Telehealth Cognitive Behavioral Therapy for Depression in Parkinson's Disease (PD)

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1. Purpose/Specific Aims

There is a critical need for treatments that address depression and barriers to mental health care among the nearly 100,000 Veterans with Parkinson's disease (PD) served by the VA. Depression in PD (dPD) is a major complicating factor in the movement disorder, affecting several key functional outcomes such as motor disability, cognitive status, quality of life, and Care-partner relationships.[1-4] The challenge to meeting the treatment needs of Veterans with dPD centers on the lack of clinicians who are knowledgeable about the interactions of PD and depression, the considerable transportation barriers faced by this population, combined with the geographical dispersion of specialized services within the VA, and the paucity of effectiveness research that informs treatments for dPD. [5]

To address this problem, we propose to conduct a randomized controlled trial (RCT) to test the effectiveness of a psychotherapeutic intervention aimed at treating depression in Parkinson's disease (dPD) in Veterans. The proposed study treatment consists of a 10-session cognitive-behavioral treatment (CBT) package that has been tailored to address the unique needs of depressed Veterans with PD. Also, the treatment seeks to overcome treatment access barriers by a using telehealth delivery platform (i.e., video-to-home telehealth technology). In addition, the proposed treatment package provides support and skills-training to the Veteran's Care-partner (3 sessions).

1.1 Objectives

AIM 1: To evaluate the effectiveness of TH-CBT (telehealth-cognitive behavioral therapy) for improving Veteran outcomes in dPD (depression in Parkinson's Disease).

AIM 2: To examine the impact of TH-CBT for dPD on a variety of Care-partner outcomes.

AIM 3: To assess Veteran and Care-partner perspectives on TH-CBT using qualitative, semi-structured interviews.

1.2 Hypotheses

Primary Hypotheses: Depressive symptoms will decrease more for Veterans receiving TH-CBT (the "intervention group"), than for Veterans receiving standard care only (the "control group").

Secondary Hypotheses: There will be more treatment responders in the TH-CBT group (the "intervention group") than in the standard care group (the "control group)." Psychiatric and functional correlates of dPD for Veterans receiving TH-CBT will show greater improvement (anxiety, quality of life) or stabilization (motor disability) over time than those for Veterans in the standard care group.

Care-partner Hypotheses: Care-partners in the TH-CBT condition(the "intervention group") will feel more empowered, report less distress and be less critical (towards the Veteran) relative to Care-partners in the standard care group (the "control group").

2. Background and Significance

Depression, the most common non-motor complaint in PD, [1] affects up to 50% of PD patients.[6] Depression in PD (dPD) is associated with rapid physical and cognitive decline,[2] poorer quality of life,[7] increased healthcare costs,[8] earlier initiation of dopaminergic replacement,[9] and notable Care-partner distress.[3] Depression is therefore a key intervention target for improving a range of PD complications.

Yet, unfortunately, depression treatment is the one quality standard inadequately addressed in VA PD care, including in its PD specialty centers.[10,11] Sub-optimally treated dPD aggravates physical and cognitive PD morbidity, thereby undermining all of the VA's other evidence-based efforts to improve non-mental health disturbances for PD Veterans.[2,10,12] Thus, there is a critical need for treatments that address depression and barriers to care among the approximately 100,000 Veterans with PD.[13]

The challenge to addressing depression in PD centers on the lack of mental health clinicians who are knowledgeable about the movement disorder (a prerequisite to effective care), the transportation barriers faced by Veterans, the geographical dispersion of VA services, and the paucity of effectiveness research that informs depression treatments for PD Veterans.[5]

The proposed study seeks to overcome these obstacles by using a telehealth delivery platform (i.e., video-to-home; "V2H" or "CVT-H") to test the effectiveness of a 10-session cognitive-behavioral treatment (CBT) package, tailored to address the unique needs of Veterans with dPD. Preliminary studies provide strong support for the current trial. **V2H allows Veterans to use their computer's webcam to interact with their providers using videoconferencing, via the VA's secure telehealth connection.**

The current trial builds on several earlier trials that have shown support for this intervention to treat depression in PD.

First, this CBT package was initially tested in a face-to-face RCT with 80 people with dPD (and Care-partners), who were randomized to receive CBT plus standard care or standard care only for 10 weeks. The Hamilton Depression Rating Scale [14] (HAM-D 17) was the primary outcome. Treatment response was defined a priori as a rating of a 1 or 2 on the Clinical Global Impression-Improvement Scale [15] (CGI-I; a 7 point scale with scores ranging from 1 [very much improved] to 7 [very much worse]) or ≥50% reduction in the baseline HAM-D 17 score. Patients were evaluated at baseline, midpoint (week 5), endpoint (week 10), and one-month follow-up (week 14). CBT was associated with greater improvements in <u>depression,</u> [HAM-D 17; F(3,215)=30.74 P<.0001; Cohen's d=1.59] & Beck Depression Inventory (BDI) F(3,210)=9.77 P=.001; Cohen's d=1.10], <u>anxiety</u> [F(3,214)=11.65 P=.001; Cohen's d=.98], <u>quality of life</u> [F(3,209)=5.07 P=.02, Cohen's d=.81], <u>coping</u> [F(3,204)=4.25, P=.05; Cohen's d=.80] , and <u>motor disability</u> [F(1,68)=5.9 P=.02; Cohen's d=.13] vs. control. At week 10, 56% patients receiving CBT and 8% receiving standard care were treatment responders, as defined above (Fisher's exact P<.0001). At week 14, 51% of CBT patients and 0% of patients in the standard group met criteria for response (Fisher's exact P <.0001).

