Protocol with Statistical Analysis Plan

Protocol Title: Efficacy of a Virtual Intervention for Informal Caregivers of Adults with Frontotemporal Dementia

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Efficacy of a Virtual Intervention for Informal Caregivers of Adults with Frontotemporal Dementia

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PROTOCOL TITLE: *Efficacy of a Virtual Intervention for Informal Caregivers of Adults with Frontotemporal Dementia*

INTRODUCTION AND PURPOSE:

Caregivers of adults with dementia report significant stress and poor self-care. Virtual Caregiver Coach for You (ViCCY ["Vicky"]), a virtual support intervention, may relieve stress and promote self-care in dementia caregivers. Even less is known about the effect of caregiver support interventions on dementia patient outcomes. Thus, we propose to extend the novel self-care support intervention ViCCY ("Vicky") to caregivers of persons with behavioral variant frontotemporal dementia (bvFTD) and we will explore the effect of caregiver outcomes on bvFTD patient outcomes. This work will allow us to develop a new and innovative way to increase support that is urgently needed to reduce poor outcomes in this distressed and underserved caregiver population.

OBJECTIVES:

Aim 1: Compare the preliminary efficacy of ViCCY vs. Health Information (HI) alone in improving self-care in FTD caregivers. We hypothesize that, at 6 months after enrollment, caregivers randomized to ViCCY vs. HI alone will have H1a: Improved self-care measured with the Self-Care Inventory (primary outcome); H1b: Reduced self-reported stress measured with the Perceived Stress Scale (secondary outcome); H1c: Reduced depression measured with Center for Epidemiologic Studies Depression Scale (CES-D; secondary outcome); H1d: Improved coping measured with the Ways of Coping Questionnaire, short form (secondary outcome); H1e: Reduced burden measured with Zarit Burden Interview (ZBI; secondary outcome); and H1f: improved perceived mental and physical health status measured with the SF-36 (secondary outcome).

Aim 2: Explore the effect of caregiver outcomes on FTD patient outcomes. We hypothesize that, at 6 months after enrollment, FTD patients whose caregivers improve vs. not improve in self-care – regardless of group – will demonstrate H2a: Fewer behavioral symptoms measured with the Frontotemporal Dementia Rating Scale (primary outcome) and Neuropsychiatric Inventory (secondary outcome).

BACKGROUND:

Informal caregivers are stressed and their self-care is poor. The number of people living with Alzheimer's disease (AD) and related disorders (ADRD) will continue to grow exponentially, with most being cared for by informal caregivers, the majority of whom are spouses. As a group, informal caregivers have more stress, worse self-care, poorer health status, and higher mortality than non-caregivers. Caregivers often feel left alone to cope with problems, which exacerbates their stress. When stressed, caregivers are less vigilant and less motivated to engage in self-care behaviors that are important for maintaining physical and emotional health. As a consequence, high levels of poor outcomes such as depression and anxiety and poor physical health have been observed in dementia caregivers. Together, these studies illustrate the risk that informal care providers face when they defer self-care in response to the stress of caregiving and highlight the urgent need to develop innovative strategies to promote self-care activities.

Informal caregivers of persons with Frontotemporal degeneration (FTD) are an understudied population with unique needs. FTD is a common cause of young-onset dementia with no known cure. Behavioral variant FTD (bvFTD) is the most common of the FTD syndromes and involves a progressive disorder of emotional regulation and personality, and significant impairment in executive function. bvFTD caregivers face unique challenges which are particularly stressful, including young age at which the disorder appears, behavioral symptoms like apathy and disinhibition that are severe and appear early in bvFTD, and the lack of appropriate supportive services. Indeed, numerous studies have demonstrated that stress, depression and burden are higher in FTD caregivers than in any of the other ADRDs, yet caregiver interventions tested in specifically in the FTD population have been limited to a few small studies that focus on education around patient behavior management, not caregiver self-care. Recent evidence suggests that the personal and societal costs of FTD substantially exceed those of dementia in the elderly, yet supportive services that are available are for older persons and thus, rarely meet the needs of this particular groups of caregivers.

Effective interventions are needed for FTD caregivers. Given the challenges outlined above, there is an urgent need to develop supportive interventions for FTD caregivers that are flexible in nature. A recent scoping review found only five intervention studies targeting FTD caregiver stress, but these were mainly limited to small pilot studies exploring the use of support groups. While support groups are an important resource for FTD caregivers, geographical barriers as well as caregiving and life demands severely limit attendance. Web-based interventions may be an effective solution to overcome these accessibility barriers as the home environment may be the best place to deliver an intervention, where distractions are predictable and privacy can be optimized. Home interventions are perceived as convenient, requiring less time commitment, travel costs, financial costs, and waiting times; duration and timing of sessions can be flexible and accommodate caregiver preferences. Indeed, web-based interventions for dementia caregivers have been reported to be convenient and beneficial in reducing caregiver depression and stress, yet these studies have been limited to forms of dementia like Alzheimer's disease

where the caregiving experience significantly differs from that of FTD. Therefore, we propose to extend the intervention, ViCCY, to address these gaps by offering: 1) a psychosocial rather than purely educational approach; 2) flexibility; 3) multidimensionality including information and support tailored for the specific needs of FTD caregivers.

Dyadic processes influence patient behavioral symptoms. Caring for a person with bvFTD is extremely challenging. Caregivers often misinterpret patient behavioral symptoms such as apathy or disinhibition as a sign of volitional opposition and poor cooperation, leading to high level of stress and dissatisfaction with caregiving. Studies have demonstrated that caregivers must adjust their own affect and demeanor to meet the needs of the patient with behavioral symptoms and negative emotional-behavioral responses and altered interactions may therefore increase behavioral and psychological symptoms of dementia (BPSD). We hypothesize that improving caregiver affect through self-care may also reduce BPSD in the care recipient.

Theoretical Framework. The proposed study is based on the Transactional Model of Stress and Coping. Stressful experiences such as caregiving demand – circumstances that give rise to real or perceived stress – are construed as person-environment transactions. Primary appraisal of demand involves assessment of its significance, which results in perceived burden. Secondary appraisal involves assessment of the resources available to cope with it. These appraisals lead to the coping effort.

