acute SNF use** | CMS | | | | | X |
| Hospice use** | CMS | | | | | X |
| Long-term nursing home use** | CMS | | | | | X |
| Caregiver Rating of Dementia Care Quality | Questionnaire | | | | X | |
| Caregiver satisfaction with dementia care | Questionnaire | | X | | X | X |
| Dementia Burden Scale-Caregiver | Composite | X | X | X | X | X |
| Clinical Benefit | Composite | X | X | X | X | X |
| Quality of Life in Alzheimer's Disease | Questionnaire | X | | | | X |
| Positive Aspects of Caregiving | Questionnaire | X | | X | | |
| Cost-effectiveness analysis | CMS | | | | | X |

CMS=Center for Medicare and Medicaid Services and site-obtained claims data;

*Switched to telephone-collected after beginning of COVID-19 pandemic, with option for in-person visits

** Also used to calculate time spent at home

** Goal Attainment Scaling will be obtained only on a subset of caregivers (i.e., it will not be performed in caregivers in the usual care group nor on all caregivers in the two active intervention groups; this will be completed by an unblinded assessor (i.e., the Dementia Care Specialist or Care Consultant with goal setting occurring at baseline, and goal attainment scaling occurring 6 months [6-12 months window] and 18 months [15-18 months window] after enrollment)

Self/caregiver-reported outcomes will be assessed at baseline and at 3, 6, 12, and 18 months. Baseline measures, which were initially conducted in person, will be collected by telephone due to COVID-19. To accommodate participants who cannot conduct the baseline interview via telephone (e.g., hearing impairment) or prefer an in-person visit, the option of conducting the baseline visit in-person will be provided but all baseline assessments must follow the telephone interview administration exactly. In-person research procedures will not commence until the clinical trial site provides CPM with written assurance of adhering to their local institution's COVID restrictions and a copy of their respective local policy/procedures. Because many persons with dementia become home bound and it is difficult for caregivers to leave the patients, all patient/caregiver outcomes will be collected over the telephone. All baseline and follow-up data collection will be completed by blinded site staff. At 59 months into the study (6 months after final outcomes have been collected to ensure completeness), Medicare claims and Medicare Advantage utilization data will be requested for all time in the trial to assess long-term nursing home placement and calculate time (in days) spent at home. Utilization data for 1 year prior to enrollment will also be collected to conduct analyses that include prior utilization as a predictor or covariate.

To minimize ascertainment bias during the collection of the 18-month outcomes, a letter will be sent at least 1 month prior to the 18-month assessment to participants in all three arms reminding them that a study team member will call to schedule their final (18-months) assessment.

For participants enrolled in the active intervention arms, the interventions will continue until each participant has completed the final (18-month) assessment.

### 6.1.1 Primary Outcomes

Because of the importance of both the patient and caregiver in dementia care, the primary outcome measures will be both the Severity scale of the Neuropsychiatric Inventory Questionnaire (NPI-Q)[5] and the Modified Caregiver Strain Index (MCSI). The NPI-Q Severity is a validated survey that assesses the caregiver's perception of the severity of 12 dementia-related psychiatric and behavioral symptoms. NPI-Q Severity score ranges from 0-36 with higher scores indicating more severe symptoms. In a nursing home population, the minimal clinically important difference (MCID) was determined to be 2.8-3.2 points.[6] The MCSI[7] is a 13-item validated tool used to assess severity of caregiver strain. The index targets financial, physical, psychological, and social aspects of strain and is scored from 0 to 26 with higher scores indicating greater levels of strain. The MCID is 1.5-2.3 points.

### 6.1.2 Secondary Outcomes

Secondary outcomes include caregiver self-efficacy, distress in response to dementia-related psychiatric and behavioral symptoms, and depressive symptoms.

The NPI-Q Distress scale is a validated survey that assesses the level of distress experienced by the caregiver in response to dementia-related psychiatric and behavioral symptoms. NPI-Q Distress score ranges from 0-60 with higher scores indicating more severe distress. In a nursing home population, the MCID was determined to be 3.1-4.0 points for distress.[6]

Caregiver Self-Efficacy is measured with a 4-item self-efficacy scale assessing the caregiver's ability to manage dementia-related problems and ability to access help, including community resources.

Patient Health Questionnaire-8 (PHQ-8)[8] is a shortened version of the PHQ-9 (item 9 is omitted) that is often used when the instrument is administered by telephone and intervention cannot be adequately provided. The PHQ-9 is 9-item validated tool used to assess depressive symptoms in the caregiver using the DSM-IV criteria for major depression and is scored from 0-27 with scores >10 indicating moderate symptoms and scores >20 indicating severe depressive symptoms. Because of the infrequency of positive responses to item-9, its deletion has minimal effect on scoring and identical scoring thresholds for depression severity can be used. [9]

### 6.1.3 Tertiary Outcomes

Tertiary outcomes include cognition and functional status, long-term nursing home placement, goal attainment (a measure developed through a previous PCORI Methodology grant), mortality, PCP and proxy ratings of care and satisfaction, quality of life in Alzheimer's Disease, positive aspects of caregiving, and a new and novel outcome, time spent at home.[10]

Montreal Cognitive Assessment (MoCA)[11] is a validated widely used test of cognition that captures mild cognitive impairment as well as dementia. This will be collected by telephone at baseline and at the end of study[12] to document disease progression. To reduce respondent burden and missing data, we will use a shortened form[13,14] for reporting study participant baseline characteristics and measuring decline in cognition, a tertiary outcome. Participants who score 8 or higher on the shortened version will receive the full telephone MOCA to determine whether they have capacity to provide informed consent (**see 11.2**).

Functional status will be measured using the Functional Activities Questionnaire (FAQ) measures functional status and ranges from 0 to 30 with higher scores indicating more functional dependence.[15] We will also measure activities of daily living[16] (Katz ADL), which has been validated and is well-established in research and clinical use.

Goal attainment scaling, developed through PCORI funding to the Principal Investigator, asks patients and caregivers to select their most important goal and assesses progress towards meeting it. These goals were identified in focus groups of caregivers and patients and additional goals were identified when integrating goal-setting into clinical care in the PCORI Methodology study. An inventory of 53 dementia goals captures virtually all goals that have been articulated.[17] For this study, we will use a shorter inventory designed to help caregivers consider categories of goals that may be important to them. *Goal attainment*, defined as whether a person's individual goals are achieved as a result of the study intervention, will be measured using a 5-point goal attainment scale (GAS). Using the SMART goal framework, GAS describes the person's expected level of goal achievement over a specified timeframe, ranging from much worse than expected (scored as -2) to much better than expected (scored as +2). Scales are dynamically set according to a person's needs, while measurement of attainment is standardized**.** The mean 6-month GAS score in a previous study of similar patients was 52.4 (SD 11.7) on a 0-100 scale with a T-score of 50 indicating that on average the expected level of goal attainment was achieved. Measurement of goal attainment will be performed with caregivers by clinicians involved in the intervention (Dementia Care Specialists and Care Consultants), who are unblinded, and can be performed over the telephone.

Conceptually, time spent at home is a composite measure of control of dementia symptoms (e.g., problem behaviors), the ability of caregivers to cope with the disease, and the success of the health system in providing

services that avoid days spent in other settings. Time spent at home has previously been operationalized[43] as within the last 6 months of life but we will modify it to include each person's total follow-up time spent after randomization that is spent at home. Total follow-up time will be determined from time of randomization to time of death, withdrawal (if CMS utilization data are allowed by the participant to be used), or to the end of the study for those who are administratively censored. Hence, the time spent at home is:

"Number of days since randomization (540) minus (1) number of inpatient days spent at an acute care hospital, inpatient rehabilitation facility, skill nursing facility, long-term care facility, or inpatient hospice unit), and (2) number of days not alive".

Caregiver Satisfaction will be collected using a 11-item questionnaire modified from the UCLA ADC, which will be collected at 3, 12, and 18 months.

Quality of Life in Alzheimer's Disease (QOL-AD)[18] is a 13-item (range 4-52) instrument that can be administered to persons with dementia and caregivers. It has demonstrated sensitivity to psychosocial intervention[19] correlates with health-utility measures, is widely translated and used internationally and can be used by people with MMSE scores as low as three[20].

Positive Aspects of Caregiving (PAC) is measured with 11 items focusing on favorable aspects of the caregiving experience,[21] with range 0-44 (most positive) and Cronbach's alpha 0.92.[22] The items ask about their mental or affective state related to their caregiving experience For example, providing help to care recipients has 'made me feel more useful', 'made me feel strong and confident', 'given more meaning to my life', 'enabled me to develop a more positive attitude toward life', and 'enabled me to learn new skills'.

Two additional tertiary outcomes will be examined that use measures described above.

Dementia Burden Scale-Caregiver (DBS-CG)[23] is a composite of the NPI-Q Distress, MCSI, and PHQ-8 scales with items transformed linearly to be on a 0-100 possible range and then averaged with higher scores indicating higher caregiver burden. The minimal clinically important difference (MCID) for the DBS-CG is 5 points.

Clinical benefit[24]- Measured patient symptoms using the NPI-Q severity scale (the only patient outcome anticipated to benefit from the program) and caregiver symptoms using the DBS-CG scale. Benefit on the NPI-Q severity scale is defined as having a 1-year score of $\leq$ 6 (the lowest tertile of symptoms) or improving by at least 3 points, the MCID. DBS-CG benefit is defined as having a 1-year score of $\leq$ 18.8 (the lowest tertile of symptoms) or improving by at least 5 points, the MCID. Defining benefit in this manner allows us to capture both preventive (those who have few symptoms at baseline and do not deteriorate) and therapeutic (those who improve) benefit from the program. We will then determine clinical benefit using 3 perspectives: patient benefit only, caregiver benefit only, patient or caregiver benefit.

