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PROTOCOL TITLE: Communication Bridge: A person-centered Internet-based intervention for individuals with primary progressive aphasia

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OBJECTIVES:
The proposed study will use a randomized controlled trial (RCT) design to evaluate whether a person-centered treatment (experimental) for adults with mild PPA maximizes functional communication participation as compared to an impairment-only treatment (control). All treatment will be provided remotely by speech language pathologists using a HIPAA compliant video-conferencing program.

Aim 1: Determine the within-group response of the Experimental and Control treatments for individuals with PPA.

- Aim 1a: To provide descriptive and quantitative characterizations of within-group responses to treatment. This data will serve to inform future clinical study design.
    - Hypothesis 1: The experimental group will show significant within-subject gains on communication participation and language performance measures, while control group gains will be restricted to language performance measures.
- Aim 1b: Determine if the magnitude of treatment response is mediated in part by participant home exercise compliance, PPA subtype, level of depression, and/or communication partner support.
    - Hypothesis 2: We hypothesize the number of times participants complete their home exercises (i.e., compliance) will be a significant mediating factor in treatment response, especially for the language performance measures.

Aim 2: Determine if a person-centered dynamic treatment approach (experimental) for adults with PPA will show more favorable communication participation outcomes as compared to a dose-matched impairment-only treatment approach (control) over a 12-month course of disease.

- Hypothesis 3: Participants in the experimental group will show more favorable communication participation outcomes relative to the control group.

This study will be one of the largest non-pharmacologic intervention studies for individuals with PPA to date. It will add critical data on the usefulness of telepractice for adults with dementia. The goal of this study is to maximize functional communication and life participation for the participants.

BACKGROUND:

Primary Progressive Aphasia. The diagnosis of primary progressive aphasia (PPA) is made when a relatively isolated progressive impairment of language occurs as a result of neurodegenerative disease[1]. It is associated with Alzheimer's disease or a form of frontotemporal lobar degeneration. Adults with PPA can have deficits in word finding, word usage, word comprehension, and/or grammar. Consensus research criteria recognize three variants of PPA based on the profile of language deficits: agrammatic (PPA-G), semantic (PPA-S) and logopenic (PPA-L)[2].

- **Agrammatic Subtype (PPA-G):** Individuals have difficulties with word production and word order.
- **Logopenic Subtype (PPA-L):** Individuals have difficulties with word finding.
- **Semantic Subtype (PPA-S):** Individuals have difficulties with word understanding.

Individuals with PPA tend to have preserved insight into their disease, which may contribute to increased risk for depression[3]. Onset of PPA tends to be before the age of 65, which is younger than those with amnestic Alzheimer's dementia[4]. This creates unique psychosocial and economic challenges since adults with PPA are commonly in the prime-earning phase of their careers and often have dependent children at home[5]. Maximizing functional abilities of individuals with PPA could have quality of life benefits including improved mood, social engagement and prolonged independence, which could translate into economic savings for the family and the medical community at large[5].

PPA Treatment. There is no cure for PPA. A few pharmacological trials have been conducted with inconclusive results[6-8]. Promising case-reports and small group studies of non-pharmacological communication interventions in PPA show positive effects of impairment-based interventions (i.e. script training to improve fluency, multi-syllabic word production training to improve articulation; for reviews see[9-11]). Barriers for individuals with PPA being referred for speech-language therapy services include therapeutic nihilism amongst healthcare providers and stakeholders[12-13], limited training for community-based speech-language pathologists (SLP's) on how to appropriately treat individuals with dementia, and decreased awareness on the part of physicians and the general public regarding the potential benefit of non-pharmacological interventions for dementia[13-14]. The American Speech-Language-Hearing Association (ASHA) and National Aphasia Association website allow users to search for SLPs who specialize in *aphasia* in their geographic area, but users are unable to search for SLPs specializing in PPA making it difficult for individuals to know if their local therapist has received specific training or experience in PPA. This pilot randomized controlled trial (RCT) will address concerns about access to non-pharmacological care and small numbers of participants in evidence-based research studies for individuals with PPA by using videoconferencing over the Internet to deliver treatment, which can reach individuals irrespective of their geographic location. Outcomes from this project have the potential to improve awareness about the relevance of non-pharmacological interventions in dementia and, if effective, will offer an evidence- based treatment model for individuals with PPA.

Telepractice model. PPA is a strong candidate for care through the telepractice model. Access to services and the ability to conduct large evidence-based studies has been limited because individuals with PPA may not live near an SLP who has experience in treating individuals with neurodegenerative aphasia[15]. In fact, >40% of the participants in our preliminary Communication Bridge study lived in rural areas and >94% lived outside

Chicago, IL, the home site for the study. Distance from a healthcare facility is one of many variables that can be alleviated using a telepractice model. For example, our participants could attend sessions while on vacation, and remain with the same therapist even from their winter homes, resulting in fewer missed sessions and better continuity of care. Additionally, since PPA is a relatively young-onset neurodegenerative disease, patients often enter clinics with expertise in mobile technology and expectations of including this modality in their communication interactions.