Without successful coping, self-care is poor, which decreases health status in caregivers. Our virtual support intervention [ViCCY ("Vicky") – Virtual Caregiver Coach for You] addresses both appraisal and coping. Because stress does not affect all people equally, the intervention is tailored to individual appraisals and the factors most likely to influence demand and perceived burden. A key strength of the Transactional Model of Stress and Coping is its recognition that both individual and environmental variables respond to coping.

Scientific premise. This study builds on a strong body of evidence that describes stress and poor self-care in FTD caregivers. Health coaching has been shown to decrease perceived stress and improve self-care and health status in Alzheimer's dementia caregivers, however FTD caregivers are a unique group who are most at-risk for poor self-care, stress and depression. Furthermore, in addition to our primary aims, we will explore the impact of caregiver mood on patient behavioral outcomes. Although a growing body of research illustrates the influence of caregivers on patients and vice versa, (i.e., dyadic processes), we are not aware of intervention studies that have explored the influence of the FTD caregiver mood on behavioral and psychological symptoms (BPSD) in the patient.

CHARACTERISTICS OF THE STUDY POPULATION:

1. Target Population and Accrual:

In the proposed randomized clinical trial, we will enroll adults who are informal caregivers of adults with bvFTD and the bvFTD patients they care for. The study focuses on the caregivers, but we will also enroll bvFTD patients because we will be collecting patient demographic and disease severity (i.e., modified Clinical Dementia Rating Scale) information.

The informal caregivers and the bvFTD patients are anticipated to be adults because bvFTD is a condition affecting adults. The mean age of bvFTD patient participants in the Penn FTD Center is 64 years and most of their caregivers are spouses of a similar age.

The sampling plan involves enrolling a consecutive sample of adult caregivers and patients with bvFTD. We will focus enrollment on caregivers. We have a large referral source from the Penn FTD Center and we will initially draw from this pool of caregivers by contacting those we know are willing to participate in research. Caregivers must be informal caregivers of patients with a confirmed diagnosis of bvFTD. They will be screened with the 10-item Health Self-Care Neglect scale. We will enroll only those who are poor in self-care using a cut-point of ≥2 based on our pilot study. Caregivers must be able to provide informed consent (speak English, see, hear, cognitively intact) and complete the protocol. We will exclude caregivers with cognitive impairment because we anticipate that they would have difficulty completing the intervention. We will exclude anyone with untreated major psychiatric illness such as psychosis. Caregivers in a competing trial testing a support intervention also will be excluded. In this way, we anticipate enrolling only caregivers who are able to provide true informed consent and those who will potentially benefit from the intervention. Any bvFTD patient cared for by an enrolled caregiver will be consented (see consent procedures).

Most caregivers will be spouses but some will be adult children. We expect to enroll slightly more female than male caregivers because most caregivers are female and support interventions are more appealing to women. We will monitor enrollment weekly to ensure that it is appropriately balanced. We will enroll 30 caregivers and patients (15 caregivers per study arm) to achieve over 90% power to detect significant overall differences in longitudinal profiles between the groups on the primary outcome of Self-Care Inventory. We estimate enrolling 10 caregivers per month over 3-4 months. We will require a minimum of 12 months for enrollment. We have conservatively allowed 6 months for enrollment and 6 months to complete the study. Duration of study participation is 6 months.

Dr. Riegel (PI) and Dr. Massimo (Co-I) will oversee the recruitment and enrollment. Participants will be primarily recruited from the Penn FTD Center located in Philadelphia, PA. The Penn FTD Center draws patients from other parts of Pennsylvania, New Jersey, and Delaware. Patient recruitment reflects the average of the population characteristics of these areas as provided by the U.S. Census Bureau (https://www.census.gov/quickfacts/table/). Recruitment, selection and enrollment into the parent study are non-discriminatory regarding race and sex. However, research suggests that members of the minority populations are less likely to participate in dementia research because, relative to their Caucasian counterparts, they are often diagnosed later and, thus do not receive specialized dementia care. We will make every effort to ensure that the subject populations conform to the NIH policy guidelines on Gender and Minority Inclusion in Research Studies, and we make special efforts to recruit women and minorities. On-going efforts to increase minority population include educational series at community centers in Philadelphia and surrounding areas to engage a community of minorities and an annual FTD Caregiver conference sponsored by the Penn FTD Center. All of these efforts will be used to aggressively increase and retain minority group representation.

We expect to enroll women more easily than men because most caregivers are women and this type of intervention is more appealing to women. Recruitment efforts will focus on enrolling a sufficient number of men so that we can analyze sex-based differences in response to the intervention. No caregivers who are < 18 years of age will be included because their stresses may be unique. The randomization sequence will be generated a priori by a statistician unassociated with the study. Caregiver participants will be notified of their group assignment by the Project Manager. Both groups will receive Health Information (HI) delivered by the Internet in addition to standard care. The intervention group will receive virtual health coaching (ViCCY) by video conferencing, with 10 front-loaded health coaching contacts over six months. This dose is based on published data demonstrating that six months of health coaching is needed to be effective. No other collaborating sites are involved.

2. Key Inclusion Criteria:

1. Informal caregiver providing care at least 8 hours/week
2. Reporting poor self-care on screening (Health Self-Care Neglect Scale, score ≥ 2)
3. Able to complete the protocol, e.g., adequate vision and hearing, English speaking
4. Caregiver of a patient diagnosed bvFTD

3. Key Exclusion Criteria:

1. Participation in another support RCT
2. Untreated major psychiatric illness (Use of anti-anxiety/anti-depressant medicines is acceptable and will be adjusted in analysis if group imbalance is identified.)
3. Caregiver with Cognitive Impairment based on Telephone Interview for Cognitive Status (TICS) score <25

4. Subject Recruitment and Screening:

We will enroll a consecutive sample of informal bvFTD caregivers identified from the Penn Frontotemporal Degeneration Center (https://ftd.med.upenn.edu), one of the largest NIH-funded centers dedicated to the study of young-onset dementias in the United States and a site where Dr. Massimo is PI of other FTD-related studies. The Penn FTD Center is actively studying 110 bvTD patients, all of whom have caregivers and we see approximately 20 bvFTD patients a year. If recruitment is slower than expected, we will identify caregivers through the Association for Frontotemporal Degeneration, a national caregiver organization, with whom Dr. Massimo works closely.