**6.2 Other measures to be collected**

We will collect baseline sociodemographic data, including zip code to determine rural/urban status, to characterize the study population and for subgroup analyses. We will also ask caregivers about several personal health items including hospitalizations and inability to get health care (e.g., missing appointments) because of caregiving demands as well as items assessing informal caregiving hours from the BRFSS Caregiver module.[25] These data sources are well validated using the data collection approaches that the study will use. As a measure of process of care, we will ask whether participant contacted the Alzheimer's Association Helpline during the 18-month interview.

**Physician Satisfaction Measures**

Physician Satisfaction will be collected using an 5-item questionnaire modified from the UCLA ADC, which will be linked to specific patients and conducted when the provider's first enrolled patient completes the study. The instrument will be revised so that the same survey can be administered to evaluate participants in all 3 arms. All providers with at least one enrolled patient in the study will be surveyed. This will be very valuable in disseminating the interventions.

**Fidelity and Quality Measures**
We will also collect fidelity measures (see above sections describing each intervention) that capture whether the interventions are being implemented as planned. In addition, at 12 months, we will collect 10 ACOVE and Physician Consortium for Performance Improvement (PCPI) quality indicators quality measures of dementia care that can be collected by self-report including:

Domain: Assessment/Screening
- Annual assessment of cognition
- Annual assessment of function
- Annual depression screening
- Annual screening for dementia-related behavioral symptoms

Domain: Counseling
- Dementia prognosis
- Community resources
- Behavioral interventions for neuropsychiatric symptoms
- Safety
- Driving
- Advance care planning or palliative care

**COVID-19 Measures for Caregivers**
To assess the potential impacts of the coronavirus pandemic on study participants, we will administer a 10-item questionnaire (modified from the Pain Management Collaboratory and National Alzheimer's Coordinating Center questionnaires) evaluating how COVID-19 has affected caregivers' emotional, physical, and social well-being (e.g. caregiver distress, ability to care for person with dementia, social support) and care recipients' mental and emotional well-being over the past 3 months. The COVID-19 Measures for Caregivers questionnaire is obtained over the telephone at the participants' next scheduled outcomes assessment call, after the change has been approved by the IRB, by a blinded assessor (e.g. the Research Assistant).

Finally, we will ascertain self-report (by caregiver) of serious adverse events (SAEs) of death and hospitalizations at each outcome assessment time point and through claims data.

## 7. STUDY PROCEDURES AND VISITS

### 7.1 Randomization

At the time of the in-person or telephone (after the start of the 2020 COVID-19 pandemic) baseline assessment, caregiver and, if the person with dementia is capable, patient informed consent will be obtained. Upon successful completion of baseline measures, eligible persons will then be randomized to either HSDC or CBDC or UC in a 7:7:1 ratio. The randomization will be stratified by site using a permuted block design with a fixed block size of 15; using variable block sizes was not practical given the size of the block and the few numbers of participants to be enrolled in the usual care arm at each site. The randomization scheme will be computer-generated and the allocation sequence concealed. Intervention assignment will be delivered by the web-based clinical trial management system. Because all of the care processes employed in all arms reflect

standard of care, the consent will focus only on the collection of data. This approach is the same as that employed in the PCORI- and NIA-funded Strategies to Reduce Injuries and Develop confidence in Elders (STRIDE) pragmatic multisite trial aimed at reducing serious falls-related injuries.

### 7.2 Schedule of Events

The trial Schedule of Events is shown in **Table 4**.

**Table 4.** Schedule of Events (see also Table 3 for timing of outcome measures)

| **Task** | **Year** | | | | | |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 |
| IRB approval | X | | | | | |
| Engaging patients and stakeholders | X | X | X | X | X | X |
| Refining the interventions and tailoring to CTS | X | | | | | |
| Training DCS' and CBDC Care Consultants | X | | | | | |
| Piloting the intervention and outcomes at CTSs | X | | | | | |
| Recruitment of participants | | X | X | | | |
| Follow-up of participants | | X | X | X | X | |
| Data collection, quality management and analysis | | X | X | X | X | |
| Data analysis | | | | | X | X |
| Write papers and dissemination | | | X | X | X | X |
| Obtain claims data | | | | | X | |
| Conduct cost-effectiveness analysis | | | | | X | X |
| Write papers and dissemination | | | X | X | X | X |
| PCORI Peer-Review Process | | | | | | X |

## 8. STATISTICAL ANALYSIS, SAMPLE SIZE AND POWER CALCULATIONS

### 8.1 Design Overview

This section describes the general approach for the analysis of the primary, secondary and tertiary outcomes, including safety. The trial will be registered on clinicaltrials.gov before the first patient is enrolled and results will be reported within one year of obtaining the primary outcome on the last patient. Current versions of SAS and R will be used for all analyses.

### 8.2 Analysis of Primary, Secondary, and Tertiary Outcomes

#### 8.2.1 Analysis of Primary Outcomes

All analyses will be according to intent-to-treat or as-randomized. The analysis of the two primary outcomes – NPI-Q Severity and MCSI scores – will be done using a constrained longitudinal repeated measures analysis[26] based on maximum likelihood methods adjusted for the stratified randomization by site. Treatment differences, averaged over all follow-up time points, will be summarized by least square means and 97.5% confidence intervals. Significance testing for each outcome will be done by the Hochberg procedure[27] using an overall type I error of 2.5% (2-sided) to control for the 3 pairwise comparisons, i.e., testing each outcome at 2.5% will maintain the overall type I error at 5% (2-sided). This analysis will be implemented as a mixed methods repeated measures (MMRM) model which uses all available records under the assumption that visit-specific data are missing at random (MAR). Inclusion of the baseline 3, 6, 12, and 18-month data as outcomes in the model will assist in meeting the MAR assumption. We will test for the treatment by time interaction at the 10% significance level. If significant, we will also report treatment differences at each time point. We will also

examine for treatment by site interactions, although there may not be power to detect them. Sensitivity analyses will investigate the MAR assumption, such as methods that jointly model missingness and outcome distributions (e.g., pattern mixture models).[28,32]

We will conduct an exploratory analysis to test whether giving any intervention is superior to usual care if there is no significant difference between the two interventions, and if neither intervention is superior to usual care for either or both outcomes. We will test this hypothesis using the same longitudinal repeated measures analysis described for the primary outcomes at the 0.05 (2-sided) level of significance uncorrected for multiplicity. The difference between giving any intervention and usual care will be reported as least square means with 95% confidence intervals.

Heterogeneity of treatment effects (HTE) for the primary outcomes will be assessed in six key subgroups of participants: higher vs. lower patient function by FAQ, independent vs. dependent patient function by ADL, more vs less NPI-Q Severity, more vs less MCSI at baseline, spouse caregiver vs. other caregiver, and white non-Latino vs. nonwhite or Latino. These subgroup analyses are aimed at determining whether there is differential effectiveness of the interventions among patients with more and less severe disease, perhaps elucidating a preventive (if effect is greater among those with less severe disease) versus therapeutic (if effect is greater among those with more severe disease) effect. Similarly, the high vs low distress subgroup comparison will determine whether the intervention is more effective among those with more distress at baseline (a therapeutic benefit) versus less distress (a preventive benefit). Evidence of HTE will be based on tests of interaction within the longitudinal model structure described above. Because six tests of interaction will be conducted, we will use the Hochberg procedure to control for multiplicity using an overall type I error of 2.5% (2-sided) for each outcome; subgroup treatment differences will be reported using 99% confidence intervals.

Exploratory analyses to assess HTE for the primary outcomes will be also be conducted in demographic subgroups (e.g., age, race and ethnicity) as well as the effects of the COVID-19 pandemic and not adjusted for multiplicity.

### 8.2.2 Analysis of Secondary Outcomes

The analysis of the continuous secondary outcomes – NPI-Q Distress, caregiver depression (PHQ-8), Caregiver self-efficacy– will be analyzed like the primary outcomes. The Hochberg procedure will be used to control for the testing of each secondary outcome using an overall type I error of 5% (2-sided); treatment differences will be reported using 95% confidence intervals.

### 8.2.3 Analysis of Tertiary Outcomes

The analysis of tertiary outcomes will be considered exploratory and, thus, no control for multiplicity will be done. Continuous outcomes will be analyzed by longitudinal methods, time to event data by survival methods and count data by Poisson, Negative Binomial, hurdle models or rank based methods depending on the distribution of the counts. Time spent at home is calculated as 540 minus (1) the number of days in a health care facility, including hospital, nursing home, acute rehabilitation, and inpatient hospice, and (2) the number of days not alive. The analytical approach will depend on the distribution of the outcome (e.g., skewed distributions will require rank-based methods.)

### 8.2.4 Missing Data

Several strategies will be implemented to address the issue of missing data during this study. Prevention is the most obvious and effective manner to control bias and loss of power from missing data.[29] (see section 9.1.7 “Data Quality Control” for a discussion of our plans to minimize missing data and other errors during data

collection). This protocol will follow the intent-to-treat principle, requiring follow-up of all participants randomized regardless of the actual treatment received.[30] The primary source of missing data will result from death since we expect relatively few dropouts (< 10%). Whenever a participant drops out of the study, we will document the specific reason for dropout, who decided that the participant would drop out, and whether the dropout involves some or all types of participation. For example, some participants may drop out of the patient/caregiver-reported outcomes but permit use of claims data to determine some secondary and tertiary outcomes.

The follow-up period of 18 months was set to capture the time period during which treatment benefits would be maximized while minimizing the impact of deaths. Also, the timing and frequency of follow-up assessments at 3, 6, 12, and 18 months was designed to minimize missing primary outcome data on participants by having measurements at early time points.

