Study Title: Cluster Randomized Controlled Trial to Test the Efficacy of a Psychosocial Intervention (REACH VN) to Support Alzheimer's Family Caregivers in Vietnam

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1) Protocol Title

Title: Cluster RCT to test the efficacy of a psychosocial intervention to support Alzheimer's family caregivers in Vietnam

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2) Objectives

The objective of this study is to conduct a cluster randomized controlled trial to test the efficacy of a psychosocial intervention to support Alzheimer's family caregivers in Vietnam. The cluster RCT will test the hypothesis that family caregivers who receive the intervention will show lower psychological distress and lower caregiver burden compared with those in the control group (primary outcomes). In addition, we will conduct secondary analyses to examine whether intervention group has lower perceived stress and somatic symptoms. Exploratory analyses will be conducted to determine if intervention effects are mediated by caregiver self-efficacy or knowledge gain.

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, over the next several decades. Dementia is among the most disabling and costly neurodegenerative brain diseases. Strengthening LMIC capacity to support family caregivers of persons 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.

This project addresses these gaps by testing a community-based and culturally adapted behavioral family caregiver intervention for use in Vietnam. The intervention has several components (psychoeducation, stress reduction, skill-building) and is designed to reduce caregiver stress and burden. This project also builds directly on a pilot cluster RCT that found evidence for feasibility and preliminary efficacy of the intervention.

4) Inclusion and Exclusion Criteria

To be eligible for the cluster RCT, the family member will need to be the identified adult (age 18 and above) primary caregiver (i.e., the person spending who provides the most time day-to-day providing care) to an older adult with dementia who is living in the community. In the event that the primary caregiver

is not available to participate, an alternate family member who providing substantial (i.e., at least 4 hours/day) of care to the older adult with dementia will be eligible. Caregivers will need to score ≥ 6 on the Zarit Burden Inventory 4-item version. All participants will be living in designated clusters in Hai Duong, Vietnam. To be eligible, clusters will have a minimum of 5 participants and a maximum of 15 participants. Clusters will be defined as geographic areas serving local health stations.

The final sample for the cluster RCT will be 350 family caregivers of persons diagnosed with dementia (175 in the active intervention and 175 in the control group). The RCT will exclude:

- Caregivers who are unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Prisoners

5) Study Timelines

- We will begin recruitment in August of 2020.
- We will complete recruitment by September of 2023.
- We will complete all data collection and intervention activities by March of 2024.
- We will complete preliminary analysis of the data by August of 2024.

6) Study Endpoints

This is a time-limited intervention lasting up to 3 months with independent assessment of outcomes at baseline, 3 months, and 6 months.

7) Procedures Involved

The study will be conducted in two districts in Hai Duong, a province located near Hanoi, Vietnam. Clusters within both districts will be defined as geographic areas served by local health clinics (commune health stations). In collaboration with commune health stations, community-based screening will be conducted to identify Alzheimer's family caregivers residing in the designated clusters who will then be invited to participate in the study. Clusters will be randomly assigned to either the intervention (approximately 21 clusters, 175 caregivers) or to the enhanced control condition (approximately 21 clusters, 175 caregivers).

Staff from the National Geriatric Hospital and Hai Duong Provincial Hospital will train local staff (e.g., village health workers) to identify persons at high risk for dementia from their caseloads, including those with a history of significant memory problems, behavioral issues and evidence of functional decline. Research staff from local health clinics will contact potential participants by phone, provide information about the project, and invite them to participate in

screening to determine their elibility. Verbal consent will be obtained from the 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, bedside cognitive testing and dementia stage using standard instruments, including the Mini-Cog, NPI-Q and CDR. Once an older adults has been determined to meet criteria for dementia (i.e, CDR≥1), we will identify the adult family member providing the most day-to-day care and invite them to participate in the study and obtain verbal consent. Because of the minimal risk of both screening and behavioral intervention, verbal consent will be obtained for both.

Family caregivers in the intervention will receive a manualized intervention that will consist of 3-6 one-hour sessions with a trained staff (e.g. nurse, social worker, or community health worker) who has been certified to deliver the intervention. The sessions will be administered at home (or other setting of the subject's choice such as a clinic) or by phone and include several components, including psychoeducation, stress reduction, skill-building. The intervention will be tailored to the needs and preferences of the caregiver. As part of the intervention, participants will receive a caregiver notebook with information about dementia and management of common problems. Participants in the control clusters will receive a single session in which they will receive education about Alzheimer's disease including written materials.

Outcomes will be assessed by research staff from the Institute of Population Health and Development who are masked to allocation. Participants in both clusters will be assessed at baseline, 3 months, and 6 months to assess primary and secondary outcomes using standardized instruments, including the PHQ-4, Zarit Burden Interview-12, Perceived Stress Scale-10, PHQ-15 (a somatic symptoms scale). In addition, we will assess two different potential mediators using the Caregiving Self-Efficacy Scale and Dementia Knowledge Scale. Assessments will be conducted by research staff who are masked to allocation.