To obtain a consecutive sample we will seek a HIPAA waiver to screen the FTD Center clinic daily appointment schedule to identify every patient with a potentially eligible caregiver. FTD Center clinic providers and staff will identify potential caregiver participants (e.g., speak English) and determine their interest in speaking with research staff about the study. If caregivers agree to speak with research staff, the RA will explain the study and screen the caregiver for inclusion and exclusion criteria with standardized testing (e.g., Health Self-Care Neglect scale) and interview (e.g., hearing). Fully eligible caregivers who provide informed consent (see Human Subjects) will complete the virtual baseline assessment before being randomized to study arm. After all baseline data are collected, the caregiver will be randomized to study arm. At that time, participants will be trained in tablet use and how to access the Health Information website.

To safeguard confidentiality and privacy we have planned a 2 step screening process:

1. The RA will obtain Verbal Consent from interested caregivers to conduct preliminary screening for eligibility using study inclusion and exclusion criteria:
   - Caregiver is providing care at least 8 hours /week
   - Able to see, hear, speak and read English
   - Not planning to move out of the area soon
   - Not participating in another support study

2. If appropriate, RA will continue with the full screening process by assessing the following:
   - Reporting poor self-care on screening (Health Self-Care Neglect scale score greater than or equal to 2)
   - Telephone Interview for Cognitive Status (TICS) score <25

After screening, the RA will obtain informed consent from caregivers to continue with study procedures. Those who agree to participate will be asked to read and sign the consent form with integrated HIPAA authorization information (i.e., specifics about data elements to be collected and use of the private information). Fully eligible caregivers who provide informed consent will complete the baseline assessment before being randomized to study arm. After all baseline data is collected the caregiver will be randomized to study arm. At that time, participants will be trained in tablet use and how to access the Health Information website. We will seek bvFTD patient consent to review their medical records and to complete the modified Clinical Dementia Rating Scale (mCDR).

Remote enrollment. In the event that written consent cannot be obtained in person due to safety or practical reasons we will telephone caregivers who have expressed a willingness to speak with us about the study or were referred to us by clinical or other research staff. We will explain the study and screen those who are interested in participating. The screening will be done by telephone. Those who are eligible to participate will be pushed an electronic link that begins with the consent form. Staff will talk through the consent in detail. If the caregiver wishes to think about the study but not commit at this time, we will contact him/her at a later date. If the caregiver immediately decides to participate, the consent can be signed electronically. Once signed, the full enrollment survey will be available for completion. Staff will offer to stay connected and support survey completion for those who wish support.

5. Early Withdrawal of Subjects:

Participants may withdraw from the study at any time without impact to their care. They may also be discontinued from the study at the discretion of the Investigator for lack of adherence to intervention or study procedures or visit schedules or AEs. The Investigator may also withdraw subjects who violate the study plan, to protect the subject for reasons related to safety or for administrative reasons. It will be documented whether or not each subject completes the study. Participants who withdraw early will not be compensated for research activities they did not yet complete.

6. Vulnerable Populations:

Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

7. Populations vulnerable to undue influence or coercion:

The following populations will not be included in the study: children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

STUDY DESIGN:

This study is funded by NIH Grant # 3R01NR018196 - 02W1. In the proposed RCT we will enroll adults who are informal caregivers of adults with behavioral variant frontotemporal degeneration (bvFTD) and the bvFTD patients they care for. The study focuses on the caregivers, but we will also enroll the bvFTD patients to address our exploratory aim. We will seek bvFTD patient consent to review their medical records for factors anticipated to add to the demand of caregiving (e.g., dementia severity on mCDR).

Caregivers must be informal caregivers of patients with a confirmed diagnosis of bvFTD. They will be screened with the 10-item Health Self-Care Neglect scale; we will enroll only those who are poor in selfcare using a cut-point of 2 based on our pilot study. Caregivers must be able to provide informed consent (speak English, see, hear, cognitively intact) and complete the protocol. We will exclude caregivers with cognitive impairment because we anticipate that they would have difficulty completing the intervention. We will exclude anyone with untreated major psychiatric illness such as psychosis. Anyone who

is planning to move out of the area will not be enrolled. Anyone in a competing trial testing a support intervention also will be excluded. In this way, we anticipate enrolling only caregivers who are able to provide true informed consent and those who will potentially benefit from the intervention.

Caregivers in both the intervention and control arms will receive augmented standard care content (Health Information [HI]) through the Internet. In addition, caregivers randomized to the intervention [ViCCY ("Vicky") - Virtual Caregiver Coach for You] will receive 10 front-loaded sessions of virtual health coaching by trained Health Coaches over 6 months with content based on the theoretical framework our prior research. Sessions are provided using tablets. Initially, sessions are weekly to build the relationship, but the frequency of sessions decreases over time. A document of the detailed description of the health coaching intervention content is attached.

We help caregivers gain the knowledge and skills needed to achieve self-identified health goals through self-care using motivational interviewing. We focus on identifying personal values, solving problems, and transforming goals into action using a combination of psychological and behavioral interventions. ViCCY is standardized in a treatment manual. Because stress does not affect all people equally, the intervention is tailored to individual appraisals and the factors most likely to influence demand and perceived burden.

METHODS:

1. Study Instruments:

Self-care refers to those behaviors undertaken to maintain health. In this study we will measure self-care using the Health Self-Care Neglect (HSCN) scale, a 10-item dichotomous scale. This scale has been demonstrated to be reliable (alpha 0.76) have content validity. This will be augmented with the Self-care Inventory (SCI), a 5-point likert scale assessment consisting of 20 items.

Self-reported stress will be measured with the Perceived Stress Scale, a 14-item instrument that provides a global rating of an individual's belief in the severity and frequency of stressful experiences during the last month. The Perceived Stress Scale includes 14 items designed to assess symptoms of stress and global measures of the degree of stress experienced in the past month. Each item is scored from 0 (never) to 4 (very often), with total sum scores ranging from 0 to 56; higher scores indicate higher perceived stress. Cronbachs alpha of the scale ranges from 0.84 to 0.86 and was 0.91 for older African American and European American females.