Because the study population has dementia, the primary source of data collection (including primary and all secondary outcomes) will be from caregivers. To minimize missing data, all follow-up data will be collected by telephone, making it much easier, compared to in person visits, for participants (and caregivers) to complete the outcomes assessments. Because most instruments, including the two primary outcome measures are self-administered, we can also offer the options of collecting these data by fax, secure website, or secure email, which will also reduce the likelihood of missing data. We will also employ a risk-based approach to trial monitoring with timely data entry combined with weekly missing data reports that will trigger protocols for tracking and obtaining missing data items or outcome assessments[31] data.

Despite these prevention efforts, it is reasonable to assume missing data will occur. Our primary analysis is valid under the assumption that missing data is missing at random (MAR). Sensitivity analyses will investigate the MAR assumption, such as methods that jointly model missingness and outcome distributions(e.g., pattern mixture models).[29,31] . The results of these techniques to account for missing data will be incorporated into the interpretation of findings and conclusions of the study.

### 8.3 Sample Size

#### 8.3.1 Primary Outcomes

The assumptions used to determine sample size for testing differences among the three treatment arms for the two primary outcomes were: 1) type I error 0.05/6 = 0.0083 adjusted for 3 treatment comparisons (HSDC vs. CBDC, HSDC vs. UC and CBDC vs. UC) times 2 primary outcomes, 2) standard deviation (SD) for NPI-Q severity of 6.5 units and SD for MCSI of 6.7 units, 3) treatment difference for HSDC vs. CBDC of 1.5 units, 4) treatment difference for HSDC and CBDC vs. UC = 3 and 5) lost to follow up over 18 months because of death and dropout of 25%. The detectable treatment difference of 1.5 units for HSDC vs. CBDC is based on data reported in the literature suggesting a minimally clinical important difference (MCID) ranging from 2.8 to 4.0.[6] Given that both intervention arms will be receiving an intervention, we reduced the detectable difference in half to 1.5. Data from two studies[32, 33] indicate that the expected benefit between HSDC and UC would be 3.2 units for NPI-Q Severity score. Based on these data we used a difference of 3 units for comparisons with UC. The estimates of the standard deviations (SD) for the 18-month NPI-Q Severity score and MCSI are 6.5 and 6.7, respectively, based on UCLA pilot data. An 18-month censoring rate of 25% was assumed because of death (15%) and dropout (10%). The death rate was taken from fee-for-service claims data on 274 UCLA patients with a mean survival time of 1.5 years.

Sample size was first determined for the comparison between HSDC and CBDC because the effect size is smaller. The goal was to achieve at least 90% overall power for testing both outcomes. Testing each outcome at 95% power with a sample size of 1000 subjects per treatment group (adjusted for censoring) gives at least 90% overall power for testing both outcomes. Given these sample sizes, the sample size is 150 (for UC

adjusted for censoring) for comparisons with the two interventions giving an overall power of at least 90%. For conservativism, we assumed the same effect size for both interventions compared with UC even though we hypothesize that HSDC will be superior to CBDC. The total sample size for the trial is 2150 individuals (adjusted for censoring).

**Table 5**:Power and Sample Size for the Two Primary Outcomes

| Comparison | Difference to be detected | Power for MCSI | Power for NPI-Q Severity | Overall Power | Adjusted Sample Sizes |
|---|---|---|---|---|---|
| HSDC vs. CBDC | 1.5 | 95% | 95% | 90% | 1000 per group |
| HSDC or CBDC vs. UC | 3.0 | 95% | 95% | 90% | 1000 HSDC and CBDC vs. 150 UC |

The inflation of sample size for censoring due to deaths and losses is conservative because the data will be analyzed using longitudinal methods under the MAR assumption that include all available data on each participant. Considering the first patient follow-up for the two primary outcomes is at 3 months, the effective censoring rate for analytical purposes is approximately 5% for the primary analysis (i.e., those without any primary outcome follow-up data).

Heterogeneity of treatment effects (HTE) for the two primary outcomes will be assessed in six subgroups of participants: high vs. low patient function by FAQ, high vs. low patient function by ADL, high vs. low NPI-Q Severity, high vs low MCSI at baseline, spouse caregiver vs. other caregiver, and white non-Latino vs. nonwhite or Latino. The study will have approximately 90% power to detect interactions (differences in treatment effects between subgroup categories) of about 3 units for both NPI-Q severity and MCSI for the HSDC vs. CBDC comparisons. Interactions on the order of 6 units can be detected with approximately 90% power for comparisons of HSBC and CBDC with UC for the two primary outcomes. These detectable interactions assume a conservative Bonferroni adjusted type I error of 0.05/(6x3x2) = 0.0014 to control for multiplicity. (In the analysis, we will conduct one global test of interaction per subgroup for 6 subgroups). Using an anchor-based approach that compares changes in NPI-Q measures with other clinical measures, the MCID for the severity scale is 3.2.[6] Hence, based on this range of MCID, the study will have adequate power to detect clinically meaningful differences in subgroups for comparisons between the two interventions. However, only large interactions can be detected for the comparisons with UC because of the smaller sample size in this arm. Although equal subgroup sample sizes were assumed in the calculations, power will not be greatly affected if the imbalance in subgroup sample sizes is not more extreme than a ratio of 2:1.

### 8.3.2 Secondary and Tertiary Outcomes

For the three secondary outcomes (NPI-Q Distress, caregiver depression (PHQ-8), Caregiver self-efficacy), we determined the detectable effect sizes assuming a Bonferroni adjusted type I error of 0.05/(3x3) = 0.006 to control for multiplicity. The detectable effect sizes with 90% power for the three continuous measures (NPI-Q Distress, caregiver depression (PHQ-8), Caregiver self-efficacy) are on the order of 0.20 for testing HSDC vs. CBDC. For testing HSDC/CBDC vs. UC, there will be approximately 90% power to detect effect sizes on the order of 0.40. Thus, we will have good power to detect small to moderate effects for the three continuous outcomes.

The goal attainment scaling (GAS) tertiary outcome will be collected only from caregivers (in the two active intervention groups) enrolled through December 15th, 2020. Goals will be set at baseline and will be assessed at two follow-up time points: at 6-12 months and 15-18 months after enrollment. After considering the expected loss to follow up, we anticipate 80% power (appropriate for a tertiary outcome) to detect a 10% difference between HSDC and CBDC arms.

Power determinations for tertiary outcomes were not performed because these are considered exploratory. Sample size and power were calculated using Power and Sample Size (PASS) software (Kaysville, UT, 2013).

### 8.4 Cost-effectiveness and utilization analysis

The cost-effectiveness of the interventions compared to UC is the ratio of incremental net costs to incremental effects of the two primary outcomes. Thus, the ratio will be the net costs per X point change in NPI-Q-Severity and Y point change in MCSI. Costs will be taken from the perspective of Medicare. The net costs of the interventions are the costs of training for and doing the intervention less the cost offsets of reduced medical care and caregiving, if any, they bring about. The intervention costs, primarily labor, will be collected at the sites. The cost offsets come from changes in various kinds of utilization, which will primarily be based on the Medicare claims of participants in FFS, MA, or commercial health plans, or records of utilization priced using Medicare prices. We will model the cost offsets using differences in differences using general estimating equations with a gamma family and log link, as was done in a prior CMMI analysis that showed significant cost savings.[34] The cost effectiveness ratio can be transformed into the clinical benefit gained (patient, caregiver) per $1000 investment per year. After we have calculated intervention costs and savings, we will compute return on investment = (cost savings – intervention costs)/(intervention costs).

We will use the Master Beneficiary Summary File (MBSF), Medicare Provider Analysis and Review (MedPAR) file, Outpatient file, Hospice file, and Carrier file (non-institutional providers) to determine costs and utilization. The MBSF includes the base segment with beneficiary demographic information, date of death, and chronic conditions, and a costs and use segment with payment and utilization information. The costs will be computed as total Medicare payments across all services (hospital outpatient, acute inpatient, other inpatient, skilled nursing facility, hospice, home health, Part B carrier, and durable medical equipment). The MedPAR files contain inpatient hospital and skilled nursing facility (SNF) records for all Medicare beneficiaries, the outpatient files include claims submitted by emergency departments, and the hospice file contains claims for hospice stays. For participants in MA or commercial health plans, we will use internal records of utilization, and compute costs using Medicare prices.

Secondary analyses will be from a societal perspective and include costs to Medicaid and consumers as well as Medicare. Long-stay nursing home stays will be identified using place of service codes and Current Procedural Terminology (CPT) codes for nursing facility services (from carrier and outpatient claims), and the absence of SNF claims in an initial month.[35] To compute nursing home costs, nursing home stays will be multiplied by a weighted average reimbursement rate paid by Medicaid and private plans. Costs to consumers will include beneficiary cost-sharing payments for services as well as caregiving costs using questions from the Aging, Demographics, and Memory Study.[25] The cost of paid caregiving will be estimated based on average hourly rates from caregiver agencies, and the cost of family care will be estimated based on the market wage paid to formal caregivers or the cost of foregone wages by caregivers based on average market wages.[36]

In tertiary analyses to understand where the cost savings arise, we will study changes in utilization by type of use including all-cause hospital admission rate stratified by psychiatric versus general hospital admission, 30-day hospital readmission rate, ambulatory-care sensitive hospital admissions, length of hospital stay, ED visit rate, ICU use, post-acute nursing home admission rate and length of stay, proportion of enrollees institutionalized in nursing homes, and hospice enrollment. Analyzing the types of utilization will allow us to have a better understanding of the drivers behind the overall cost offsets. We will model expected utilization, adjusted for hospital and ED use in the 12 months prior to date of enrollment for each participant. We will inspect the actual distribution of our data to guide statistical modeling but expect to use negative binomial regression to model utilization rates (i.e., count of hospitalizations). Negative binomial regression will allow us to account for heterogeneity in individual rates, repeated events within patients, and different months of available claims data for each patient.