Second, this treatment was repeated in an uncontrolled trial, where the intervention was delivered via telephone. Within group CBT effect sizes for telephone delivery showed a similar treatment effect, compared to effect sizes obtained via face-to-face delivery. This telephone-based CBT protocol was provided to 21 patients and Care-partners, resulting in significant improvements in depression [HAM-D

17: F (3,56)=18.50, P<.0001; Cohen's d=1.21 and BDI: F(3,53)=23.68, P<.0001]. This trial demonstrated that the same treatment can be delivered remotely with a similar level of treatment impact.

Combined, these initial studies provide support for the CBT package and for its remote delivery (i.e., telehealth). The current trial therefore proposed to test the delivery of this treatment via video-to-home telehealth. This modality of care has been rolled out by the VHA and therefore provides an existing infrastructure to make this intervention available to Veterans with dPD, who face access barriers to treatment. For example, at VA New Jersey, 583 mental health encounters have been conducted via video-to-home telehealth in FY14.

3. Research Design and Methods

Participants will include 90 Veterans (ages 35-85) with dPD and their Care-partners (N=180 total: 90 Veterans with PD and 90 Care-partners). Since Care-partners will be designated by their Veteran with PD, they will not likely be Veterans themselves. The justification for including nonveterans is due to the fact that Care-partners serve as an integral part of the treatment team for Veterans with dPD. Thus, we are evaluating the clinical effectiveness of an intervention that involves Care-partners in order to optimize Veteran depression treatment response and Care-partner well-being.

The clinical effectiveness of a 10-session telehealth-based cognitive-behavioral treatment package (TH-CBT) for dPD will be evaluated. Study conditions are as follows:

- [Intervention] Half of the Veterans will receive telehealth-based CBT, in addition to their standard care (i.e., treatment-as-usual under the care of their personal physicians).
- [Control] The other half will receive their standard care only during the study period. Participants will be randomly assigned to treatment group via computer generated random assignment. Randomization will be stratified by antidepressant use at baseline (yes/no).

Veterans will be evaluated remotely, via telephone, prior to treatment (week 0), mid-way through treatment (week 5), immediately after treatment (week 10), one month following treatment, and six months following treatment by raters who are blind to treatment condition. A purposive subsample of 40 treatment recipients (20 Veterans/20 Care-partners; will receive a semi-structured interview (i.e., exit interview) at Week 10, in order to generate qualitative data on their experience with the study. Specifically, these interviews will focus on 10 Veterans (and their Care-partner) who respond at endpoint (i.e., CGI-I of 1 or 2) and 10 (and their Care-partner) who do not respond (i.e. CGI-I of 4 or 5) to TH-CBT.

Participants will receive the study treatment at no cost. Veterans and Care-partners will each receive $45 per outcome assessment completed. Data collection ends for all participants at the 6-month follow-up. However, since we expect that our Veteran population will not have access to a needed tailored psychotherapy for dPD (TH-CBT), we will offer this clinical care to control group participants, after the data collection period. However, no additional data will be collected. The total duration of the protocol is9 months for all participants.

3.1. Duration of Study

This is a four-year study that will actively recruit subjects for a period of approximately 3.5 years. Subjects enrolled in the study will participate in the protocol for approximately 9 months.

3.2 Study Sites

Subjects will be Veterans of VA New Jersey Healthcare System. VA New Jersey will be the only site engaged in Human subjects research.

3.3 Sample Size Justification & Subject Selection

The study will enroll a total of 180 subjects (90 Veterans + 90 of their Care-partners), from VA New Jersey, who have Parkinson's Disease and depression. 1,199 Veterans with dPD were served in VA New Jersey during the last four fiscal years. Several methods of recruitment (see Recruitment and Consent below) will be used to enroll this pool of Veterans.

Our Power Analyses assume 180 participants (90 enrolled dyads) with 144 participants (72 dyads, 36 dyads each arm), completing the study. Observed standard deviations in the power calculations that follow are taken from control group baseline data in Dobkin et al.[16] For the primary test of treatment differences in HAM-D scores, controlling for baseline HAM-D scores and demographic covariates, the current study is powered to detect a 2.5 point HAM-D treatment difference between groups. For comparison, we observed a group difference of 7.30 in Dobkin et al.[16] For the secondary test of responder/nonresponder, we considered clinical response rates of 0.05 and 0.10 for the control group and .35, .40, and .45 for the treatment group. Power was greater than .95 in call cases. For comparison, we observed rates of 0.08 and 0.56 in the control and treatment groups, respectively, in Dobkin et al. (2011).

3.4.1 Inclusion Criteria

Veteran Inclusion Criteria:

1) Confirmed PD diagnosis in the VA medical record;
2) Primary Major Depression, Dysthymia, or Depression NOS of at least moderate severity per the SCID;87
3) Access to a computer/tablet with high-speed internet access. Comorbid anxiety disorders are not exclusionary if the depressive disorder is primary.
4) Ages 35-85;
5) Stable medication and mental health regimen (including applicable antidepressants, other psychotropic agents, movement disorder drugs, clinic-based psychotherapies) ≥ 6 weeks). This means that the medication regimen and treatment plan have been consistent for at least 6 weeks.
6) Family member or friend willing to participate;

Veteran Exclusion Criteria:

1) Possible dementia or marked cognitive impairment [Montreal Cognitive Assessment Score (MoCA) < 21]. [17]
2) Motor fluctuations ≥ 50% of the day;
3) Acute suicidal plans or intent (determined by clinical interview);
4) Unstable medical conditions;
5) Bipolar, Psychotic Spectrum, or Substance Use Disorders.