Coping will be measured using the Ways of Coping Questionnaire, short form. This 42-item questionnaire measures the use of five different coping styles: avoidance, problem-focused, seeking social support, self-blame, and wishful thinking. The original scale has been used widely since developed by Lazarus in 1985. The short version (30 items) uses a 4-point Likert-scale response format (0 = not used to 3 = used a great deal); higher scores indicate greater coping. It is reliable (alpha 0.95) and has construct validity. This instrument has been used numerous times in studies with older adult caregivers.

Health status (physical and mental health). Medical Outcomes Study Short form (SF)-36. The SF-36 has 36 items formatted in scales of varied format (3-, 5- and 6-pt scales and dichotomous [yes/no] scales). each component score is standardized a 0-100 point scale. Reliability is varied samples is typically 0.80. Convergent and divergent validity have been demonstrated in various populations, including caregivers. A benefit of using the SF-36 is that it is one of the common data elements.

Depression will be assessed with the Center for Epidemiological Studies – Depression (CES-D). The CES-D is a valid and reliable scale for detecting caregiver depression in dementia. It has added utility, beyond that of a caregiver burden scale, in identifying a subgroup of caregivers with depression but not burden. This measure uses 20, 3-point Likert scale response items and is reliable (alpha = 0.90).

Burden will be measured with the Zarit-Burden-Interview (ZBI). The ZBI has been used in numerous informal dementia caregiver studies to capture burden associated with providing care to a loved one. Total scores are summed and a range is provided for little to no burden (0-21) to severe burden (61-88). This is a reliable scale (alpha = 0.86) consisting of 22 items rated on a 5-point likert scale (0=never to 4=nearly always).

Quality of caregiver-patient relationship will be measured with the Mutuality scale. The Mutuality Scale is a valid and reliable scale that captures the quality of the relationship between the patient and caregiver regarding dimensions of love and affection, shared pleasurable activities, shared values, and reciprocity. This measures uses 15 item scored on a 5 point Likert scale and is reliable and valid in patient-caregiver dyads.

Evaluation of perceived efficacy of the intervention at 1 month will be evaluated with the Credibility-Expectancy scale to measure intervention credibility and treatment expectancy early on in the study. The Credibility-Expectancy scale is reliable (alpha=0.84) and consists of 6 items scored on a 9 point Likert scale.

Caregiving characteristics will be collected at baseline in a sociodemographic survey interview format to assess work performance with the 7-day work performance questionnaire. This measure has 13 items of 10-pt scale, dichotomous assessment, and a record of number hours spent performing paid and unpaid work; alpha = 0.73.

The Protocol for Responding to and Assessing Patients Risk and Experiences (PRAPARE) is a tool kit developed by the National Coalition on Community Health Centers to standardize the collection of data on social determinants of health (SDH) and facilitate its integration into health records, as a response to recommendations from the National Academy of Medicine. The PRAPARE has 16 core domains (Race, Ethnicity, Education, Employment, Insurance, Income, Material Security, Transportation, Stress, Housing stability, Housing status, Language, Veteran status, Address/Neighborhood, Migrant/seasonal farm work and Social integration/support) and four optional domains (Incarceration history, Safety, Refugee status and Domestic Violence) that align with Healthy People 2020 and the Center for Disease Control and Preventions agenda for prioritizing SDH in health centers.

Patient characteristics and outcomes will be assessed at baseline with the modified Clinical Dementia Rating Scale (mCDR) which includes behavior and language domains. We will also use the Frontotemporal Dementia Functional Rating Scale (FTD-FRS) and the Neuropsychiatric Inventory (NPI) to measure behavioral and psychological symptoms of dementia

2. Group Modifications:

No modifications have been made for the study instruments described above.

3. Method for Assigning Subjects to Groups:

Fully eligible caregivers who provide informed consent will complete the baseline assessment before being randomized to study arm. The Project Manager will open a numbered sealed envelope, prepared by the team in advance, which assigns caregivers to their study arm. The Project Manager will then notify the study staff and participants of their group assignment (ViCCY or HI only) by telephone, email or message. The Project Manager will notify the study staff and participants of their group assignment (ViCCY or HI only) by telephone, email or message, as preferred by the individual. Although balance in sample size can be achieved with block randomization, the groups may not be fully comparable on other factors. Initial comparison of the groups will allow us to control for important covariates in the analyses. Investigators and all staff involved in collecting assessment data will be blinded to group assignment until after the data are locked. The Health Coaches providing the intervention and the caregiver participants will not be blinded. All baseline data will be collected prior to randomizing. Timing of follow-up assessments will be based on day of randomization

4. Administration of Surveys and/or Process:

We will enroll 30 informal bvFTD caregivers and the bvFTD patients for whom they care. After collecting baseline data, we will block randomize the caregivers 1:1 to the intervention or control group, stratifying randomization by caregiver sex and relationship to the patient (e.g., spouse, adult child) factors known to influence caregiving burden, perceived stress, and receptivity to the intervention.

We will provide tablet devices with wireless network access and connect caregivers in both conditions to the Internet so they can access the Internet site providing Health Information (HI) content for 6 months of the study. A data plan will be provided and is included on the tablets. Research staff will provide instruction on how to use the tablet and how to access the HI website. A research diary will also be provided to aid tracking of healthcare resources used and costs. Participating caregivers in both study arms will be encouraged to spend at least 30 minutes weekly using the Internet modules or books for six months. Those who choose to use books rather than the website will be asked to keep track of the number of book chapters reviewed each month. Use of the website or book chapters will be used as a measure of fidelity in both arms. After six months, we will collect all tablet devices (both groups) to minimize bleeding of the intervention into the follow-up period, and we will continue to track use of the website to identify if bleeding occurs.