### 8.5 Safety

Because this is a minimal risk trial, we will ascertain self-report (by caregiver) of SAEs of death and hospitalizations at each outcome assessment time point, which will be monitored by the DSMB. At the end of the follow-up, we will confirm any between-group differences in self-reported SAEs by examining data on mortality and hospitalizations from CMS data files and site-obtained utilization data. In addition, if a caregiver's, PHQ-8 score is >14, Research Assistants will immediately (that day) notify the site's clinical director (or covering physician) and this clinician can decide on next appropriate steps.

### 8.6 INTERIM MONITORING

Interim monitoring will focus on safety, recruitment, adherence to protocol, baseline comparability of treatment groups, data quality, and uptake of the assigned intervention. A set of monitoring tables will be generated for this purpose. Because this is a minimal risk trial and the follow-up period is relatively short (18 months), no monitoring for efficacy or futility is being proposed.

## 9. DATA COLLECTION AND MANAGEMENT

### 9.1 Data Collection

All data collection and data entry will be performed by site research staff, using tools and standard operating procedures (SOPs) provided jointly by the Central Project Management (CPM) and by the Data Coordinating Center (DCC). The primary mode of data collection will be directly onto electronic forms, through a device that is encrypted and secured according to site institutional standards for information security. The DCC will also provide equivalent paper forms, for use in situations where a suitably secure, internet-connected device is unavailable (e.g., a telephone interview conducted after hours at home). Access to all data collection and data entry services will be through a study portal website Patient dashboard, described below. Staff will be trained in the proper handling of paper forms (i.e., storage in secured participant jackets, no identifying information, all notations in permanent ink, all modifications initialed and dated in red ink).

#### 9.1.1 D-CARE Study Portal Website

Most of the DCC data management services will be organized and delivered through the *D-CARE Study Portal Website*, a secure web tool that will be available to study staff. Role-based access to DCC services will require login through Yale's Central Authentication Service (CAS), using Yale Research Affiliate user accounts (netids) that will be issued to staff as required. The portal website will be hosted by Yale Information Technology Services (ITS) and certified as HIPAA-compliant by the Yale Information Security Office (ISO). ISO will scan the portal website for vulnerabilities throughout the study period.

#### 9.1.2 REDCap

All data collection systems and services will be based on REDCap, the CTSA-supported data management tool (http://project-redcap.org). While REDCap provides many essential features, its main strength is its open architecture and support for user-designed extensions ("plugins" and "hooks"). Many of the services described below are highly customized REDCap extensions that appear to the user as stand-alone web applications. Through these extensions, we can customize the interface of any REDCap-based web tool to match the workflow of the study activity.

#### 9.1.3 Site Management Services

The portal website will be the means for disseminating *site metrics* such as accrual progress; interviewer performance; error rates; error closure statistics; and other performance measures. Detailed reports will be

distributed to sites and comparative reports and charts ("site report cards") will be available on an "all sites" page. We will post relevant administrative forms on the study portal website, as well as important study documents such as the MOP, and study forms.

### 9.1.4 Staff Management Services

DCC will provide, through the D-CARE portal website, tools for managing site study staff. Basic information such as role on study, email address, and active status will be editable by site coordinators, but staff training will be a particular focus of this module. The DCC will work with CPM to develop training certification standards and curricula for site staff involved in data collection and will provide means for accessing tutorials and signing up for training webinars. Training certificates will be issued, sent to staff by email, and tracked. Only certified staff will have access to the REDCap-based data collection tools. Interview staff will be monitored on key performance factors such as refusal rate, data completion rate, adherence to rules for contacting patients (e.g., at least one weekend, one evening attempt), adherence to interview windows, and metrics assessing the measurement of key outcomes. Staff will be re-trained as indicated by monitoring results.

### 9.1.5 Data Quality Control

#### 9.1.5.1 Preventive Data Quality Control

Clear, unambiguous, and uniform procedures that all study personnel can follow are essential to maintaining data quality.[37] DCC will provide DCS site staff with SOPs and standardized training, and all staff will follow identical procedures for data collection. Staff will be continuously monitored according to interview performance and measurement metrics, and interviewers showing significant departures from group medians will be evaluated for additional training or other action.

Interview design will be partly guided by two principles that have large effects on data quality: *parsimony* and *specification completeness*. Keeping the number of data elements to the minimum required to accomplish study goals reduces the overall participant, site staff, and data management burden in terms of time and efforts necessary to process data for analysis. Wherever possible, responses that are open to interpretation (e.g., free text responses, non-exhaustive choice sets) will be avoided.

#### 9.1.5.2 Proactive Data Quality Control

Comprehensive point-of-entry error checks will be built into the electronic forms. REDCap provides for range checks and branching logic enforcement and has limited support for higher-dimension data pattern actions. For example, branching logic may be defined based on data "piped in" from other forms.

#### 9.1.5.3 Batch Error Checks and Error Resolution

Batch error processing is a necessary component of data quality control. It has been reported that batch data cleaning can reduce the median transcription data entry error rate by as much as seven-fold.[38] A substantial portion of D-CARE data will be entered via transcription from paper forms (e.g., after hours assessments), so batch error checks problematic data patterns will be a vital component of the QC system. Finally, by design, real-time errors can be overridden by interviewers (e.g., a lab value outside the range allowed). These (apparent) errors must still be resolved.

The D-CARE tool for daily batch error detection, tracking and resolution will be a web-based tool under development by DCC that is based on the "Data Quality Control Query" (DQCQ) utility implemented in the SILVER-AMI study: http://medicine.yale.edu/intmed/geriatrics/silver_ami/about/. DQCQ is a REDCap-based web tool that manages a database of error conditions detected by SAS programs that use a standard DQCQ code (macro) library. All errors are viewable and tracked by DCC staff, and can be conditionally exposed to site staff for resolution. Site staff can correct most errors through "mini forms" rendered directly on the DQCQ

interface using REDCap metadata, or they may use the normal REDCap interface. Site staff can also declare errors as "unrecoverable" or "resolved as an outlier," in which cases explanations are required. DQCQ errors can only be closed by DCC staff. DQCQ works with built-in REDCap QA/QC features, such as explanatory "field notes" that can be entered onto any REDCap form. Updates are audited through the normal REDCap logging feature. Site staff are incentivized to address open DQCQ queries though performance summaries (open queries, 30-day resolution rate, etc) displayed on the portal website dashboards, and on comparative reports that rank sites on these important metrics.

### 9.2 Intervention Support

HSDC Management Services The primary tool for HSDC intervention workflow and task management will be a specialized software application developed by a third-party vendor (High5LA) working with the DCC. This application is a modification of the software system, also developed by High5LA, in use by the UCLA dementia care team. The workflow/task management software will be integrated with a REDCap-based electronic data capture module (EDC), following methods worked out for STRIDE.

DCC will work with CPM and CTS's to develop and maintain training standards for software and will provide means for accessing tutorial and training webinars. The DCC, High5LA (the software vendor), and CPM will coordinate user support efforts for the software.

CBDC Management Services The study will use existing BRI Care Consultation Information System software and relevant data will be exported. This software tracks all contacts, action steps, assessment domains, direct and indirect time, and other processes completed as part of the program. Built in reports are generated by Care Consultants, supervisors, and administrators that provide results for these data in aggregate form, which can be exported as individual case-level data to statistical software for analyses.

### 9.2 The Data Mart

DCC will maintain a read-only snapshot or "data mart" for use by DCC data managers and statisticians for analyses, batch error checks and study conduct reports. The data mart will be regenerated each night and will be in SAS format. The data mart will include all assessment and outcome data, as well as fidelity measures from the HSDC and CBDC systems. Specific data mart snapshots used for DSMB reports, interim analyses, manuscripts and other specialized purposes will be permanently saved.

## 10. SAFETY AND ADVERSE EVENTS

### 10.1 Background

This section describes the requirements and processes for reporting adverse events (AE), serious AE (SAE) and unanticipated problems to the Institutional Review Board (IRB) of record and DSMB. It incorporates guidelines provided by the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) and Food and Drug Administration (FDA) reporting requirements. NIH is obligated to ensure that researchers comply with their approved reporting procedures. Because this is a minimal risk trial, we will ascertain self-report (by caregiver) of SAEs of death and hospitalizations at each outcome assessment time point, which will be monitored by the DSMB. At the end of the follow-up, we will confirm any between-group differences in SAEs by examining data on mortality and hospitalizations from CMS data files and site-obtained utilization data.

### 10.2 Definitions

**Adverse Event:** Because 45 CFR 46 does not provide a specific definition for an adverse event (AE), the definition of an AE will conform to the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. The same definition is used by the U.S. Food and Drug Administration (FDA) except that

"drug" is typically used instead of the term "intervention." An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an intervention and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational intervention, whether or not related to the intervention.

**Serious Adverse Event (SAE):** Any AE that:

- Results in death;
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred;
- Requires or prolongs hospitalization;
- Causes persistent or significant disability or incapacity;
- Results in congenital anomalies or birth defects;
- Is another condition, which the investigators judge to represent significant hazards.

**Unanticipated Problem:** any incident, experience, or outcome that meets all of the following criteria:

- 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 study population;
- related or possibly related to participation in the research; in this guidance document, 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;
- 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.

**Adverse Event Reporting Period**: The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up.

**Preexisting Condition**: A preexisting condition is one that is present at the time of providing the consent for the study. A preexisting condition is considered an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

### 10.3 Responsibilities

**Investigators conducting clinical research are responsible for:**

- Assurance that their procedures are conducted in compliance with these guidelines.
- Creating a DSMP that describes the plans for adverse events, serious adverse events, and unanticipated problems commensurate with the nature and complexity of the study.
    - Recipients of Serious Adverse Event and Unanticipated Problem reports must include the IRB and DSMB
    - Adherence to the DSMP with respect to timely submission of adverse events, serious adverse events, and unanticipated problems.