Preliminary Data. Our initial study was an uncontrolled trial and demonstrated that web-based person-centered treatment using impairment-based strategies, compensatory-based strategies and communication partner-training strategies was feasible in 31 PPA participants across subtypes[16]. SLP-assessed and self-reported functional gains, improved retrieval and/or pronunciation of words, and increased confidence in communication (using the same measure proposed in this project) were documented at 2 months and maintained at 6 months post-enrollment. More specifically, there was significant improvement on the Communication Confidence Rating Scale for Aphasia (CCRSA) from baseline to 2 months (mean scores at baseline = 68.2 +/- 2.7, 2months = 73.3 +/- 2.6, $p = 0.018$) and no significant decline at 6 months (mean score = 70.9 +/- 2.9, $p > 0.4$). All participants maintained or improved their level of functioning in their most challenging language domain from the initial evaluation to 2 months (65% improved and 35% maintained) on the ASHA-Functional Communication Measure (ASHA-FCM). At the 6-month evaluation, only 13% declined by one level on the ASHA-FCM compared with the initial evaluation.

Participant feedback from our preliminary project was overwhelmingly positive with >90% families reporting that our Internet-based person-centered speech-language therapy intervention met or exceeded their expectations. Participants commonly reported improvements in completing functional daily communication tasks they had previously abandoned. One participant reported being able to email family and friends after therapy. Another participant was able to generate her own To-Do list on paper, an activity that she required assistance with prior to treatment. Most participants (69%) have continued to use the Communication Bridge web-application after therapy ended. One participant, who completed the study 8 months ago, still uses the web-application to practice her target word cards daily. Another practices an average of 8 times per month since therapy ended 84 weeks ago.

INCLUSION AND EXCLUSION CRITERIA:

Screening. Participants and communication partners will be given a complete overview of the study and an opportunity to ask questions when they are being consented to complete the screening procedures for the study. They will be informed that they could be deemed ineligible to participate at certain points of this process.

Medical Record Review. Interested participants will be asked to send their medical records to Northwestern University, which will be reviewed by medical professionals on the study team to confirm the PPA diagnosis.

Technology Screening. Technology proficiency will be examined using a guided interactive interview, which includes the participant and communication partner's previous or current history working with video-chat programs, their frequency of email use, and the

strength and type of Internet connections they have available to them. Using their personal computer, participants receive a link via email to a videoconference. The success of signing on and completing a short call via videoconference will serve several purposes. First, it will allow for the research team to determine how comfortable the participant and communication partner are with using a computer and email to start a video-chat. Secondly, the audio/video quality of the video-chat will be a good indicator of the participant and communication partner's strength and quality of Internet connection. During the session, participants and communication partners will also be asked to complete an Internet speed test (www.speedtest.net) to ensure their Internet bandwidth can support uninterrupted video-chat. Participants are required to have at least 1 Mbps upload and 4 Mbps download of available Internet bandwidth as recommended by the HIPAA compliant video-chat software program used in this study. A strong Internet connection is important to ensure uninterrupted Treatment Sessions with consistent audio and video feed. Insufficient Internet connection will be remedied prior to enrollment. A Technology Proficiency screening was implemented during our preliminary study and has been successful at identifying appropriate candidates for treatment over videoconference.

Cognitive Screening. A brief cognitive screening (about 30 minutes) will be administered to participants over videoconference. This assessment will serve to confirm mild impairment of PPA.

Depression Screening. Individuals will be given the 15-item Geriatric Depression Scale to screen for depression. Indications of depression are categorized into mild, moderate and severe as follows: 5-8 mild depression, 9-11 moderate depression, and 12-15 severe depression; Sheikh & Yesavage, 1986). If an individual scores a 9 or above and their depression is untreated, they will be ineligible for the study.

SLP Screening. The screening with the speech-language therapist will be the last screening activity. SLP's will confirm PPA subtype at this screening.

At any point during screening, a participant may be determined to be ineligible. They will be informed of the reason they are ineligible for the study. If a participant is eligible, they will be consented into the study and randomized to study group (experimental vs. control).

Inclusion/Exclusion Criteria:

- Must be English speakers
- Hearing adequate to have a conversation in a crowded room (correction permitted)
- Reported vision adequate to read the newspaper (correction permitted)
- If Bilingual, must use English daily
- Must have a communication partner (spouse, family member, close friend) who is willing to participate in the study
- Adequate experience with computers (tech screening)
- Diagnosis of PPA must be made by a clinician (we will require medical records for review).
- There is no age requirement. However, most individuals that are diagnosed with PPA are in their 50s – 70s. This is a neurodegenerative disease so we do not anticipate participants younger than their late 40s.