Exclusion Criterion 1 above is due to dementia being associated with numerous clinical variables (e.g., motor fluctuations, delusions) that make the rating of depression difficult. Dementia may also compromise the clinical effectiveness of a non-pharmacological treatment due to its impact on cognitive processes. As dementia is not typically seen in the early stages of PD, results from the current study should generalize to the larger PD population without dementia.

Care-partner Inclusion Criteria:

1) Ages 25-85;
2) Daily contact with Veteran

Care-partner Exclusion Criteria:

1) Unstable medical/psychiatric conditions (clinical interview).

3.4.3 Subject Recruitment and Consent

180 participants (90 Veterans with PD and 90 Care-partners) will be recruited from the New Jersey area (2 VAMCs and 9 CBOCs), using several recruitment strategies. A DSS report will be generated with contact information of Veterans in VANJ who had a visit with a diagnosis of PD, during the previous 4 fiscal years (a HIPAA waiver has been submitted). Letters will be mailed informing them of the study, and study staff will contact them by telephone to determine if they would be interested in and eligible to participate. If there is no contact by the Veteran, the research team will call the Veteran after waiting a period of 2 weeks, unless the veteran notifies the study team that he/she does not wish to receive a phone call.

Recruitment will also take place through Neurology and Primary Care Clinics at VA New Jersey. Veterans will be recruited from these sites via recruitment flyers (attached). Also, providers may refer potential candidates to the research team. This will be done by either instructing the Veteran to contact the research team or alerting the research team via CPRS that the Veteran is interested. In case of the latter, the research team will send a letter (see attached) to the potential candidate that includes the name of the referring provider. As above, phone contact will not be initiated earlier than two weeks and in cases where the Veteran notifies the study team that he/she does not wish to be contacted.

Candidates identified with the methods described above will be informed of the study. If they are interested, a phone script will guide the candidate through informed consent for the phone screen (see attached Waiver of documentation of consent). If verbal consent is provided, they will be screened by telephone (see attached phone screen) for basic eligibility criteria. For those who meet basic eligibility and remain interested, consent forms will be mailed to potential participants. At a later time (allowing for consent forms to arrive at candidate's homes), study staff will then review the consent form with the potential participant over the phone. After all questions are answered, the participant will sign the consent form and mail it back to the study team, so that they can later be formally evaluated for study eligibility (i.e,. baseline evaluation). This same consent process will also be conducted for the Care-partner.

<u>Other Procedures:</u>

<u>Baseline Assessment:</u> After the screening and consent, appropriate individuals will be scheduled for a telephone appointment. Demographic information will be obtained, and inclusion/exclusion criteria will

be assessed. A detailed medical (i.e., number of medical conditions, duration and stage of PD) and psychiatric history (i.e., number past depressive episodes, past treatments), and a current list of all prescription and over-the-counter medications will be gathered. Clinician-administered rating scales and self-report measures will be completed. The screening appointment typically lasts between 2 and 3 hours. If participants are unable to complete the entire screening evaluation in one day, a second telephone appointment will be scheduled within the next 7 days to complete the remainder of the screening procedures.

Randomization: All appropriate candidates will be randomly assigned to receive either: 1) telehealth-based cognitive-behavioral therapy plus standard care (the "intervention") or 2) standard care, based on computer generated random assignment, after the screening appointment (the "control group" treatment). Randomization will be stratified by antidepressant medication (ADM) use at baseline (yes or no) such that patients taking ADMs are equally represented in both treatment conditions. Patients will be notified of their assignment to group via telephone in the week following their baseline assessment.

Assessments: Participants will be assessed at baseline (week 0), midpoint (week 5), endpoint (week 10), and follow-up (1 and 6 months post-treatment). Follow-up assessments will be conducted via telephone for the clinician-rated instruments (i.e., HAM-D, HAM-A). Self-report questionnaires will be mailed to participants with a self-addressed envelope that can be returned to the research team upon completion. If participants request assistance with the self-report questionnaires, they will be mailed to them and also read aloud to them by telephone. These assessments will last 1-2 hours.

Qualitative Data: Semi-structured interviews will be used to study participants' perspectives in terms of treatment effectiveness. Specifically, selecting from the study's treatment arm, quantitative data will be used to identify a purposive subsample of participants for qualitative interviews, where 10 Veterans who respond at endpoint (i.e., CGI-I of 1 or 2) and 10 who do not respond (i.e. CGI-I of 4 or 5) to TH-CBT will be identified. Once identified, qualitative data will consist of semi-structured interviews conducted separately with these Veterans and their Care-partners. A total of 40 interviews will be conducted (10 responder Veterans + their 10 Care-partners; 10 non-responder Veterans + their 10 Care-partners).

Blinding: All follow-up (i.e., post-baseline) assessments will be conducted by independent evaluators without knowledge of treatment condition. Veterans will be instructed not to reveal group assignment to raters. Veterans and therapists will not be blind given the nature of the treatment. Information regarding the integrity of the blind (patient revealing group assignment to rater) and the blind raters' guess regarding group assignment will be collected after each study evaluation. In rare cases in which the blind may be broken, the interview recording (with unblinding information removed) will be presented to a second rater for coding. Therefore, all final score determinations will be made by an independent evaluator with no knowledge of group assignment.

