INVESTIGATOR STUDY PLAN – REQUIRED

ID: H00011523	**Speech, Linguistic and Acoustic Markers in Parkinson's Disease**	**NCT04273672**

1) Title

Speech, language and acoustic markers in Parkinson disease (SLAM-PD)

2) IRB Review History*

NA, this is the initial application.

3) Objectives*

1) To develop markers of cognitive function in Parkinson's disease (PD) that can be assessed through speech and language

We hypothesize that speech and language tasks will yield biomarkers that can serve as proxies for performance on standard cognitive measures

2) To assess the feasibility of implementing technology such as smartphone applications and tablet-based tasks to aid in the monitoring of vocal biomarkers in PD

We hypothesize PD patients will be amenable and able to perform mobile app collection of vocal biomarker data.

3) To evaluate the impact of motor, cognitive, and affective symptoms and therapy on vocal biomarkers.

We hypothesize that vocal biomarkers of disease burden will fluctuate based on therapeutic response and will correlate to severity of motor, cognitive, and affective symptoms.

4) Background*

Speech impairment occurs in almost 90% of individuals with Parkinson disease (PD)[1]. PD patients have characteristic changes in speech, including changes in the coordination, changes in frequency and amplitude, changes in rhythm and rate, and changes in vocal quality, including breathiness, harshness, and hypernasality[2]. Changes in PD speech are thought to be caused by the neurodegenerative process of PD, specifically the impact on dopaminergic neurons in the substantia nigra and the subsequent dysfunction in the basal ganglia, a brain circuit involved in motor and cognitive control. While general speech impairment in PD has been characterized relative to healthy individuals, it is unknown if certain speech characteristics reflect particular motor or cognitive symptoms. Additionally, speech impairment may vary within an individual in response to medications and other therapies.

Changes in speech may also be sensitive to subtle, early symptoms in PD such as cognitive dysfunction. While it is known that cognitive changes frequently occur early in the course of PD, these subtle deficits may be difficult to detect clinically. For instance,

PD patients may report word finding difficulty (WFD) during spontaneous speech before objective cognitive deficits develop. Spontaneous speech may be a powerful tool to assess a range of cognitive functions because it requires multiple simultaneous cognitive processes (e.g. lexical retrieval, grammatical and syntactical structing, organization of narrative) occurring in real-time to attain fluency and accuracy.

Previous work in this area has focused on the relationship between vocal biomarkers and motor symptoms. Authors have successfully predicted PD motor severity based on several vocal features[3,4]. An observational study has recently identified a link between clinician-rated speech symptoms and cognitive decline[5]. However, rating scales do not capture the data-rich acoustic and linguistic characteristics of speech. To our knowledge, there are no published reports using quantitative, objective speech parameters to monitor cognitive function in PD. In preliminary work, we have identified a potential relationship between WFD and pausing in speech that may depend on the location of the pause within the sentence structure[6]. We have also identified a cluster of acoustic and phoneme-related parameters that correlate significantly with global cognition independently of motor severity[7]. We therefore hypothesize that by combining quantitative speech and language assessment, we will be able to develop valid, sensitive tools to detect, monitor and predict cognitive changes in PD. Since PD symptoms vary both within and between days, and in response to medications, we will also use smartphone and tablet technology to obtain quick, remote and frequent speech data. By capitalizing on the ability to easily monitor speech remotely, we will develop assessment tools that can be implemented broadly.

We propose to enroll PD patients with (n=50) and without (n=50) MCI and controls (n=50). We will compare speech acoustic and linguistic measures in tasks that evaluate speech production and comprehension. We will combine measures into models to discriminate by disease and cognitive status. Acoustic data will also be automated and assessed using machine-learning methods to enable future large scale data analysis.

5) Inclusion and Exclusion Criteria*

This study will include adult patients >18 years of age with no upper age limit with PD (diagnosed by a Movement Disorders specialist according to standard clinical diagnostic methods) and healthy controls (HC) who do not have PD or other neurological disorders.

Patients and controls with dementia based on screening assessment (Montreal Cognitive Assessment, MoCA, score < 21) will be excluded.

Patients without smartphone access will be excluded from the smartphone sub-study.

The following special populations will not be included: Adults unable to consent, individuals who are not yet adults (i.e., younger than 18 years: infants, children, teenagers), pregnant women, and prisoners.

Non-English speaking individuals will be excluded from this study since our linguistics outcomes of interest are based on norms and preliminary data from English speakers, and are specific to the grammatical and syntactic structure of the English language.

