Study Title: A pilot cluster randomized controlled trial of a phone intervention supporting family caregivers of people living with dementia in Vietnam: Resources for Enhancing Alzheimer's Caregiver Health in Vietnam (REACH VN)

NCT#: NCT05481320

Document Date: November 16, 2022

Document Type: Study Protocol

1) Protocol Title

Title: A Phone Intervention for Family Dementia Caregivers in Vietnam

Protocol Version Date: *11/16/2022*

2) Objectives

The objective of this study is to examine the feasibility, acceptability, and preliminary efficacy of the phone version of REACH VN, a psychosocial culturally adapted Alzheimer's family caregiving intervention that will be delivered over the phone with an enhanced control as the comparison. The pilot cluster RCT will test the hypothesis that family caregivers who receive the intervention will show lower caregiver burden (primary outcome) and lower depressive/anxiety symptoms (secondary outcome) compared with those in the control group.

3) Background

Low- and middle-income countries (LMIC) such as Vietnam are undergoing a dramatic demographic transition that will result in a substantial increase in the number of older adults, including those afflicted with Alzheimer's disease and related dementias (ADRD), over the next several decades. Dementia is among the most disabling and costly neurodegenerative brain diseases. Strengthening LMIC capacity to support family caregivers of people with dementia through low-cost and sustainable non-pharmacological approaches, such as education and skill-building to deal with difficult behaviors, is vital to avoid costly and ineffective alternatives such as psychotropic medications or institutionalization, and to reduce caregiver burdens and depression. While evidence-based non-pharmacological treatments exist in high income countries (HIC), these interventions have not been adapted for use in Vietnam and other LMIC.

Delivery of interventions through telehealth and other types of technology (e.g., online, mobile apps) holds considerable promise for the field because of lower costs and greater reach, particularly for those living in rural areas. These considerations are particularly important in Vietnam and other LMIC because most older adults reside in rural areas. With the rapid adoption of mobile phones, tablets, and smartphones, family caregiver interventions hold considerable promise for closing gaps in dementia care and services for these countries. The COVID-19 pandemic has also reinforced the need for interventions that can be delivered at a distance to maintain support for caregivers and reduce their social isolation.

To our knowledge, our study will be the first study in Vietnam or other LMIC in Asia to examine the efficacy of multicomponent family caregiver intervention delivered remotely. The intervention has several components (e.g.,

psychoeducation, stress reduction, skill-building) and is designed to reduce caregiver stress and burden.

4) Inclusion and Exclusion Criteria

Inclusion criteria:

To be eligible to participate, a family member will need to be the identified adult (i.e., age 18 and above) who is the primary informal (i.e., unpaid family member) caregiver (i.e., the person who provides the most time day-to-day care) to an older adult (i.e., age 60 and above) with dementia living in the community. If the primary caregiver is not available to participate, an alternate family member who provides substantial care (i.e., at least 4 h/day) to an older adult with dementia will be eligible to participate. In addition, caregivers will need to score ≥ 6 on the Zarit Burden Interview-4 (ZBI-4). All participants will be living in clusters in Thach That District, a semi-rural area in Hanoi.

Exclusion criteria:

The study will exclude:

- Caregivers with difficulties in the consent process due to cognitive impairment or severe sensory impairment (i.e., visual, hearing)
- Caregivers don't have access to phone
- Individuals who are not yet adults (i.e., infants, children, teenagers)
- Prisoners

5) Study Timelines

- We plan to begin recruitment in August of 2022.
- We plan to complete recruitment by January of 2023.
- We plan to complete all data collection and intervention activities by April of 2023.
- We plan to complete preliminary analyses of the data by July of 2023.

6) Study Endpoints

This is a time-limited intervention lasting up to 3 months with independent assessment of outcomes at baseline and 3 months.

7) Procedures Involved

Study design: A two arm, 3-month follow up, cluster randomized controlled trial of 60 caregivers (30 in REACH VN phone intervention group and 30 in enhanced control group) will be conducted.