STUDY-WIDE NUMBER OF PARTICIPANTS:

Up to 100 individuals with mild PPA and their communication partners (spouse, family member, or close friend).

STUDY-WIDE RECRUITMENT METHODS:

Recruitment sources will include Clinical Core participants at the Alzheimer's Disease Centers at Northwestern University (NU) and Oregon Health & Science University (OHSU), clinical referral (including NU and OHSU Clinics), Clinicaltrials.gov, NUCATS, the Alzheimer's Association TrialMatch website, as well as the Association for Frontotemporal Degeneration (AFTD).

Potential participants will be provided contact information of the research coordinator at the recruitment sources mentioned above. We will also have a recruitment flyer,recruitment postcard, and recruitment brochure with information about the study available at these recruitment sources.

Additionally, we will have a Constant Contact email recruitment flyer that will be sent out to neurologists at Northwestern University and other neurologists and speech-language pathologists at associated Alzheimer's Disease Centers. Additionally, the email recruitment flyer will be sent to individuals on the Northwestern University's Alzheimer's Disease Center mailing list. These individuals have indicated they are interested in updates about research at our center.

Additional locations where recruitment fliers, postcards, and brochures may be handed out are academic conferences or lectures given by members of the study team.

MULTI-SITE RESEARCH:
The individuals from OHSU are clinicians on the current study. However, all hard copies of data and coordination for the study will take place at NU. All recruitment will come from NU and then participants will be assigned to one of the clinicians. Enrollment decisions will be made by the team at NU. We are using these clinicians because they are experts in treating individuals with primary progressive aphasia, which is rare in the speech pathology field. If individuals are referred from OHSU, the NU team will complete all screening procedures to determine eligibility for the study.

The researchers joining us from OHSU (Aimee Mooney, M.S., CCC-SLP, speech-pathologist) who will be seeing patients is a Co-Investigator on the study. Dr. Melanie Fried-Oken (Co-Investigator) on the study will also be covered by this IAA. She will not see patients for the study, but is a part of the study team who will have access to participant data. Aimee's interactions with participants, and Melanie's data access for this study will be overseen by the Northwestern IRB. An IAA between Northwestern University and OHSU has been established between the two universities IRBs.

STUDY TIMELINES:

Participant participation in this study will last 1 year.

90 participants are intended to be enrolled over 5 years.

STUDY ENDPOINTS:
The primary endpoint of being able to discern differences between the treatment groups will occur when all 90 participants complete the research protocol. We intend to have the majority of patients (80/90) to have completed the interventions by the end of year 4.

PROCEDURES INVOLVED:

Study Design. Up to 100 participants will be randomized, 60% to the experimental group and 40% to the control group. The rationale for using an unequal enrollment design is to maximize the number of observations in the Experimental group for individuals with PPA, which may allow for further refinement and may mitigate study drop-out rates. Randomization will be blocked and stratified by subtype (PPA-L, PPA-G, PPA-S). Within each subtype, blocks will maintain the 60%:40% split of experimental:control, respectively.

- ***Experimental Group.*** Individuals in the experimental group will receive a person-centered intervention. A person-centered intervention includes a combination of therapy approaches to maximize functional communication and life participation. This intervention will include, but not be limited to, impairment-based strategies, compensatory strategies, communication partner training, and disease education. Communication partners will be required to attend all evaluation and therapy sessions over the course of the study.
- ***Control Group.*** Individuals in the control group will receive impairment-based treatment that will target areas of weakness in a rehabilitation approach to improve function of a specific cognitive domain. They will receive disease-education at the first treatment session. Communication partners will attend the first treatment session and a portion of subsequent therapy sessions.

Study Procedures

All evaluations and therapy sessions will take place over a HIPAA compliant video-conferencing program. All sessions will be video-recorded through this program.

Orientation and Training:

Participants and communication partners will undergo an orientation to the technological aspects of the study over two one-hour sessions. At the initial orientation, participants will be consented to the study, complete demographic questionnaires, and if randomized to the experimental group, they will be instructed on how to fill out the brainstorming form for their personally relevant words that will be targeted in therapy. After this session, the participant and communication partner will work on the brainstorming form while the research coordinator assembles and mails the participant laptop computer with a webcam and Ethernet plug, technology guides, and self-report questionnaires. Participants and communication partners are asked to complete their brainstorming form in a 3-week time period and return it to the study team.

