PROTOCOL TITLE:

Phase 2 development of a spoken language biomarker of cognitive impairment in Parkinson's disease.

PRINCIPAL INVESTIGATOR:

Angela Roberts, Ph.D.
Assistant Professor
Communication Sciences and Disorders

CO-INVESTIGATOR:

Dr. Tanya Simuni, Northwestern University
Dr. Leora Cherney, Northwestern University and Shirley Ryan AbilityLab

STUDENT INVESTIGATOR:

N/A

VERSION DATE:

November 17, 2021

1.0 Purpose of the study:

Aim 1 will characterize PD-MCI (Parkinson's disease mild cognitive impairment), PDN (Parkinson's disease without cognitive impairment), and HA (healthy adult) spoken discourse, cognitive, and motor speech profiles. Phase 2 biomarker development requires robustly characterized cohorts in which to test candidate biomarkers. Using a standardized battery of cognitive, language, and motor speech tests PD participants will be assigned to PD-MCI (single/multi-domain) or PDN groups. We propose collecting spoken discourse samples using standardized elicitation protocols. The same tasks will be extracted from the extant HA database. Researchers will transcribe, code, and analyze discourse samples. Group differences (including sub-analyses for single and multi-domain MCI subtypes), elicitation stimuli effects, and group x stimuli interactions will be examined using multivariate and mixed-design ANOVA procedures.

Aim 2 will develop and evaluate the classification accuracy of an optimally weighted discourse classification function for PD-MCI and PDN. We propose using discriminant function analysis to identify an optimized composite variable that best predicts PD-MCI, PDN, and HA group membership. Sensitivity/specificity analyses, positive/negative predictive values, and receiver operating characteristic curves will be used to evaluate the discourse classification function properties.

The **primary endpoint** is an optimally weighted discourse function that can classify PD-MCI with > 80% sensitivity/specificity.

2.0 Background / Literature Review / Rationale for the study:

Individuals with Parkinson's disease (PD) have a 6-fold increased risk of dementia.[1] PD mild cognitive impairment (PD-MCI) is thought to be a transitional state to dementia for

many of those affected.[1-2] **Difficulties monitoring early cognitive impairments, and concomitant delays in treatment initiation, are major barriers** to the accurate diagnosis of and the development of interventions for cognitive impairments in PD.[3-5] A biomarker is any characteristic that can be objectively measured and indicates normal/pathogenic processes or responses to therapeutic interventions.[6] Biomarkers can be genetic markers, neural markers, and observable behaviors.[6] In the absence of neuropsychological findings, early dementia can still be detected in spoken discourse.[7-10] Thus, a **spoken discourse biomarker** can be a valuable supplement to extant neuropsychological evaluation for **monitoring cognitive-linguistic changes in real world environments**. The **long-term objective** of this research is to improve the early and accurate diagnosis of PD cognitive impairment with a reliable spoken discourse biomarker. Research shows that discourse features including grammar errors, information content/efficiency, coherence, and verbal disfluencies hold promise for detecting PD cognitive impairments.[14-28] Additionally, our pilot suggests that an optimally weighted composite variable, and no one single variable, is best able to discriminate PD spoken discourse. A **major barrier** is the absence of a spoken discourse biomarker that has been rigorously developed and tested on a meticulously-characterized cohort of PD-MCI, PD without cognitive impairment (PDN), and healthy adults (HA). Using the Fit-for-Purpose framework, **the goal of the proposed research is to complete a Phase 2 spoken discourse biomarker study**.[29] The **overarching hypothesis** is that PD-MCI and PDN will have unique profiles of spoken discourse impairments that are distinguishable from each other and from HA.

3.0 Inclusion and Exclusion Criteria:

Only individuals with PD will be newly recruited and enrolled as part of the study.
Healthy adult data will be extracted from extant databases (publicly available) from NIH-funded studies.

Inclusion Criteria Person with Parkinson's disease without cognitive impairment

- Age 50-90 years
- Diagnosis of idiopathic Parkinson's disease (UK Brain Bank criteria) made by a movement disorders specialist
- Under the care of a movement disorders specialist for a minimum of 1-year duration
- Native monolingual English speaker
- Hoehn & Yahr score between 1.5 and 4
- Grade 10 education, or higher
- Sufficient vision and hearing (aided or unaided) for all experiment tasks
- Montreal Cognitive Assessment (or MoCA-converted MMSE score) greater than or equal to 25
- No subjective complaints of cognitive difficulty or word finding issues

Inclusion Criteria Person with Parkinson's disease mild cognitive impairment

- Age 50-90 years
- Diagnosis of idiopathic Parkinson's disease (UK Brain Bank criteria) made by a movement disorders specialist

- Under the care of a movement disorders specialist for a minimum of 1-year duration
- Native monolingual English speaker
- Hoehn & Yahr score between 1.5 and 4
- Grade 10 education, or higher
- Sufficient vision and hearing (aided or unaided) for all experiment tasks
- Montreal Cognitive Assessment (or MoCA-converted MMSE score) greater than or equal to 17
- Subjective complaints of cognitive difficulty or word finding issues, without significant impact on activities of daily living

