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PRIMA Intervention for Adults With Mild Cognitive Impairment and Their Caregivers

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Abbreviations

AE	Adverse Event
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

1.0 Background & Rationale

Approximately 20% of Americans over 65 have mild cognitive impairment (MCI), defined as experiencing more memory problems than normally expected with aging, but no other symptoms of dementia such as impaired judgment or reasoning.^{1,2} Persons with MCI (patients) are at great risk for developing dementia (10-33% per year).³ Memory problem (poor executive function) diminish the patient's confidence and ability to perform meaningful and/or important activities (e.g. socialization, medication management).⁴⁻⁶

Deteriorating life satisfaction in patients⁷⁻¹⁰ and care partners (caregivers)^{11,12} is a prevalent problem due to diminished meaningful activity engagement which occurs as a result of patient frustration and embarrassment,⁵ lack of self-efficacy (confidence), and diminishing activity performance.⁴⁻⁶ As a result, patients experience additional negative health outcomes: 38% report depressive symptoms¹³ and anxiety.¹³ Caregivers often lack confidence to manage their own and the patient's daily challenges and meaningful activity engagement, leading to high caregiver burden, depressive symptoms, and anxiety.¹⁴⁻¹⁸ As a dyad, both patients and caregivers report diminished satisfaction within their communication and relationship due to disagreement about the patient's functional ability to effectively and safely perform meaningful activities.¹⁹⁻²²

Emerging evidence indicates regular engagement in social, physical or cognitive activities can improve life satisfaction, activity performance, depressive symptoms, anxiety, and dyad communication; health outcomes are even better when the activities are self-selected and meaningful.²³⁻²⁶ To promote patients' and caregivers' life satisfaction and health outcomes, interventions to maximize patients' capacity for full engagement in meaningful activities are essential; yet, there is a marked absence of such empirically validated interventions.

We developed and tested the Daily Engagement in Meaningful Activities (DEMA) intervention to improve life satisfaction and health outcomes for participants and study partners. DEMA is a positive health focused, theoretically grounded, tailored, family-centered, multi-faceted intervention.^{27,28} Over 7 session, dyads work with a nurse to 1) identify meaningful activities, assess capacity, problem-solve barriers, and establish routines for engagement and 2) learn more about MCI by working through six Self-Management Toolkit topics (e.g., benefits of meaningful activity; planning the future).

Our purpose is to evaluate the efficacy of DEMA in a two-group randomized controlled trial with 210 patient/caregiver dyads (DEMA intervention vs. the information support (IS) attention control group).

Objective(s)

1.1 Primary Objective.

Aim 1 (Primary): Test DEMA's efficacy for improving life satisfaction in patients and their caregivers over time.

Hypotheses 1: Patients and caregivers in the DEMA group will have greater improvement in life satisfaction over time compared to the IS group.

1.2 Secondary Objective.

Aim 2 (Secondary): Over time, evaluate DEMA's efficacy for patient and caregiver to:

- 1) increase patient activity performance and diminish depressive symptoms and anxiety.

Hypothesis 2.1: Compared to the IS group, patients receiving DEMA will have improved activity performance and decreased depressive symptoms and anxiety.

- 2) decrease caregivers burden, depressive symptoms, and anxiety .

Hypothesis 2.2: Compared to the IS group, caregivers receiving DEMA will have decreased burden, depressive symptoms, and anxiety.

2.3. Tertiary/Exploratory/Correlative Objectives.

Aim 3: Explore improvement in health outcomes over time in the sub-sample of patients with depressive symptoms using the (PHQ)-9 ≥ 5 at baseline) and explore the burden on caregivers when patients have PHQ-9 is >5 . Compared to the non-depressed participants:

Hypothesis 3.1. Patients with depressive symptoms (scores > 5 on PHQ-9 measured at baseline) will have improved activity performance.

Hypothesis 3.2 Caregivers of patients with depressed symptoms (scores > 5 on PHQ-9 measured at baseline) will report reduced burden.

Hypotheses 3.3. Patients with depressive symptoms (scores > 5 on PHQ-9 measured at baseline) and their caregivers randomized to DEMA will report improved: confidence to manage daily challenges, communication satisfaction, life satisfaction, relationship satisfaction, decreased depressive symptoms and anxiety.

2.0 Outcome Measures/Endpoints

2.1 Primary Outcome Measures

Measure Name	Time Frame	Completed by
Life Satisfaction Index for the Third Age (LSITA) Scale—Short Form	Time 1 (T1) = pre-intervention evaluation, Time 2 (T2) = 10 days post-intervention evaluation, Time 3 (T3) = 3 months post-intervention, and Time 4 (T4) = 6 months post-intervention	Patient Caregiver

2.2 Secondary Outcome Measures

Measure Name	Time Frame	Completed by
Patient Health Questionnaire-9 Items (PHQ-9)	T1 = pre-intervention evaluation, T2 = 10 days post-intervention evaluation, T3 = 3 months post-intervention, and T4 = 6 months post-intervention	Patient Caregiver
The General Anxiety Disorder 7-item (GAD-7)	T1 , T2 , T3, and T4	Patient Caregiver
Alzheimer Disease Cooperative Study MCI-Activities of Daily Living Inventory [ADCS-MCI-ADL Scale]	T1 , T2 , T3, and T4	Caregiver
Relationship Assessment Scale (RAS)	T1 , T2 , T3, and T4	Patient Caregiver
Caregiving Outcomes Scale (COS)	T1 , T2 , T3, and T4	Caregiver

2.3 Tertiary/Exploratory/Correlative Outcome Measures

Measure Name	Time Frame	Completed by
Six-item Screener	Pre-consent	Caregiver

The Montreal Cognitive Assessment (MoCA) ^a	Pre-consent	Patient
Functional Activities Questionnaire (FAQ) ^a	Pre-consent	Patient
University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) ^b	Pre-consent	Patient
Demographic Profile and Comorbidity Condition	Time 1-Pre-intervention Evaluation	caregiver
Patient's Anti-depression medication, Anxiety Medication, and FDA medications for the treatment for Alzheimer's Disease and Related Dementia (ADRD) - (Medication type, dosage, and using time frame),	T1 = pre-intervention evaluation, T2 = 10 days post-intervention evaluation, T3 = 3 months post-intervention, and T4 = 6 months post-intervention	Caregiver Patient
Confidence Scale	T1 , T2 , T3, and T4	Patient Caregiver
The subscale of Communication and Affective Responsiveness (CAR)	T1 , T2 , T3, and T4	Patient Caregiver
Dementia Deficits Scale (DDS) (Patient vs. Caregiver Versions)	T1 , T2 , T3, and T4	Patient Caregiver
The Canadian Occupational Performance Measure (COPM)	T1 = pre-intervention evaluation, All Sessions: Session 1 at Week 1, Session 2 at Week 2, Session 3 at Week 4, Session 4 at Week 6, Session 5 at Week 8, Session 6 at Week 10; Session 7 at Week 12 T2 = 10 days post-intervention evaluation, T3 = 3 months post-intervention, and T4 = 6 months post-intervention	Patient Caregiver
The modified Credibility/Expectancy Questionnaire (CEQ)	T 2 = 10 days post-intervention evaluation	Patient Caregiver

Note: ^aThe MoCA and Functional Activity Assessment scores are obtained from patient record or referral record. ^bThe University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) will be collected by research staff through either in-person or telephone. Other measures will be collected by research staff through telephone.