Once the participants receive the computer, they will undergo their second orientation session. At this session, the research coordinators will show the participant and communication partner how to log-in to their laptop and the Communication Bridge web-application. This web-application is the main resource for the study and is where individuals access their therapy sessions, instructional videos, and interactive web exercises. Next, the research coordinator will walk the participant and communication partner through signing onto a therapy session through the Communication Bridge web-application, using HIPAA compliant video-conference

software. Once the participant and communication partner have successfully signed onto the video-conference meeting, the research coordinator will share their screen with the participant and walk through the entire Communication Bridge web-application. Next, the research coordinator will go through a troubleshooting guide with the participant and communication partner for the video-chat sessions. This troubleshooting guide will include teaching the participant and communication partner how to check their microphone and camera, sign out of session and sign back in, how to share their screen, and how to use the chat function within the video-conference software.

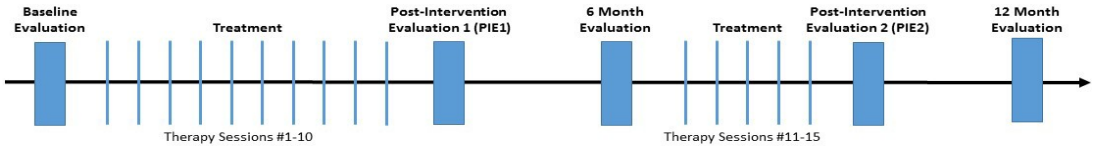

Figure 1. Timeline of Study

***Baseline Evaluation*:**
The baseline evaluation for both groups will contain three components (listed below). In total these sessions will last approximately four hours, and will be split across multiple sessions. There will be no more than one session on a given day.

1) *Neuropsychological Testing.* Participants will complete neuropsychological tests relevant for assessing someone with primary progressive aphasia[17-21]. Administered by a research coordinator.

2) *Questionnaires.* A research coordinator will administer the questionnaires[22-24] to the participant at the neuropsychological testing session. The communication partner will fill out self-report questionnaires including measures of communication/behavioral/cognitive abilities of the individual with a diagnosis and estimates of caregiver burden. Assistance will be provided as requested.

3) *Speech-Language Pathology (SLP) Evaluation.* At this evaluation, the SLP will complete several assessments including the Assessment for Living with Aphasia, the Social Networks Inventory, and the Progressive Aphasia Severity Scale. They will also begin discussions regarding personal goals (participant and communication partner) as related to *Goal Attainment Scaling.* They will also identify the 30 target words, which will be used for the language performance measures for each group.

Intervention Block 1 (Therapy Sessions 1-10):

- ***Intervention Sessions:*** This block will be composed of 10 once-weekly therapy sessions. The intervention sessions are approximately 1 hour long and will happen once a week for 10 weeks. For the control group, these sessions will be composed of impairment-based strategies: script training and training of target-words. The experimental group (person-centered) will use an approach where the clinician and participant will collaboratively identify the most appropriate treatment strategies

from other evidence-based therapy approaches (conversation strategies, impairment-based strategies, compensatory strategies).

Post-Intervention Evaluation 1: This evaluation session will occur over two session lasting no more than 2 hours per session. They will occur approximately 1 week after completion of the 10 intervention sessions. Post-Intervention Evaluation 1 outcomes will be measured through the standardized evaluation measures, communication participation measures, and language performance measures given at the Baseline Evaluation

6-month Evaluation: This evaluation will be identical to the ***Post-Intervention Evaluation 1*** in Block 1 and will also include the neuropsychological testing given during the Baseline Evaluation. It will occur approximately 6-months after the Baseline Evaluation. Identical to other evaluations, this will occur over two sessions lasting no more than 2 hours per session (4 hours in total).

Intervention Block 2 (Intervention Sessions 11-15).

- ***Intervention Sessions:*** There will be 5 intervention sessions in Block 2 that will occur once a week. The approach will be the same as intervention sessions in Block 1 with control participants working on impairment-based strategies and experimental participants working on a combination of strategies from different intervention approaches.

Post-Intervention Evaluation 2: This evaluation will be identical to the ***Post-Intervention Evaluation 1*** in Block 1. This evaluation will take place approximately one week following the 5 weekly therapy sessions of Intervention Block 2. Identical to other evaluations, this will occur over two sessions lasting no more than 2 hours per session (4 hours in total).

12-month Evaluation: *Approximately* one year after the Baseline Evaluation, the participant will take part in a final evaluation. Post-treatment outcomes will be measured through standardized evaluation measures, communication participation measures, and language performance measures that have been given throughout the course of the study. Identical to other evaluations, this will occur over two sessions lasting no more than 2 hours per session (4 hours in total).

Scheduling Compliance:

Sessions: To successfully complete the trial, participants must complete 10 visits within 12 weeks for the first treatment block and 5 visits within 7 weeks for the second treatment block. Circumstances may arise that require the re-scheduling of visits. When this occurs, the following rules apply:

- No more than 2 visits may be scheduled within a 5-day window
- Sessions on consecutive days should be avoided

Visits that cannot be scheduled within these rules will be considered ‘missed’ visits. In the case of a missed visit, the visit will not be re-scheduled. Dosing effects resulting from missed visits will be accounted for in the statistical analyses. Participants with more than 2 missed visits will be asked if they would like to continue to receive the intervention as part of routine clinical care; however, the participant will be withdrawn from the study analysis.