Video-to-home telehealth V2H): Inclusion criteria require that all participants will need a home computer or tablet with a webcam to participate in the study. If they do not have a webcam, one will be provided to them. V2H set up for Veterans will follow established procedures in place at VANJ, which is supported by the facility's telehealth lead ([redacted]). This includes signing the facility's video-to-home consent form and application, documenting which records are needed, including emergency contacts for the participant (included as an attachment). Veterans will need to download the software (i.e., Jabber) for connecting with the study team. They will be assisted with self-help instructions, study team telephone guidance, and/or a home visit, depending on the level of assistance needed with V2H installation procedures.

As documented in the VHA's Clinical Video Telehealth in the Home Manual, prior to the initiation of telehealth sessions, information will be obtained pertaining to emergency contacts that can be called in case of emergency.

Contact for appointments related to treatment and assessments:
This research is being carried out with a population that requires active engagement to mental health services. In standard VA NJ mental health care, this is reflected in policies requiring at least three follow-up phone calls and/or a letter after a no-show to standard mental health appointment. Our research team will adopt a similar approach to maintaining engagement, utilizing telephone calls and letters to arrange for appointments. Our philosophy will be guided by a person-centered, relationship-building approach. For example, we anticipate that there will be several missed appointments and our interactions with study participants will convey empathy and understanding for missed appointments, as well as flexibility and accommodation for rescheduling. On the other hand, our research staff will also be sensitive to indications that participants no longer wish to participate and will cease contact efforts once that appears to be the case.

3.4.5 Subject Costs and Compensation

There will be no cost to subjects for the study treatment sessions. Veterans and Care-partners will each receive $45 per outcome assessment completed. Subjects selected for the semi-structured interviews will receive an additional $20.

3.5 Chart Review Selection

Research staff will also perform retrospective chart reviews on all enrolled study subjects for the purpose of documenting the standard care that participants received during the study. Standard care will focus on mental health standard care. Because our study occurs within the context of standard care, data will be collected to describe the standard care received and/or control for potential standard care covariates. Specifically, we will gather detailed standard VA medical care information pertaining to: a) psychotropic medication use (dose, type, frequency); b) number of medication management visits; c) number of standard care psychotherapy visits (i.e., non-TH-CBT). Non-VA standard mental health care will be assessed via interview.

As with our primary data, all medical records data will have identifiers removed and data storage will occur by ID number, rather than name. Also, the data will be stored on a secure server that is maintained by the VA's IRM (Information Resource Management) and has up to date security protections. Within this server, the data will be placed on a secured folder [redacted] that is restricted for only users that are part of the VANJHCS Dual Diagnosis Unit, which is our local research unit. Data will also be stored in VINCI, which is the VA's computer infrastructure that allows data storage, analysis, and sharing, while maintaining privacy and security.

4. Study Variables

4.1 Interventions

Study Conditions

Control Group: Standard Care. Standard Care is defined as medical and psychiatric treatment provided by patients' personal doctors (e.g., neurologists, psychiatrists, therapists). Veterans will continue to receive routine clinical care and will remain on all depression treatments that they were receiving prior to their study (e.g., stable ADMs, established psychotherapy, clinical monitoring). Care-partners will continue to receive all non-clinical services for which they qualify through the VA, including services offered through the Office of Caregiver Support, as well as PD caregiving resources, support groups, and referral information provided by the American Parkinson's Disease Association.

Intervention Group: TH-CBT + Standard Care: The TH-CBT group will receive the study intervention and standard care. The study treatment has been previously manualized and modified for remote administration. dPD Veterans will receive 10 weekly individual sessions (60 minutes each) of CBT, delivered via V2H. Treatment will incorporate behavioral activation, exercise, thought monitoring and restructuring, relaxation training, worry control, and sleep hygiene (emphasis dictated by patient preference), and will be augmented with 3 separate Care-partner educational sessions (30-60 minutes each), that are evenly dispersed throughout the Veterans' treatment. The Care-partner sessions are intended to provide Care-partners with the skills needed to facilitate the Veterans' practice of self-management techniques (i.e., exercise, socializing, reframing thoughts) both between sessions and after treatment had ended, in order to empower the Care-partner in the helping role. The intervention will be provided by IRB-approved licensed clinical social workers and doctoral level clinicians under the supervision of Drs. Interian and Dobkin.

The CBT package employed in this trial is tailored to the unique needs of the Parkinson's population. In brief, PD specific modifications include a stronger emphasis on behavioral and anxiety management techniques than traditionally integrated into CBT protocols for depression, and the inclusion of a supplemental Care-partner educational program. These changes have been successfully implemented in our prior clinical studies of CBT for dPD and are intended to address the psychiatric complexity and executive dysfunction that characterize these patients, as well as to effectively mobilize the patients' social supports, in order to optimize treatment response. For example, the inclusion of family members in psychosocial interventions for chronic medical conditions has been linked with improved patient outcomes across a range of physical illnesses versus standard care[18]. Estimates also suggest that informal Care-partners assist people with PD an average of 11 times per day in early PD and up to 30 times per day in later stage disease.[19] The beneficial impact of Care-partner involvement on mental and physical health in PD has been well demonstrated. [20] Moreover, as described above, dPD is characterized by high rates of executive dysfunction and psychiatric comorbidity, factors which have been negatively associated with depression treatment response in older adults [21] and in the few pharmacologic studies that have examined these relationships in PD. [22] Thus, more intensive behavioral strategies which target these clinical correlates of dPD are warranted.