Inclusion Healthy Adults (**from extant data base – no new recruiting**)

- Age 50-90 years
- Montreal Cognitive Assessment (or MoCA-converted MMSE score) greater than or equal to 26
- Native monolingual English speaker
- Grade 10 education, or higher
- Sufficient vision and hearing (aided or unaided) for all experiment tasks

Exclusion Criteria Neurological injury or disease (other than PD for the PD cohort)

- History of unmanaged or untreated depression or major psychiatric illness
- History of deep brain stimulation surgery (DBS)
- Diagnosis of Dementia with Lewy Bodies

Hearing and Vision Screening. PD participants will complete the protocol using their typical vision and hearing devices. PD participants with pure tone averages > 41 dB (either ear), who do not have their own assisted listening device, will be fitted with a personal amplifier only during test/task instructions and test item presentation. Participants will complete vision acuity and field screening tasks to confirm sufficient visual acuity (aided or unaided) and in-tact visual fields for the discourse tasks.

4.0 Sample Size:

We will enroll 86 PD participants (43 individuals with PD and normal cognition and 43 individuals with PD mild cognitive impairment). Data from 43 age/education/sex matched HA will be sampled from an extant repository.

Sample sizes for ANOVA and DFA were calculated using G*Power. For Aim 1, a sample of 129 participants for MANOVA procedures with 3 IVs (PD-MCI, PDN, HA), 15 dependent variables (6 canonical variables), and up to 3 covariates will detect a minimum *of*^{2} of 0.16 (medium-sized effects) with power of 0.90, and α=0.05. The available effect size estimates for the 8 candidate discourse variables range from f^2 of 0.33 to 0.50 (medium to large effects). With the smallest anticipated effect size based on our pilot data (f^2 =.33) 129 participants in a mixed ANOVA with 2 IVs (Group [3 levels]) and Task [2 levels]) with up to 2 covariates will yield power of 0.86, α=0.05. At the highest estimated effect size (f^2 =.50), the same sample size will yield power of 0.99, α=0.05. For **Aim 2**, DFA procedures with 3 groups and 8 discourse variables with 129

participants will detect f^2 of .10 (small-medium effects) with power of 0.90, α=0.05 and power of 0.85, if α=0.025. For the sensitivity and specificity analyses a sample of 129 participants will detect sensitivity and specificity values of 0.83 or higher with a 90% confidence interval precision of 0.10, given an expected disease (PD-MCI) prevalence of 30%, a conservative prevalence estimate. This precision level is consistent with guidelines for Phase 2 studies.

5.0 Research Locations:

New Data Collection
All data collection will take place at Northwestern University, Evanston campus, the Northwestern University Department of Communication Sciences and Disorders flexible laboratory research space located in Abbott Hall on the Chicago campus, or alternatively in participant homes through in-person or virtual visits if individuals are not able to physically travel to our locations.

Data will be collected in a dedicated research space (or participant home). Data will be collected in a low distraction, accessible environment specifically designed for the collection of discourse and neuropsychology testing data. If data are collected in a participant's home, efforts will be made to create a low-distraction quiet environment consistent with the research spaces located on the Evanston and Chicago campuses.

Data will also be collected virtually through Zoom videoconferencing. Similar efforts to in-person data collection in participants' homes will be made to replicate low-distraction environments consistent with the research spaces on the Evanston and Chicago campuses. A HIPAA-compliant, end-to-end encrypted version of Zoom will be used for study visits to comply with strict personal health information protection guidelines. If participants do not have access to a personal computer capable of running the necessary videoconferencing software, a microphone for audio recording, or a webcam for videorecording we mail or drop off necessary hardware to their homes.

Extant Data Collection (Healthy Adult data)
Demographic data and neuropsychology testing measures for the healthy control sample will be secured from an extant dataset in a secure repository ICPSR 3664 (Harris Wright, Heather, and Capilouto, Gilson J. Discourse Processing in Healthy Aging in the United States. Ann Arbor, MI: Inter-university Consortium for Political and Social Research [distributor], 2017-03-02. https://doi.org/10.3886/ICPSR36634.v1). Audio and video files of spoken discourse samples for the same study (study of normal aging and discourse) are curated with the Carolina Conversations Collection and are available for use in research with an approved IRB (http://carolinaconversations.musc.edu/about/).

6.0 Multiple sites:

Shirley Ryan AbilityLab – Dr. Leora Cherney who has faculty appointments at both NU Evanston (Communication Sciences and Disorders) and the Shirley Ryan AbilityLab is a co-investigator. Dr. Cherney's involvement is limited to providing mentorship to the PI on grant administration, serving in a consultative role for resolving discourse coding ambiguities, and supporting the PI in interpreting the study results. While Dr. Cherney may have a limited role in recruiting participants with Parkinson's disease, no data will

be collected from, nor will any health records be required from, the Shirley Ryan AbilityLab.