### 10.4 Level of Monitoring in this Study

Data and Safety Monitoring Board The study will convene a Data and Safety Monitoring Board (DSMB) that will meet once in year 1 and twice a year thereafter. The DSMB will monitor participants' safety and study

progress, and make recommendations to the project team regarding participants' safety and continuation of the trial. The DSMB will include experts in dementia care (including investigators), clinical trials and statistics.

General Description/Overview: This pragmatic trial differs from a typical randomized, controlled trial (RCT) in important ways. First, no experimental interventions are used. All interventions are standard of care and not research. Indeed, the consent form does not include language for consent to an intervention, only for collecting data. Thus, the definitions of research and therefore AE, SAE, Unanticipated Problems and Pre-existing conditions do not apply to the intervention. However, this appraisal does not preclude the need to monitor the study and its impact on participant safety. There are no in-person study visits other than the baselines conducted prior to the 2020 COVID-19 pandemic; the only data collection methodologies are questionnaires and examination of claims data. Therefore, our safety monitoring procedures focus on data collection via the methodologies available in the protocol design. Our plan is based upon the following principles:

1) It is not feasible or necessary for participant safety to monitor AEs as the definitions above do not apply because the intervention is not research.

2) Limited monitoring is justified for serious adverse events (SAEs) as many of these will not occur in our study population (e.g. congenital anomalies) AND this is not a trial that has implications for FDA approval. Thus, only Good Clinical Practice (GCP) need dictate the level of monitoring in accordance with Federal Registry Title 21.

3) It is not necessary to assign monitored SAEs as "related" or "unrelated" to the study protocol because there is inherent bias in this assessment, attribution of "relatedness" would be a tremendous burden, and whether a difference in SAE burden is considered "related" or not, a significant difference between groups would be treated with similar concern by the DSMB.

4) Mechanisms for timely reporting after SAE ascertainment are important, but collective totals of monitored SAEs at assigned intervals will meet "timeliness" for the purposes of this study.

5) The primary and secondary study outcomes will not require additional SAE reporting.

### 10.5 Ascertainment of AE, Unanticipated Problems (UP), and SAE

#### 10.5.1 Adverse events

As noted in **10.4**, AEs will not be collected in this trial since "any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the intervention" will be occurring in the course of routine care, not research. Limited SAEs will be collected and reported as outlined in 11.5.3.

#### 10.5.1 Unanticipated Problems (UP)

Investigator institutions must have written procedures for ensuring prompt reporting to the IRB and others as appropriate, of any Unanticipated Problem involving risks to study participants or others (45 CFR 46.103(b)(5)). As shown in **Table 6**, if the site PI or study coordinator has an individual concern, they will be required to contact the Medical Safety Officer (MSO) within 48 hours of first knowledge of the event. An UP form must be completed by the site investigator and faxed to the PI/Study Director (SD) within 48 hours. The site PI will keep a copy of this UP form on file at the study site. The SD will confirm that the UP is an anticipated event and, if confirmed, report the UP to the DSMB within 48 hours of its notification. An UP will result in corrective plans and measures to prevent reoccurrence. An electronic record of such concerns and the action plan will be filed by the SD with the DCC so that concerns can be tabulated and reported as outlined below.

**Table 6. Methods to ascertain safety concerns and SAEs**

- Site PI has specific concern → contact SD directly;
- Outcomes telephone interview reported hospitalizations or deaths confirmed by CMS Master Beneficiary file for patients

### 10.5.2 Ascertainment of SAEs and Deaths

Given the principles in **10.2**, our plan focuses on a limited set of SAEs. Only hospitalizations and deaths will be collected, which will ensure the protection of participants from potential harm but remain feasible within the study design. The vast majority of SAE ascertainment will occur from telephone interviews per the outcomes assessment schedule. Self-reported hospitalizations and death will be reviewed by the SD by the SD on schedule determined by DSMB (e.g., every 6 months).

Participants who die within the participating health care systems will be verified CMS Master Beneficiary Summary File at the end of the study.

As outlined in the safety plan below, SAEs will be reported to the DSMB, and the IRB of record in accordance with NIH and local regulations, and in conformity with the Data and Safety Monitoring Plan developed by the DSMB and approved by NIA and PCORI.

### 10.6 Safety Personnel

**Study Director (SD)**: The SD will coordinate reporting of the safety data. The SD will monitor and evaluate all collected UPs and SAEs from all sites efficiently and effectively by regular review/monitoring of reports of monitored SAEs or UP reported directly by site PIs/personnel. The SD may suggest measures to the PIs to improve monitoring or prevent risk to participants. Upon approval by the DSMB, these modifications may be submitted as protocol modifications to the IRB of record. The SD will review reports of UPs and SAEs (in total, but not segregated by treatment assignment) and submit these to the DSMB, the IRB of record and the DCC for distribution to Reporting of Unanticipated Problems and Serious Adverse Events

Deaths learned by the Clinical Trial Site, Dementia Care Specialists and Care Consultants are to be reported to Central Project Management (CPM) as soon as learning of it. CPM is responsible for notifying the DSMB Chair and NIA via email with death details (Dyad ID #, date of death and classified as related or unrelated to research participation or intervention related.

Each CTS is required to maintain a log of deaths that occur at their site. Information on the log should include:

- Date learned of death
- Dyad ID
- Date of Death
- Cause of death (if known)
- Related or Unrelated to study participation or intervention

Similarly, hospitalizations should only be reported to the cIRB *if* they are related or possibly related to research participation. If the hospitalization is *unexpected*, and related or possibly related to research participation, it

should be submitted to the IRB within 3 working days. The CTS should report the unexpected, and related or possibly related hospitalizations to CPM immediately upon knowledge of it.

Determination of reporting hospitalizations to CPM will be made by the Clinical Trial Site. The Clinical Trial Site will ONLY report hospitalizations that are directly related to research participation or intervention of the study. CPM is responsible for notifying the appropriate entity.

CPM will also maintain an on-going log of hospitalizations for each CTS with the abovementioned information and will be responsible for communicating the information to the DSMB, NIA, and IRB, as appropriate.
A summary report of the UP and SAE collected by all methods of ascertainment will be prepared by the SD and DCC for submission to the DSMB and IRB of record in accordance with the Safety Monitoring Plan.

## 11. ETHICAL AND REGULATORY CONSIDERATIONS

### 11.1 Good Clinical Practice Statement

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for Good Clinical Practice (GCP) and all federal as well as local regulatory requirements.

### 11.2 Informed Consent

The principles of informed consent are described in ICH guidelines for GCP (ICH E6[R1]). The ICH used by the investigators at the trial sites will be reviewed and approved by the Trial's DSMB prior to submission to the IRB and Informed Consent.

As noted previously in the screening procedures outlined above, potential participants and their identified caregivers, referred by physicians will be contacted by telephone if they do not otherwise opt out. Informed consent will be obtained by trained study personnel with all caregivers and participants who are able to consent. At the time of the COVID-19 pandemic, consenting and baseline interviews were switched to telephonic. Initially, each site differed with respect to the Legally Authorized Representative consenting. Currently, all four clinical trial sites have approval to obtain verbal consents from care recipients (who have the ability to consent), caregivers, and Legally Authorized Representatives (LAR) using an electronic consent process (through RedCap). In the event that the caregiver is not the LAR, verbal consent from the LAR will be obtained prior to the baseline interview being conducted.

After consenting, they will receive a general description of the study, including the baseline and surveillance evaluations, along with the study specific evaluations. The IRB agreed that consent for the interventions is not considered necessary since these are facilitating standard of care in a consistent fashion, not providing an experimental intervention. Of course, data collection does require consent and thus will be the primary focus of the consenting process.

Decisional capacity and proxy consent: For all potential participants who score 8 or higher on the short version of the MOCA, cognitive status will be assessed by administration of the full 22-item telephone MOCA prior to consenting and those scoring $\leq$ 16 will be considered incapable of consenting for participating in the study and providing patient-reported outcomes.[39] Those unable to consent will be asked for assent using the *question* "We would to ask your [caregiver relationship or name] some questions. Would that be ok?" If the person with dementia says "no", then the patient and caregiver will not be enrolled in the study. All caregivers will be consented for providing caregiver-reported outcomes and for obtaining caregiver utilization data (for spouses only).

## 11.3 Institutional Review Board

### 11.3.1 IRB of Record

All identified participating sites have agreed to rely on the review of the IRB at the primary site, UCLA. Any sites added after the study has begun will be required to rely on the same IRB. This application is a multi-site study involving non-exempt human subjects research. Therefore, all sites confirm compliance with the NIH Policy on the Use of a Single Institutional Review Board of Record for Multi-Site Research consistent with 45 CFR Part 46.114.

As required by 45 CFR 46 Part E, all UCLA IRBs are registered with the federal Office for Human Research Protections. The IRB that will review this study has appropriate membership, including the professional competence necessary to review the proposed research.

### 11.3.2 Authorization/Reliance Agreement

The participating sites are all signatories to the SMART IRB agreement (NIH's National Center for Advancing Translational Sciences (NCATS) Streamlined, Multi-site, Accelerated Resource for Trials (SMART) IRB Reliance Platform). This means that an agreement is already in place and related documentation (including joinder agreements and general standard operating procedures) is centrally available to all sites. All sites also have access to the SMART IRB platform to properly document their acceptance of the arrangement for this particular proposal and track the status of the reliance. The UCLA IRB office will download and maintain a local copy of such documentation.