Setting: Thach That District, a semi-rural area in Hanoi, Vietnam.

Recruitment:

In collaboration with commune health stations, community-based screening will be conducted to identify "at risk" older adults with dementia and their family caregivers.

Staff from the National Geriatric Hospital (NGH) will train local staff (e.g., village health workers) to identify people at high risk for dementia from their caseloads, including those with a history of significant memory problems, behavioral issues and evidence of functional decline. Staff from local health clinics will contact potential participants by phone or in-person, provide information about the project, and invite them to participate in screening to determine their eligibility. Verbal consent will be obtained from an older adult and a family member prior to screening by research staff. Those who consent to participate in the screening will undergo an assessment including a brief neurological exam, cognitive testing and dementia stage using standardized instruments, including the Mini-Cog, NPI-Q, and CDR. The assessments will be conducted by physicians, neurologists, or healthcare professionals trained by NGH. Once an older adult has been determined to meet criteria for dementia (i.e., CDR $\geq$ 1), we will identify the adult family member who is providing the most day-to-day care and invite them to participate in a brief screening to determine their eligibility. If they are eligible, we will invite them to participate in the study and obtain verbal consent.

A screening log will be kept to document number and reasons of participants who do not meet the inclusion criteria, decline to participate, or any other reasons.

Consent:

Because of the minimal risk of both screening and behavioral intervention, verbal consent will be obtained for both. As part of the consent process, all caregivers will be informed that this is a voluntary study and that they can withdraw at any time.

Randomization:

Communes will be the unit of randomization and randomization assignments will be generated using a block randomization function in R for each stratum with a 1:1 ratio for two groups: intervention (n= approximately 8 clusters or 30 caregivers) or enhanced usual care (n= approximately 8 clusters or 30 caregivers). The UC Davis Biostatistician will be responsible for generating randomization codes and assigning randomization codes to communes. The biostatistician will communicate cluster assignment to the principal investigator (PI) to convey to the study team in Vietnam of when communes have been randomized.

Clusters will need to be in Thach That District and have a minimum of 3 participants and a maximum of 15 participants.

Blinding:

A trained outcome assessor who conducts data collection will be blinded regarding group assignments.

REACH VN Phone Intervention:

Family caregivers in the intervention will receive a manualized multicomponent intervention, including psychoeducation, stress reduction, and skill-building, that will consist of 4-6 "core" sessions with the option for 1-2 "maintenance" sessions based on caregiver needs and clinical judgment with a trained staff (e.g., nurse, social worker, or community health worker) who has been certified to deliver the intervention. Interventionists will follow the interventionist manual that includes scripts, detailed descriptions of the goals for each session, and standardized forms.

The enrollment session (session 0) will be conducted face-to-face. Interventionists with village health workers will come to caregivers' home to provide a caregiver notebook with information about dementia and management of common problems, check phone issues and signals, and conduct the risk priority intake assessment. The intervention sessions will be conducted over the phone with either audio or video call over the course of 1-3 months. The sessions will occur every 1–2 weeks depending on the needs and availability of family caregivers. Each intervention session will last between 30 minutes to an hour. In case caregivers are not able to concentrate on the session after the first 20-30 minutes, interventionists can end the session and make appointment to call back within 2-4 days (or whenever it is possible) to complete the session.

At the beginning of the intervention, we will emphasize to caregivers that text message is only allowed for scheduling or making changes to scheduled intervention times, not for other purposes. In case caregivers would like other family members to attend the intervention with them, interventionists will inform caregivers in advance that the intervention includes components that ask caregivers about caregiving difficulties, private psychological issues, or family problems; thus, it is up to caregivers to decide whether to include family members into the calls. If they feel comfortable sharing when there are with other family members, they may choose so to let other family members attend the intervention. However, if caregivers are not comfortable, we will advise them to attend the intervention by themselves.

Quality control of the intervention

At the end of each session, interventionists will complete a standardized treatment form (i.e., Interventionist Delivery Assessment (IA)) that summarizes the session either on REDCap or hardcopy.