Intervention details. Behavioral strategies for increasing meaningful, pleasurable, and social activities will be addressed early in therapy in order to help Veterans maintain and/or increase a sense of purpose and fulfillment in their lives, despite the limitations of their medical condition. Collaborative goal-setting to safely increase physical activity (i.e., exercise) will be emphasized. Problem-solving regarding physical limitations (i.e., ordering food that does not need to be cut in a restaurant, walking for 10 minutes three times a day, instead of 30 minutes at one time), as well as strategies for pacing daily activities, and setting realistic daily goals, will be conducted to help facilitate these healthy behavioral changes. Throughout the course of treatment, Veterans will also be asked to monitor the thoughts (i.e., My life is

meaningless) and feelings (i.e., depressed) that they have in response to stressful situations. The Veterans' negative thoughts will be evaluated via the use of a variety of cognitive restructuring techniques and replaced with more accurate alternatives as appropriate ("I will still be able to have a meaningful life despite the limitations associated with my medical condition"). A major focus will be on the modification of thoughts leading to excessive disability, helplessness, loss of control, and dependency.

The Veterans' individual treatment will also incorporate relaxation techniques, such as diaphragmatic breathing, progressive muscle relaxation, and guided visualization, in order to address the high prevalence of anxiety and somatic complaints found in the PD population. All 3 techniques will be sequentially introduced and emphasis will be dictated by Veteran preference. Separate recordings of each relaxation exercise will be made to facilitate both practice and mastery. In order to best manage the physical symptoms of anxiety, Veterans will be encouraged to regularly incorporate these relaxation strategies into their daily routines and to apply them when confronting stress. Behavioral worry control techniques, such as thought stopping, scheduling and postponing worry, and the use of positive affirmations, will also be implemented as needed. For Veterans with sleep difficulties, sleep hygiene techniques, such as avoiding daytime naps, and establishing bedtime-wakeup routines, will be introduced.

Care-partner Sessions: During initial sessions, Care-partners are provided with information regarding the psychiatric complications in PD and the CBT model of depression. In later sessions, Care-partners are trained to recognize the Veterans' negative thoughts such as "I am rapidly deteriorating" and to help the Veteran replace their negative thoughts with more balanced alternatives (i.e., "I am not rapidly deteriorating. My neurologist said I am the same as I was six months ago and did not change my medication."). Techniques for supporting the Veterans in the application of their newly acquired self-management skills (e.g., daily walks, calling a friend weekly, going to Physical Therapy) are addressed, as well as strategies for minimizing the Veterans' sense of helplessness (e.g., not offering assistance when it is not needed). Ways to decrease negative social exchanges (e.g. risk factors for depression like criticism) between the Veteran and Care-partner are also targeted.

4.1.1 Drug or Device Interventions

None

4.2 Dependent Variables or Outcome Measures

The table below illustrates how the study measures will be administered across the study protocol. Further description of each measure appears further below.

Table 1: Summary of Measures						
Domain	Measure	Week 0 (Baseline)	Week 5 (Mid-Treatment)	Week 10 (Post-Treatment)	1 Month f/u	6 Month f/u
Aim 1 - Veteran Outcomes						
Psychiatric Diagnosis	SCID	V				
Depression	HAM-D; BDI-II	V	V	V	V	V
Anxiety	HAM-A	V	V	V	V	V
Quality of Life	SF-36	V	V	V	V	V

Cognitive Functioning	MoCA	V				
Aim 2 -- Care-partner Outcomes						
Care-partner Burden	CDS	C		C	C	C
Empowerment	FES	C		C	C	C
Criticism	PCS	V:C	V	V:C	V:C	V:C
Aim 3 - Mixed-Methods Veteran and Care-partner Perspective						
Telehealth Satisfaction	Satisfaction Questions			V:C		
Therapeutic Alliance	Working Alliance Inventory		V	V		
Semi-structured Interview				V:C		
Note: TH-CBT will occur between Weeks 0 and 10. V=measure will be given to Veteran. C=measure will be given to Care-partner. Aim 3 measure will only be given to participants in the TH-CBT condition.						

Screening Assessments:

Structured Clinical Interview for DSM-IV (SCID-IV).[23] The SCID is a semi-structured interview for assessing the DSM Axis I psychiatric diagnoses and the depression inclusion criterion . As many symptoms of depression (i.e., fatigue, psychomotor retardation) overlap with physical aspects of PD, an NIH working group has recommended taking an inclusive approach when making a psychiatric diagnosis in PD.90 Thus, all mood symptoms are counted towards the depressive disorder diagnosis, despite the potential overlap of mood symptoms with core PD symptoms as long as one of the two key features of a DSM depressive disturbance (i.e., sad mood, loss of interest/enjoyment) are present.