Any sites added after award will be expected to sign on to SMART IRB if they have not already done so. If such sites are ineligible to sign on to SMART IRB, an appropriate agreement will be negotiated.

### 11.3.3 Communication Plan

The UCLA Principal Investigator will designate a central point of contact on the UCLA study team, the Study Director, to:

- Coordinate communications with reliance sites
- Request and receive information and documentation from relying sites
- Develop template materials for review by the UCLA IRB and for limited modification by relying sites
- Submit materials from all sites to the UCLA IRB and coordinate responses to any IRB queries
- Provide documentation to relying sites

Reliance sites will follow local procedures to coordinate, collect and verify information such as:

- Local context
- Site variations in areas such as recruiting, informed consent, HIPAA, populations
- Conflict of Interest disclosure and management
- Completion of ancillary reviews
- Training and qualifications of study team
- Continuing Review or Closure information
- Reportable Events

Reliance sites will provide necessary information or assurances to the UCLA study team for submission to the UCLA IRB. The UCLA IRB office will communicate directly with the UCLA study team as the proxy for all relying sites.

UCLA has dedicated reliance points of contact within its IRB office. Sections of UCLA's web-based IRB system are designed for submissions, reviews and documentation related to relying sites. When appropriate,

the UCLA IRB office will communicate directly with relying site Human Research Protection Program offices. Relying sites will follow their local procedures for dissemination of information and documentation (e.g., if the local IRB office or ancillary services require copies of the UCLA IRB approval).

### 11.4 Protocol Changes

Any change in the study protocol must be approved by the DSMB, PCORI, and the Project's Study Advisory Committee and approved by the cIRB and trial sites' before it can be implemented.

### 11.5 Risks to Human Subjects

The risks associated with participation in the study intervention itself are deemed to be minimal because: 1) the intervention is aimed at maximizing participation in components of current standard of care; and 2) the intervention is being implemented by trained professionals in the care setting in which they typically provide care. Our assessment of minimal risk does not, however, preclude the possibility that adverse events, and serious adverse events could occur. Therefore, a comprehensive data safety monitoring plan is outlined in the following sections. Authority for monitoring the safety of the protocol will reside in an independent DSMB responsible for holding the PIs accountable for data quality and completeness and assessing the ongoing safety of the trial participants through periodic meetings/review. Ongoing participant safety monitoring is the responsibility of site PIs who will report adverse events to the SD. The SD has the authority to directly report concerns to the DSMB if they arise.

There are potential risks associated with data collection and information management and, in fact, these risks are the major reason consent will be required in this trial. These include inadvertent disclosure of personal health information or research data collected. Every effort will be made to inform the participant of this potential and minimize the risks as outlined below.

#### 11.5.1 Protection Against Risks

**Minimizing Risks:** The study protocol will be implemented at each clinic only after the PI, and study coordinator have undergone rigorous protocol training. The training and monitoring of performance in accordance with the Manual of Procedures for the study will be the responsibility of the study PI and SD. All efforts will be made to minimize risks and participant inconvenience and mitigate interruptions of therapy. Risks will be minimized by: 1) adequate training of all staff with proficiency testing; 2) frequently encouraging participant questions throughout the interventions; and 4) Serious Adverse Event (SAE) Reporting and monitoring overall study safety by a DSMB as outlined below.

#### 11.5.2 Potential Benefits of the Proposed Research to Human Participants and Others

There are a number of potential benefits of the study for the participants including: 1) enhanced care by receiving one of two effective dementia care interventions, 2) receiving close monitoring of the participant during the trial, and 3) preventing or reducing caregiver stress and depression.

There are also potential societal benefits from the proposed research. Optimizing models of care for providing effective comprehensive dementia care has the potential to greatly enhance patient care – including the potential to reduce morbidity both for the patient and caregiver as well as reduce costs.

#### 11.5.3 Importance of the Knowledge to be Gained

The knowledge to be gained from this trial is substantial. It addresses a critically important clinical question, the care of the burgeoning population of persons afflicted with dementia. It also is a head-to-head comparison of

two evidence-based approaches to determine comparative effectiveness using a pragmatic design in clinical practice settings representing diverse geography and patient populations.

### 11.6 Safety Monitoring Protocol

Safety monitoring will be accomplished in accordance with the Safety Monitoring Plan included in the Manual of Procedures (MOP) to be approved by the DSMB.

### 11.7 Inclusion of Women and Minorities

As shown in **Table 8**, women are expected to constitute 67% of the overall sample, consistent with higher life expectancy of women than men. Also, women are more likely to participate in clinical trials than men. **Table 8** also summarizes the racial and ethnic background of the potential participants at each of the 4 trial sites.

**Table 8: Estimated Final Racial/Ethnic and Gender Enrollment Table:**

| | Ethnic Categories | | | | |
|---|---|---|---|---|---|
| | Not Hispanic | | Hispanic or Latino | | Total |
| Racial Categories | Male | Female | Male | Female | |
| American Indian/Alaska Native | 7 | 14 | 0 | 0 | 21 |
| Asian | 22 | 44 | 0 | 0 | 66 |
| Black/African American | 102 | 208 | 15 | 30 | 355 |
| Hawaiian/Pacific Islander | 10 | 21 | 0 | 0 | 31 |
| White | 473 | 979 | 71 | 151 | 1674 |
| More than one race | 1 | 1 | | 1 | 3 |
| **Total** | **615** | **1267** | **86** | **182** | **2150** |

## 12. STUDY DOCUMENTS

### 12.1 Retention of Records

The site PI will retain all study-related documents for at least seven years (7) following the completion or discontinuation of the study. If the site PI's personal situation is such that such archiving can no longer be ensured, the PI will inform the Central Project Management and the relevant records will be transferred to a central secure location for storage.

## 13. PUBLICATION AND DISSEMINATION POLICY

The project PIs in discussion with the Study Advisory Committee will establish a Publication and Dissemination Committee, which will set the rules for publication of the data and authorship in conformity with PCORI policies. In accordance with PCORI's legislative mandate on public dissemination, we will make the study's findings available to clinicians, patients, and the general public not later than 90 days after the completion of the study on September 30, 2024.

### 13.1 Dissemination

The findings of this trial have important implications for public health and policy, requiring wide dissemination; additionally, several aspects of this trial's approach and implementation will shape clinical practice and form the basis for dissemination after the trial. First, the screening methods will be built to interface with major EHR

vendor software and will be readily transferable to any site using similar software. Second, instruments used for risk assessment and intervention management by the DCS can be used in any health system. Third, patient materials will be adapted and used in the program and will be exportable after the trial. Fourth, training materials and procedures will be available for propagating "train the trainer" programs.

A Publication and Dissemination Committee (PDC) will be established to oversee the dissemination of the study's findings. The PDC will include members of the National Patients and Stakeholders Council (NPSC) and investigators with content expertise. This structure will allow the stakeholders and investigators to jointly address how to disseminate study findings to influence clinicians, patients, policy makers, communities, CMS and other third-party payers. Also, local councils will work with investigators from the trial site to plan dissemination and implementation in local communities.

Dissemination of study results will be accomplished through traditional routes (e.g. scientific meeting presentations, publications), but also through novel routes felt to be most effective by our patients and other stakeholder partners using the PCORI Dissemination and Implementation Action Plan begun through a recent roundtable.

A particularly valuable asset for dissemination of this project is the Pepper Older Americans Independence Centers, which form a network of fourteen key academic institutions and thought leaders who are likely to be early adopters of this program if proven effective. Three other potential resources for dissemination will be the Health Care Systems Research Network (HCSRN), PCORI Patient Powered Research Network (PPRN) and the Clinical Data Research Network (CDRN).

## 14. ORGANIZATIONAL FRAMEWORK OF AN INTERDISCIPLINARY TEAM OF INVESTIGATORS, PATIENTS, AND STAKEHOLDERS

The research will have four major partners: Patients and Stakeholders, Clinical Trial Sites (CTS) Central Project Management (CPM), and the Data Coordinating Center (DCC) and will be overseen by a Study Advisory Committee (SAC). The SAC will advise the study before it goes into the field and will monitor all progress to ensure that patient and other stakeholder views are continually integrated into the research. The tasks and responsibilities of each of CPM, CTS, and DCC are presented in **Table 9**.

**Table 9:** Tasks and responsibilities (all tasks will be guided by the SAC)

| **Task** | **Lead Responsibility** | | |
|---|---|---|---|
| | CPM | CTS | DCC |
| Convene Study Advisory Committee | X | | |
| Convene national Patient and Stakeholder council | X | | |
| Convene local Patient and Stakeholder councils | | X | |
| Coordinate IRB | X | | |
| Convene DSMB | X | | |
| Develop HSDC and CBDC | X | X | |
| Adapt and implement HSDC and CBDC | | X | |
| Train DCS' and DCS Assistants | X | | X |
| Develop randomization procedures | | | X |
| Create data collection instruments and standardize collection of outcomes | | | X |
| Recruit participants | | X | |
| Collect baseline and outcome measures and data entry | | X | |
| Ongoing reporting of recruitment and patients seen | | | X |
| Prepare materials for DSMB | | | X |
| Data analysis | | | X |

An Operations Committee will include the study PI (Reuben), the project director, a CTS PI, the DCC PI (Peduzzi), and Co-I (Gill) and will meet weekly to make decisions about the day-to-day conduct of the study, prepare for SAC and DSMB meetings.

The Operations Committee is responsible for overall operational management and coordination of the entire project, synthesizing information from various committees, preparing and executing operational plans, identifying problems and disseminating information to the other Committees.

In addition, the following committees will be convened during Year 1 and maintained for the duration of the study: Local Patient and Stakeholders, National Patient and Stakeholder, Clinical Trial Sites, Recruitment and Retention, Interventions and Training, and Assessment and Outcomes.