In addition to augmented standard care HI, caregivers randomized to ViCCY will receive 10 front-loaded sessions of virtual health coaching by trained RNs over the first 6 months with content based on the theoretical framework and our prior research. Health coaching sessions will be provided though the tablets via Zoom conferencing software. Sessions are weekly initially and decrease in frequency over time. Because maintaining contact is important to the success of stress reduction interventions, the assigned Health Coaches will check in with caregivers between intervention sessions. We will offer booster sessions to any caregiver in the ViCCY arm who wishes to receive additional support during the 6-month intervention interval. We will track the number of sessions and test for differential effectiveness based on the dose received. If a brief check-in call becomes an intervention session, it will be tracked for use in analysis. We will mail monthly newsletters to maximize retention.

5. Data Management:

The research team at the University of Pennsylvania will create and maintain a Redcap research database for all participant and adherence data collected during the trial. The database will be stored electronically in the School of Nursing, on a Nursing institutionally secured and managed network drive. Please note that all data entered into the research database will be password-protected with several levels of protection: first, a password will be required to access the computer of the user who has access to the database; second, a password will be required to access the database.

The research team at the University of Pennsylvania will identify potential participants and assign a unique participant identification number. This information will be stored in a password-protected document that is only accessible to research team members. A member of the University of Pennsylvania research team will approach each potential participant and administer informed consent via a paper document. These consent forms will be stored at the University of Pennsylvania in a locked file cabinet.

Paper forms will be used to collect participant information during the initial interview and all subsequent interviews, and from the medical chart extraction process. These forms will also be kept in a locked file cabinet and the information entered into the research database by a member of the University of Pennsylvania research team. We will use standard operating procedures to guide all data management activities, such as the naming of variables, data cleaning and handling of missing data. Missing fields will not be allowed except in certain pre-specified cases (e.g., income).

6. Subject Follow-up:

Assessments of self-care, perceived stress, depression, burden, coping, relationship quality, and health status will be conducted at baseline (after enrollment but prior to randomization) and by phone at 3 and 6 months. We will also collect the credibility-expectancy scale at 1 month to evaluate treatment expectancy. Using contrasts within a mixed-effect modeling framework, we will assess intervention efficacy at 6 months using intention-to-treat analysis. We provide 10 health coaching sessions based on pilot data and literature demonstrating that a shorter duration of health coaching is not routinely effective. We chose to assess the primary aim at 6 months based on prior psychosocial intervention studies, but we will also assess outcomes at 3-months based on this rationale: baseline (enrollment), to generate consistent profiles of all enrollees at a consistent point in time and prior to implementation of the intervention; at 3-months to evaluate very early effects; and at 6-months to demonstrate efficacy of the intervention. Our goal is to establish preliminary efficacy and in a future study we will evaluate longer terms effects of ViCCY vs. HI at 6-months.

If a subject can no longer participate in the study safely or due to changes in circumstance that prevents participation (e.g., imprisonment, long term hospitalization, etc.) they will be withdrawn from the study. Data collection will not continue for participants who are withdrawn from the study. If applicable, research staff will arrange to collect study equipment from the participants who are withdrawing.

STUDY PROCEDURES:

1. Detailed Description:

We will use a RCT design to achieve robust and unbiased results, as detailed below. We will enroll 30 informal bvFTD caregivers and the bvFTD patients for whom they care. After collecting baseline data, we will block randomize the caregivers 1:1 to the intervention or control group, stratifying randomization by caregiver sex and relationship to the patient (e.g., spouse, adult child) factors known to influence caregiving burden, perceived stress, and receptivity to the intervention. We will provide tablet devices with wireless network access and connect caregivers in both conditions to the Internet so they can access the Internet site providing Health Information (HI) content, which will be the only content provided to caregivers in the control group. In addition to HI, the intervention group will receive 10 front-loaded sessions of ViCCY over 6 months. To safeguard confidentiality, tablets provided to caregivers can only be used for the study. Assessments of self-care, perceived

stress, coping, and health status will be conducted at baseline (after enrollment but prior to randomization) and by phone at 3 and 6 months. Using contrasts within a mixed-effect modeling framework, we will assess intervention efficacy at 6 months using intention-to-treat analysis. We chose to provide 10 health coaching sessions based on our pilot data and literature demonstrating that a shorter duration of health coaching is not routinely effective. We chose to assess the primary aim at 6 months based on prior psychosocial intervention studies, but we will assess outcomes at 3-months based on this rationale: baseline (enrollment), to generate consistent profiles of all enrollees at a consistent point in time and prior to implementation of the new intervention; at 3-months, very early effects, at 6-months longer-term effects of ViCCY. We will pull resource use data from the electronic medical record (EMR) in 30-day increments and validated these data during routine follow-up calls with caregivers. We expect the proposed study to require 5 years for completion.

2. Data Collection:

A separate database will contain PHI and the link to the assigned patient identifier. Only the PI and the research staff will be able to access the PHI data. This information will be maintained by the PI upon the completion of this study; however, this data will not be shared or identified for secondary use without IRB approval. Data from the participating subjects will be stored in a password protected limited access human subject research database. Original source records will be maintained in locked offices.

3. Genetic Testing:

Not applicable

4. Use of Deception:

None

5. Statistical Analysis:

All analyses will use an intent-to-treat approach. Descriptive statistics will be used to characterize the sample, with measures of central tendency and variation for continuous measures, and frequencies and percentages for categorical variables. Distributional properties will be examined to determine if variance stabilizing or normalizing transformations should be applied. Non-inferential interim analyses will be performed to ensure data collection and archiving procedures are operating correctly. Outliers will be assessed by visual inspection and checked for accuracy. Once the database is locked, comparisons by group will assess for balance and identify multi-collinearity and areas requiring statistical adjustment. For comparisons involving continuous variables, homoscedasticity will be evaluated using Levines tests. Normality will be assessed using Shapiro-Wilk tests. Should violations emerge, transformations will be applied, or nonparametric tests used.

While every effort will be made to obtain complete data on every participant, some missing data are inevitable. The underlying mechanism missing completely at random (MCAR), nonignorable or not missing at random (NMAR)will be evaluated prior to adjusting to minimize bias from missing data. We expect most missing data to be MCAR (e.g., finding data collection burdensome). However, systematic bias may exist for those who withdraw so baseline characteristics will be compared among those with and without complete follow-up data. To assess potential biases, we will compare withdrawal rates and time to withdrawal. If the number lost to follow-up is small (5%) and the missing observations can be considered MCAR, then the primary hypotheses will be tested using the complete observed data. If missing observations cannot be assumed to be MCAR, more complex approaches will be considered such as shared parameter models or random pattern-mixture models. Sensitivity analyses for these models will be performed. These approaches assume that participants dropped out for either informative (e.g., illness exacerbation) or non-informative reasons (e.g., withdrawing consent). If dropouts are informative, we will adjust for this potential bias by introducing a covariate(s) into the analysis to help to explain why participants dropped out early.