6-Month and 12-Month Evaluations: These evaluations should be scheduled within a time window that includes the 2-weeks prior to or following the actual 6 or 12 month follow-up date.

Schedule procedures to minimize missed visits: As part of enrollment, participants should confirm they are able to attend 10 sessions with a 12-week window for the first treatment block and 5 visits within a 7-week window for the second treatment block. Participant scheduling should take into account the potential for disruptions due to travel plans, holidays, potential work schedule constraints, medical procedures, moving/relocation, etc. This may require delaying the start of the intervention until a suitable 12-week window and subsequent 7-week window is available.

DATA AND SPECIMEN BANKING:

Each participant will receive a study ID number. Data will be collected, entered, and stored securely in REDCap (Research Electronic Data Capture) database using the study ID number. Data will be de-identified and entered into the password protected REDCap database within 48 hours of collection. Over the next three days, all participant data are checked for accuracy. Data are maintained in a format that is easily transferred to statistical software (e.g., SPSS) for analysis. The database will be password protected and accessible only to the principal investigator and approved study personnel. Paper copies of any measures will be kept in locked files in our research offices and will only be accessible to the PI and study personnel.

Data from the web-application will be constructed using an industry-standard software platform (PostgresSQL, Ruby On Rails, Apache, Linux). Participant data from the web-application will be de-identified through the use of the assigned study ID number. Data obtained through the web-application infrastructure will be stored and managed by Table XI, a product development and software consultant firm, and will be protected via IP restriction and on a Virtual Private Network accessible only to study-authorized staff. Data from the web-application will be stored independently of protected health information (PHI) and can only be combined with PHI offline by study staff. Performance data from the web-application can be downloaded according to the participant study ID by the PI or approved study personnel into files that are easily used for data analysis (e.g., .csv, .xls.). All access to this application will be provided over encrypted-TLS communication and all servers are locked and managed in a physically secure facility with Marlok identity management.

DATA AND SPECIMEN MANAGEMENT:

Aim 1: Determine the within-group response of the Experimental and Control treatments for adults with PPA. Aim 1a will provide a descriptive and quantitative characterization of the response to treatment including within- group effect sizes.

Statistical analysis Aim 1a: The primary analysis goals for Aim 1a will be (i) the estimation of the within-person change and the variability in this change along with the statistical significance of the change within each treatment group and (ii) the estimation of the within-group effect size for each treatment group. These analyses will be done for all outcomes.

Power calculation for Aim 1: In preliminary data, the Pearson correlation between the initial and 6 month CCRSA was 0.70. Assuming a standard deviation of σ for an outcome at one time, and assuming a correlation of 0.50 between the initial and 12 month measure (since follow-up is longer), then the standard deviation of the change is also σ. Similar assumptions will be made for all outcomes. The Experimental group with a sample size of 51 would have 80% power to detect a mean change that is 0.4 σ while the Control group with a sample size of 34 would have 80% power to detect a mean change of 0.5 σ. For testing correlations between the change in an outcome and a continuous measure, the Experimental group (n=51) would have 80% power to detect a correlation of 0.38 while the Control group (n=34) would have 80% power to detect a correlation of 0.46. Two-tailed tests and a Type I error rate of 5% are assumed for all calculations for Aim 1.

Aim 2: Determine if a person-centered dynamic treatment approach (Experimental) for adults with PPA will show more favorable communication participation outcomes as compared to an impairment-only treatment approach (Control) over a 12-month course of disease.

Specific Aim 2 Analysis: The group statistical analysis will focus on two participation measures (CCRSA, Goal Attainment Scaling [GAS]) and two language performance measures (% target word accuracy and % script accuracy). All outcomes are continuous measures except for GAS which is ordinal. The primary analyses will focus on the initial and 12-month time points. Secondary analyses will be done using all time points, specifying certain post-hoc comparisons of interest (e.g. comparing the effect of the pre- and post-evaluations for the 6-month Treatment Sessions between groups).

Power Calculation for Aim 2: Power will be based on a sample size of 51 in the Experimental arm and 34 in the Control arm. For all language and participation outcomes, preliminary data were used to estimate unadjusted standard deviations (SDs). It is expected that analysis of covariance would reduce the unadjusted SDs but since longitudinal data were not available on all measures, the conservative approach will be to use the unadjusted SDs in the power calculation. The Table below gives the between-group effect size (in units of the scale) detectable with 80% power for each outcome measure using a two-tailed test and a Type I error rate of 0.017. For example, for the CCRSA scale, there is 80% power to detect an Experimental minus Control difference of 12% in the 12-month mean adjusted by analysis of covariance for the initial evaluation CCRSA level.