**Table 10** displays the functions of the current committees. The committees include scientific chairs, other highly regarded experts in the area of dementia, and patient and stakeholder representatives. The Committees conduct their business through regularly scheduled conference calls; their approved minutes are posted on the study's internal website/ portal.

### 14.1 Reporting Structure

The various committees, DCC, and IT Management Group report to the Operations Committee, which in turn reports to the Study Advisory Committee and to the National Institute on Aging Program Officer. The PCORI program officers interface with the study leadership through the SAC and directly with the PI on a monthly call.

**Table 10: Functions of the Committees**

| Committee | Committee Function |
|---|---|
| Study Advisory | Advises the study before it goes into the field and monitors all progress to ensure that patient and other stakeholder views are continually integrated into the research. |
| Operations | Includes the study PI (Reuben), the Study Director, a CTS PI, the DCC PI (Peduzzi), and Co-I (Gill) meets weekly to make decisions about the day-to-day conduct of the study, prepare for SAC and DSMB meetings. |
| Clinical Trial Sites | Provides a venue for bidirectional flow of information between site PIs and the study's leadership. It includes all site PIs and provides high-level guidance for the trial's implementation at the trial sites. |
| Recruitment and Retention | Responsible for high-level guidance on recruitment and retention activities. |
| Intervention | Responsible for developing the protocols for the intervention. It has two distinct sub-committees focusing on the separate intervention arms and overseeing the implementation of the intervention at the trial sites. |
| Health Systems-based Dementia care | Responsible for developing the protocols and implementation, including DCS training, of the HSDC arm |
| Community-based Dementia care | Responsible for developing the protocols and implementation for the CBDC arm of the study. |
| National Patient Stakeholders Council | Responsible for developing protocols for patient and stakeholder engagement, overseeing the formation and training of local patient and stakeholder councils, providing input into protocol development and all aspects of trial's implementation. |
| Assessment and Outcomes | Responsible for selection of measures and protocols for collecting data, sample size estimation, power calculation, and data analyses. |
| Data Management and Operations Support | Responsible for building the IT infrastructure for data collection and management, staff training in data recording, building appropriate interfaces with the EHRs at sites to allow data collection, creating data forms, ensuring data security, and overseeing FCM software development. Also responsible for providing web tools for workflow management. |

| | |
|---|---|
| Ancillary Studies | Reviews ancillary studies proposals and make recommendations to the investigators on the approval of ancillary studies to the trial. |
| Publications and Presentations | To review and coordinate publications and major presentations from the study. |

### 14.2 Meeting Schedule and Functions of the Leadership

The Operations Committee holds a conference call weekly to review progress, establish work objectives, and discuss operational problems. Other committees meet monthly or more often, if needed. In addition, all investigators meet monthly during the planning year to monitor progress and provide additional input. The SAC meets twice yearly in person. We plan to hold an investigators' meeting once yearly.

### 14.3 Integration of Patient and Stakeholders in the Trial's Planning, Implementation, Analyses and Dissemination

In accordance with the model set forth by Curtis et al,[40] patient engagement will occur at two levels – locally, at the clinical trial sites, and nationally, at the central project management level. To provide integration between the local and national patient and stakeholder councils, the local councils at the 4 trial sites have chosen representatives to serve on the National Patient and Stakeholder Council (NPSC).

Year 1 will focus on 1) development of local patient and stakeholder councils; 2) development of national patient and stakeholder council (NPSC); 3) training of investigators and stakeholders to work in partnership; 4) refining methods for eliciting patients' and stakeholders' voices, and 5) setting up structures to assure patients and stakeholders engagement with investigators to: (a) formulate the final research questions; (b) finalize study design with attention to recruitment of participants, the planned intervention, the comparators, and the outcomes; (c) monitor study's progress and interim results; and (d) help disseminate the results of the study.

#### 14.3.1 Local Patient and Stakeholder Councils

The LPSCs are comprised of 7 persons drawn from the constituencies described in **Table 11**.

**Table 11. Composition of Local Patient and Stakeholder Committees**

| LPSC Role | Description |
|---|---|
| Chair | Facilitate the group and provide linkages with the investigative team (e.g. engagement professional) and NPSC. The facilitator should have expertise in engaging patients and other stakeholders in research. This is essential to promote timely communication, interaction and connections among scientists and the local stakeholders. The Chair should be able to translate between research language and lay language for effective communication between investigative team and LPSC. |
| Trial key personnel | Dementia Care Specialist providing Health System-based Dementia Care (HSDC intervention<br>Social Worker or Case/Care Manager Consultant providing Community-based Dementia Care (CBDC) |
| Patient and Caregiver stakeholders | Patient/caregiver stakeholders (personal experience with dementia): consider diversity of representation for dementia stages, male/female, and communication preferences (computer/email vs. phone/mail). |
| Community stakeholders | Volunteers or representatives from sites where the community-based interventions will be in place such as local community centers, adult day cares, respite programs, churches or senior centers that provide resources for dementia care |
| Area Agency on Aging | The local Area Agency on Aging or other agency that provides applicable resources |

| | |
|---|---|
| Alzheimer's Association | The Alzheimer's Association or equivalent |
| Primary health provider stakeholder | Primary Care Physician who has patients including those with dementia |
| Other health provider stakeholder | A home health agency who has experience receiving referrals for patients with dementia |

### 14.3.2 National Patient and Stakeholder Council

The NPSC is comprised of 6 persons, 2 Co-chairs and a representative from each LPSC. The NPSC: 1) serves in a consultative capacity to local councils and site PIs, various work group committees and study leadership; 2) integrates the input from the 4 local councils and communicates that to the trial's PI and committees; and; 3) coordinates activities initially for a) formulating the final research questions; b) finalizing study design; c) monitors study progress, and suggests changes and edits of all participant-facing print materials and d) provides recommendations for disseminating the results.

### 14.3.3 Training patients, stakeholders, and investigators

During Year 1, investigators, patients and stakeholders will undergo training, focusing on communicating what it means to be partners in patient-centered research. The training emphasized an authentic communication paradigm that builds and maintains trust, respect, and mutual understanding.

### 14.3.4 Engaging patients and other stakeholders as partners in all phases of the research

The bidirectional process of engaging patients and other stakeholders will take place in local councils and the NPSC throughout the duration of the project. The local councils will meet 4 times a year during years 1-4 and twice during year 5. The NPSC will continue to meet monthly throughout the duration of the study.

After year 1, the local councils will focus on refining their trial sites' local resources that support screening and recruitment strategies, the intervention(s), assessment and outcomes, and strategies for disseminating the trial's findings. These local councils will provide recommendations to the NPSC and to site PIs and continually support the local Dementia Care Specialists and Care Consultants. The NPSC will collate the information from all local councils and provide guidance to the PI and various committees.

### 14.3.5 Monitoring the study's progress

During recruitment, the Operations Committee will review the accrual of participants weekly and after recruitment, the collection of outcomes at its weekly meeting. The SAC and DSMB will also review the study's progress. In addition, each committee will review progress of its responsibilities at the monthly meetings.

### 14.3.6 Dissemination and implementation of study findings

The project team will prepare a summary of findings that will be sent by mail to all study participants, including their caregivers. This summary will be reviewed and vetted by the National and Local Patient/Family Stakeholder Committees to ensure that the reading level, formatting, and content of the material are appropriate for the target group of participants. The project team has had experience providing updates of findings about improved dementia care through the UCLA ADC newsletters. This summary of findings will be

translated into Spanish and, if appropriate, adapted to suit the population of a specific region. In addition to an individual mailing to each participant/caregiver, this information will be conveyed through the project's website.

A Publications Committee will be established to oversee the dissemination of the study findings. It will include members of the NPSC and investigators with content expertise. This structure will allow the stakeholders and investigators to jointly address 1) how to disseminate the study findings to impact clinicians, patients, policy makers, communities, CMS and other payers; and 2) how study interventions can be scaled up for wider implementation. Also, LPSCs will work with site investigators to plan dissemination in their local communities. The patients and stakeholders can be effective particularly in influencing the policies of CMS and other payers, which can facilitate the adoption of the intervention. In addition to publications in scientific journals, the Publications Committee will plan presentations at scientific meetings, and orchestrate presentations to stakeholders, the media, payers, and policymakers.

If HSDC proves to be superior, dissemination will be less of an issue for systems that serve high percentages of capitated patients (i.e. Medicare Advantage), since the program would achieve cost savings if it is as effective as the original UCLA demonstration ($2100 per year cost savings, CMS unpublished data). However, an initial upfront investment will be required. Work on disseminating HSDC, funded by the Commonwealth Fund, will create business cases for adopting organizations to determine how soon they will be able to recapture their investment. In addition, some healthcare systems that have strong cultures of team care may want to adapt the intervention by using BSN registered nurses as Dementia Care Specialists, thereby reducing staffing costs and addressing access in areas that may lack advance practice nurses. If major departures occur (e.g., substituting a BSN registered nurse for a nurse practitioner DCS), then the model would need to be evaluated for fidelity to ensure that similar care is provided. In fee-for-service environments, under the current reimbursement structure, HSBC would likely not generate revenue after costs of the intervention are considered. Nevertheless, there are new and emerging cost reimbursement mechanisms (e.g. 99483 cognitive assessment code, Chronic Care Management) that can be used to offset significant costs. Other obstacles to disseminating HSDC include the lack of a trained workforce and the availability of nurse practitioners who can fill the Dementia Care Specialist role. A grant under consideration by the John A. Hartford foundation for their December 2018 Board meeting would fund the development of a hands-on, in-person skill-building sessions to train nurse practitioners to become Dementia Care Specialists.