The interventionists will follow a manual (Interventionist Manual) that includes scripts, detailed descriptions of the goals for each session, and standardized forms. The interventionists will provide the caregivers with a detailed notebook with helpful cargiving information (Caregiver Notebook).

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 6 months and then destroyed. Participants may continue their participation in this study without consenting to these recordings and having any impact on their participation.

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 or 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 in Vietnam will participate in the local equivalent of this training.

9) Data and/or Specimen Banking

a) Will the data or specimens ever be used by you or other researchers to answer a different research aim that is not included in this study?

☒ Yes - Complete the remainder of Section 9.

☐ No - Do not complete Section 9. Go to section 10.

b) What will be banked for future use?

☒ De-identified data/specimens. Banked data/specimens cannot be linked to an individual.

☐ Identifiable data/specimens – Banked data/specimens will include identifying information.

☐ Coded data/specimens – Banked data/specimens will be stripped of identifiers and assigned a code. A key will be maintained that links the identifiers to the data/specimens.

☐ Contact information will be banked for future research opportunities.

c) Where will the data/specimens be banked?

Computer files are password protected, and data are maintained on a secure firewall-protected network of the UC Davis Health System, REDCap.

d) How long will the data/specimens be banked?

After the study, the key linking personal identifiers to the survey data will be destroyed. De-identified data will be kept indefinitely.

e) Who will have access to the banked data/specimens?

Only select researchers involved in the project will have access to these data. Only de-identified data will be shared to other researchers who wish to access banked data.

f) Describe the procedures to release data/specimens. Include the process to request a release, approvals required for release, who can obtain data/specimens, and the data/specimens to be provided.

- Recipient investigators who wish to access banked data will need to contact PIs (Dr. Ladson Hinton and Dr. Huong Nguyen) for an inquiry.

- If PIs agree for accessing banked data, the following approval steps will be taken:

+ Recipient investigators will submit a proposal to PIs with the following information:

- Title
- Recipient PI's contact information and team members/co-authors
- Introduction
- Research questions
- Data variables
- Analysis plan
- References

+ Recipient investigators will submit an IRB approval letter from their local institution.

+ PIs will submit the UC Davis Data Use Agreement request to UC Davis Innovation Access for recipient investigators to complete the Data Use Agreement Form.

+ After recipient investigators receive approval documents, de-identified data will be transferred to them electronically through a password encrypted zip file.

- Recipient investigators are:

+ required to safeguard data provided to them and ensure deletion/destruction of the data upon completion of their project

+ restricted from attempting to identify participants using the data provided to them

+ restricted from presenting data in any manner which could identify participants

+ restricted from further distribution of the data.

+ required to acknowledge the funding in any publication or presentation "Research reported in this publication was supported by the National Institute on Aging (NIA) of the National Institutes of Health (NIH) under award number R01AG064688 (Hinton/Nguyen MPI). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIA and the NIH."

Note: Identifiable protected health information extracted from the UCDH EMR under an IRB-issued waiver of HIPAA Authorization may not be re-disclosed/released outside the study team.

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

The goal of this cluster randomized controlled trial care is to assess the efficacy of the psychosocial intervention to support Alzheimer's family caregivers. Case review will occur on a weekly basis with a team that includes the care manager and the local PI and investigators from the UC Davis 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 Office (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 Hai Duong project lead (i.e, Dr. Bien) within 48 hours. Dr. Bien will send all AE Field Report Forms to NGH RCT leads (i.e, Dr. Ngoc and Dr. Hung), and the interventionist supervisors within 48 hours. Upon receiving the report from Dr. Bien, 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 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 institutional 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.

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. Interventionist 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: To address the inconvenience associate with completing study questionnaires, we will give subjects the option of completing these in the home or by phone. In addition, 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.

13) Potential Benefits to Subjects

There are several potential direct benefits to subjects. Subjects 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.

Participants will receive $4 at the end of the screening session and $8 at the end of each study visit (including intervention sessions and visits for administration of assessments).

14) Multi-Site Research

This is a single-site, multiple PI, 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

Describe the steps that will be taken to protect subjects' privacy interests. "Privacy interest" refers to a person's desire to place limits on whom they interact or whom they provide personal information.

Describe what steps you will take to make the subjects feel at ease with the research situation in terms of the questions being asked and the procedures being performed. "At ease" does not refer to physical discomfort, but the sense of intrusiveness a subject might experience in response to questions, examinations, and procedures.

Indicate how the research team is permitted to access any sources of information about the subjects.

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.