To assess changes in each of the primary and secondary outcomes over time, separate mixed effects regression models will be generated with SAS Proc Mixed. We are not powered for secondary outcomes (e.g., stress, coping, health status), but we will examine effect sizes and confidence intervals (CIs) to determine if lack of power is driving nonsignificant results. Mixed models can account for correlation between repeated measures and handle non-excessive MAR or MCAR data better than traditional models and allow for use of time-independent and time-dependent covariates. Both random slopes and random intercepts will be modeled to represent deviations from the average, or fixed-effect, slope over time and intercept, respectively. REML will be used for parameter estimation and the most appropriate covariance structure will be examined. Scores will be analyzed as repeated observations, with mean-centered baseline outcome scores serving as a covariate. Other predictor variables will include group, assessment time, and the interaction of group time (primary effect of interest). Baseline measures and group will be analyzed as time-independent covariates. The evaluation of differences in outcome profiles over time according to group will rely on the group x time interaction terms, while differences by the balancing

variables will rely on the mixed-effects modeling of higher order interaction terms. Statistical significance for individual intervention contrasts will be evaluated for each outcome, applying the Benjamini & Hochberg method to control for the type I error rate at 5%. The Akaike information criterion (AIC) will be used to evaluate overall model fit and to select the best-fitting longitudinal change pattern. We expect the groups to be balanced on baseline characteristics due to randomization; however, imbalances that occur by chance will be adjusted for in all analyses. To evaluate patient outcomes (Aim 2) over time we will use mixed effects regression modeling. As described above, scores will be analyzed as repeated observations, with mean-centered baseline outcome scores serving as a covariate. Other predictor variables will include time-dependent caregiver variables, assessment time, and the corresponding two-way interaction term (primary effect of interest).

RISK/BENEFIT ASSESSMENT:

1. Risks:

Protection Against Risk:

Fatigue- To minimize the most likely risk of fatigue during data collection, we selected surveys that are as short as possible. Completion of the self-report survey packet requires less than one hour. Testing will be scheduled at a time that is convenient for subjects. If participants are too fatigued to complete all measures, sociodemographic and clinical data will be administered at enrollment and the baseline surveys will be gathered in a subsequent telephone call (but before randomization). All delayed data collection will occur within a two-week interval. The RAs will be trained to be sensitive to signals from participants that a break is needed during testing. All participants will be informed that they can stop their participation in the study at any time. For subjects who find data collection too fatiguing, we will offer the option of providing only the most essential data reflecting the key outcome variables (e.g., health self-care neglect).

Stress- To minimize the risk of stress during data collection the RAs will be trained to be supportive and helpful to participants with questions about data collection. If a participant becomes stressed during data collection because of the questions asked, the burden of data collection, or for other personal reasons, data collection will be terminated, delayed, or abbreviated to only the most essential items (e.g. primary outcome variable). Significant stress will be reported to the Project Manager who will contact the caregiver to discuss the issue if indicated (the PI is blinded). The RAs will be trained to detect any signals that the participant is becoming upset before stress escalates. In a prior study, we hired nursing and psychology students as RAs, which facilitated the assessment and management of participant stress during data collection. RAs will be required to have sufficient maturity and background to interact appropriately with ill, aging, stressed individuals. The protocol for the training of RAs, detailed in our operations manual, addresses enrollment methods and the collection of data in a uniform manner. Training for RAs in data collection will occur during a two-day period prior to beginning subject enrollment. Training will begin with classroom instruction, including the purpose and background on each measure, importance of strict adherence to the standardized protocol, step-by-step instruction for survey administration, criteria for aborting testing and the procedure for audiotaping sessions and transmitting data. RAs will be trained to ensure that they do not prompt subjects with verbal or nonverbal cues. Training will include practice administering all tests. Consistency in data collection procedures will be assessed and reinforced during routine staff meetings. Retraining and retesting will be done immediately if a new RA is hired and annually thereafter. The PI and the Project Manager will meet weekly or bi-weekly with staff (in-person or by video) to discuss issues of enrollment and data collection. All decisions will be logged and filed for future reference. All issues will be reported immediately to the IRB and the Data Safety Monitoring Board, as discussed in that plan.

We will be enrolling a sample of stressed individuals and it is possible that we will identify someone with severe distress. Dr. Riegel (PI) has previously tested a detailed safety plan, which has been refined for use in this study. This safety plan addresses the concerns associated with severe stress that need to be handled in order to ensure that the research participants needs are addressed. This plan includes the requirement that research staff undergo training in this safety protocol and participate in ongoing regular supervision by Dr. Massimo (Co-I) on these procedures. In addition, for participants randomized to the ViCCY group, specific rules to ensure privacy and safety will be discussed in the first session, such as being in a private place during sessions and not engaging in discussions while driving.

2. Benefits:

We cannot guarantee that any participant will benefit by participating in this study, although all of the caregivers will receive health information. We acknowledge that subject burden may be an issue for these already-burdened caregivers. However, we believe that the benefits of the knowledge gained will outweigh the burden and the risks to participants. A Data and Safety Monitoring Board will be used to ensure the validity and integrity of the data. We anticipate that the results of this study will benefit society most, by helping to improve the support provided to caregivers of bvFTD patients.

3. Subject Privacy:

Data will be compiled from all of the subjects in the study and aggregated for analysis and publication. All identifying data will be eliminated from files before data are electronically transferred to the biostatistician. As a result of aggregation, no individual subjects will be identifiable from the written materials. Audiotaped interviews will be assigned a unique identifier; any identifiable information in the interviews will be deleted during the transcription process. All videoconferencing sessions will be conducted using secure encrypted platforms. All companies providing third-party platforms used for this study completed the Vendor Security Technical Assessment of Risk (V-STAR) forms and have been vetted by SONs IT Department. And tablets provided to caregivers can only be used for the study.