Montreal Cognitive Assessment Scale (MoCA).[24] The MoCA is a brief cognitive screening tool that is sensitive to the effects of cognitive decline in PD. A score of 21 has been identified as an optimal cut-off for possible dementia in PD (sensitivity 81%, specificity 95%).88 **This cut-off score will allow us to exclude patients with more serious cognitive limitations who may not be appropriate for this type of treatment,2 while still allowing patients with a broad range of cognitive abilities to participate. As a result of this exclusion, we will not be enrolling participants with impaired capacity to consent.**

Outcome Assessments:
The following outcomes measures will be administered to the Veteran. The primary outcome will be change in clinician-rated depression, as measured by the Hamilton Depression Rating Scale (HAM-D), which is a well-established clinician-rated instrument for depression.[25] Secondary clinical outcomes include responder status [15] (defined a priori as depression very much improved (1) or much improved (2) on the CGI-Improvement Scale; CGI-I:, depression severity (as assessed by the Beck Depression Inventory-II, which is a well-established self-report measure of depression), [26] clinician-rated anxiety (Hamilton Anxiety Rating Scale (HAMA),[27] quality of life (Medical Outcome Study Short Form [SF-36]),[28]

The Veteran will also complete a measure of Perceived Criticism.[29] The scale consists of ratings of perceived criticism and reactivity to criticism. The respondent completes the following two items: 1) How critical do you think you are of your family member?; 2) How critical do you think your family member is of you? For reactivity to criticism, Veterans completed the following two items: 1) When your

family member criticizes you, how upset do you get?; 2) When you criticize your family member, how upset does he/she get? For perceived criticism and reactivity to criticism, items are rated 1-10 and were summed to generate a score ranging from 1-20 with higher scores indicating greater perceived problems.

Finally, Veterans will also complete treatment Satisfaction measures, [30,31], as well as the Working Alliance Inventory-Short Form. [32] The qualitative data will be assessed with a semi-structured interview that will elicit a narrative on their experience with the treatment (see Measures). The qualitative interview will only be give to a subsample and will take place at endpoint (see Research Design and Methods, 3rd paragraph).

The following outcome measures will be administered to the Care-partner. Family Empowerment will be assessed with the 12-item family subscale from the Family Empowerment Scale.[33] Each item is rated from 1 (not at all) to 5 (very true), resulting in a sum score of 12 - 60. This measure captures the degree to which Care-partners feeling they understand and respond to their Veterans' illness. Care-partners will also complete a measure of Caregiver Distress [34] and Perceived Criticism (same measure as Veteran).[29]

Qualitative Data: The qualitative interviews (see attached) will be theme-driven, with participants being prompted to discuss their perceptions of TH-CBT. The analysis section below describes the qualitative analytic process.

4.3 Risk of Harm and Protections Against Risk

The proposed study involves non-invasive interview assessment measures and a psychosocial intervention, both of which are associated with minimal risk. The risk associated with each component of the research is outlined below, followed by the steps we will take to minimize these risks.

Structured Interviews, Rating Scales, Questionnaires, and Electronic Medical Record Review:
These types of assessment procedures are commonly used in psychiatric research and are generally associated with minimal risk. Problems that might arise during research assessments or therapy sessions would be related to emotional distress. To address this risk, all assessors and therapists will receive training and supervision pertaining to depression in Parkinson's disease from Co-Investigator Dr. Roseanne Dobkin, and on assessing and responding to suicide risk, from the PI, Dr. Alejandro Interian. Thus, staff will be trained and closely supervised to directly intervene with any emergent emotional distress in a manner consistent with standard clinical practice. Study clinicians, [redacted] and [redacted], are both licensed clinical social workers. At the same time, Dr. Interian will be accessible to intervene with any psychiatric emergent events and will do so in a manner consistent with standard clinical practice, including the full range of clinical options (i.e., crisis assessment, crisis counseling, and intervention, providing safety planning, contacting family for support, linkage to indicated treatment, use of emergency services). In addition, the research team members are experienced in working with veterans on the facility high-risk list, have had training in VA crisis and suicide prevention protocols, and work closely with the VA Suicide Prevention Team.
In addition, Dr. Margery Mark (Co-Investigator) is our study's movement disorder specialist who will provide consultation for the team, to allow for identification of need to coordinate with the participant's usual care neurologist/physician with emergent issues pertaining to PD. She will not interact with patients or access PHI.

The other primary foreseeable risk is associated with breaches of confidentiality of study data or personal information.

In order to protect the privacy of participants, we will closely adhere to VA regulations. The recruitment process will entail the use of a contact spreadsheet that contains protected health information (minimal PHI needed to consider basic eligibility and contact information for recruitment). This administrative spreadsheet will be stored separately from the study's research data. No protected or personal health information will ever be recorded or stored in a permanent research database. The contact spreadsheet will be placed on a secure VA server. The spreadsheet will not be downloaded to a personal computer and will only be used by authorized members of the research team. The database containing demographic information and interview responses will be saved separately. This process ensures that protected health identifiers are never recorded in the research database. The data will be destroyed following the release of VA regulations on retention of research records and will follow the VA's policy for destruction of study records.

With respect to other data, all paper-based information containing personal identifiers (such as consent forms) collected in this study will be kept in locked filing cabinets accessible only to the research staff of the VA NJ Health Care System. All assessment data will be collected in a private VA office and directly entered into a computer database, and stored in password-protected VA files on the secure VA server. This will include the study teams secure network folder as well as VINCI. VINCI is the VA's secure VPN portal for research data and can be used to allow approved VA collaborators to access data, without the data leaving the secure VA computing environment. We will use VINCI to share de-identified interview transcripts with [redacted]. Assessment data will be identified by ID number only and will not be associated with any personal identifying information. The database that contains the link between the subjects' names and their ID numbers will be maintained on a separate password-protected spreadsheet on the secure VA network. The final research database will not contain any PHI. No personal identifying information will be included in published findings from the study or in reports to the funding agency. The specific time frame for destruction of identifiers will be determined following the release of VA regulations on retention of research records and will follow the VA's policy for destruction of study records.