People with visual impairment may be excluded because the speech and cognitive tasks are reaction timed measures and it would not be scientifically useful to include any subjects that require extra time for reading due to their vision or required use of braille. There are no standard norms available for these measures to correct for vision impairment, and the sample size will not be large enough for the study team to create those norms. However, reasonable accommodations will otherwise be made to include individuals with some degree of visual impairment.

Table 5.1 Inclusion and Exclusion Criteria

Group	Inclusion Criteria	Exclusion Criteria
PD	Diagnosis of PD (UK PD Brain Bank Criteria)[8]	Any neurological disorder other than PD
	Disease duration ≥ 2 years[9]	Deep brain stimulator placement
		Severe, unstable psychiatric disorder
		Unintelligible speech due to effects of PD
PD and controls	MCI or normal cognition (MDS Task Force Level II criteria)[10]	Diagnosis of dementia (DSM-5)
	Age of PD onset >35 yrs or age>35 yrs (control)	Non-English primary language speaker
		Visual acuity or color vision impairment that would interfere with cognitive testing
		Other voice, speech or swallowing disorders or history of surgery involving palate/nasopharynx/larynx/vocal cords
Controls		Current or past history of any neurological disorder

6) Study-Wide Number of Subjects*

N/A

7) Study-Wide Recruitment Methods*

N/A This is not a multicenter study.

8) Study Timelines*

Planned enrollment duration- 24 months

Planned duration of study for each participant- main study: 1 screening session and 1 study visit less than 3 months apart; smartphone app sub-study: 4 weeks following the study visit

Planned duration of the study- approximately 48 months. Approximately 24 months to enroll and approximately 24 months for complex data analysis and development of analytical software and computerized algorithms.

The goal is to begin actively enrolling into this study once IRB approval is received or November 2019 whichever comes first. Enrollment is estimated to be achieved by the fall of 2021. Data analysis is estimated to be completed by the fall of 2023.

9) Study Endpoints*

The primary outcomes will be 1) development of a model using speech acoustic markers to classify PD participants by cognitive status, 2) identification of linguistic markers (pausing, syntax) associated with cognitive status, and 3) identification of changes in speed and accuracy of syntax comprehension that correlate with cognitive status.

10) Procedures Involved*

Potential participants will undergo a preliminary screening session. Interested participants will be asked if they have Parkinson disease, their year of clinical diagnosis, and if they have deep brain stimulation for any indication. PD and control participant will be asked questions about neurological and psychiatric disorders and disorders or procedures that may have affected their voice (see screening questionnaire). Both groups will be asked if they have a smartphone that is compatible with the Speech Vitals app (Aural Analytics, iOS running 12.4 or later, Andriod devices running 6.0 or later).

If the potential participant meets all criteria, t, they will undergo a screening global cognitive assessment (Montreal Cognitive Assessment, MoCA). They will be excluded if MoCA <21. They will also be excluded if they have severe visual impairment such that they cannot comfortably read the text of the MoCA. , Screening sessions will occur in the offices of study personnel at UMass Memorial Medical Center or remotely via videoconference and will take approximately 30 minutes total. This video will not be stored. If time and space allow, this visit may be conducted on the same day as a participant's regularly scheduled Neurology clinic visit, either before or after the physician visit. The participant's name, phone number, appointment date/time, and yes/no if they were eligible will be recorded in a screening log. When enrollment is complete, the screening call log will be disposed of in a UMass Memorial Medical Center HIPAA-compliant bin. Any collected data from participants who were ineligible or chose not to participate will thereby be destroyed.

All participants who remain eligible will be educated about the study and undergo the informed consent procedure. Both the MoCA and HIPAA authorization are paper forms. If the participant is unable to come to UMass to complete these forms, they can be mailed or emailed to the participant prior to the initial visit and discussed in detail over videoconference to simulate the experience that would occur in the clinic setting. Any uncertainties regarding participant eligibility will be discussed directly with the study PI before any further study activities occur.

The team plans to provide study documents such as the consent form and prompts for speech protocol in large font print for those with visual impairments. Similiarly, the language comprehension task on the laptop will be programmed with the largest font that is practical.