A strength of our previous study was having over 90% completed measures across all time points.²⁸ Our patients and caregivers reported perceived benefits of and high satisfaction with DEMA and no burden associated with data collection. We also train our staff to monitor and prevent burden.

3.0 Eligibility Criteria.

We report MCI patient/caregiver eligibility together because we will be recruiting MCI patient/caregiver participants in pairs. Eligibility criteria must be met by both the patient and the family caregiver.

3.1 Inclusion Criteria.

Both the MCI patient and caregiver must consent to participate and have a phone at home or daily access to a telephone to be eligible for the study.

MCI patients will be eligible, if they:

- are aged > 59 years old;
- able to speak and read English;
- have both self or informant reported cognitive complaints,
- Cognitive Change Index (CCI-20-I and CCI-20-S) scores > or = 20
- have MoCA score = 15 to 25
- are in the normal range in performance of daily living tasks based on functional impairment absent: a check box of Functional Activities Questionnaire (FAQ) has no score ≥ 2 ;

Family caregivers (spouse, other family members or friends) will be eligible, if they

- self-identify as care partner
- are aged ≥ 18 years old,
- have primary responsibility for providing care to an MCI patient, along with monitoring safety and providing social support;
- are able to speak and read English;
- are oriented to persons, places, and time (having a 6-item Screener score of 4 or above).

3.2 Exclusion Criteria.

MCI patients and family caregivers will be excluded, if the MCI patient or family caregiver dyads participants are:

- a diagnosed untreated severe major depression, or receiving advanced cancer treatment or hospice care,
- receiving dialysis,
- severe hearing loss and no hearing aids,
- have no access to a telephone
- the family caregiver has significant cognitive impairment that may hinder participation (6-item MMSE < 4).²⁹

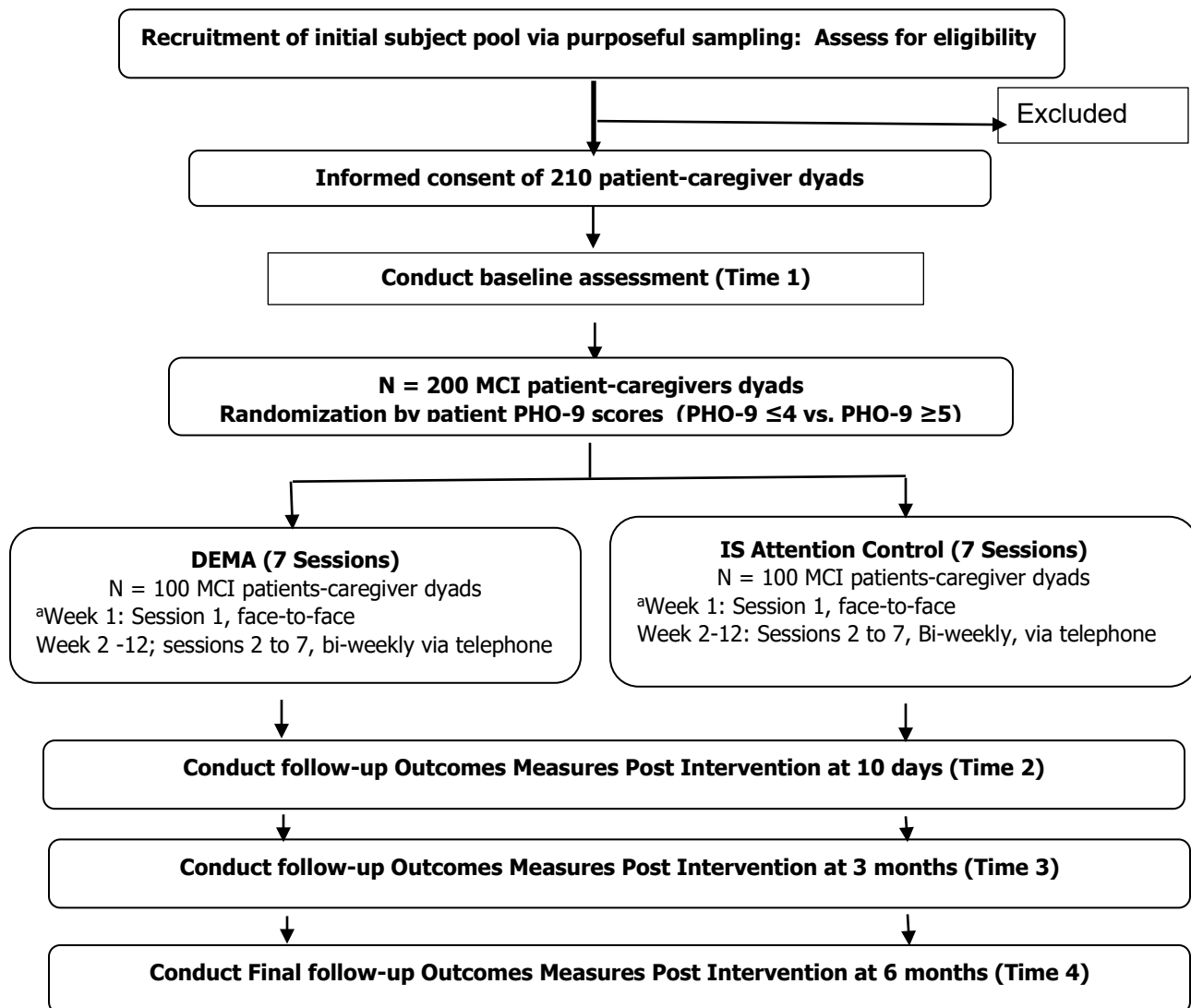
Rationale: From our preliminary studies, we learned that when MCI patients have underlying, untreated mental illness, or the caregiver also has significant cognitive impairment, DEMA is not likely to be delivered as planned in terms of content or dosage.

