Outreach-ER: A Dementia Care Intervention Program

Short Title: Outreach-ER

Protocol Number: Version 1.2

National Clinical Trial (NCT) Identified Number: NCT05451693

Principal Investigator: Bhavani Kashyap, MBBS, PhD

Sponsor: HealthPartners Neuroscience Research

Institutional Review Board Number: A22-086

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the terms of the award.

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46) All personnel involved in the conduct of this study have completed human subjects protection training.

INVESTIGATOR'S SIGNATURE

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

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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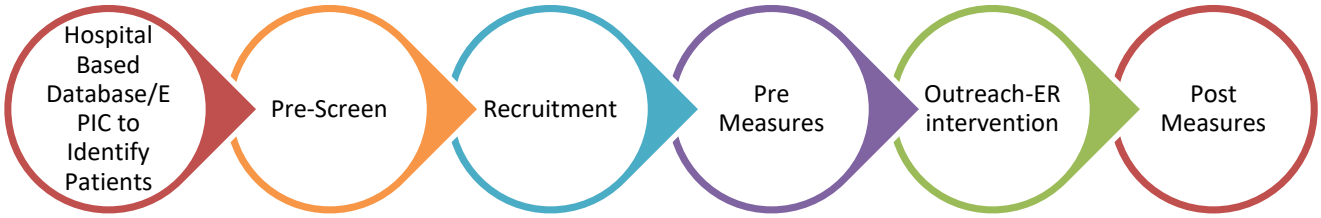
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Outreach-ER: A Dementia Care Intervention Program
IRB Number:	A# 22-086
Study Description:	This is a feasibility/pilot, prospective cohort study to determine how to implement and refine Outreach-ER intervention for a larger clinical study. A key feature of Outreach-ER is to reach out to PLWD and their families following an emergency room visit or hospitalization. The outcome of this study will help in the overall goal of studying the impact of Outreach-ER in a larger clinical study and focus on outcomes relevant to PLWD and their care partners.
Specific Aims and Outcomes:	Aim 1: To assess the feasibility and acceptability of Outreach-ER. This aim will be accomplished by collecting detailed process data which will allow the assessment of registration, enrollment, retention, and adherence/fidelity to the program Aim 2: To assess feasibility of collecting outcomes and explore the effectiveness of Outreach-ER. In care partners, we will evaluate the pre-post benefits of Outreach-ER to improve mood (Center for Epidemiologic Studies Depression Scale-10), reduce burden (Zarit Burden Interview-12), reduce stress (Perceived Stress Scale) and improve quality of life. We will describe and report healthcare utilization in PLWD, such as 30-day hospital readmissions and number of emergency room visits.
Study Population:	*Inclusion Criteria* • *PLWD with a recent Emergency department visit or admission at Regions Hospital or Methodist Hospital* • *Diagnosis of dementia based on ICD Codes in the medical record* • *Provides informed consent prior to participation* • *Must be able to read and speak English* • *PLWD Living at Home* • *Age >=18 years for PLWD and their care partner* *Exclusion* • *PLWD living in a nursing home/Long term care – Assisted living facility* • *Current involvement in another clinical research study/trial for care partners* • *PLWD MRN on the HP exclusion list* Sample Size: We plan to enroll 30 PLWD and their families.
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at HealthPartners Neuroscience Center, located at 295 Phalen Blvd., St. Paul, MN 55130.
Study Duration:	The duration of this study is 1.5 years.
Participant Duration:	Participants are in the study for 5-6 months

1.2 SCHEMA



2 INTRODUCTION

2.1 BACKGROUND & STUDY RATIONALE

Alzheimer's disease affects 6.2 million individuals in the United States and results in an annual cost of care of $355 billion, including $239 billion in Medicare and Medicaid payments combined ("2021 Alzheimer's disease facts and figures," 2021). People living with dementia (PLWD) often receive poorly coordinated and fragmented care that can lead to ineffective care and poor health outcomes, including trips to the emergency department and hospitalizations (Hirschman & Hodgson, 2018). Care for PLWD is demanding and stressful, as the needs of those with dementia are constantly evolving as their behavior and abilities change. Caregivers often experience mental health concerns such as anxiety and depression, poor physical health, compromised immune system, and emotional and social issues due to the demands and stress of caregiving (Elliott, Burgio, & DeCoster, 2010; Ferrara et al., 2008).