4. Subject Confidentiality:

A trained research assistant will review the electronic medical record to make sure that the caregivers approached qualify to be participants before we invite them to join the study (eg. the patient has bvFTD). Accessing the EMR means that we will see PHI but we will limit our review to only those elements essential to establish eligibility. If the record review indicates that a caregiver is not eligible, we will note this on our paper-and-pencil log so that we do not need to repeat the review the next time the patient comes into the clinic. That paper log will be transported back to the School of Nursing and locked in a drawer until the next scheduled day of enrollment. We will not disclose the information on the log to anyone not directly involved in the study.

To protect against any risk to subject confidentiality, all printed data forms will be coded with unique identifiers. The unique identification number will be kept separate from the files with protected health information (PHI) to protect subject confidentiality. Every effort will be made to prevent anyone who is not on the research team from knowing what information was collected from a particular subject. As part of the consent process, subjects will be made aware of the fact that there are some circumstances where the research team may have to provide subject information to other people (regulatory or legal circumstances). In addition, as we are unable to ensure total Internet security, this limitation of privacy will be noted in the informed consent. In this manner caregivers will be informed that although it is highly unlikely that anyone would access an audiotaped session, the prevention of such intrusions cannot be guaranteed. The content of the intervention sessions is not anticipated to be confidential in nature.

Since this data storage system is behind multiple firewalls, is monitored regularly, and is accessible only to key personnel who receive private network/firewall, server/password, and data directory access rights, the risk of unlawful penetration is not a significant data safeguard concern. Individually identifiable or deducible data will not be transmitted by unsecured telecommunications, which include the Internet, email, and electronic File Transfer Protocol (FTP). Further, the data will not be physically moved or transmitted in any way from the server without written approval from the project manager. All output containing individual identifiable information is treated as confidential data. This information is never transferred electronically via email or other protocols.

All data will be backed up daily and system backups will be done weekly. Batch validity checks will be run on the database at periodic intervals to identify data that violate predefined rules. Data will be de-identified and stored on the database server with strong access controls, software firewall, secure file transfer protocols, network-wide virus protection software, and daily back-ups. The computers will be password-protected and maintained in a secure, locked location at the School of Nursing. Interim checks will be conducted regularly to ensure that data collection and archiving procedures are operating correctly and security and confidentiality are not compromised. All information obtained on paper (e.g., consent forms) will be numerically coded and locked in a secure location, as described further below.

Signed consent forms and other subject-specific information containing names will be kept separate from the subject identification numbers. The master list and subject information will be stored in different locked file cabinets in the PIs research offices at the University of Pennsylvania, School of Nursing. Access to these master files will be limited to those directly involved in the study.

Regarding internet access and video-conferencing sessions, study tablet devices, which are versatile for allowing privacy, will be provided to all participants and can only be used for the study. Health coaching sessions will be provided through the tablets via Secure VidyoConferencing software. Sessions are weekly initially and decrease in frequency over time. The tablet uses an embedded computer camera capable of full 2-way duplex video and audio transmissions for real-time communication. Existing broadband Internet connection is not required because we supply devices with mobile connectivity. Technology experts (Caryl Technologies, with whom we have worked in the past) will train research staff to set up Internet service.

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.

☒ Whenever feasible, identifiers will be removed from study-related information.

☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.

☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)

☒ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.

☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

☐ Other (specify):

5. Protected Health Information

Name
Street address, city, county, precinct, zip code, and equivalent geocodes
All elements of dates (except year) for dates directly related to an individual and all ages over 89
Telephone and fax number
Electronic mail addresses
Medical record numbers

6. Compensation:

As data collection is anticipated to require significant commitment and effort on the part of subjects, remuneration will be provided. We carefully considered the amount to pay participants using the guidelines from Dickert and Grady. Because of the potential burden of data collection, we chose a market model of payment where the amount serves as an incentive rather than a reward. The advantage is more rapid recruitment and avoidance of subject financial sacrifice. Further, a completion bonus encourages subject retention. Using this model, caregivers will receive $25 at enrollment, $25 at 3 months and $75 when they complete the study for a total remuneration of $125 for a 6-month commitment. This amount is not anticipated to be undue inducement, considering the effort and commitment required of participants.

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7. Data and Safety Monitoring:

We will use a Data Monitoring Committee as described in the attached document.

8. Investigator's Risk/Benefit Assessment:

It is our judgment that benefits outweigh the risk to study participants.

INFORMED CONSENT:

1. Consent Process:

After approval by the Institutional Review Board (IRB) at Penn, the research staff will work with clinical staff to identify eligible caregivers for referral to us. To obtain a consecutive sample we will seek a HIPAA waiver to screen the clinics daily appointment schedule to identify every patient with a confirmed diagnosis of bvFTD and a potentially eligible caregiver. If enrollment from the clinic is slow we will also look for bvFTD patients participating in research at the Penn Frontotemporal

Degeneration center. Once identified, clinic or research staff will ask potential caregiver participants (e.g., those who speak English) and determine their willingness to speak with research staff about the study. Those agreeing to speak with us will have the study carefully explained to them by the research staff. Potential participants will be fully informed regarding the interventions and the schedule of the data collection. Those willing to be screened will provide verbal consent to undergo screening to assess inclusion and exclusion criteria.

After screening, the RA will obtain written informed consent from caregivers and bvFTD patients. Those who agree to participate will be asked to read and sign the consent form with integrated HIPAA authorization information (i.e., specifics about data elements to be collected and use of the private information). The consent form will specify that some intervention sessions will be audiotaped to ensure the quality of the intervention and judge treatment fidelity. We will explain that these audiotapes will be transcribed for analysis and then destroyed. We will use SameDay transcription for our audio recordings. They are a HIPAA-compliant company that has been vetted by SON's IT Department. The RAs will answer questions and make sure that the procedures that are to be used are fully understood.