Feinberg – Dr. Tanya Simuni is on faculty at Feinberg. Dr. Simuni will be involved with recruiting (not enrolling) participants. She will also be involved with the design of the study and the interpretation of the results. Dr. Simuni will also provide medical guidance and PD expertise as required during the study. The study does not require access to patient records at NMH.

7.0 Reliance Agreements/Single IRB:

NU is the IRB of record for both the Shirley Ryan AbilityLab and Feinberg. To the PIs knowledge no additional IRB permissions or reliance agreements are required.

8.0 Procedures Involved:

The proposed study is not a clinical trial and was not deemed as such by the NIH.

C. APPROACH

Observational, cross-sectional study with three cohorts: healthy older adults, individuals with Parkinson's disease without cognitive impairment, and individuals with Parkinson's disease with mild cognitive impairment.

Data Sources

Measures collected **on all PD participants**. Only PD participants will be recruited locally. All healthy control data will be extracted from extant databases available through data sharing agreements or publicly accessible datasets. All measures will be audio and video recorded in order to facilitate off-line data analysis for standardized measures and orthographic transcription of discourse samples. If the participant has completed any of the neuropsychological testing measures in our lab within the last 6-months, and a suitable alternate version of that test is not available, we will use their previous data in order to reduce participant burden and data contamination (e.g., learning effects from previous test administrations).

In the PD group measures will be collected over 1 or 2 visits (conducted within a 4-week window), depending on participant fatigue levels/scheduling. Each participant's total involvement is anticipated at 3 to 3.5 hours in duration. The typical participant is anticipated to complete the protocol in one visit.

All tests will be administered by trained research staff. All measures will be administered and scored in accordance with their published manuals/scoring instructions.

Participants may complete the protocol in our Evanston lab, satellite lab in Abbott Hall, or their home through in-person or remote visits. Participants will be able to select a time of day of their choosing for completing the protocol.

The total duration of the research project is estimated at 36 months.

The study visit will be conducted in two stages: a screening portion and the experiment portion. With the exception of the cognitive testing, hearing testing, and vision testing all other inclusion criteria will be evaluated during the initial phone, email, or in-person contact with the participant when interest in the study is expressed.

Participants will receive reminder calls regarding upcoming appointments. These will typically occur within 72 hours of the scheduled appointment. During the telephone reminder call, staff members will complete the Participant/Visitor health screener for (attached to protocol). If participants answer 'yes' to any item, staff members will request that their study visit be rescheduled at a time that is convenient for the participant. If the participant answers 'yes' to any of the questions under the 'Travel' heading then they will be provided with the COVID-19 contact information handout (attached). This information will be emailed to the participant if required. Information will also be provided over the telephone including the email and telephone contacts for the Illinois Department of Public Health.

Descriptive Variables
Geriatric Depression Scale – brief depression screening tool. Depression can interact with language production abilities.
MDS-Unified Parkinson Disease Rating Scale – measure of PD motor symptoms. Completed through physical exam by a certified research assistant or the PI.
Hoehn and Yahr scale – PD staging tool completed as part of the motor exam
Communication Participation Item Bank measure – pen and paper tool measuring communication quality of life

If the participant cannot be contacted by telephone, the screening form can be completed in person at the time of the study visit (but prior to initiating any substantial participant contact). Visitors who accompany the participant will also be asked to complete a health screener, if they intend to wait in the research lab lobby space. Health screening tools will be stored in a locked filing cabinet in the PIs lab for a period of 60 days following the participant's visit. Following this period, forms will be shredded using secure shredding boxes located in the NUCASLL clinic/PIs home department (CSD).

During the **screening portion** of the visit, participants will complete the Montreal Cognitive Assessment (MoCA), an audiometric hearing assessment, and a vision screening using a Snellen eye chart. Participants meeting the inclusion criteria for the study will advance immediately to the experiment tasks. Those not meeting the inclusion criteria will be provided summary results, including the criteria that they did not meet (i.e., cognition, hearing, vision) and will be advised to discuss these results with their healthcare team.

During the **experiment portion** of the visit participants will complete the following tasks:

Descriptive and Neuropsychological Testing Measures – The measures in the table below are standard descriptive measures for the population and the research aims under study. These are all standard clinical measures in PD clinical practice. Standardized language and cognitive neuropsychological measures will be used to stratify participants into PD-MCI and PD normal cognition groups using the Movement Disorders Society Task Force published guidelines.