4.0 Study Design

This is a two-group, single-blind, randomized controlled trial to determine the efficacy of DEMA compared to Information Support (IS) attention control (n=210 patient/caregiver dyads). Two strata are based on depression scores from the PHQ-9 scores, PHQ-9 ≤ 4 vs. PHQ-9 ≥ 5 .^{30,31} Immediately after consent, eligible dyads will complete baseline data collection (T1) and then be randomized. Following randomization, both groups will receive seven 60-minute sessions (1 face-to-face, 6 via telephone) over 12 weeks. This is one session more than our pilot study and based on pilot study post-intervention qualitative data indicating that participants would benefit

from more time to establish their pattern of meaningful engagement.^{28,32} To evaluate immediate and carry-over effects and determine sustainability of meaningful activity with caregiver support, intervention evaluations will occur: within 10 days of intervention completion (T2), and 3-months (T3) and 6-months (T4) post-intervention.^{33,34} Design rationale. Our prior studies suggest that an attention control condition is acceptable to participants without benefit and likely to have similar attrition to our pilot study.^{28,32} Previous problem-solving therapy studies suggest that a usual care condition would likely negatively affect study accrual.^{35,36} The number of sessions and amount of contact time are based on data from our preliminary studies,^{32,37} a systematic review of stroke caregiver interventions,³⁸ and other problem-solving clinical trials with older adults.³⁹⁻⁴¹ During COVID-19 crisis, the subjects can do the first session by phone or zoom for DEMA or IS group.

Figure 1 Study Schema



5.0 Enrollment/Randomization

Recruitment Plan. For this study, 210 MCI patients (patients) and 210 of their caregivers will be recruited from the Indiana Alzheimer Disease Center (IADC) (P30 AG10133) Clinic Core, outpatient memory and neuropsychology clinics, IADC Outreach and Recruitment Core, and the IADC Research Participant Database (See letter of support). Our recruitment and outreach core team will closely cooperate with the IADC support team and follow the recruitment protocol to complete the recruitment process and ensure to meet the goals of our study recruitment and retention (Human Subjects 3.5). The recruitment procedures will be reviewed and approved by the Indiana University Purdue University at Indianapolis Institutional Review Board (IRB) prior to beginning the study.

Following IRB approval, research coordinators staffed by the clinics will use the eligibility checklist to identify potential participants, verify eligibility with Co-I, Dr. Apostolova, and the faculty of the IADRC Clinical Core and, then provide the initial invitation and the initial study

introduction brochure for them to participate. With the potential participant's permission, Dr. Apostolova and the faculty of IADRC will provide the PI and the DEMA project manager with the dyads' signed authorizations for the release of the health information for research forms. After participants consent to be contacted, the project manager and/or trained research staff will contact the patient-caregiver dyads and send either the introduction letter to identified potential participants, and furthermore the recruitment packet to by mail, email or in-person, whichever is most convenient. The recruitment packet includes the study brochure, cover letter, two copies of the authorization for the release of the health information for research forms, and two copies of the informed consent forms. The brochure emphasizes that participation in the study is voluntary and will not affect the care that they will receive in any way, regardless of whether they decide to participate or not. Approximately one week after the study recruitment package is sent, the project manager or trained research staff will contact potential participants by phone and/or follow up via email and explain the study, answer questions, determine their interest, screen for eligibility, and obtained verbal informed consent from those who are eligible and interested in the study. Research staff will make sure to give the patient-caregiver dyads full information about the nature, purpose, and possible risks and benefits of the study by reading the consent form and answering their questions related to the study via telephone. All patients and their caregivers will also be informed that participation in the study is voluntary and they are free to withdraw from the study at any time. In our previous pilot study, we learned that MCI patients and their family caregivers preferred to have time to look over the information, ask questions, and consider participation after receiving the invitation and recruitment package from their physicians.

Although patients suffer some impairment, they are generally capable of providing informed consent and making decisions as documented in many studies, as well as in the PI's previous pilot studies¹⁷⁵⁻¹⁷⁸ as well as in the PI's previous pilot studies.^{23,24} However, to make sure of patients' functional ability to provide informed consent, the research staff will institute the following precautions: 1) All subjects will be asked to be accompanied by a significant other who will be asked to attest by signature to the subject's ability to provide fully informed consent; 2) A series of questions of the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) will be asked by research staff through either in-person or telephone to assure comprehension and capacity to provide consent; 3) all subjects' continued assent will be monitored by the research staff during the study period and subjects will be reminded that they can discontinue participation at any time with no repercussions.

Since the capacity to provide consent may change or fluctuate in individuals with cognitive impairment over the course of the study, it is important to have a legally authorized representative (LAR) involved in the consent process in order to ensure that the best interests of the subject are represented in accordance with the person's premorbid wishes. For this reason, the information on the study is presented to both the potential subject and the LAR at the beginning of the consent process, as well as in an ongoing fashion over the course of the study. In addition, the LAR will be required to sign all documents, and if the subject is capable, he/she must personally sign his/her name and date the main study informed consent, any additional consents specific to the study, and the authorization.

Screening and participant enrollment. If necessary to meet recruitment goals, recruitment will be extended to include the Indiana Clinical and Translational Sciences Institute (CTSI) ResNet (Research Network), partnership with the Wellness on Wheels program with the IU Center of Excellence of Women's Health (See letter of support), our IADC Research Participant