Table 1. Power Calculations

Measure	Type	SD	Between-group effect size with n=51 and 34 per arm[A]
Lexical Retrieval	Language	19 [16]	13
Script Performance	Language	14 [25]	10
Confidence Rating Scale for Aphasia (CCRSA)	Participation	16 [16]	12
Goal Attainment Scaling (T-Score)	Participation	10 [26]	7
[A]80% power, 2-tailed p<0.025 for language measures and *p<0.017* for participation measures			

All members of the study team will be trained on the procedures of how data are stored and managed. Members of the study team that are approved by the Northwestern IRB will have access to the REDcap database and to the web-application database. All access to these applications will be provided over encrypted-TLS communication and all servers are locked and managed in a physically secure facility with Marlok identity management. All data will be de-identified and stored as much.

All data will be checked by a research assistant who is different from the individual who administered the tests. This checking will take place on hard copies of outcome measures and data stored in REDcap. Discrepancies between raters will be recorded by a crossing out of original score and initialing the new score with the checkers initials. REDcap includes a feature where data can be marked as “unchecked” or “checked”. Once data are checked by a second scorer, they will be marked as “checked” in REDcap.

Participants will be asked if they are willing to share data from the study with other researchers within the CNADC. If so, researchers will not receive any identifiable information.

PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:
A data safety and monitoring board (DSMB) has been established for the proposed study. The members of this committee are not associated with the research project and work independently of the PI. They are all qualified to review the patient safety data generated by this study because of their unique expertise in the areas of statistics, speech-language therapy, primary progressive aphasia, dementia, treatment efficacy/outcomes and clinical trials. The committee will meet at least annually to review study data concerning recruitment, randomization, retention, compliance form completion, gender and minority inclusion, intervention effects and safety. The committee will be available at any time to advise on these issues.

At each meeting the committee will vote whether to continue the trial. Reasons for early termination of the study may include concerns about safety of the intervention or an early convincing beneficial effect of intervention. The committee may also recommend amendments to the study protocol if it appears that such are necessary for safety of scientific validity of the trial. Committee minutes will be part of annual Institutional Review Board review.

WITHDRAWAL OF PARTICIPANTS:

Participants can be withdrawn from the study for the following reasons: 1) Lost contact; 2) Missed visits due to: a) “no show” without rescheduling for two treatment sessions; or b) not adhering to scheduling compliance rules (see above); 3) Obtaining outside speech-language therapy during the study.

If individuals are withdrawn from the study, they will be sent a FedEx Airbill to send their laptop computer provided by the study back to Northwestern. They will be informed of the reasons why they were withdrawn. These reasons for possible withdrawal will be clearly stated in the consent form.

Data collected up until the point of lost contact with the participant will be used in analyses for the study.

RISKS TO PARTICIPANTS:
The risks for participation in the proposed research are minimal. Potential adverse events associated with this research include:

1. Loss of confidentiality
2. Fatigue and/or frustration in performing the online intervention
3. Depression and Anxiety: Caregivers of individuals with PPA and living with PPA can both be psychologically taxing experiences. It is not abnormal for individuals in these

circumstances to express negative emotions, including hopelessness, sadness, anger, or frustration. It is important to recognize when these symptoms go beyond what is normally expected.

These risks will be minimized in the following ways:

1. Data will be stored securely, and any data sharing agreements will adhere to NU's strict policies on privacy protection.
2. This risk of fatigue is considered to be minimal and is addressed in the consent form. Fatigue will be minimized by advising the participant and caregiver that they should rest if they feel fatigued, before continuing with any component of the intervention. Participants will be working with licensed speech-language pathologists who are trained to identify fatigue and frustration and they will modify the plan accordingly. Participants will be informed of this risk when consenting to join the study.
3. The risk of depression and anxiety is considered to be minimal. Depression and Anxiety measures are completed with both the participant and communication partner at every evaluation (Baseline, Post Intervention Evaluations, 6 month evaluation, and 12 month evaluation). Specifically, the CAT-version of the PROMIS Depression and Anxiety Sub-tests are given to participants and communication partners (Cella et al., 2010). If the measures reveal a clinically relevant level of anxiety or depression (based on normative values), the research team will follow a risk-specific protocol outlined in the Risk Identification and Response Plan (attached in Supplemental Materials on eIRB). The Risk Identification and Response Plan identifies unanticipated risks that go beyond what is expected in this study. However, if any verbal/behavioral indication of suicidal/homicidal thoughts are observed by the speech-language pathologists in the study, measures will be taken to alert the appropriate people. A licensed clinical social worker, Darby Morhardt, Ph.D., is a Co-Investigator on this study. She will be consulted according to the plan and will meet with our participants for a session. Since Dr. Morhardt is a member of the study team, this information will be kept with the participant records.