Sentence Intelligibility Test (SIT-5). Set of 11-sentences generated for each participant. Sentences are phonetically balanced and are read aloud by the participant. Measure of speech intelligibility
Standardized oral reading passage (speech rate and intelligibility)
Brief motor speech exam
Demographic form (attached)
National Adult Reading Test
Neuropsychological Measures Used in Primary Analyses and to Classify Participants into MCI-PD from PDN (no cognitive impairment) groups
Trail Making Test-A (In-person testing)
Trail Making Test-B (In person testing)
10-points Clock Drawing Test + Clock copying
Free and Cued Selective Reminding Test from the Arizona Battery of Communication Disorders of Dementia (In-person testing)
Brief Visuospatial Memory Test-Revised
Semantic Fluency-animals
Digit span forward and backward
Stroop Color-word Interference
Boston Naming Test (30-item version)
Verb Naming Subtest – Northwestern Assessment of Verbs and Sentences
Sentence Production Priming subtest of the Northwestern Assessment of Verbs and Sentences
Pyramids and Palm Trees Test - object semantics
CERAD 10-Word List (Remote testing)

Discourse Sampling (main study outcome measure)

Using standardized spoken discourse elicitation stimuli and instructions, participants will be asked to generate a story about a series of events occurring in: 1) a series of six black and white line drawings and 2) a wordless picture book. Participants will generate a maximum of four spoken discourse samples. Each discourse sample is estimated at 2 to 4 minutes in length. Audio files will be transcribed using a HIPAA compliant transcription service/software. Once transcribed, files will be coded in Dr. Roberts' lab for a number of discourse (e.g., story structure, information content), speech (e.g., pauses, number of words), and language variables (e.g., grammar/syntax).

Proposed Data Analysis

Aim 1

Multivariate ANOVA statistical procedures will be used to examine group differences on neuropsychological test measures and spoken discourse measures. Follow-up univariate ANOVAs and Tukey's post-hoc tests will be used to further examine significant individual variables from the multivariate testing and to examine group contrasts (healthy controls, PD without cognitive impairment, and PD-MCI). If required based on group differences in descriptive variables age, sex, depression measure scores, and education will be entered as covariates.

Aim 2

The spoken discourse measure data will be used in a canonical discriminant function analysis (DFA) to identify the optimal discourse classification functions that separate groups. DFA is a multivariate procedure that is used to predict group membership. In our

case, where there are > 2 diagnostic groups, Wilks' lambda values, in a stepwise approach, will be used to identify the final set of variables that account for the maximal variance for group differences. This step will eliminate variables that do not contribute significantly to group variance. Redundant variables will also be deleted. The DFA approach will yield multiple potential models that will be evaluated for classification accuracy using sensitivity and specificity analyses. Receiver operating characteristic curves will be used to evaluate discriminant function accuracies as discrimination thresholds vary.

Vulnerable Populations

All consent procedures for individuals with cognitive impairment will be conducted by individuals who are experienced in facilitating communication with individuals who have communication and cognitive difficulties. Family members of those with cognitive impairment may be present during the consent process if requested. The study will recruit individuals with normal cognition and those with mild cognitive impairment. While it is possible that we will need to use alternate consent procedures, the mild severity of cognitive issues in this population, leads us to anticipate that participants will be able to provide their own consent (with supported communication). We anticipate only rare cases where this will not be true.

9.0 Incomplete Disclosure or Deception:

N/A

10.0 Recruitment Methods:

Participants will be recruited through their primary care provider (or associated clinic), through movement disorders specialists (or associated clinic), through community-based support groups/wellness programs that serve individuals with Parkinson's disease, through formal research participation registries, through community outreach activities (e.g., health fairs, education events), through social media/community postings, and through senior community living facilities. A variety of methods including direct referral by a health care professional, flyers, on-line advertising (PI's website and approved social media), and recruiting events held at local support groups/wellness centers will be used to optimize recruitment. Participants recruited through support/wellness groups or other community resources will contact the PI or study coordinator/team member directly to confirm their interest in the study and will be invited to participate if they meet the eligibility criteria. Only materials approved by the IRB at Northwestern University will be used.

11.0 Consent Process:

Written consent will be obtained from all participants completing in-person assessments, or their surrogate decision makers (when appropriate). Participants completing the virtual assessment may provide either written or verbal consent, based on their preference and ease of using the REDCap interface. Consent will be obtained by a research study team member and will be secured in one of the three potential study locations: PI's lab on the Evanston campus, satellite lab in Abbott Hall, or the participant's home. When requested, consent documents may be sent to the participant ahead of their scheduled screening appointment for advanced review. If enrolled in the remote protocol, participants will be scheduled for two videoconferencing sessions. The

first session will be held prior to their study visit to acquire consent from the participant. If completing the protocol remotely, and written consent is the chosen mode of providing consent, consent forms will be sent to participants through email and e-consent will be received through a REDCap survey during their first study visit before any tests are administered. Otherwise, if choosing verbal consent, consent will be obtained, noted on the consent form, and captured in the recording of the video conference session.

The consent process indicates that participation is voluntary and that he/she has the right to withdraw from the study at any time or to refuse any procedure within the study. Risks and benefits of the study are conveyed in a written consent document and also described orally during the consent process.

Multi-modality communication supports are used by trained personnel (speech-language pathologists or experienced research staff) who are experienced with facilitating communication in individuals with cognitive and language impairments in order to facilitate a participant's ability to understand the consent documents.