Database, the IADC FaceBook page, the Alzheimer's Association's TrialMatch and clinicaltrials.gov, and outreach to the Alzheimer's Association of Greater Indiana (AAGI; see letter of support). If patient-caregiver dyads are recruited from these sources, participants will be screened for cognitive impairment using a six-item screener by telephone or in-person in a private setting. Rationale. Using a cut-off of ≥ 3 errors on the six-item screener, the sensitivity and specificity for a diagnosis of dementia in this patient population is 88.7 and 88.0, respectively.¹³⁶ It is possible to increase the sensitivity of the screener by lowering the cut-off score to one or two errors but then one loses efficiency by identifying a large number of false positives.¹³⁶ Patients screening positive will complete the MoCA test and the caregiver will complete the patient's Functional Activity Assessment Questionnaire, administered by trained research staff in a private setting (e.g. a conference room or at IADC Clinic or in a private room on the IUPUI Campus). The trained research staff will also use the eligibility checklist with the results of MoCA test and FAQ, and then verify eligibility with Co-I, Dr. Apostolova, and the faculty of the IADC Clinical Core and, then provide the initial invitation and study introduction brochure to potential participants. Those meeting the eligibility criteria, will receive the recruitment package and will follow our recruitment protocol of giving the MCI patient-caregiver dyads full information about the nature, purpose, and possible risks and benefits of the study by reading the consent form and answering questions related to the study by telephone or in person, whichever is most convenient to the dyad. In addition, those meeting the eligibility criteria, will also be invited to receive advanced clinical diagnosis procedure from the IADC Clinic Core, if they are interested in doing so. All MCI patients and their caregivers will also be informed that participation in the study is voluntary and they are free to withdraw from the study at any time. As in our past studies,^{23,24} we will use several strategies to ensure high accrual and retention of participants and minorities:^{140,141} 1) cultural competence training for study staff to increase minority participant recruitment; 2) in-person contact with potential participants to build trust and rapport; 3) large print recruitment material presented to potential participants at the IADC, the Wellness on Wheels program with the IU Center of Excellence of Women's Health, and the Alzheimer's Association of Greater Indiana; as well as frequent clinic staff contact to provide outreach and information to prevent misunderstandings about the study purpose, design, inclusion or exclusion criteria; 4) posting the study on the Alzheimer's Association's TrialMatch and clinicaltrials.gov; the IADC FaceBook page, the Alzheimer's Association's TrialMatch and clinicaltrials.gov, Indiana CTSI study listing called the All IN for Health TrialX iConnect, CICOA (CICOA Aging & In-Home Solutions, Inc.) staff will approach their existing clients over the phone, IU Health Database, local churches, libraries, community centers, retirement centers, advertising the study in a local newspaper, research volunteer websites (researchmatch.org), flyer distribution in various clinician offices; 5) frequent IADRC clinic staff contact to assure full understanding and prevent miss understanding about the study purpose, design, inclusion or exclusion criteria; 6) flexible and convenient scheduling for study related activities.

Randomization. Following consent, the project manager will arrange a time convenient for patient-caregiver dyads to separately complete the baseline (T1) measures by phone. A trained data collector, blinded to randomization status, will administer all measures at all time points via phone interviews in a quiet, private setting and be available for questions following data collection. Immediately following completion of the T1 measures, the data collector will enter patient scores on the PHQ-9 depression scale³¹ directly to the database. A web-based computer-generated stratified randomization scheme will be used to assign the patient-caregiver dyads to DEMA or the IS group in 1:1 ratio using a block-randomized approach

stratified on a depression score PHQ-9 ≤ 4 vs. PHQ-9 ≥ 5 . SAS PROC PLAN version 9.3 or higher will be used to determine the randomization scheme.⁴² The Project Manager will immediately schedule Session 1. Data collectors will be blinded to the group assignments of study participants. Only the statistician, PI, project manager, and the intervener will know the MCI patient-caregiver dyad's randomization status.

6.0 Study Procedures

DEMA. This group will receive 7 individualized sessions, 7 bi weekly telephone sessions delivered by a trained intervener. The DEMA protocol is in Appendix 3 and the DEMA Self-management Toolkit is in Appendix 4. All 7 sessions will be conducted over the phone. To tailor DEMA, patients and caregivers will separately complete the Dementia Deficit Scale to appraise the patients' level of awareness of his or her functional ability and the Canadian Occupational Performance Measure to assess the types and frequencies of daily meaningful activities and barriers to engage in these activities. DEMA will use the principles of problem-solving therapy and consistent with the overall goals of this intervention, DEMA will provide autonomy support by helping patients to identify and prioritize activities, classify needs and goals, generalize manageable solutions, engage in self-selected activities under family support, and self-evaluate failure and success or renew problem-solving as needed.

Session 1 focuses on introducing the MCI dyad to the intervention and meaningful activity concepts, reviewing patient meaningful activity history, and establishing a realistic and manageable weekly meaningful activity plan. Sessions 2 to 7 have two components in each session. First, MCI dyads are guided to use the principles of problem-solving therapy to review their personalized, self-selected meaningful activities and plan next steps to continue the activity and/or identify and establish a plan for additional activities. Second, the intervener and dyad discuss one of the 6 topics in the Toolkit relevant to understanding MCI, its treatments, management, resources, and planning for the future. Patient-caregiver dyads are encouraged to use the DEMA activity log at home, and the self-reported frequency and duration of activities will be collected at Time 2, Time 3, and Time 4 through telephone. To evaluate immediate and carry-over effects and determine sustainability of meaningful activity with caregiver support, intervention evaluations will occur: within 10 days of intervention completion (T2), and 3-months (T3) and 6-months (T4) post-intervention.^{127,128} At the completion of Session 7, study staff may ask permission to use shared photographs of patient-caregiver dyads' meaningful activities for future educational purposes, academic conferences, presentations, and trainings.

Information Support (IS). All 7 sessions will be conducted over the phone on a bi-weekly basis. Patients and caregivers will have the opportunity to ask questions related to the educational materials. The patient-caregivers will complete outcomes measures by the trained research staff through telephone separately that will occur: within 10 days of intervention completion (T2), and 3-months (T3) and 6-months (T4) post-intervention. After completing Time 4 data collection, the patient-caregiver dyads will receive DEMA Self-Management Tool kit package through mail.

7.0 Study Calendar

8.0 Reportable Events

Risks to the participants are considered minimal and include: 1) breach of confidentiality; 2) increasing fatigue for patient or caregiver as a result of participating in the study session activities or completing measures; and 3) psychological discomfort for the patients and their caregivers when responding to evaluation questions.

Protection against Risk:

Confidentiality. To minimize the possibility that a breach in confidentiality will occur, data for this study will be kept separate from any subject identifiers and will be kept in a locked file cabinet. Digital audio recordings of patient/caregiver participation in study sessions will also be uploaded on a secure, password protected computer server that is backed up by the university's main computer system. Only the PI, Co-I, project manager, and designated study staff will have access to the data. Computers where data will be entered will be accessed through passwords and kept in locked offices. Data monitoring will occur in three stages: 1) field editing for missing data by evaluators; 2) office editing by a designated research evaluators after instruments are returned to the office; and 3) listening to random samples of 25% of the audio-taped evaluation sessions and intervention sessions by the PI or Co-I.

Fatigue or burden. To prevent and reduce burden, the interveners and data collectors will be trained to: 1) inform the participants (patients and caregivers about their role as research participants and the process of intervention/ data collection and discuss anticipated barriers to

attending appointments for the intervention session or data collection; 2) provide a routine and convenient schedule for participants to engage in all intervention sessions and data collections while maintaining flexibility; 3) use a reminder letters and phone calls for all appointments and rapid follow-up of missed appointments should be incorporated into the protocol and participants' convenience schedule; 4) inform participants that if they have any concerns (i.e. conflicting schedule, sick) that cause them to be unable to attend sessions, they can call or email the program manager to reschedule the appointments at a convenient time for participants; 5) inform the participant that they can take breaks during intervention session or data collection to meet their needs (e.g., go to rest room or drink a cup of water). Participants will also be told that, if they become tired during a session, the rest of the session can be rescheduled at their convenience with the next week.