POTENTIAL BENEFITS TO PARTICIPANTS:

By participating in this study, participants will learn new strategies for coping with their communication difficulties caused by the disease. These new strategies may allow the individuals to engage more actively in their lives by facilitating communication. In our pilot study, we saw increased communication confidence when comparing post-treatment measures of the CCRSA to pre-treatment measures. We also found that this increase in performance was maintained 6-months post-treatment. However, due to the progressive nature of the disease, individual's communication will get worse over time. This current study is important in determining the duration of potential benefits beyond this point.

VULNERABLE POPULATIONS:

Individuals with Primary Progressive Aphasia are cognitively impaired. However, individuals in the mild stages of Primary Progressive Aphasia have deficits primarily in the use of language. Memory, attention, and other cognitive abilities are preserved. Individuals enrolled in this study will be verified as being in the mild stages of the disease through medical records and a brief evaluation by our team. Additionally, participants with PPA will be consented with their communication partner. Their communication partner will also be consented into the study. This

study provides an intervention for a population that has no pharmacological treatment for their disease, and thus a benefit for them to more effectively cope with their symptoms.

Individuals will be provided with the opportunity to speak with members of the study team, including speech-language pathologists, prior to consent and enrollment to ask any questions they have. The study team members, including SLPs, are trained in communicating with individuals of this population. We believe that these steps will ensure that the participants (patient and communication partner) have sufficient information to participant in the study.

COMMUNITY-BASED PARTICIPATORY RESEARCH:
n/a

SHARING OF RESULTS WITH PARTICIPANTS:

Results will not be shared with the participants.

SETTING:
The research team will be located at the Mesulam Center for Cognitive Neurology and Alzheimer's Disease. This is where all consent forms and data from the study will be stored. Speech language pathologists that provide treatment for the study will come from Northwestern University and Oregon Health and Science University.

Participants will be recruited through the following sources: Clinical Core participants at the Alzheimer's Disease Centers at Northwestern University (NU) and Oregon Health & Science University (OHSU), clinical referral (including NU and OHSU Clinics), Clinicaltrials.gov, NUCATS, the Alzheimer's Association TrialMatch website, as well as the Association for Frontotemporal Degeneration (AFTD).

All sessions for the intervention will take place remotely over a HIPAA compliant video-conferencing program. Therefore, participants will be located all over the United States. We will also enroll international participants.

RESOURCES AVAILABLE:
The Mesulam Center for Cognitive Neurology and Alzheimer's Disease, where this research will take place, is one of approximately 30 NIH-funded AD Centers and the investigators on this proposal are experts in neurodegenerative dementia syndromes including PPA, which was initially described in the modern literature by Dr. Marsel Mesulam (project Co-I and CNADC Director). The CNADC has one of the largest research programs for PPA. The current project will leverage the existing infrastructure of the CNADC and its affiliated grants. The CNADC PPA Research Program has enrolled and followed over 150 PPA participants and communication partners, who come from across the United States and Canada. Enrollment by PPA subtype has been relatively equal in our PPA research program. Retention has been excellent and the PPA Research Program has been highly successful yielding over 50 peer-reviewed publications that have made important contributions to the understanding of the disease, its diagnosis, and also in providing education and support to individuals with a dementia diagnosis, their families and professionals.

The investigators are well equipped to conduct this trial since they have expertise in developing web-based Behavioral Intervention Technologies (BITs) that help people make

positive behavior changes to support health and wellness; forging strategies for improving diagnosis in dementia; charting the course of the disease; identifying risk factors; identifying potential avenues for treatment for individuals with a PPA diagnosis; and improving education for families faced with a PPA diagnosis as well as professionals who may treat them. Our speech-language pathologists have over 10 years of experience in treating hundreds of individuals with dementia. The project has the support of the Northwestern University Clinical and Translational Sciences (NUCATS) Institute, our CTSA-funded hub for supporting clinical and translational science. NUCATS will provide support for recruitment as well as data collection, data storage and data safety & monitoring.

We are confident about subject recruitment for this study since we enrolled 50 participants with PPA into our preliminary study over 3 years and currently have a waiting list for enrollment. Consistent with our goal to improve access to care, we expect >80% of the research participants for this project will reside out of town. In fact, 94% of the participants to date (n=47/50) came from outside of Chicago, residing in 21 different states, Canada and Singapore.

Study personnel include trained speech-language therapists and a licensed clinical social worker who will be able to intervene and recommend social, emotional, or psychological resources, if necessary. All of these individuals have worked extensively with individuals with PPA. They are all trained to identify and intervene in the event that a risk of self-harm, harm to others, and/or depression/anxiety is observed. Research assistants who collect data on the PROMIS anxiety/depression levels, are trained to alert the team (PI, therapists, social worker) if scores are above the normative range. Scores on this measure are converted to T-scores on REDcap. If a t-score indicates that the individual is over 1 standard deviation over the mean on depression/anxiety, the research team will be alerted and the Risk Plan will be followed as applicable.