The study will provide tablet devices with wireless network access and active antivirus to all participants. The tablets will only be able to be used for the study. Caregivers in both conditions will be able to access the Internet site providing Health Information (HI) content for 6 months of the study. A data plan will be provided and is included on the tablets. Research staff will provide instruction on how to use the tablet and how to access the HI website and assist participants to access the HI site if necessary. A research diary will also be provided to aid tracking of health care resources used.

In the case that participants cannot be consented in-person, participants may be consented remotely at the PI’s discretion. Screening will be done by telephone and those who are eligible to participate will be pushed an electronic link that begins with the consent form. Staff will talk through the consent in detail. If the caregiver wishes to think about the study but not commit at this time, we will contact him/her at a later date. If the caregiver immediately decides to participate, the consent can be signed electronically.

2. Waiver of Informed Consent:

No waiver requested.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION:

OVERALL STRUCTURE OF THE STUDY TEAM
This is a single site clinical trial with a Clinical Coordinating Center (CCC) with direct oversight by Dr. Massimo and Dr. Reigel and a Data Coordinating Center (DCC) with oversight by Co-Investigator Dr. Aryal. Enrollment will take place primarily at the Penn Frontotemporal Degeneration Center. Oversight of the clinical intervention will be done by Dr. Reigel and Dr. Massimo.

The Project Manager will identify training requirements relevant to the study activities and develop a training plan and process for providing and documenting training activities. This includes developing training materials (checklists, manuals, slides, and FAQs) and implementing a process for tracking. She will oversee participant enrollment, data collection, data entry and cleaning, and analysis efforts to assure that these activities take place as planned. In addition, a clinical research coordinator will be hired to facilitate smooth and efficient data collection, help with recruitment and identification of potential subjects.

Health coaches. We will hire 2-3 experienced health coaches with excellent interpersonal communication skills, and comfort with technology. The coaches will receive two days of initial training in health coaching from Dr. Riegel and her team and then completed 7 hours of online training in motivational interviewing provided by the University of Colorado, College of Nursing. Dr. Massimo will also provide the coaches with a day of training related to FTD and they will receive the book, “What if it’s Not Alzheimer’s,” developed for FTD families, which contains a chapter written by Dr. Massimo on common behavioral symptoms in persons with FTD. Thereafter, weekly training and supervision will be conducted by Drs. Riegel, Hirschman and Massimo as the coaches begin sessions with the caregivers. As part of this supervision, audio-recordings of coaching sessions will be reviewed by independent raters using the Behavior Change Technique taxonomy. Two trained raters have judged randomly selected session recordings for each coach, assessing completeness and thoroughness of the therapeutic techniques used. We will continue to assess the quality of the coaching as we add this group of caregivers with unique issues.

Internet Access. We will leverage the current technology infrastructure from R01NR01819. We will provide tablet devices to all participating caregivers. Tablets are versatile, allowing privacy for coaching sessions and website access to those in the HI group. The tablet uses an embedded computer camera capable of full 2-way duplex video and audio transmissions for real-time communication. Existing broadband Internet connection is not required because we supply devices with mobile connectivity. Technology experts (Caryl Technologies, with whom the team currently work) will train research staff to set up

Internet service and devices with Caregivers during a virtual visit. Caregivers will be left with a step-by-step manual and the research assistant phone number in case technology issues occur.

Data Coordinating Center - Data coordination for the trial will be done by the BECCA (Biostatistics * Evaluation * Collaboration * Consultation * Analysis) Lab in the School of Nursing. The BECCA Lab is comprised of a team of highly skilled doctoral and masters level statisticians, along with Penn Nursing research assistants and biostatistics graduate interns who oversee data management and analytic activities. The lead statistician and Co-Investigator, Dr. Aryal will ensure statistical rigor and appropriateness of all analyses.

Research Technology staff will develop and maintain a REDCap data management system. They will collaborate with the investigators to identify relevant clinical data from electronic medical record data (EMR) in the Penn Data Store and design, test and implement a process to import data at a scheduled frequency to data tables, which will be part of the research database. Research Technology staff will also develop programs to identify new hospital encounters for study participants using EMR information in order to initiate communication to the research staff that follow up action may be required.

Data Management staff will develop the case report forms and modify standard or template questionnaires as needed. They will design and develop the trial database and required modules. All research data for the trial will be stored in an electronic database that is managed by BECCA Lab. The database will be hosted on secure School of Nursing computing servers with access restricted to only those individuals who are authorized to work on the trial. Individual user accounts with passwords will be used to restrict access to the database. Specific privilege assignments within the database will be employed to limit the types of functions that authorized users can perform to those functions that are appropriate for their role in the trial. Additional measures to prevent unauthorized external access to the database environment will be employed using network firewall technologies.

BECCA Lab personnel will work closely with Dr. Massimo, Dr. Riegel, and the Project Manager to design, develop, and test an appropriate database structure to support the requirements of the study to promote data security and integrity. Electronic audit trails of changes to database contents are incorporated into the design and will capture and record those changes automatically. BECCA Lab personnel will configure a module to allow remote data entry from the enrollment sites. The module will be available to any computer with a persistent internet connection and will be run using standard web browser software. The data entry screens will look like the existing or reconfigured data collection forms and will allow for direct source-to database data entry, eliminating the need for paper Case Report Forms (CRFs). Data entry checks will be included in the entry screen designs where appropriate to limit the opportunity for erroneous entries due to mistyping. Such data entry checks would include value range comparisons, valid data type checks, required value checks, and skip pattern enforcement. This data entry module will be configured for single data entry.

BECCA Lab personnel will configure a module to assess data entered into the database in relation to a set of rules that describe expectations for those data items. This set of data validation rules will be defined by clinical data management personnel, working closely with Dr. Riegel and the Project Manager, to identify data items that may have been collected incorrectly or entered into the database inaccurately. The module will inspect all newly entered or modified data. Clinical data management staff will review the results of the data validation and contact research staff to request corrective action for invalid data. All changes made will be recorded in an electronic audit trail and documented using change control procedures. Prior to deployment and use in the trial, the database will be subjected to extensive functional testing. Testing will include an evaluation by representative users.

Trial Close-Out: Once all data have been collected, BECCA Lab staff will lock the database. Trial data will be packaged for data sharing purposes. A snapshot of the database will be taken and stored in a secure folder.