For training purposes only and quality control of the intervention, we will audio record a subsample of the intervention sessions. These audio recordings will be stored securely and will not be linked to participant's name or other identifying information. These will not be used for research purposes. The recordings will be reviewed within 3 months and then destroyed. Participants may continue their

participation in this study without consenting to these recordings and having any impact on their participation.

In general, a session will be conducted by one interventionist. However, in some cases, there will be another interventionist who will join the session as a supportive person to enhance the quality control of the intervention.

Supervision of all interventionists will take place during a weekly supervision meeting (in-person or by phone) with senior members of the research team.

Enhanced Control:

Caregivers in the enhanced control group will receive a single phone session in which they will receive education about ADRD including written materials.

Outcome assessments:

A research assistant at the National Geriatric Hospital who is trained and certified will conduct outcome assessments over the phone. An outcome assessor will be masked to group assignment status. We will remind caregivers not to tell an outcome assessor their group assignment status to minimize bias. Caregivers in both groups will be assessed at baseline and 3 months. The primary outcome will be caregiver burden as assessed by the Zarit 6-item burden scale (ZBI-6) and the secondary outcome will be depressive/anxiety symptoms as assessed by the four-item Patient Health Questionnaire (PHQ-4). We will use previously developed Vietnamese versions of study instruments.

Feasibility, fidelity, and acceptability assessments:

Feasibility metrics will include recruitment, randomization, retention, treatment adherence, treatment fidelity, and assessment processes. *Fidelity assessment* will be based on review of standardized treatment delivery forms completed by interventionists and an independent observer of a random subset of sessions. Prior to the RCT, interventionists who are already certified in face-to-face REACH VN intervention will need to be trained in phone delivery. *Acceptability* will be assessed through semi-structured interviews with a random subset of participants who have completed the intervention group (n=10) and REACH VN interventionists (n=5). These interviews will include questions on satisfaction, aspects of the intervention that participants found most helpful, challenges, and opportunities for improvement. We will inquire about any issues related to intervention delivery by audio or video call.

Reimbursement:

Participants will receive $4 (or 100,000 VND) at the end of the screening session and $8 (or 200,000 VND) at the end of each study visit/session (including intervention sessions and outcome assessments).

8) Data and/or Specimen Management and Confidentiality

REDCap will be used to collect outcomes data. Procedures for maintenance and confidentiality include 1) assigning each participant a unique identifier, 2) data collected will be labeled using the unique identifier and will be stored separately

from the key linking personal information (e.g., name, date of birth, address, phone number) and identifiers, 3) data will be kept on a secure server that is only accessible to research staff, 4) at the conclusion of the study, the key linking identifiers and personal information will be destroyed, 5) all research personnel in the U.S. who have access to the patient data will receive training on conducting human research (e.g., NIH online course) – all investigators and research staff in Vietnam will participate in the local equivalent of this training.

9) Data and/or Specimen Banking

All data will be stored on a secure server at in Vietnam. De-identified data will be transferred to UC Davis and the University of Minnesota (UMN) electronically through an encrypted zip file. After the study, the key linking personal identifiers to the survey data will be destroyed.

10) Provisions to Monitor the Data to Ensure the Safety of Subjects

Case review will occur on a weekly basis with a team that includes the interventionists, the PI and investigators from the NGH, UCD, and UMN. The caregiver's level of distress and any indicators of elder abuse/neglect will be reviewed at each session.

This study will have a Safety Officer (SO), who will meet 1-2 times each year to review the progress of the study, including adverse events, procedures for maintaining the confidentiality of data, and the quality of data collection, management, and analyses. The SO will also review any issues that arise in terms of conflict of interest or serious adverse events as needed. The SO will report directly to the funder (i.e., NIA).

Dr. Hinton will be responsible for overall monitoring and appropriate reporting of adverse events including serious adverse events that occur during the study. Plans regarding reporting of adverse events will follow guidelines and policies of UC Davis as well as NIH.