To address any fatigue or burden, interveners and data collectors will be trained to observe for increasing fatigue or burden in session one and ask persons with patient /caregiver participants to indicate if the patient's or caregiver's own fatigue or burden is at a level where the activity should be stopped or take a short break during intervention or data collection. Also, intervention sessions or attention control sessions, and evaluations will be stopped if the intervener or evaluator assesses a level of fatigue or burden in the patient or caregiver that precludes their ability to participate. Participants will be informed they can stop the session at any time and/or stop their involvement in the study at any time.

Psychological Discomfort. Study personnel, interveners, evaluators, and data collectors, will receive specific training in identifying and responding to psychological discomfort related to intervention sessions and to evaluation. Patient and their caregivers will be informed they can stop the session at any time and/or stop their involvement in the study at any time, if they become uncomfortable. Study personnel will be alert to any signs of anxiety, anger, or burden from patient -caregiver dyads and tell them that they may terminate participation in this study at any time during the interview. Patient -caregiver dyads will have the opportunity to decline to answer questions that they feel are objectionable. Participants will understand the general nature of the research before agreeing to participate. The possibility of a serious adverse event is low. Study personnel will be trained in basic first aid and will know how to access emergency assistance in the event of a coincidental health emergency (e.g., fall or heart attack) during the first face-to-face session. Should psychological discomfort be identified (i.e., suicidal idea), a protocol will be in place to notify the PI.

Plan for managing adverse events. The possibility of a serious adverse event is low, but an adverse event during randomized treatment (i.e. suicidal idea) did occur in our previous pilot study. Thus we will train our research staff follow the plan of managing adverse events (severe depression or suicidal tendencies) and following suicide protocol. Study personnel will be trained: 1) in basic first aid and will know how to access emergency assistance in the event of a coincidental health emergency (e.g., fall or heart attack) during the first face-to-face session; and 2) how to identify adverse events (e.g., severe depression: PHQ-9 Score >15)³¹ or suicidal tendencies).

All adverse events (e.g., severe depression or suicidal tendencies) and unanticipated problems will be monitored through the nurse intervener delivering the sessions and the research staff during the course study. Current and any changes to anti-depression medication status and comorbidity conditions will be recorded. Any concerns will be documented and reported to the PI and the Data and Safety Monitoring Committee Chair immediately by email or phone call. In

the unlikely event that a patient or caregiver appears to be distressed or an adverse event occurs (e.g., severe depression or suicidal tendencies), participants will be told that they have right to stop treatment and/or measurements at any time as needed, if they experience any adverse events. She or he will be also encouraged to contact his or her primary physicians or be given the telephone number for Eskenazi Mental Health Center (317-880-8491) or the Crisis Hotline 24 hours (317-621-5700, or 1-800-662-3445). If PHQ-9 depression scores are higher than 19, the same procedures will be used.

The PI will inform the faculty of the IADC Clinical Core and the IRB of any adverse events and/or any amendments to the protocol. In addition, the data collectors and interveners will receive training about how to respond to any potential adverse events experienced by family caregivers, such as severe depression or suicidal tendencies. Patients or caregivers with these types of problems will be given information about how to seek help and will be encouraged to inquire whether medication and/or psychological counseling would be helpful. In the event of severe depression or suicidal thoughts, the PI or her research staff may contact the faculty of IADC Clinical Core on the patient and their family caregiver's behalf so that they can contact them directly to determine if treatment is necessary. Training on how to respond to these types of issues for data collectors and nurse interveners will also include a detailed suicide protocol and role-playing.

9.0 Data Safety Monitoring

This study involves minimal risk. Minimal risk is defined as the probability and magnitude of physical or psychological harm that does not exceed that encountered in ordinary, everyday life or in the performance of routine medical or psychological examinations.

Monitoring entity or who will monitor the study

The Principal Investigator (PI) will be responsible for executing the Data and Safety Monitoring Plan and complying with the reporting requirements. Our DSMP will be included as part of the protocol and submitted to the Indiana University-Purdue University Indianapolis (IUPUI) Institutional Review Board (IRB) for review and approval. The Data and Safety Monitoring Plan includes twice per year data safety monitoring by the Data and Safety Monitoring Committee (DSMC), which includes three internal research team members and three external scientists. The internal research team includes the PI, Dr. Gao (statistician), co-investigators, Haase, and Apostolova. The three external research scientists are Drs. Susan Hickman (Chair), Sheri Robb, and Janet Carpenter. Dr. Hickman has a strong research background in ethics, and she is currently the Co-Director of Research in Palliative and End-of-Life Communication and Training Center at IUPUI. Dr. Robb is a senior investigator and has a background in quality-of-life research with children, adolescents and young adults with cancer. Dr. Carpenter is a senior investigator and has very strong background in preventing breast cancer through identifying non-hormonal treatments for menopausal hot flashes. Dr. Hickman will be the Chair of the DSMC. Drs. Hickman and Robb served as external scientists of the DSMC for our previous R21 pilot study (2012-14). Data quality, subject recruitment, retention, outcomes, adverse events, scientific reports that indicate potential subject safety impact, and privacy monitoring will be provided by the DSMC.

There are five groups of personnel in this study: 1) Administrative team consisting of Lu, PI; Co-I: Gao (the statistician), Haase, Austrom, and Apostolova; and Project Manager (PM). 2) Recruitment & Outreach core team consists PI, Co-Is: Apostolova, and PM. This team will work with IADC Support Team closely to ensure goals of recruitment and retention are met and to minimize burdens on patient and their caregivers. 3) Intervention team consisting of 4 nurse interveners (2 FTE) (2 trained to deliver DEMA and 2 trained to IS conditions). In addition to

initial and then random self-evaluation of quality of protocol delivery by interveners, data collectors, and evaluators, Lu will monitor intervention and control session integrity (intervention consistency) and the PM will monitor adherence to study session timelines. 4) Evaluation team consisting of 2 data collectors to complete data collections and the certified evaluator(s) to monitor quality of both intervention data collection sessions based on the audio-recordings. 5) Data core team including 1 data manager and 1 master level of statistician who are supervised by Dr. Gao. The data management team will design and test the REDCap data system using standard operating procedures to manage data collection and ensure data integrity, security, and quality assurance; investigate and resolve data questions; identify any outliers or errors; and conduct data analysis. Lu will monitor data integrity (evaluator consistency) and the PM will monitor adherence to data collection timelines. In addition, Gitline (Consultant) will consult with Lu (PI) and provide bi-monthly conference/Zoom calls and as needed conference calls or emails to discuss progress and process of the intervention, including content, delivery, fidelity, and outcomes throughout the study.