After explaining the study protocol, participants will be interviewed to assess their understanding of the study aims, the requirements of the study protocol, potential risks, potential benefits, that participation is voluntary, and that they are able to withdraw at any time using a lab-developed questionnaire for obtaining informed consent from individuals with cognitive impairments (see uploaded documents). If potential participants are not able to answer these questions, the research team will provide further education to raise their understanding to sufficient levels for making an informed consent about study participation. Procedures may include repeating information, simplification of language form/content, segmenting content into small units of information, and multi-modal communication support (e.g., pictures, gestures). The estimated duration of the consent process is between 20 and 30 minutes, but this is highly variable across individuals.

It is likely that participants will be able to provide their own consent. However, if not able to do so, participants may choose to have another party sign/provide consent on their behalf. This individual would be the authorized decision maker for the affected person (e.g., spouse, child, or SDM if appropriate).

HIPAA consent is not applicable.

12.0 Financial Compensation:

Participants will have no direct cost associated with the study. Participant parking will be covered if they are required to travel to the downtown or Evanston lab spaces. Participants will be compensated in the form of a $25.00 Stored Value Card (purchased through NU Research Services) to account for time and travel costs. Stored Value Cards will be provided at the conclusion of the study protocol (typically one study visit). Compensation will not be prorated.

13.0 Audio/Video Recording/Photography

Neuropsychological testing will be audio and video recorded. This is essential because:

a) Some items in these tests require off-line assessment to verify participant responses and to ensure rigorous scoring of the test measures used to stratify

participants. Audio and video recordings allow us to disambiguate any questionable responses.

b) As part of our research protocols, we double-score a percentage of the test measures to increase the rigor of the data set.
c) Audio and Video recordings are reviewed regularly, as part of the study protocol, to assess test administration fidelity throughout the duration of the study.
d) Consenting to the use of audio and video recordings of the neuropsychological testing for the purposes of data analysis is mandatory.

Spoken discourse samples will be audio and video recorded. This is essential because:

a) The primary analyses conducted on these data require off-line orthographic transcription and fine-grain coding of linguistic and speech errors.
b) Audio and video recording of discourse samples is a standard procedure for discourse analysis research and considered an essential step in rigorous research.
c) Consenting to the use of audio and video recordings of the discourse data for the purpose of data analysis is mandatory.

Presentations (optional)

a) Audio recordings only (no video) of the discourse samples only may be used for presentations where research generated from these recordings is being presented. There are elements of these analyses (e.g., pausing, verbal disfluencies, speech errors) that are best exemplified through the original source records (i.e., audio recordings) vs. the orthographic transcription.
b) When used for illustrating study results/findings, audio recordings will not be distributed to the audience broadly. They will be played as part of the presentation, but the audio file will not be embedded into the slide deck or distributed in any way to the attendees.
c) Participants will be allowed to opt out of the use of audio recordings for presentations. This is not a mandatory element of the study.

Audio and video recordings will be stored on the LCAN (Dr. Roberts') research server. Only approved study personnel (listed on the IRB application) will have access to the audio and video recordings. Recordings will be stored for a duration of at least 7-years (and potentially longer) following the end of the NIH grant funding period. When destroyed, audio and video recordings will be destroyed using the most up-to-date and secure procedures for doing so at the time of their destruction and will be completed in consultation with local University IT services.

14.0 Potential Benefits to Participants:

Although there is no direct benefit to participants, they and their families often consider us an unbiased source of disease-related education on communication impairments in Parkinson's disease. When requested, our team is able to provide contacts to participants for foundations and agencies that focus on Parkinson's disease education (e.g., local support groups, printed education materials, national/local education events and materials).

15.0 Risks to Participants:

The risks involved with this study are not substantially different from those associated with typical clinic visits. Participants may experience fatigue owing to the duration of the protocol. If enrolled in the remote protocol, participants may experience fatigue commonly associated with using videoconferencing software for extended periods of time. In our experience administering a similar duration neuropsychological assessment protocol within the Ontario Neurodegeneration Diseases Initiative, fewer than 5% of 160 PD participants required two data collection visits.

Some participants may experience a sense of emotional discomfort from being video/audio recorded during these sessions. Video and audio recording are routine during Parkinson's-disease related clinical sessions.

We anticipate that all participants with cognitive impairments will be aware that they have cognitive issues. However, it is possible that our testing may reveal deficits of which the participant was previously unaware and thus may present a potential risk of distress associated with this concern.

Some participants may perceive a sense of nervousness when completing mood and cognitive testing, particularly the depression measure. Participants will be able to refuse any task that makes them uncomfortable.

There are no anticipated physical risks associated with this study.

While efforts will be taken to protect participant confidentiality, there is always a risk that confidentiality may be breached. The primary risk of breaching confidentiality in the current study arises from the need to audio/video record data collection sessions.

There are no anticipated social or legal risks.

There are no costs associated with the study. Participants' parking will be covered for all visits. We will also provide a nominal study participation fee to help accommodate for travel and time-related expenses.

Risk level. The overall risk level is low and impact to participants is anticipated to be minimal. This assessment is based on a number of projects in the PI's lab that employ similar procedures, research designs, and methods.