Multicomponent non-pharmacological psychosocial care interventions such as REACH (Resources for Enhancing Alzheimer's Caregiver Health), or NYUCI (NYU Caregiver Intervention) include more than one care technique or delivery method to foster support, expertise, information, or skills for caregivers to improve caregiver quality of life and health outcomes. These interventions usually include therapy and social support, education, supportive feedback, goal setting, and planning, as well as relaxation and physical exercises. These are offered as structured approaches to develop skills for problem solving, improving communication and improve relationships for caregivers and PLWD. These approaches have been recognized as high priority in the Alzheimer's research community to study the real-world effectiveness and implementation across different health care settings (Larson & Stroud, 2021). The multicomponent interventions such as REACH, NYUCI have been shown to reduce stress, improve depression, well-being of caregivers and delays nursing home placement of PLWD (OUT, 2018). Key challenges to these interventions include implementation, identifying & tailoring interventions to specific level of dementia and care partner support, and efficacy of caregiver-related interventions (Gaugler, Jutkowitz, & Gitlin, 2020; Hodgson & Gitlin, 2021). REACH-TX was effective in improving quality of life and decreasing caregiver burden when administered by a community agency, as there were

significant statistical improvements from baseline to 6 months on quality of life for caregivers (Cho, Luk-Jones, & Stevens, 2018). NYUCI has also been modified to provide support to different caregivers including adult children and families and has shown similar improvement in caregiver outcomes (Sperling et al., 2020). In Minnesota, there is currently a study in progress to adapt this intervention to be delivered in combination with adult day services (Gitlin et al., 2019). A key missing element in these clinical trials was that PLWD who have had multiple recent emergency visits or hospitalizations were excluded. In this proposed study we are utilizing a psychosocial interventional approach like REACH and NYUCI with a focus on PLWD with recent ER visits or hospitalizations and their care partners, as the needs and burden are different (Benner, Steiner, & Pierce, 2018).

Multicomponent intervention-based studies have focused on caregiver outcomes and have specifically not examined the effects on PLWD healthcare utilization outcomes. Individuals with dementia are more often hospitalized than those without dementia. In many cases, these hospitalizations are avoidable (Phelan, Borson, Grothaus, Balch, & Larson, 2012). In 2013, 21% of hospitalizations for fee-for-service Medicare enrollees with Alzheimer's or dementia were either unplanned readmissions within 30 days of prior hospitalization, or an ambulatory care visit for a condition that was potentially avoidable with effective outpatient care ("2021 Alzheimer's disease facts and figures," 2021). Studies suggest that caregiver burden and stress may be associated with healthcare utilization of PLWD (Guterman et al., 2019; Lau et al., 2021). In a cross-sectional survey with 399 PLWD and their caregivers, caregiver distress from behavioral and psychological symptoms (BPSD) was positively associated with emergency room utilization, while caregiver burden was positively associated with length of hospital stay (Lau et al., 2021).

We propose to study a new care intervention called Outreach-ER. A key feature of Outreach-ER is to reach out to PLWD and their families following an emergency room visit or hospitalization. In this study, we will assess the feasibility of identifying and recruiting PLWD and their families and collect health-related outcomes to explore its effectiveness. The outcome of this study will help in the overall goal of studying the impact of Outreach-ER in a larger clinical study and focus on outcomes relevant to PLWD and their care partners.

2.2 RISK/BENEFIT ASSESSMENT

2.2.1 KNOWN POTENTIAL RISKS

There are minimal risks associated with participation in this study

Survey and Assesments
The questions on these assessments may make participants feel uncomfortable because some parts may be easy to answer, while some parts may be difficult or tiring. It may also cause individuals to feel uncomfortable or upset. The health history survey probes for personal health history information that may be sensitive information. Participants may skip any questions that make them feel uncomfortable.