Training. All personnel (PM, nurse interveners, data collectors, evaluators) will attend separate, one-day training sessions at start-up of the grant. Similar training was successfully implemented and evaluated for our previous trial (R21NR013755-02). The training consists of 1) an overview of grant objectives, theoretical framework, research design, and rationale; 2) background and training on collecting data free from bias (evaluators); 3) basic information on scale and item response issues (evaluators and data collectors); 4) delivery of study conditions based on specified protocols (nurse interveners); protection of human subjects and confidentiality issues; and 5) data monitoring and quality assurance procedures (evaluators). Activities for training will consist of lectures, discussions, computer data base training, and role-play with feedback.

Database Tracking of Recruitment, Accrual, and Retention. The PI (Lu) and PM will monitor and review reports on weekly recruitment, as well as enrollment and accrual activities with monthly goals. Our data management staff will create an on-line REDCap system to monitor timeliness of evaluation, intervention activities based on protocol-defined time limits, retention based on assumptions about anticipated patient /caregiver participant attrition, and tracking of refusals and attrition (including rationale statement) in order to discern early patterns that may be minimized by focused recruitment and retention efforts.

Data Integrity and Security. IRB approval and all informed consents will be kept in a locked file cabinet in a secure, key-entry, location. All computers will be password-protected. Only trained grant personnel will have access to data. Once call data have been linked to individuals, all identifiers will be deleted. Additional precautions will be taken with digital audio data; these data will be stored in a separate, password-protected file on a computer server that is backed up by the university's main computer system.

All interviewers will be required to audio record all data collection sessions, which will be reviewed for quality assurance. All interveners will be required to audio record all intervention session, which will be reviewed for intervention protocol adherence and quality assurances. The PI, project manager, and evaluators will use an evaluation checklist to assess the quality of data collection interviews and adherence to study protocol. Any unusual events or questions that arise from the evaluation checklist of interviewer notes will be shared with the data safety and management committee.

Data from all telephone interviews will be directly entered into REDCap by trained research staff using a password-protected computer that is backed up regularly by the University. The REDCap system will be used to manage study data. Paper forms will be available should there

be any technical difficulties during the intervention and data collection process. A telephone log and Participant Calendar will be used to track and schedule participants' meetings. We will review and process data using multiple verifications and edit-checking programs. After exporting data from REDCap into a SAS-format data set, descriptive statistics will be used to identify patterns of missing and outlying values. Questionable values in the exported data will be verified using hard copy forms.

All data will be linked to subjects via a unique subject ID. A list of coded numbers identifying names, telephone numbers, and addresses will be kept in a locked file cabinet in the project manager's office. The data collectors will collect all study data confidentially through phone interviews in a secure office. Once obtained, separate file cabinets will be used for personal identifiers and data collection forms that have just the study ID numbers. All material will be stored in locked file cabinets or secure rooms with controlled access. This information will be destroyed after all relevant data have been collected. The REDCap database and digital audio-recordings will be housed in password protected files on a secure server at the IU School of Nursing. All completed digital audio-recordings, data coding sheets, and computer files will be kept secured per the required length of time set by the IRB and then properly destroyed accordingly. Only authorized study personnel will have access to the database or contact information for the participants enrolled in the study. The results of the study will be analyzed and reported only as group data. No individual or individual responses will be identified.

In bi-weekly in-person, virtual, or phone meetings, we will discuss any potential or existing problems. In additionally, the University has a process in place where random monitoring for data integrity will be occur by a committee to the grant staff.

To minimize the risk of experimental drift and diffusion, interveners, data collectors, and evaluators will all have self and external quality assurance monitoring for all intervention or measurements sessions of their first three dyads and then randomly selected monitoring of 25% of subsequent interventions/evaluations by the external monitor. And they will receive written and verbal feedback. Interveners and data collectors are located in different areas and are not likely have opportunities to interact, since most activities are by phone. Risk for experimental drift, bias, and diffusion will be addressed through twice per year assurance monitoring procedures established in our previous study.

Missing Data and Multiple Comparison. Based on our pilot studies with very few missing data^{27,28} and the Little et al' recommendation,⁴³ several strategies for preventing missing data and managing missing data were developed. We will ensure participants fully understand the consent information to enhance their commitment to complete study; provide convenient times for intervention and data collection sessions; ensure availability of make-up sessions; track reasons for drop-out to identify any changes to study flow that may influence retention; keep up-to-date participant contact information; and provide assistive devices (headphone or speakerphones) if a participant's auditory acuity declines and interferes with interventions or outcome assessments. Our research team will follow the principles for drawing inferences; estimate the treatment effect in the key domains (Life Satisfaction and PHQ-9); document the reasons of missing data; conduct a statistically valid analysis under primary missing-data assumptions; assess the robustness of inferences about treatment effects to various missing-data.

The mixed effects model⁴⁴ approach we plan to use is robust under the missing at random assumption (i.e. the probability of missing is not related to the missing observations). We will compare baseline characteristics of dyads who drop out during follow-up with those who complete the trial to detect potential violation to the missing at random assumption. Intention to treat analysis will be used in all analyses.^{45,46} Further sensitivity analyses will be performed using imputations or a full parametric likelihood approach assuming various patterns of missing data. Our sample size and power estimation had accounted for 20% attrition rate during follow-up and should remain adequately powered with moderate drop-out. For the primary and secondary aims, we did not propose multiple comparison adjustment as these are focused hypotheses based on our pilot studies. We will adjust for multiple comparisons in the exploratory aim.

Identification of Adverse Events.

For this study, any Adverse Event will be defined as any reaction or undesirable even that occurs while a subject is on the research protocol whether or not is considered relate to the study intervention (DEMA). Such events could include illness, signs, symptoms, or abnormal laboratory tests that have appeared or worsened during the course of the trial regardless if any causal relationship to the study can be made.

All adverse events (e.g. severe depression or suicidal tendencies) and unanticipated problems (e.g., heart attack, stroke) will be monitored through the nurse intervener delivering the sessions and the data collector(s) during the course study. The PI, project manager, the intervener(s), and the evaluators (s) will be alert to any signs of adverse events by using adverse event grading scale.