Minimizing Risks.
Fatigue. To minimize fatigue, participants will be offered rest breaks every 60 minutes. However, participants may request and be granted a rest break at any time. If the testing session is too long for some participants, we will break testing into two data collection visits. Participants will be allowed to select their 'best' time of day for their data collection session. This step will allow participants to complete the protocol at their typical peak performance time of day. The protocol will be conducted with PD participants in their 'on' medication state. Doing so will promote participant comfort and minimize mobility/pain risks associated with 'off' medication states. When required, participants will be provided with a break for taking medications during the data collection session.

Emotional discomfort audio/video recording. Some participants may experience a sense of emotional discomfort from being video/audio recorded during these sessions.

To minimize any sense of emotional discomfort, the audio/video recording equipment will be positioned discretely in the lab (or home) environment.

Unmasking of previously unknown deficits or emotional distress associated with completing measures of cognition/depression. In cases where the participant demonstrates (or voices) emotional distress over the challenges of living with communication, mood, or cognitive difficulties or where specific tests trigger unpleasant feelings over concerns with these issues, appropriate counseling will be provided by the PI (a SLP or the medical consultant Dr. Simuni). Issues falling outside of the PI's scope of practice (e.g., indicators of significant depression) will be discussed with Dr. Simuni and further follow-up planned. In cases where a participant fails the cognition, vision, and/or hearing screenings they will be provided with a summary of these findings that they can share with their healthcare team to facilitate appropriate follow-up. In cases, where risk of self-harm (including suicidal ideations) or a Geriatric Depression Screening score is > 10 participants will be provided with a Mental Health recommendation form based on the NIH standard (see attached). Participants at elevated risk for self-harm (frank voicing of suicidal ideations or plans to self-harm) will be referred to the nearest emergency room (Northshore Evanston Hospital), in addition to the other procedures.

Potential Confidentiality Breaches. See below

Withdrawing from the Study. Consent is voluntary. A participant is free to withdraw from the study at any point in time. If a participant withdraws from the study, a summary of their treatment progress (up to the point of withdrawal) will remain in the research record and may be included in the analysis. However, no further data will be collected. The data collected from the participants up and until the point of withdrawal will remain in the study.

16.0 Provisions to Protect the Privacy and Confidentiality of Participants and the Research Data:

All study procedures will be conducted in private research/clinical facilities with no general public access.

To ensure that participants feel comfortable during the administration of study tasks, individuals collecting data will be experienced study team members from the PI's lab. They have experience interacting with older adults and those with communication difficulties. Task instructions will be provided both verbally and in writing to elevate participant understanding, and to minimize any perceived or real intrusion into privacy. Questions posed as part of the study are limited in intrusiveness. All interviews will be conducted in a relaxed environment without time pressure for responding. Participants may refuse to provide a response to a question and or to complete any task asked of them.

Only research team members directly involved with the project will have access to participant data. Data (specifically any audio files) will be accessed from a secure research server or from the project-specific REDCap database using a secure Northwestern University network access.

At times, participants may request, or we may have need to, share information with the participant's medical team (e.g., indication of severe depression). In these unusual circumstances, we will obtain explicit permission from the participant to do so.

Protection of source materials

Pen and paper test forms, questionnaires, demographic history forms. These source materials will be labelled using unique participant numbers that do not contain any personal health information. All information will be entered into, stored, and accessed via a study-specific REDCap database. Only study personnel will have access to the database. Data will be entered into fillable fields, and original .pdf forms of all measures uploaded to the secure REDCap database for storage.

If enrolled in the remote protocol, participants will be mailed paper test forms for demographic measures through a local mail courier to be filled out after they have been consented and before their study visit. Participants will then mail these forms back to the main lab location on Northwestern's Evanston campus in a prepaid envelope. As soon as the paper measures arrive at the Evanston campus, research personnel will handle the forms in the same manner as paper measures from the in-person protocol.

Audio/Video files. These source materials will be labelled using unique participant numbers that do not contain any personal health information. This will facilitate linking the audio/video data to the other source materials collected from participants. All study related audio/video recordings will be archived on the PI's secure research server (see Facilities document).

Orthographic transcription will be completed using a combination of automated and post-automated manual correction procedures. Only the audio files (no video) will be used in any of the automated applications. The automated analysis application selected for this project is a HIPAA compliant service. Specific mechanisms will be used to ensure data safety during this process including secure physical access, authenticated access privileges and secure file transfer, audit trails, and data encryption through upload and download processes (on both ends of the data management chain) using 128-bit encryption and 128-bit SSL encryption. Once transcribed orthographic representations of the audio files will be realigned with the video files (stored only on PI Roberts' server) and then used in the linguistic coding and analysis procedures. All secondary file editing (post automatic transcription) and coding of the orthographic transcriptions will be handled in Dr. Roberts' lab by trained, qualified research personnel.

For all audio/video recordings taking place in participant homes (if participant is unable to come into the lab), care will be taken in the recording setup to scan and remove from the recording environment any materials that may reveal personal health information (e.g., mail with an address label, medical visit reminder), pictures of other individuals not consented into the study (e.g., pictures of children), and any other similar potential identifying materials.