One risk is that participants may experience discomfort or fatigue in having research staff call or visits to your home.

Loss of Confidentiality
There may be a slight possibility of breach of confidential information that was collected. However, the following procedures will be implemented to reduce this risk:

- Data collection and reporting tools will be developed and stored internally.
- Data collected and stored electronically will remain confidential and secure (e.g. secured server and password protected files [REDCap]).
- Study binders will be stored in a locked file cabinet within a locked office.
- After the study is closed, all subject identifiers will be destroyed.

2.2.2 KNOWN POTENTIAL BENEFITS

Participants may or may not benefit from this study. Similar interventions have shown benefits with regard to care partner outcomes such as reducing burden, improving mood and reducing stress. The participants will receive the written care plan from experts. The results of this may aid in future clinical research studies for care intervention programs for People living with Dementia and their families.

2.2.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

We believe the potential risks to the participants in this study are minimal.

The following measures will be taken to protect providers and patients from the risk of breach of confidentiality:

- A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient and used to link data from various sources and needed for analysis. The study number will be used on the RedCap database.
- All field notes and assessment data from the consultants will be uploaded/transcribed in REDcap.

3 OBJECTIVES AND ENDPOINTS

Aim 1: To assess the feasibility and acceptability of Outreach-ER.
• Recruitment rate • Participation rate • Completion rate • Session completion rate • Questionnaire specific response rate
Aim 2:
Care Partners • Rate of completion for all scales • Exploratory- effectiveness
PLWD • 30-day hospital readmission rate

- Number of ED visits in 6 months before and 3-month period following the intervention
- Number of ED to Hospital admission in 6 months before and 3-month period following the intervention
- Number of Clinic visits (planned/unplanned) 6 months before and in a 3-month period following the intervention

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a feasibility/pilot, prospective cohort study to determine how to implement and refine Outreach-ER intervention for a larger clinical study.

Aim 1
To assess the feasibility and acceptability of Outreach-ER. This aim will be accomplished by collecting detailed process data which will allow the assessment of registration, enrollment, retention, and adherence/fidelity to the program. This is an important step prior to moving forward with a larger trial. We will also utilize mixed methods approach, including semi-structured interviews and surveys to assess the acceptability and experience of participants.

Aim 2
To assess feasibility of collecting outcomes and explore the effectiveness of Outreach-ER. In care partners, we will evaluate the pre-post benefits of Outreach-ER to improve mood (Center for Epidemiologic Studies Depression Scale-10), reduce burden (Zarit Burden Interview-12), reduce stress (Perceived Stress Scale) and improve quality of life. We will describe and report healthcare utilization in PLWD, such as 30-day hospital readmissions and number of emergency room visits.

4.2 OVERVIEW – STUDY PROCEDURES/DATA COLLECTION

The cohort of PLWD will be identified through the Regions and Methodist Hospital administrative database/EPIC Clarity report following acute care. This research investigation will take place mostly virtual or in-home.

4.3 END-OF-STUDY DEFINITION

A participant is considered to have completed the study 3 months after completing the final study visit, or 3 months after the final study visit

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a dyad must meet all of the following criteria:

1. *PLWD with a recent Emergency department visit or admission at Regions Hospital or Methodist Hospital*

2. *Diagnosis of dementia based on ICD Codes in the medical record*
3. *Provides informed consent prior to participation*
4. *Must be able to read and speak English*
5. *PLWD Living at Home*
6. *Age >=18 years for PLWD and their care partner*

5.2 EXCLUSION CRITERIA

A dyad who meets any of the following criteria will be excluded from participation in this study:

1. *PLWD living in a nursing home/Long term care – Assisted living facility*
2. *Current involvement in another clinical research study/trial for care partners*
3. *PLWD MRN on the HP exclusion list*

5.3 LIFESTYLE CONSIDERATIONS

NA

5.4 SCREEN FAILURES

Pre-screening: All potential participants will undergo a pre-screening chart review and a phone or a video call to determine whether they meet the inclusion/exclusion criteria. Patients will be considered ineligible if they do not meet one or more of the inclusion/exclusion criteria during pre-screening. We will collect information on why participants are ineligible or decide not to move forward with the trial.