In addition to the above data, we will also be audio-recording TH-CBT sessions and semi-structured interviews for the purpose of conducting fidelity reviews to ensure clinicians are following the protocol in delivering the treatment and for qualitative analysis. All assessment interviews will also be audiorecorded to allow for quality control. In addition, this will allow a second rating by a blind rater, in instances where the experimental blind is broken.

Individuals will not be identified by name during assessment interviews. Participants will be aware that some sessions will be recorded and will be requested to provide signed consent when consenting to participate in the research study and verbal assent prior to initiating each recording. Following each recording, we will immediately transfer the recordings from the digital recorder to the VA secure server and the audio file will be assigned a code name. The recording will be deleted from the original device according to VA protocol. The digital recorder will be kept in a locked cabinet in the VA office of the interviewer. The file name for each recording will not contain PHI and will coded by research ID.

Review of deidentified audiorecordings will be conducted by our Co-Investigator, Dr. Roseanne Dobkin, Rutgers-Robert Wood Johnson Medical School. Dr. Dobkin will be credentialed at VANJHCS (i.e., WOC)

and will be able to access the team's files and folder on the secured server. Audiorecordings will not be sent outside of VA New Jersey.

4.4 Potential for Benefit

Study Veterans and non-participating depressed PD Veterans and their Care-partners may benefit from the proposed project. Prior research with the study intervention indicates that at least some benefit is likely. Specifically, the proposed telehealth CBT treatment package has the potential to enhance emotional and physical health for Veterans with PD through the alleviation of depression and its associated psychiatric and functional correlates, as well as to improve access to evidence-based mental health care in PD. There is also the potential for benefit to Care-partners, in terms of empowerment, reduced burden, and improved communication patterns with their Veteran with dPD. Finally, participants in both study conditions will be receiving greater clinical monitoring of depressive symptoms, relative to standard care, via the study assessment. Greater monitoring will help detect clinical worsening and mental health crisis, allowing for appropriate care to be provided and coordinated, thereby providing additional benefit.

If the treatment coincides with clinically significant improvements, the results will be published so that other mental health professionals can more successfully treat dPD and other complex medical and geriatric conditions. The improved functioning of PD patients will also benefit society, larger family units, and the healthcare system. Neurologists, psychiatrists, psychologists, and primary care physicians will also benefit in that they will ultimately have additional empirically validated treatment options from which to choose when working with depressed PD patients and Care-partners, as well as research support for alternative methods of treatment delivery that have the potential to reduce access barriers to mental health treatment in this and other geriatric and medically complex populations.

5. Data Handling and Statistical Analysis

Unless otherwise indicated, all of the analyses below will use mixed models analysis to examine treatment effects on the specified dependent variable. There will be one between-group variable (TH-CBT versus control), one repeated measure variable (time), and group-by-time interactions (effect of interest). We will consider several correlational structures between repeated measures (e.g., compound symmetry) and determine the best structure using the Akaike's Information Criterion (AIC). Random effects will be specified for each subject. For each dependent variable, we will analyze the effect of interest (i.e., group X time) separately at each post-randomization assessment point. The models will include demographic covariates (age, sex) as indicated. Standard residual diagnostics will be applied. In the event of unaccounted-for outliers, analyses will be run with and without the outliers. Should the residuals deviate unacceptably from normality assumptions, we will use robust estimation as described and catalogued by Wilcox.[35]

AIM 1: To evaluate the effectiveness of TH-CBT for improving Veteran outcomes in dPD. Primary Hypothesis: Depressive symptoms will decrease more for Veterans receiving TH-CBT, than for Veterans in the control group. The HAM-D is the primary depression outcome measure. Secondary Hypotheses. There will be more treatment responders in the TH-CBT group. Analyses examining depression treatment response will utilize the CGI-I (response equals CGI-I score of 1- 2). [36] Fisher's exact test will be used to test the hypothesis related to treatment response. A sensitivity analysis will be performed using logistic regression to examine the possible importance of covariates. Secondary Hypotheses: Secondary

outcome measures for Veterans receiving TH-CBT will show greater improvement (BDI, HAM-A, SF-36) over time than for those of Veterans in the control group. As these measures can be expected to be correlated, the significance threshold adjusting for multiple-testing will be determined by permutation-based analysis.

AIM 2: To examine the impact of TH-CBT for dPD on a variety of Care-partner outcomes. Hypotheses: TH-CBT Care-partners will feel more empowered (FES), report less distress (CDS) and be less critical (to the Veteran; PCS) relative to controls. The analysis approach will be the same as in Specific Aim 1

AIM 3: The following analytic process will be used to qualitatively analyze data collected from semi-structured interviews. Interviews will be audiorecorded, transcribed, and imported into a qualitative analysis software program (i.e., Atlast.ti). Analytic methods will be guided by grounded theory,[37] using an open, inductive coding approach. Coding will be iterative, will rely on the constant comparison method, and will utilize multiple raters. Regular meetings will be utilized to build the coding framework and achieve consensus between raters when coding disagreements occur. Once the qualitative data have been coded, indices (e.g., number and % of statements within each narrative) will capture the extent to which each participants' narrative responses fall into each thematic category. This will allow for comparisons to be made between groups established by the quantitative data (e.g., themes according to responder versus nonresponder) and analysis of associations among quantitative variables (e.g., Care-partner burden, client satisfaction) and qualitative themes. The aim of this integration will be for the qualitative data to generate a contextualized understanding, based on participants' perspectives, on the themes associated with the objectively measured (i.e., CGI response) success of the treatment.