Audio and video recording for the virtual protocol will be done through a HIPAA compliant, encrypted videoconferencing software using a lab supplied microphone and webcam. Recording equipment will be dropped off at participants' homes if they are local to the area or mailed to participants with a prepaid return label through a courier service. Audio and video recordings will be stored on the research administrator's security-

compliant, Northwestern University provided computer and then transferred to the secure lab server after each session.

Orthographic transcriptions. The discourse elicitation tasks used in the protocol have been used previously in the PI's lab. These stimuli elicit stories about the characters portrayed in the picture stimuli. In our experience, it is very rare that individuals add or augment these stories with personal information. However, if this does occur, we will redact all personally identifying comments from the orthographically transcribed files.

Data handling. Data from paper forms of tests/tasks will be entered into REDCap within 72 hours of data collection. Once the data are entered into REDCap, verified, and all reliability testing completed the original paper versions of the forms will be stored in a locked filing cabinet in the PI's lab located at Northwestern University. Paper copies of REDCap stored data will be stored for 7 years following the conclusion of the funding period and then destroyed using HIPAA compliant receptacles and procedures located in the Northwestern University Center for Audiology Speech Language and Learning.

Audio/video files will be stored on Dr. Roberts' secure lab research server maintained by Northwestern University and accessible only by those with access through the study. All audio and video recordings will be made using equipment that has redundant recording channels (two copies of all data files) to minimize data loss.

To further minimize confidentiality breaches, audio/video files collected in the lab space in Abbott Hall will be uploaded to the LCAN (Dr. Roberts) secure research server prior to the study team returning to the Evanston campus. SD drives used to collect the audio/video data will be erased prior to transporting to the Evanston campus. Paper test forms (de-identified) and consent forms will be transported in a locked case that will remain in the possession of the study team member until the information can be secured in the PI's main lab located on the Evanston campus. The same procedures will be followed when data are collected in the participant's home with the exception of the audio/video files. Uploading data from the participant's home is not feasible based on a) the lack of access to a secure server and b) the time required to upload data files. In these cases, we will encrypt the audio/video data prior to leaving the participant's home and transport it in an encrypted format to the Evanston campus using the same locked case for transporting paper forms.

Basic personal information (e.g., first name, contact information) will be collected for the purposes of scheduling study visits. This information will be stored electronically on the LCAN server, accessed only by lab personnel, and will not be linked to the unique participant identifiers.

Given the possibility that individuals may need to complete data collection in their homes (e.g., weather, mobility issues), we may need to retain information such as address and phone numbers to facilitate study logistics. These data will be stored on the secure lab server. Research staff in the 'field' will have access to this information but only when logging into the server using a secure Northwestern University VPN. Study personnel may enter the address into a GPS based device for direction-finding purposes but will be prohibited from storing the address or contact information in any identifiable manner on any portable device (e.g., cell phone). Phone devices will be supplied by the study. Following the completion of the study, these devices will be 'wiped' and reset to delete

any cached files. Staff personnel will be prohibited from storing any identifiable information on these portable devices.

17.0 Data Monitoring Plan to Ensure the Safety of Participants:

We will provide training to all personnel who handle data that includes HIPAA training, Good Clinical Practice (GCP) training and Social and Behavioral Science IRB training.

Overall framework for safety monitoring. Adverse events (AE), serious adverse events (SAE), unanticipated problems, unusual participant behavior, and protocol exceptions will be documented in an online database (REDCap) after every session. Adverse events include: (a) participant psychological stress (crying that last more than 5 minutes), (b) an episode of physical or verbal aggression and/or resistance by the participant or their accompanying partner, and (c) minor injury to the participant or the research staff member that does not require medical treatment. In this trial, serious adverse events include: (a) more than minor injury to the participant or the intervention provider that requires any form of medical treatment and (b) hospitalization, institutional care, or death of a participant due to natural progression of underlying health conditions or accidental injury unrelated to the study protocol (e.g., automobile accident).

Frequency of monitoring. The PI (or her proxy designate) will receive an automatic email notification each time an AE or SAE report is completed in the study's electronic documentation system (REDCap). Additionally, aggregate safety and protocol exception monitoring reports will be gathered weekly, placed into a central document, and reviewed by the PI during weekly research meetings. In consultation with Dr. Simuni, documentable action plans will be generated from these meetings to minimize future safety issues.

Process for managing and reporting adverse events/protocol exceptions. After each visit, research staff will complete an on-line session log in which they are prompted to report if an adverse event or protocol exception occurred. AEs and SAEs are predefined before the start of the study (as described above). Protocol exceptions are predefined as any variation from the documented study procedures/IRB approved protocol. Session logs will be monitored weekly by the project coordinator and the PI (as noted above). After documenting the AE/SAE/protocol exception on the session log, staff members will be required to complete an AE/SAE/protocol exception survey using the study's REDCap on-line documentation tool. The survey tool will prompt for all required reporting information. The PI (or her designate) will follow up on all AEs/SAEs by calling or emailing the participant within 24 hours. The PI (or her designate) will follow up with staff members regarding all protocol exception reports within 48 hours. Follow-up steps will also be documented in REDCap. Compliance to these steps will be monitored as part of weekly monitoring procedures.