Screen failures are defined as participants who are considered eligible during the pre-screening, but it was subsequently determined that they do not meet one or more of the inclusion/exclusion criteria. We will collect information on why participants screen fail or decide not to move forward with the trial.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Recruitment: A recruitment letter and flyer will be sent out to patients identified as eligible. Within a few days after discharge (2 days to 2 weeks) research staff will reach out to patients and their caregivers via a phone call. If interested, the caregiver and patient will be provided with informed consent to review on their own time. A video or phone encounter will be arranged to provide additional details of the study and informed consent. Participating subjects will need to explain in their own words what the study entails. A virtual consent though REDcap or a mailed consent with witness will be obtained.
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Remuneration: Participants will be provided gift cards totaling $100 per dyad for completing certain visits of the research study.

5.6 PARTICIPANT WITHDRWAL

5.6.1 REASONS FOR PARTICIPANT WITHDRWAL

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may withdraw a participant from the study if:

- Any medical condition, event or situation occurs such that continued participation in the study would not be in the best interest of the subject.
- The participant meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Significant study procedure non-compliance
- Lost-to-follow up; unable to contact subject

5.6.2 HANDLING OF PARTICIPANT WITHDRWALS

The reason for participant discontinuation or withdrawal from the study will be recorded on the relevant eCRF.

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

The following actions must be taken if a participant fails to attend any required study visit:

- Study staff will attempt to contact the participant, reschedule the missed visit, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, telephone calls or e-mail – if no answer leave a voicemail on the first and last attempt). These contact attempts will be documented.
- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

All dyads will receive the study intervention – Outreach-ER. Outreach-ER is a psychosocial intervention designed by dementia experts in the field of care partner interventions. The intervention is similar to other care intervention/support programs such as REACH or NYCUI. The Intervention is designed to be delivered over phone/virtual and in-home and will be conducted by Amplio, LLC consultants. The care plan will be personalized to the needs of the care partner/PLWD.

6.2 DISCONTINUATION OF STUDY INTERVENTION

If a significant change is noted, or any other reason as identified after enrollment, the investigator or qualified designee will determine if any change is needed for the intervention.

7 STUDY SCHEDULE

7.1 SCREENING

7.1.1 SCREENING/CONSENT VISIT (VISIT 1) (DAY 0)

- This visit may be a telephone/video visit
- Review, obtain and document consent from care partner and PLWD (e-consent)
- Review medical history, demorgraphics to determine eligibility to participate
- Schedule the next two study visits for individuals who are eligible and available for the duration of the study
- A total time of 40 minutes to an hour is anticipated for this visit

7.2 BASELINE (VISIT 2) (WITHIN 10 DAYS OF VISIT 1)

- This is a virtual visit
- A REDcap survey is sent via email including the outcome measures CES-D-10, PSS, ZBI-12
- In the case of participants unable to do via email, research staff will conduct this survey via a telephon/video visit
- This visit is about 15-30 minutes.

7.3 INTERVENTION VISITS

7.3.1 VISIT 3 (WITHIN 3 MONTHS OF DISCHARGE FROM HOSPITAL)

- This visit may be a telephone/video visit
- Initial visit by Amplio consultants
- Setup intervention visits schedules
- This visit is about 15 minutes.