6. Data and Safety Monitoring

In addition to the detailed measures described above to maintain the safety of research participants and their data, this study will have a Data and Safety Monitoring Board (DSMB), which will serve as an oversight committee, reviewing any major modifications to the research design and conduct of the study and making recommendations according to the NIH Policies for data and safety monitoring as described below. Definition of Adverse Events and Serious Adverse Events will be determined in accordance with the DSMB and the IRB. Reports of adverse events will be made to the IRB according to the standards for expedited reporting.

The individuals who will serve on the DSMB are:

[redacted]

[redacted]

[redacted]

<u>The specific goals of this joint DSMB are:</u>

1. To review new or modifications to existing risk management protocols.
2. To review procedures and decisions regarding the adequate protection of specific patients when investigators move into risk management protocols because of adverse events or clinical deterioration.
3. To review progress toward meeting enrollment goals.
4. To review procedures for maintaining the confidentiality of data, and quality of data collection, management, and analyses.
5. When appropriate, serve as final arbiters of whether individual patients should be removed from a protocol.
6. To recommend continuation, discontinuation, modification, or termination of a study based on emerging data (in the study and literature) and evaluation of risk/benefit ratio.
7. To conduct annual reviews to determine whether patient safety has been adequately safeguarded.
8. To meet at least once yearly with the principal investigator to review progress reports.

The PI will forward all DSMB reports to the IRB for review.
The general purpose of the data monitoring plan will be to maximize the safety and privacy of all study participants, and ensure the integrity, validity, and confidentiality of the data collection and analysis procedures. These objectives will be accomplished through regular monitoring and oversight by the Principal Investigator. The Principal Investigator will report any serious and unexpected adverse events and unexpected problems that involve risk to the participants or others, or any breaches in confidentiality to the Institutional Review Board (IRB).

Each year, the PI will include a summary of data safety monitoring activities in the annual progress reports to the IRB. These reports will include: (1) whether participants' safety, privacy and confidentiality has been consistently assured by the investigators; (2) review of interim data analyses that bear on outcomes of the study and risk/benefit ratios to participants, including recommendations for new statistical analyses; (3) judgment as to whether research instruments have been administered in a uniform manner and in a way that maintains the participants' privacy; (4) a review of the study's progress toward recruitment goals, quality of data (e.g., appropriate completion of forms), and participant retention/attrition rates; and, (5) a review of new scientific literature pertinent to the safety of participants or ethics of research participation.

There will be regular, ongoing communication between the PI and the local IRB. While no serious and unexpected adverse events are expected as a result of participation in the research study, any unanticipated study problems will be reported to the local IRB. As noted above, the study clinicians will take all clinically appropriate actions to prevent and treat psychiatric emergencies in participants.

7. Reporting Results

We will not be conducting medical tests or collecting any other measures that would require patient notification. In terms of professional reporting, aggregate results will be reported in a final report to the funding agency as well as in presentations at professional meetings and in peer-reviewed journals.

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Protocol Amendments

1. 8/11/16:
   We requested a full waiver of HIPAA authorization for caregiver research subjects only as we are not collecting any private health information from caregiver participants. This includes an exemption of medical record notes in the medical chart for caregiver research subjects only. We will still obtain written, informed consent from caregivers to participate in the study.

2. 10/19/16:
   First, we requested a waiver of the requirement to obtain written informed consent from both Veterans and their Care Partners, as mailing and requiring the return of signed consent forms prior to participation for this minimal risk study creates an undue burden for potential participants and a significant time lag. Second, we modified the inclusion criteria requiring a care-partner, amending the criterion to include a willingness to find a caregiver to participate in the study. Third, we removed the requirement that subjects be recruited from VA New Jersey only and expanded recruitment of subjects to Veterans enrolled in VHA, including those from other facilities. Fourth, we added language to the protocol for clarification that does not constitute a change to the content of the study protocol.

3. 1/6/16:
   First, we updated the diagnostic interview from the SCID-IV to the SCID-5 to ensure that diagnoses of subjects are up to date with current accepted standards. Second, we requested approval of additional advertising materials from the research to be used at other VA facilities. Third, we added two additional questions to the follow-up assessments about medical issues encountered and psychotropic medication changes since the last assessment. Fourth, we adapted the home telehealth survey questionnaire for both Veteran and Care Partner participants to increase the relevance to study intervention.

4. 4/6/17:
   First, we requested to add an additional recruitment procedure through Michael J. Fox Clinicial Trial finder to improve our ability to reach our recruitment target. Second, we added language to all regulatory documents and advertisements consistent with our approved previous amendment to recruit from VA facilities other than VANJ.

5. 4/21/17:
   First, we requested to add additional information in our intake assessment to assist an independent expert to confirm diagnoses of Parkinson's Disease.. Second, we specified the process by which we will have interviews transcribed by VA HSR&D transcription services.

6. 6/9/17:

We requested to modify the wording of the informed consent document to clarify the payment schedule for participant incentives and to clarify that incentives are for study assessments only and not the study treatment.

7. 9/22/17:
   We updated a previous amendment to specify that our team will utilize VA Sharepoint, a secure, VA firewall-protected link, to transfer files to HSR&D's transciption service.

8. 7/25/18:
   We added the Parkinson's Disease-Specific Anxiety Inventory (PDSAI) to the set of self-report measures completed by participants at each of three time points: at baseline (week 0), treatment endpoint (week 10) and final (six-month) follow-up.