Adverse and Serious Adverse Event Grading

The following adverse event grading scale will be used:

- Mild-Awareness of sign or symptoms, but easily tolerated.
- Moderate-Interference with normal activities
- Severe: Inability to perform normal daily activities (e.g. severe depression, PHQ-9 Score >15 or suicidal tendencies)
- Life threatening- Immediate risk of death from the reactions as it occurred

The Relationship between adverse events and the study intervention, control, and evaluation session will be determined based on clinician examination of the patient and subsequent clinical judgment. The following scale will be used to describe the relationship:

- Definite: Adverse event clearly related to study intervention (activity)
- Probable; Adverse event likely related to study intervention (activity)
- Possible: Adverse event may be related to study intervention (activity)
- Unlikely: Adverse event doubtfully related to study intervention (activity)
- Unrelated: Adverse event clearly not related to study intervention (activity)

A Serious Adverse Events is an Adverse Event that results in one of the following:

- 1). Death- death to any cause
- 2) Life-threatening condition- the subject was at potential risk of dying at the time of the adverse event or if it is suspected that the use of study intervention would result in the subject's death.

- 3). Hospitalization –this indicated the initial admission to the hospital or prolongation of hospital stay that results from the adverse event.
- 4). Disability- the adverse event has resulted in a significant/persistent/permanent change impairment, damage or destructions of subject's body function/structure, physical activities, or quality of life.

We do not anticipate any of these based upon the nature of the study and the risks to the subjects is minimal.

Adverse Event Reporting.

Adverse events will be reported to the PI or project manager within 24 hours. Decisions on grading of adverse events and the relationship of adverse events to study conditions will be done by the PI, in consultation with relevant team members. All Adverse Events that meet the criteria in the IU HRPP Reportable Events policy will be reported to the Institutional Review Board within 5 business days. All other adverse events will be reported annually with the continuing review.

Response to severe depression (PHQ-9 Score >15) or suicidal tendencies

The PI, project manager, the intervener(s), and the evaluator(s)/data collector(s) will be alert to any signs of adverse events (i.e. severe depression: PHQ-9 Score >15 or suicidal tendencies) patient-caregiver dyads and tell them that they have right to stop treatment and/or measurements at any time as needed, if they experience any adverse events. She or he will be also encouraged to contact his or her primary physicians or be given the telephone number for Sandra Eskenazi Mental Health Center (317-941-5003) or the Crisis Hotline 24 hours (317-621-5700, or 1-800-662-3445). If PHQ-9 depression scores are higher than 19, the same procedures will be used. In the event of severe depression or suicidal thoughts, the PI or her research staff may contact the faculty of IADC Clinical Core on the patient's and their family caregiver's behalf so that they can contact them directly to determine if treatment is necessary. The PI will inform the faculty of the IADC Clinical Core and the IRB of any adverse events and/or any amendments to the protocol.

Given that this study is minimum risk, no interim analysis for efficacy is planned and no stop rule will be used. The DSMC will monitor the safety of study participants on an ongoing basis and can stop the trial for safety concerns.

List of Specific Information Evaluated at the Time of each DSMP Committee Review

We (PI and PM) will examine recruitment, accrual, and dropout statistics, number and description of any adverse events (AE) or serious adverse events (SAE), comparison of AE and SAE to stopping rules of determination of needs for study close, and any other additional condition. The PI will immediately report any adverse events to the Indiana University IRB. The PI will notify the IRB and NIH any necessary modifications to this protocol. No protocol modification will be instituted without IRB approval. This plan has been successfully in monitoring all aspects of our previous R21 meaningful activity engagement intervention pilot study.

Describe which adverse events will be listed and analyzed: The adverse events review will be depend upon the specific protocol and may include:

- Any and all Adverse Events.

- A table with the number of adverse events and their severity will be used in the DSMC reports to assess the level of risk that occurred.
- List who will receive the summary of the DSMC reviews: Institutional Review Board (IRB):
 - Principal Investigator
 - Institutional Review Board (IRB)
 - Sponsor

10.0 Study Withdrawal/Discontinuation

To address any fatigue or burden, interveners and data collectors will be trained to observe for increasing fatigue or burden in session one and ask persons with patient /caregiver participants to indicate if the patient's or caregiver's own fatigue or burden is at a level where the activity should be stopped or take a short break during intervention or data collection. Also, intervention sessions or attention control sessions, and evaluations will be stopped if the intervener or evaluator assesses a level of fatigue or burden in the patient or caregiver that precludes their ability to participate. Participants will be informed they can stop the session at any time and/or stop their involvement in the study at any time.

Psychological Discomfort. Study personnel, interveners, evaluators, and data collectors, will receive specific training in identifying and responding to psychological discomfort related to intervention sessions and to evaluation. Patient and their caregivers will be informed they can stop the session at any time and/or stop their involvement in the study at any time, if they become uncomfortable. Study personnel will be alert to any signs of anxiety, anger, or burden from patient -caregiver dyads and tell them that they may terminate participation in this study at any time during the interview. Patient -caregiver dyads will have the opportunity to decline to answer questions that they feel are objectionable. Participants will understand the general nature of the research before agreeing to participate. The possibility of a serious adverse event is low. Study personnel will be trained in basic first aid and will know how to access emergency assistance in the event of a coincidental health emergency (e.g., fall or heart attack) during the first face-to-face session. Should psychological discomfort be identified (i.e., suicidal idea), a protocol will be in place to notify the PI.

11.0 Statistical Considerations

Sample Size. We will enroll **210** patients-caregiver dyads (100 dyads randomized per group) to retain 80 dyads per group at end-of-study. In our pilot trial,²⁸ 94% completed all study activities for an overall 6% attrition rate. To account for the 6th month evaluation we factored in a 20% attrition rate, which doubles the attrition rate observed in our pilot study²⁸ and doubles the reported attrition rate at 1-year in a large cognitive training trial.⁴⁷

Statistical Power: Sample size for this trial was estimated using data from our pilot study wherein the DEMA group showed an increase of 0.57 *SD* in Life Satisfaction Index for the Third Age-Short Form (LSITA) score while the IS group showed 0.21 *SD* increase in LSITA from T1 to T3. Using mean LSITA scores in the DEMA group and the IS group for times T1 to T3 and standard deviation estimated from our pilot data and assuming similar trends for the two groups at T4, we estimate that a sample size of 80 per group is required to detect a significant group and time interaction with an effect size of 0.38 *SD* at the $\alpha=0.05$ level. Since we expected

comparable baseline LSITA scores between the two groups, our projected effect size will allow 80% power to detect a difference in mean LSITA scores at T4 that is 0.38 *SD* or greater. Our pilot study, with follow-up to T3, had 6% attrition rate. Thus using an anticipated 20 % attrition rate with longer follow-up to T4, we plan to enroll **210** patient-caregiver dyads (100 dyads per group) into the study. Research Strategy B.4.2. **Table 2** includes estimated power for the hypotheses in each aim. For Aims 1 and 2, estimated power was calculated using the GLMPOWER procedure in SAS for repeated measures using either our preliminary data or reported effect sizes from previous studies. Power for Aim 3 was calculated using the POWER procedure in SAS for multivariate regression models assuming adjusting for four covariates.