7.3.2 VISIT 4 (10 DAYS ± 5 DAYS AFTER VISIT 3)

- This visit may be a telephone/video visit
- Visit by Amplio consultants
- Initial assessment (Assessment#1) with care partner only
- This visit is about 60-90 minutes.
- Field notes will be collected

7.3.3 VISIT 5 (10 DAYS ± 5 DAYS AFTER VISIT 4)

- This visit may be a telephone/video visit
- Visit by Amplio consultants

- 2nd assessment (Assessment#2) with care partner only
- This visit is about 60-90 minutes.
- Field notes will be collected

7.3.4 VISIT 6 (10 DAYS ± 5 DAYS AFTER VISIT 5)

- This visit is an in-home visit
- Visit by Amplio consultants
- Assessment#3 conducted with both care partner and PLWD
- This visit is about 2-3 hours.
- Field notes will be collected

7.3.5 VISIT 7 (10 DAYS ± 5 DAYS AFTER VISIT 6)

- This visit maybe an in-home visit or a virtual visit
- Visit by Amplio consultants
- Written care plan wil be provided and guidance on integration will be provided
- This visit is about 2-3 hours.
- Field notes will be collected

7.3.6 VISIT 8 (10 DAYS ± 5 DAYS AFTER VISIT 7)

- This visit maybe an in-home visit or a virtual visit
- Visit by Amplio consultants
- Touch points Assessment or follow-up with care partner and PLWD
- This visit is about 2-3 hours.
- Field notes will be collected

7.3.7 VISIT 9 (10 DAYS ± 5 DAYS AFTER VISIT 8)

- This visit maybe an in-home visit or a virtual visit
- Visit by Amplio consultants
- Touch points Assessment or follow-up with care partner and PLWD
- This visit is about 2-3 hours.
- Field notes will be collected

7.3.8 VISIT 10 (10 DAYS ± 5 DAYS AFTER VISIT 9)

- This visit maybe an in-home visit or a virtual visit
- This is an optional visit – only if needed by Amplio consultants, specifically based on touch point goals.
- Visit by Amplio consultants
- Touch points Assessment or follow-up with care partner and PLWD
- This visit is about 2-3 hours.
- Field notes will be collected

7.4 FINAL VISIT 11 (15-30 DAYS AFTER FINAL INTERVENTION VISIT 9/10)

- This visit is a virtual visit
- A REDcap survey is sent via email including the outcome measures CES-D-10, PSS, ZBI-12 and participant experience survey. In the case of participants unable to do via email, research staff will conduct this survey via a telephon/video visit
- A post-intervention interview will be conducted by research staff regarding experience of the participant in the study – via a telephone/video. This interview will be recorded (audio only)
- This visit is about 45 minutes

7.5 AD HOC VISITS (OPTIONAL AND AS NEEDED)

This visit can be a virtual visit or in-home visit. These are included to provide any additional support with regards to care plan implementation or any alternatives in the plan or provide additional resources or support to the dyads.

Participants will be asked to adhere to study visits and to complete study assessments. Participants will remain active unless withdrawn from the study. These will be documented in the relevant CRF.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 STUDY ASSESSMENTS FOR ENROLLED PATIENTS

8.1.1 DEMOGRAPHICS AND MEDICAL HISTORY

Demographic information will be collected, including: gender, age, race, ethnicity, height, weight, BMI, education, dementia diagnosis, co-morbidities (such as Diabetes, Hypertension) and e-mail address for consent.

8.1.2 CENTER FOR EPIDEMIOLOGIC STUDIES DEPRESSION SCALE-10 (CES-D-10)

The Center for Epidemiological Studies Depression Scale is an interview that evaluates caregiver depression through a self-report measure. Caregivers rate how they have experienced depressive symptoms in the past week, and survey scores are positively correlated with greater depressive symptoms (Radloff, 1977). The shorter 10 item version is validated in caregivers for dementia. The total score range from 0-30.

8.1.3 ZARIT BURDEN INTERVIEW-12

The Zarit Burden Inventory is an interview that evaluates caregiver burden through a self-report measure. The survey scores are positively correlated with behavior problems in older adults and depression scores of caregivers (Bedard et al., 2001). The shorter 12 item is validated in this population and total score ranges from 0-48. Higher the number, higher the burden.