If CBDC proves to be superior, health systems that serve high percentages of capitated patients may opt to contract with community-based organizations to provide this service as a member benefit. Systems that largely care for fee-for-service patients will likely have financial obstacles to implement this program. Nevertheless, if CBDC confers clinical advantages, other mechanisms through the Agency for Community Living (ACL) or new Medicare mechanisms might be created to support this program.

If either HSDC or CBDC is superior, diffusion will need to be planned and an organization will need to assume responsibility for ensuring the fidelity within adopting health systems. Such an organization will need to be identified or created.

## 15. REFERENCES

[1] http://www.alz.org/facts/overview.asp accessed 5/8/2018

[2] Pearlin LI (1989). The sociological study of stress. Journal of Health and Social Behavior, 30, 241- 256

[3] Pearlin LI, Mullan JT, Semple SJ, Skaff MM. Caregiving and the stress process: an overview of concepts and their measures. Gerontologist 1990 Oct;30(5):583-94.

[4] Darlak, L., Bass, D. M., Judge, K. S., Wilson, N., Looman, W., McCarthy, C., Morgan, R., Maslow, K., & Kunik, M. E. (2016, February 1). Engagement of veterans with dementia in Partners in Dementia Care: An evidence-based care coordination program. Journal of Applied Gerontology. Advance online publication. http://dx.doi.org/10.1177/0733464815624148

[5] Kaufer DI, Cummings JL, Ketchel P et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci 2000 Spring;12(2):233-239.

[6] Mao HF, Kuo CA, Huang WN, Cummings JL, Hwang TJ. Values of the Minimal Clinically Important Difference for the Neuropsychiatric Inventory Questionnaire in Individuals with Dementia. J Am Geriatr Soc. 2015 Jul;63(7):1448-52. doi: 10.1111/jgs.13473. Epub 2015 Jun 5. PubMed PMID: 26046666.

[7] Thornton M, Travis SS. Analysis of the reliability of the modified caregiver strain index. J Gerontol B Psychol Sci Soc Sci 2003 Mar;58(2):S127-132.

[8] Kroenke K, Strine TW, Spitzer RL, Williams JB, Berry JT, Mokdad AH. The PHQ-8 as a measure of current depression in the general population. J Affect Disord. 2009 Apr;114(1-3):163-73. doi: 0.1016/j.jad.2008.06.026. Epub 2008 Aug 27. PubMed PMID: 18752852.

**[9]** Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med 2001 Sep;16(9):606-613.

[10] Groff AC, Colla CH, Lee TH. Days Spent at Home - A Patient-Centered Goal and Outcome. N Engl J Med. 2016 Oct 27;375(17):1610-1612. PubMed PMID: 27783911.

[11] Nasreddine ZS, Phillips NA, Bedirian V et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc005;53(4): 695-699.

[12] Pendlebury S. T., Welch S. J., Cuthbertson F. C., Mariz J., Mehta Z., Rothwell P. M. (2013). Telephone assessment of cognition after transient ischemic attack and stroke: modified telephone interview of cognitive

status and telephone montreal cognitive assessment versus face-to-face montreal cognitive assessment and neuropsychological battery. Stroke 44, 227–229 10.1161/STROKEAHA.112.673384

[13] Dong Y, Xu J, Chan BP, et al. The Montreal Cognitive Assessment is superior to National Institute of Neurological Disease and Stroke. Canadian Stroke Network 5-minute protocol in predicting vascular cognitive impairment at 1 year. BMC Neurol 2016;16:46.

[14] Liew TM. The Optimal Short Version of Montreal Cognitive Assessment in Diagnosing Mild Cognitive Impairment and Dementia. *J Am Med Dir Assoc*. 2019;20(8):1055.e1–1055.e8. doi:10.1016/j.jamda.2019.02.004

[15] Pfeffer RI, Kurosaki TT, Harrah CH, Jr. et al. Measurement of functional activities in older adults in the community. J Gerontol 1982 May;37(3):323-329.

[16] Katz S, Downs TD, Cash HR, Grotz RC. Progress in development of the index of ADL. Gerontologist. 1970 Spring;10(1):20-30. PubMed PMID: 5420677.

[17] Jennings LA, Palimaru A, Corona MG, Cagigas XE, Ramirez KD, Zhao T, Hays RD, Wenger NS, Reuben DB. Patient and caregiver goals for dementia care. Qual Life Res. 2017 Mar;26(3):685-693. doi: 10.1007/s11136-016-1471-7. Epub 2016 Dec 20. PubMed PMID: 28000094; PubMed Central PMCID: PMC5382930.

[18] Logsdon RG, Gibbons LE, McCurry SM, Teri L. Assessing quality of life in older adults with cognitive impairment. *Psychosom Med*. 2002;64(3):510-519. doi:10.1097/00006842-200205000-00016

[19] Logsdon RG, McCurry SM, Teri L. Evidence-Based Interventions to Improve Quality of Life for Individuals with Dementia. Alzheimers care today. 2007;8(4):309-318. PMID: 19030120; PMCID: PMC2585781.

[20] Hoe, J, Katona, C, Roch, B and Livingston, G. 2005. Use of the QOL-AD for measuring quality of life in people with severe dementia-the LASER-AD study. *Age & Ageing*, 34: 130–135.

[21] Tarlow, B. J., Wisniewski, S. R., Belle, S. H., Rubert, M., Ory, M. G., & Gallgher-Thompson, D. (2004). Positive aspects of caregiving: Con-tributions of the REACH project to the development of a new measure for Alzheimer's caregiving. Research on Aging, 26, 429–453. doi:10.1177/0164027504264493

[22] Roth DL, Dilworth-Anderson P, Huang J, Gross AL, Gitlin LN. Positive Aspects of Family Caregiving for Dementia: Differential Item Functioning by Race. J Gerontol B Psychol Sci Soc Sci. 2015 Nov;70(6):813-9. doi: 10.1093/geronb/gbv034. Epub 2015 Jun 1. PubMed PMID: 26033356; PubMed Central PMCID: PMC4841161.

[23] Peipert JD, Jennings LA, Hays RD, Wenger NS, Keeler E, Reuben DB. A Composite Measure of Caregiver Burden in Dementia: The Dementia Burden Scale-Caregiver. J Am Geriatr Soc. 2018 Sep;66(9):1785-1789. doi: 10.1111/jgs.15502. Epub 2018 Aug 10. PubMed PMID: 30094817.

[24] Reuben DB, Tan ZS, Romero T, Wenger NS, Keeler E, Jennings LA. Patient and Caregiver Benefit From a Comprehensive Dementia Care Program: 1-Year Results From the UCLA Alzheimer's and Dementia Care Program. *J Am Geriatr Soc*. 2019;67(11):2267–2273. doi:10.1111/jgs.16085

[25] Rabarison KM, Bouldin ED, Bish CL, McGuire LC, Taylor CA, Greenlund KJ. The Economic Value of Informal Caregiving for Persons With Dementia: Results From 38 States, the District of Columbia, and Puerto Rico, 2015 and 2016 BRFSS. Am J Public Health. 2018 Aug 23:e1-e8. doi: 10.2105/AJPH.2018.304573. [Epub ahead of print] PubMed PMID: 30138069.

[26] Fitzmaurice GM, Laird NM, Ware JH. Applied longitudinal analysis. Hoboken, NJ: Wiley, 2011.

[27] Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika. 75:800-802, 1988.

[28] Henderson R, Diggle P, Dobson A. Joint modeling of longitudinal measurements and event time data. Biostatistics. 2000;1:465–480.

[29] National Research Council (2010). The Prevention and Treatment of Missing Data in Clinical Trials. Panel on Handling Missing Data in Clinical Trials. Committee on National Statistics, Division of Behavioral and Social Sciences and Education. Washington, DC: The National Academies Press.

[30] Lachin JM. Statistical considerations in the intent-to-treat principle. Controlled Clinical Trials, 21: 167-89, 2000.

[31] FDA Guidance for Industry. Oversight of Clinical Investigations - A Risk-Based Approach to Monitoring. August 2013.

[32] Callahan CM, Boustani MA, Unverzagt FW, Austrom MG, Damush TM, Perkins AJ, Fultz BA, Hui SL, Counsell SR, Hendrie HC. Effectiveness of collaborative care for older adults with Alzheimer disease in primary care: a randomized controlled trial. JAMA. 2006 May 10;295(18):2148-57. PubMed PMID: 16684985.

[33] Reuben DB. Final Progress report for 1C1CMS330982 “UCLA Alzheimer’s and Dementia Care: Comprehensive coordinated, patient-centered” submitted to CMS March 31, 2016.

[34] https://downloads.cms.gov/files/cmmi/hcia-diseasespecific-thirdannualrpt.pdf

[35] Yun, H., Kilgore, M.L., Curtis, J.R. et al. Health Serv Outcomes Res Method (2010) 10: 100. https://doi.org/10.1007/s10742-010-0060-4

[36] Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. N Engl J Med. 2013 Apr 4;368(14):1326-34. doi: 10.1056/NEJMsa1204629. PubMed PMID: 23550670; PubMed Central PMCID: PMC3959992.

[37] Richesson R, Andrews J. *Clinical Research Informatics*. (c) 2012 Springer-Verlag London Ltd

[38] Nahm, M. Data Accuracy in Medical Record Abstraction. Doctoral Dissertation, University of Texas at Houston, School of Biomedical Informatics, Houston Texas, May 6, 2010

[39] Karlawish J, Cary M, Moelter ST, et al. Cognitive impairment and PD patients’ capacity to consent to research. *Neurology*. 2013;81(9):801-807. doi:10.1212/WNL.0b013e3182a05ba5.

[40.] Curtis P, Slaughter-Mason S, Thielke A, et al. *PCORI Expert Interviews Project: Final Report* 2012.