The PI (or her designated proxy) will generate reports on the following schedule:

- Anticipated SAE reported within 48 hours of study's knowledge to the IRB, with the exception that all deaths will be reported within 24 hours of study's knowledge.
- Unanticipated SAE reported within 48 hours of study's knowledge to the IRB.
- All protocol exceptions will be reported to Northwestern University's IRB (using IRB approved processes) within 7 days.

Summary report of all other AEs/SAEs/protocol exceptions annually to the NIH Program Officer unless requested at a higher frequency.

Conditions where the research team may intervene. Referrals made to outside resources as a result of information discovered during the study (e.g., hearing loss, elevated depression screening scores) will be documented. Each case will be reviewed by the Participants will be provided written documentation of the concern and will be encouraged to follow up with their health care practitioner for further referrals.

If a study team member determines that the study protocol (neuropsychological testing or discourse sampling) is too distressing for the participant (e.g., excessive crying, fatigue that is not recoverable following a break/rest) then the protocol will be terminated.

Suicidal Ideation Plan. Items on measures of depression (GDS) will be reviewed by research staff at the time of data collection for any indicators of suicidal ideations. If the participant screens positive for depression and/or self-identifies suicidal ideations during these measures (or at any time during the protocol), the PI (or her designate) and the study medical doctor (Collaborator: Simuni) will be notified immediately to determine appropriate follow-up (> 10 on the GDS). Before leaving the study visit, all participants failing the depression screen will be encouraged to contact their family physician and will be provided with a list of mental health resources (see attached).

18.0 Data, and if applicable, Specimen Banking:

All raw datasets will be archived for a minimum duration of seven years after the completion of this project but will likely be archived for public access indefinitely through the Inter-University Consortium for Political and Social Research (ICPSR) at the University of Michigan. Data location and access procedures will be made available in any publications and presentations that are authored or co-authored by key investigators. Most data (video/audio data are exceptions) are collected and stored in de-identified formats. That is, no information regarding participant's identity is stored along with datasets. Each participant is assigned a participation code and demographic information is linked to the code, but the code is not linked to any personally identifying information.

For the audio/video recordings of the neuropsychological testing and spoken discourse samples, de-identification through masking the identity of participants' voices would impact negatively on data analyses. For this reason, these data will not be shared or archived in a public database. They will remain stored on the PI's server for a minimum of 7-years.

Analyzed orthographic transcripts and summary data from the spoken discourse samples will be made available through the NIH-funded data repository.

Summary data and individual item responses for the neuropsychological measures will be archived for researcher access. However, actual copies (i.e., pdfs or images) of the test forms cannot be made available due to publishers' copyright restrictions.

We will document all data files using standardized, high-fidelity methods to increase efficiencies in accessing archived data and in data sharing. We will use the ICPSR

Guide to Archiving, which defines industry standards for data archiving documentation (http://www.icpsr.umich.edu/icpsrweb/content/deposit/guide/), to thoroughly document all data files and meet data archiving standards.

19.0 Data Sharing:

Data associated with the proposed research project will be shared by depositing these data at the Inter-University Consortium for Political and Social Research (ICPSR) at the University of Michigan, which is an NIH-funded repository. Data documentation and de-identified data will be deposited for sharing, along with participant demographics, consistent with applicable laws and regulations. Summary data suitable for meta-analysis and associated secondary analysis of data (if any), along with data content, format, and organization, will be available at ICPSR. Submitted data will conform to relevant data and terminology standards. Data will be deposited into the ICPSR repository as soon as possible after the end of the 3-year project period, but no later than 24 months following the completion of the funded project period or upon acceptance of the data for publication, whichever is earlier.

Requests for accessing these data will require approval by the PI (or her designate) through the ICPSR. Requests will only be granted to individuals with IRB or similar agency approval indicating that the requesting research has met all ethical requirements. Only de-identified data will be made available to others. Audio/video recordings will not be shared.

20.0 Qualifications of Research Team to Conduct the Research:

The PI has a full-time tenure appointment with 40% dedicated research time. The PI is a trained speech-language pathologist with extensive experience working with the populations under study. Additionally, a part time research coordinator who is also a speech-language pathologist will be hired as part of the project budget. The graduate students who will be working with the project also has extensive experience with this population by virtue of lab training. The PI and Collaborator Cherney are both well versed in the procedures used in the protocol (akin to typical clinical procedures), recording methods, and also facilitating communication with adults who have cognitive impairment. The procedures for facilitating consent (described earlier in the document) are well within Dr. Roberts' clinical skill set. The analyses proposed are clinical measures used commonly in Dr. Roberts' and Dr. Cherney's research. Collaborator Simuni is a medical physician with expertise in Parkinson's disease and will provide clinical support to the study protocol.