Adverse events will include events untoward or unfavorable mental or physical health-related occurrence in a human subject that is temporally associated with the subject's participation in the research, regardless of whether they are considered related to the subject's participation in the research. Examples of such events that might occur include incidents of brief hospitalization, caregiver distress or depression, instances of elder abuse or neglect, and other unanticipated events. Serious adverse events will be further defined as those events that seriously jeopardize the participant's health, including prolonged hospitalization, suicide attempts, and death. The overall goal of this plan is to have both serious adverse events (SAE) and non-serious adverse events (NSAE) that are viewed as likely (i.e., 50% or higher) related to study participation reported to both the UCD IRB and NIH in a timely fashion.

As a routine part of training, intervention study staff will be educated to monitor for these events and to report them to the research staff. Interventionists or other research staff will complete AE Field Report Form and provide this to NGH RCT leads (i.e., Dr. Ngoc and Dr. Hung) within 48 hours. Upon receiving the report, Dr. Ngoc must confirm that she has received the report and is available to act upon it. Dr. Ngoc will review AE Field Report Form, complete AE Form and, if it is a SAE, complete SAE Form and send to study PIs (Dr. Hinton, Dr. Huong Nguyen, and Dr. Trung Anh) within 48 hours. Dr. Hung will serve as back-up in case Dr. Ngoc is not available. Within 2 working days of receipt of the information about the SAE, Dr. Hinton will share this information with the research team and the SO. If the SAE is viewed as likely (i.e., >50% probability) of being related to participation in the study, the SAE will be reported to the UCD IRB and to NIH within 2 working days of this determination with the goal of reporting all such events to UCD IRB and to the NIH PO within 5 working days of the time Dr. Hinton became aware of the event. NSAE will be shared with the core members of the research team, including Drs. Hinton, Trung Anh and Huong Nguyen, at their regular biweekly meetings. If NSAE are deemed as possibly related to study participation they will be reported to the SO within one week and, if the SO views them as "probably" (i.e., >50% likelihood) of being related to study participation, to the UCD IRB and NIH PO within 5 working days. All SAE and NSAE that are viewed as not likely to be related to research participation will be reported on an annual basis to the NIH PO as part of the progress report as well as to the IRBs.

11) Withdrawal of Subjects

Subjects (patients and family members) may withdraw at any time. If they withdraw from the study, they will be given the option of having their records destroyed.

12) Risks to Subjects

The main risks associated with this study: 1) discomfort or mild distress because of the intervention, 2) inconvenience because of the need to fill out the study questionnaires, and 3) loss of confidentiality. These risks are similar to the risk of undergoing routine assessments in healthcare clinics in Vietnam. Specific steps are being taken to address each category of risk (please see Section 16).

13) Potential Benefits to Subjects

There are several potential direct benefits to subjects. Caregivers may experience an increase in their knowledge and skills because of the intervention. In addition, caregivers will learn stress reduction techniques that may help reduce caregiving-related distress. Older adults participating in screening will be given the option of

having information about their cognitive testing be provided to their primary care physician.

14) Multi-Site Research

This is a single-site, multiple PIs, international study with Dr. Hinton as the lead investigator. Approval for the study will be obtained by both the UC Davis IRB and the Vietnam National Geriatric Hospital IRB. Dr. Hinton will be responsible for coordinating with the international site to ensure that the most current version of the protocol and consent document are used. He will work with the PI at the Vietnam National Geriatric Hospital to ensure that 1) Participating sites will safeguard data as required by local information security policies, 2) All local site investigators conduct the study appropriately, and 3) All non-compliance with the study protocol or applicable requirements will reported in accordance with local policy.

15) Community-Based Participatory Research

NA

16) Provisions to Protect the Privacy Interests of Subjects

Discomfort due to the intervention: Even though this study builds on evidence-based strategies for support of family caregivers, subjects may experience discomfort or mild distress when discussing their caregiving experience or because of concerns about confidentiality. These risks will be minimized in several ways. Interventionists will be trained to enhance their skills to be empathic listeners to create an emotionally comfortable environment for family caregivers. Interventionists will be trained to remind patients that they are not required to answer any questions and can withdraw from the intervention at any time or choose to end a session early. For extreme situations of emotional stress (e.g., involving threats of self-harm), interventionists will have an established protocol in emergency situations to minimize risk of harm.