8.1.4 PERCEIVED STRESS SCALE

The Perceived Stress Scale is a 10-item survey that evaluates perception of stress in the last month. The survey asks about how often someone had particular feelings and thought in the last month (0= never,

4= very often). The numerical response for question 4,5,7, and 8 is reversed (0 counts for 4 points), and then all the numerical responses are added together (Cohen, Kamarck, & Mermelstein, 1983).

8.1.5 INTERVENTION ASSESSMENTS

There are specific assessments for each of the intervention visits. These asssements will help evaluate and write the comprehensive care plan tailored to the dyad.

Specific assessments (see uploaded docs in the application) include

Assessment #1: With Care Partner Only

- Life Story
- Review Hospitalization info
- Review Diagnosis of Dementia
- Stress coping strategies

Assessment #2: With Care Partner Only

- Personal care/grooming
- Mobility
- Continence
- Eating Habits
- Sleep Pattern
- Senses
- Pain Intensity
- Assess Care Partners skill/approach
- Assess social support and self-care for care partners

Assessment #3: With Care Partner and PLWD

- Assess level of cognition, insight
- Review well-being, safety, comfort, depression/anxiety, sleep patterns, movement patterns, food/hydration plan
- Review environment for safety, including lighting, functionality, etc.
- Assess current purpose and engagement routine

Comprehensive Care Plan: With Care Partner and PLWD

- Written personalized care plan

Touch Point Assessment: With Care Partner and PLWD

- An opportunity to identify barriers and success associated with implementing the care plan, help improve competency.

- 2-3 touch points but will be based on involvement and challenges of the PLWD and care partners.

8.1.6 CARE EXPERIENCE SURVEY AND INTERVIEW

A 4 question survey is utuilized to evaluate the program. In addition, a semi-structure 30 minute interview will be conducted by the research staff to understand the experience of the dyad in the study. This will be audio recorded and transcribed using software. The research staff will code the data and identify any themes to improve the intervention and study for a larger clinical trial

8.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event is any symptom, sign, illness or experience which develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- Results in study withdrawal.
- Is associated with clinical signs or symptoms.
- Leads to treatment or to further diagnostic tests.
- Is considered by the investigator to be of clinical significance.

8.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (AE)

Adverse events are classified as either serious or non-serious. A serious adverse event is any event that results in:

- Death.
- Life-threatening situation.
- Hospitalization or prolongation of hospitalization.
- Disability or incapacitation.

Other events determined by investigator to be medically significant in which subject's well-being is jeopardized (e.g. events that have high likelihood of escalating to the point of meeting criteria outlined above.

8.2.3 EXPECTEDNESS

PI will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

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

Upon consenting, a subject is considered to be a participant in the study, and until that person either withdraws or completes study, AEs and SAEs will be recorded. The investigational team will promptly report any AE/SAE as required per federal guidelines.

8.3 UNANTICIPATED PROBLEMS

8.3.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as defined by the Office for Human Research Protections (OHRP). OHRP considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
2. Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. 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.

8.3.2 UNANTICIPATED PROBLEMS REPORTING

The PI will report unanticipated problems (UPs) to the reviewing IRB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number
- A detailed description of the event, incident, experience, or outcome
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs will be reported to the IRB as soon as possible, but no later than 10 working days after the investigator first learns of the event

8.3.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Following IRB review of any unanticipated problems, the PI will follow the IRB's recommended actions. This may include, but is not limited to, modifying the informed consent document or process, re-consenting current participants, providing information to past or current participants (e.g. whenever the information may relate to the participant's willingness to continue participants), and modifications to the protocol/research plan.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL ANALYSIS PLAN