PRIOR APPROVALS:
We have received a restricted notice of award from NIH to fund this project. Approval from our DSMB is required before we enroll participants into this study.

RECRUITMENT METHODS:
Recruitment sources will include Clinical Core participants at the Alzheimer's Disease Centers at Northwestern University (NU) and Oregon Health & Science University (OHSU), clinical referral (including NU and OHSU Clinics), Clinicaltrials.gov, NUCATS, the Alzheimer's Association TrialMatch website, as well as the Association for Frontotemporal Degeneration (AFTD).

Potential participants will be provided contact information of the research coordinator at the recruitment sources mentioned above. We will also have a recruitment flier, postcard, and brochure with information about the study available at these recruitment sources.

Additionally, we will have a Constant Contact email recruitment flyer that will be send out to individuals within Northwestern University and individuals on the CNADC mailing list.

Additional locations were recruitment fliers, postcards, and brochures may be handed out are academic conferences or lectures given by members of the study team.

If participants are eligible to participate in the study, they will be provided with a $50 payment for their 1-year participation. This payment will come in the form of a check processed by Northwestern Accounting.

NUMBER OF LOCAL PARTICIPANTS:
n/a

CONFIDENTIALITY:
Data will be collected, entered, and stored securely on a REDcap (www.redcap.nubic.northwestern.edu) database. The database will be password protected and accessible only to the principal investigator and study personnel. Paper copies of any measures will be kept in locked files in the Mesulam Center for Cognitive Neurology and Alzheimer's Disease. All video files will be stored on a locked computer and will be coded by study identity. Any names or identifying information will not be shared or disclosed. Only the PI and approved study personnel will be able to access these files.

PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:
The consent form will list, in detail, who has access to medical records and personal identifiable information within the study team. Participants will be given the opportunity to ask questions and will be provided with a signed copy of their consent form.

Medical records will be sent to the study team by the participants, if they are not seen by a doctor affiliated with Northwestern Memorial Hospital. Individuals who saw Northwestern University doctors will consent to have their medical records shared with the study team for review. No one outside the PI or study team will have access to the medical records.

COMPENSATION FOR RESEARCH-RELATED INJURY:
The research study does not pose more than a minimal risk.

ECONOMIC BURDEN TO PARTICIPANTS:
Participants will have no expenses to participate in the study.

CONSENT PROCESS:
Participants (individuals with PPA and their communication partners) will be consented verbally over video-chat with a research coordinator. The consent forms will be housed within REDcap. During this video-chat consent, participants will have the study explained to them in detail and they will have ample time to ask for questions or clarifications. A research coordinator will go through the REDcap consent (sent via link to the participant) with the participants. The participants will electronically sign the consent forms. Participants will be emailed their signed informed consent from REDcap after completion of the form.

Participants (individuals with PPA and their communication partners) will be asked to consent to an optional element on the consent form that asks if they would be willing to allow their audio and/or video recordings from sessions to be used in scholarly presentations or publications. These recordings could potentially be shown at disease-related conferences and speech-language pathology professional conferences in order to help professionals in the field understand the research and/or aid in training purposes. Because of the unique and rare presentation of PPA, speech samples and/or video recordings that display the effortful motor movements in producing words are often the best way to convey how the disease presents itself. In order to thoroughly explain our research methods and describe the speech therapy strategies used, it will be most beneficial to provide audio and/or video recordings during presentations to explain what written or verbal text cannot accomplish. If the participant answers "I agree," he or she is indicating they understand the risks associated with identification.

Participants (individuals with PPA and their communication partners) will complete an optional section on the consent forms that asks if participants would be willing to share their data with other researchers at the CNADC. If the participant answers “yes”, their data can be shared, if requested, from other researchers at the CNADC. This will not include identifiable information. Participants will initial whether they agree or disagree on the REDcap form via the electronic signature function in REDcap.

A Certificate of Confidentiality (COC) is in place for the current clinical trial and will be explained to participants during the consent process.

Cognitively Impaired Adults
Even though our participants have a cognitive impairment, they will be screened for eligibility prior to enrollment. At the mild stages of PPA, individuals have deficits in their affected language domain, but their other domains of language and cognition are relatively preserved. Additionally, participants will be consented into the study with a communication partner who can aid the research staff in clarifying any study components that are unclear. Our participants signed their own consent forms in the pilot study with no issues.

PROCESS TO DOCUMENT CONSENT IN WRITING:
Participants will be mailed a copy of the informed consent form. A research coordinator will administer informed consent over the video-conferencing program. Participants will mail their signed informed consent back to us in a prepaid envelope that is provided to them. A copy of the consent form will be mailed to the participants via postal mail or scanned via e-mail.

DRUGS OR DEVICES:
n/a

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