Inconvenience due to questionnaires: Some of the survey questions might make participants feel uncomfortable or upset. During the consent process, participants will be advised that they can choose not to answer any questions that make them feel uncomfortable. Risks to subjects are minimal for several reasons.

Loss of confidentiality: Steps will also be taken to protect against risk regarding loss of confidentiality which is particularly important in Vietnam where staff may not be as familiar with research and the importance of confidentiality. All staff will receive training and education about the importance of maintaining confidentiality as a core aspect of the research to minimize of risk. When conducting interviews, staff will try to maintain a private space and discuss the participant's level of comfort in talking to the interviewer or interventionist if others are within earshot. In the consent process, participants will be informed

about loss of confidentiality as a risk and the precautions being taken to minimize this.

Other: This is a behavioral intervention and does not involve drug treatment. In prior studies conducted with multi-cultural populations in the United States, there have not been any serious adverse side events attributable to the intervention (personal communication with one of the PIs of a large-scale national study). Similarly, in a pilot study there were no serious adverse events related to this intervention. It is also possible that elder/abuse or neglect may be detected during the study and require intervention. A protocol for handling cases of abuse/neglect according to local norms/resources has been developed in collaboration with our colleagues in Vietnam.

17) Compensation for Research-Related Injury

NA – minimal risk study

18) Economic Burden to Subjects

There are no costs that subjects may be responsible for because of participation in the research.

19) Drugs or Devices

NA

20) ClinicalTrials.gov Registration

Section 1: NIH Funded Studies

If yes to BOTH, the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study is funded by the NIH. (If this study is not funded by NIH, go to Section 2.)
☒	One or more human subjects will be prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

Section 2: Studies subject to FDA jurisdiction

If yes to ANY the study must be registered on Clinicaltrials.gov.

Yes	
☐	This is a prospective clinical study of health outcomes in human subjects that compares an intervention with an FDA-regulated device against a control. This is not a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes.
☐	This is a pediatric postmarket surveillance of a device as required under section 522 of the Federal Food, Drug, and Cosmetic Act.

☐	This is a controlled clinical investigation, other than a phase I clinical investigation, of a drug subject to section 505 of the Federal Food, Drug, and Cosmetic Act or to section 351 of the Public Health Service Act.

To view a flowchart describing applicable clinical trials subject to FDA jurisdiction click here.

Section 3: Publishing the results

If yes to BOTH the study must be registered on Clinicaltrials.gov.

Yes	
☒	This study prospectively assigns people or a group of people to an intervention, with or without concurrent comparison or control groups, to study the cause-and-effect relationship between a health-related intervention *and* a health outcome.
☒	The PI has access to and control over all the data from the clinical trial and has the right to publish the results of the trial and plans to publish the results in a journal that follows the ICMJE recommendations.

This requirement includes studies of behavioral interventions.

Section 4: Registration on Clinicaltrials.gov is not required

Yes	
☐	I have read sections 1-3 above and registration on clinicaltrials.gov is not required for this research.

21) Criteria for 10 Year Approval

If yes to all items below this research may qualify for a 10-year approval period.

Yes	
☒	This research involves no more than minimal risk.
☐	This research does not receive any federal or state government funding or funding from a private funder who requires annual review per contract.
☒	This research is not subject to FDA jurisdiction.
☒	This research does not include prisoners as participants.
☒	This research is not subject to SCRO oversight.
☒	This research is not subject to oversight by the Research Advisory Panel of California (RAP of C).
☒	This research does not involve identifiable information held by the State of California Department or Agency
☒	No personnel involved in the design, conduct, or reporting of this research have a new unreported related financial interest (RFI) in this study.