Aim 1: To assess the feasibility, acceptability, and fidelity of implementation of the Outreach-ER program we will beginning by measuring the absolute number of potential care dyads of care partners (CP) and PLWD contacted for recruitment and the number of those who consent and enroll. These will be used to calculate the overall rate of program registration. The feasibility of collecting CP provided data will be evaluated by quantifying the missingness in the registration materials as well the response rate to the two questionnaires. Fidelity of the intervention will be assessed by describing CP attendance rates, length of intervention, and number of sessions as recorded by Outreach-ER staff. Completion patterns will be summarized overall and stratified by patient demographics. Any differences in intervention fidelity associated with CP and PLWD demographics will be described and discussed. Acceptability of the intervention will be assessed using data gathered through the post-intervention interview. The interviews will be transcribed, and recurring themes will be identified by the study team. If a participant withdraws before completion of the intervention this data will be solicited via telephone contact. Table 1 gives an example of how counts will be utilized throughout Aim 1 to describe the recruitment, enrollment, and adherence.

Table 2.

	Counts for feasibility	Use in analysis
Participants contacted	N	Total number of attempted recruits
Participants who enroll and consent	a	Recruitment rate: a/N
Participants who start Outreach-ER programming	b	Participation rate: b/N, compare to a/N
Participants who complete intervention (7+ visits)	c	Completion rate: c/b, used as main progression criteria Overall successful enrollment rate: c/N
Number who complete each intervention visit – k = 1, …, 7	dk	Session specific completion rate: dk/b
Number who complete each questionnaire – m = 1,2	em	Questionnaire specific response rate: em/a and/or em/b if a ≠b

Aim 2: The completeness of the CED-D-10, ZBI-12, and PSS outcomes will be quantified by calculating the rate of CPs that respond to all items on each scale (CES-D-10: 10 items, ZBI: 12 items, PSS: 10 items) at each assessment. The rate of completion for both scales will be presented overall and stratified by questionnaire and by CP demographics. Preliminary efficacy analysis will utilize the total scores for the CES-D-10 (range: 0 to 30), ZBI (range: 0 to 48), and PSS (range: 0 to 40) calculated for all completed questionnaires. All outcomes will be summarized at both questionnaire timepoints using means and/or

medians, as appropriate. Change over the study timeframe (Q2-Q1) will be calculated for each CP and summarized for the sample. To evaluate change in efficacy outcomes, the pre and post scores of each instrument will be compared using paired t-tests. If there is no difference in outcomes, we expect Scorepre = Scorepost.

To determine the feasibly of collecting utilization outcomes, the proportion of enrolled CP/PLWDs who are eligible and consent to research access will be calculated. We will collect utilization data from the EHR including number of inpatient, outpatient, and ER visits for the PLWD in the 6 months before and the 3 months during as well as after participation. These counts will be summarized to describe the patterns in utilization associated with participating in the Outreach-ER programming.

Sensitivity analysis will remove those who do not complete the intervention (early withdrawal or <6 sessions). All analysis will be performed in SAS 9.4 and significance determined using a two-sided alpha of 0.05.

To explore the feasibility of obtaining online consent for research access to CP healthcare utilization records. healthcare utilization as an outcome in a full-scale ePCT. Any differences in CP/PLWD demographics between enrollees who opt-in and those who do not will be assessed.

9.2 POWER ANALYSIS OR STATEMENT OF PRECISION

Sample size rationale: The sample size is largely determined by the logistics of the pilot award funding and time period. We plan to enroll up to 30 dyads. While this pilot is not formally powered for efficacy, we estimate that our sample size would allow detection of a 2-point change in CES-D-10 scores associated with the intervention and CES-D-10 score standard deviation of 4, with 80% power and a two-sided alpha of 0.05. Table 2 provides estimates of the current study's expected effect size with a range of assumptions for SD value (2 to 6) as well as for a reduced sample size our drop out rate reaches 20%.