12.0 Statistical Data Management

Database Tracking of Recruitment, Accrual, and Retention. The PI (Lu) and PM will monitor and review reports on weekly recruitment, as well as enrollment and accrual activities with monthly goals. Our data management staff will create an on-line REDCap system to monitor timeliness of evaluation, intervention activities based on protocol-defined time limits, retention based on assumptions about anticipated patient /caregiver participant attrition, and tracking of refusals and attrition (including rationale statement) in order to discern early patterns that may be minimized by focused recruitment and retention efforts.

Data Integrity and Security. IRB approval and all informed consents will be kept in a locked file cabinet in a secure, key-entry, location. All computers will be password-protected. Only trained grant personnel will have access to data. Once call data have been linked to individuals, all identifiers will be deleted. Additional precautions will be taken with digital audio data; these data will be stored in a separate, password-protected file on a computer server that is backed up by the university's main computer system.

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All data will be linked to subjects via a unique subject ID. A list of coded numbers identifying names, telephone numbers, and addresses will be kept in a locked file cabinet in the project manager's office. The data collectors will collect all study data confidentially through phone interviews in a secure office. Once obtained, separate file cabinets will be used for personal identifiers and data collection forms that have just the study ID numbers. All material will be stored in locked file cabinets or secure rooms with controlled access. This information will be destroyed after all relevant data have been collected. The REDCap database and digital audio-

recordings will be housed in password protected files on a secure server at the IU School of Nursing. All completed digital audio-recordings, data coding sheets, and computer files will be kept secured per the required length of time set by the IRB and then properly destroyed accordingly. Only authorized study personnel will have access to the database or contact information for the participants enrolled in the study. The results of the study will be analyzed and reported only as group data. No individual or individual responses will be identified.

In bi-weekly in-person or phone meetings, we will discuss any potential or existing problems. In additionally, the University has a process in place where random monitoring for data integrity will be occur by a committee to the grant staff.

To minimize the risk of experimental drift and diffusion, interveners, data collectors, and evaluators will all have self and external quality assurance monitoring for all intervention or measurements sessions of their first three dyads and then randomly selected monitoring of 25% of subsequent interventions/evaluations by the external monitor. And they will receive written and verbal feedback. Interveners and data collectors are located in different areas and are not likely have opportunities to interact, since most activities are by phone. Risk for experimental drift, bias, and diffusion will be addressed through twice per year assurance monitoring procedures established in our previous study.

Missing Data and Multiple Comparison. Based on our pilot studies with very few missing data^{27,28} and the Little et al' recommendation,⁴³ several strategies for preventing missing data and managing missing data were developed. We will ensure participants fully understand the consent information to enhance their commitment to complete study; provide convenient times for intervention and data collection sessions; ensure availability of make-up sessions; track reasons for drop-out to identify any changes to study flow that may influence retention; keep up-to-date participant contact information; and provide assistive devices (headphone or speakerphones) if a participant's auditory acuity declines and interferes with interventions or outcome assessments. Our research team will follow the principles for drawing inferences; estimate the treatment effect in the key domains (Life Satisfaction and PHQ-9); document the reasons of missing data; conduct a statistically valid analysis under primary missing-data assumptions; assess the robustness of inferences about treatment effects to various missing-data.

The mixed effects model⁴⁴ approach we plan to use is robust under the missing at random assumption (i.e. the probability of missing is not related to the missing observations). We will compare baseline characteristics of dyads who drop out during follow-up with those who complete the trial to detect potential violation to the missing at random assumption. Intention to treat analysis will be used in all analyses.^{45,46} Further sensitivity analyses will be performed using imputations or a full parametric likelihood approach assuming various patterns of missing data. Our sample size and power estimation had accounted for 20% attrition rate during follow-up and should remain adequately powered with moderate drop-out. For the primary and secondary aims, we did not propose multiple comparison adjustment as these are focused hypotheses based on our pilot studies. We will adjust for multiple comparisons in the exploratory aim.

13.0 Privacy/Confidentiality Issues

To protect privacy, the face-to-face session will be held at a private and quiet conference or clinical room at IADC clinical site and the IUPUI campus conference room. For the telephone intervention sessions and evaluations, the participants will be asked to use a private and quiet room in their homes and the interveners/evaluators will also use a private and quiet room.

To minimize the possibility that a breach in confidentiality will occur, data for this study will be kept separate from any subject identifiers and will be kept in a locked file cabinet. Digital audio recordings of patient/caregiver participation in study sessions will also be uploaded on a secure, password protected computer server that is backed up by the university's main computer system. Only the PI, Co-I, project manager, and designated study staff will have access to the data. Computers where data will be entered will be accessed through passwords and kept in locked offices. Data monitoring will occur in three stages: 1) field editing for missing data by evaluators; 2) office editing by a designated research evaluators after instruments are returned to the office; and 3) listening to random samples of 25% of the audio-taped evaluation sessions and intervention sessions by the PI or Co-I.

14.0 Follow-up and Record Retention

Retention Plan. As in our past studies^{27,28} and other scholars suggestions,⁴⁸⁻⁵⁰ strategies to ensure high accrual (98%) and retention (94%) will include: 1) cultural competence training to increase the recruitment of African-American and Hispanic participants, 2) in-person contact with participants in the first face-to-face session to develop trust relationship; 3) ensuring that participants fully understand the study propose and design to prevent misunderstanding;⁵¹ 4) using large print on study materials (e.g. educational materials); 5) following the intervention/data collection protocol to identify and manage any signs of adverse events; 6) verbal thanks and confirmation of the next scheduled session from research staff through phone calls after each intervention session and data collection; 7) reminder phone calls from research staff to participants at least 1-2 days prior to each data collection and intervention session; and 8) Thank you cards from research staff mailed to the participants after each intervention session and data collection. The PI, project manager, and a Data and Safety Monitoring Committee (DSMC) will monitor recruitment and retention.

Finally, after receiving the signed consent form from patient-caregiver dyads in person, by mail or fax within 10 days, our project manager/trained research staff will contact and schedule pre-intervention evaluation (baseline data collection) by telephone.

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16.0 Appendix

- Appendix 1 Measurement
- Appendix 2 DEMA Self-Management Toolkits
- Appendix 3 Treatment Fidelity Strategies
- Appendix 4 Suicide Protocol