Table 3. Effect size estimates for pilot study with a range of variation and enrollment assumptions

	Effect Size: Difference in CES-D-10 change	
SD	N = 30	N = 24
2	1.1	1.2
4	2.1	2.4
6	3.2	3.6

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

All research study staff will maintain certification in human subject's protection. All study investigators and staff will take an active role in developing procedures to protect against or minimize potential risks to the safety and well-being of enrolled participants. Potential research dyads will be informed that participation in this study is voluntary and will not be discriminated against if they choose not to participate. Written informed or electronic consent and assent will be obtained from participants, and family member/caregivers or legally authorized representatives (LAR). Participants will be asked to describe in their own words the study's expectations. Dyads will be informed that they can withdraw from the study at any time and will be given a copy of the consent form. Subjects will have written assurance that while de-identified individual subject data may be available to other researchers for research purposes, or used to improve the software program, only a summary of the results will ever be published or otherwise publicly released. Subjects will be assured that participation in the study will be strictly confidential, that any identifying information will be available to the study staff only, and that no identifying information concerning the data and results will be made known.

Potential research subjects will be informed that participation in this study is voluntary and that their decision to participate will not reflect upon their relationships with the Center for Memory and Aging, Regions Hospital, Methodist Hospital, or HealthPartners. Subjects will be informed that they can withdraw from the study at any time and will be given a copy of the consent form.

With the electronic consent via REDCap the dyad providing consent will be able to review the consent form themselves and sign electronically with a stylus, touch screen, or cursor using a signature field in REDCap. After the individual has received the link and can view the consent form, the research staff member will go through the consent form with the individual as would be typical in person. Following the consent conversation, the staff member will sign and e-mail the consent and HIPPA electronically to the patient. The patient will electronically sign, certify, and submit the consent and HIPPA in REDCap. A fully executed PDF copy of the consent and HIPPA will be provided electronically to the patient for their records as well as saved via the auto-archiver function in REDCap.

10.1.2 CONFIDENTIALITY AND PRIVACY

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

All research activities will be conducted in as private a setting as possible.

All study regulatory binders will be stored in a locked file cabinet within a secure office. The internal study monitor, representatives of the IRB, or regulatory agencies, may inspect all documents and records required to be maintained by the investigator, for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor/funding agency requirements.

A unique study ID code unrelated to the medical record number or other study subject-specific information will be assigned to each patient and used to link data from various sources and needed for analysis. The study number will be used on the RedCap database

The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

10.1.3 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator
Bhavani Kashyap, MBBS, PhD
HealthPartners Neuroscience Center
295 Phalen Blvd. St. Paul, MN 55130

10.1.4 SAFETY OVERSIGHT

There is no Data Safety Monitoring Board for this study, as this study has minimal risks

10.1.5 CLINICAL MONITORING

N/A, refer to next section.

10.1.6 QUALITY ASSURANCE AND QUALITY CONTROL

Study staff will perform internal quality management of study conduct, data collection, documentation and completion.

Quality control (QC) procedures will be implemented as follows:

Informed consent --- Study staff will review both the documentation of the consenting process and 10% of the completed consent documents. Feedback will be provided to study staff to ensure proper consenting procedures are followed.

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

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

10.1.7 DATA HANDLING AND RECORD KEEPING

10.1.7.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the research study staff under the supervision of the PI. The PI will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Data collection/reporting tools will be developed internally (i.e. CRFs or eCRFs (RedCap Database) and source documents). Data collected and stored electronically will remain confidential and secure (e.g. secured server, encrypted data, password protected file).

10.1.7.2 STUDY RECORDS RETENTION

Investigator records will be retained in accordance with regulatory, organizational and sponsor or grantor requirements. All records will be maintained securely with limited access. Disposal of investigator records will be done in such a manner that no identifying information can be linked to research data.

10.1.8 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the study protocol. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

10.1.9 PUBLICATION AND DATA SHARING POLICY

This study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

Data from the de-identifed images may be utilized by Omniscent for improvement of Infinitome program and potential future imaging research studies.

10.1.10 CONFLICT OF INTEREST POLICY

The study leadership in conjunction with HealthPartners Institute has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
1.1	March 3, 2022	Adding an exclusion criteria with PLWD MRN on HP exclusion list	Admin Review change. Amending the process to keep with institutional processes. MRN will be run against the list prior to recruitment flyer/letter
		Change in version number & date and added an IRB #	Admin changes

11 REFERENCES

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