Once a participant has signed the informed consent and HIPAA authorization, the following data will be collected by a member of the study team:

- Basic demographic information: sex, age, years of education, duration of PD if applicable, list of medical conditions medication list (PD and controls, all medications) (<5 min)
- Rating scale for symptom assessment and motor examination will be performed and rated by an experienced clinician on the study team (Movement Disorders Society Unified Parkinson Disease Rating Scale, MDS-UPDRS[11]) (<10 min)
- Timed up and go (TUG)[12], a timed mobility assessment of gait (<15 min)
    - For the TUG, participants will wear 4 wireless, Opal inertial sensors (APDM, Inc. sampling at 128Hz) mounted on the sternum, waist, and on each foot, to quantify gait and joint kinematics.
    - The participants will perform the TUG once and the total time will be recorded. The participants will then perform the TUG while performing a dual-task of simultaneously listing words that begin with the letter "S" and the total time will be recorded.
- Core cognitive/neuropsychological assessments (approx. 60 min)- MoCA[13], Trail-making test A & B, Symbol digit modalities test, Clock copy, Boston Naming Test (30 item odd), Animal naming, Letter-guided verbal fluency, Judgement of Line Orientation (15 item odd), Boston Diagnostic Aphasia Examination[14] (BDAE; verb naming

and fluency, embedded sentences), digit span (WAIS-R),Hopkins verbal learning test – R immediate, letter number sequencing, HVLT-R Delay and Recognition, brief visual memory test-R), BVMT-R Delayed and Recognition. Other tests may be added if time permits-logical memory I (WMS-R, Anna Thompson story, logical memory II, Stroop (golden version), Shipley-2 vocab subtest) Participants will be recorded while performing certain oral portions of the above measures.

- Penn Daily Activities Questionnaire for Parkinson's Disease[17] (PDAQ) (5 min)
- Geriatric depression scale[18] (GDS) (1-2 min)
- Parkinson's Anxiety Scale[19] (1-2 min)
- Clinical Dementia Rating (CDR) worksheet: The participants will complete the subject section of the questionnaire during the study visit, and an informant or caregiver will also be contacted by phone after the study visit or in person if present at the study visit to complete the informant section of the questionnaire. During the visit, the CDR should only take 5 minutes with the participant. The CDR administered during the follow-up phone call to the informant or caregiver should take between 10 and 15 minutes.
- Speech and language production measures: participants will be recorded while performing a variety of standard speech and language tests (including but not limited to sustained phonation of vowel sounds, reading nonsense words, reading sentences and passages, description of a picture of a scene, sentences that include a Stroop color-word task)
- After the study visit, please note that the study team may re-contact participants via phone if further color discrimination testing is deemed necessary based on subject results. The rationale for further color discrimination testing is based on prior research showing that Parkinson's disease contributes to some degree of color discrimination deficit. If participants agree to do the color discrimination testing, they will take a D15 Color Hue Test and a traditional Stroop Test via Zoom. Each assessment should take no more than 5 minutes to complete.

- Participants will be asked to perform manual copying and drawing tasks on a Microsoft Surface tablet while speaking. The tablet will

record voice, facial expression, and kinematics of writing/drawing. (<15 min)

- Respiratory function will be assessed by incentive spirometry measuring peak inspiratory volume (<5 min)
- To assess language processing, subjects will perform a self-paced reading task. On a computer screen, subjects will be presented with a word that is part of a sentence. They will read the word and then push a button to advance to the next word. Sentences will vary in syntactical complexity. Comprehension will be assessed by instructing the subject to select the picture correctly illustrating the sentence from multiple choices. We will optimize experimental set-up for PD patients (e.g. large, easy-to-push button).(20 min) If time allows, participants may also complete a guided sentence completion task in which they will be asked to construct a sentence to describe a series of pictures. (5 min)

A sub-group of participants will be invited to participate in an extension study using a smartphone application called Speech Vitals (Aural Analytics). These participants will use the app on their personal smartphone once weekly for 4 weeks (or 4 times total over 8 weeks if they have difficulty with weekly measurements). The app will prompt the user through about 10 minutes of speaking tasks.

- A blood sample will be drawn from peripheral venous stick to send for genetic analysis for PD and dementia-related genes.

Participants will be assigned to either the PD or HC groups depending on their clinical interview / exam.

Estimated total study visit time is 3-4 hours. Participants will be asked frequently if they require a break. If a participant asks to stop the study protocol due to fatigue, they will be allowed to return another day to complete the protocol if they wish. Participants will be compensated for a single study visit, with a $20 gift card.

All speech recordings will be performed using a head-mounted voice recorder.

Due to the COVID-19 pandemic, we will allow participants to complete the screening visit and portions of the study visit remotely via password-secured Zoom videoconference. These virtual participants must have a device with camera to be able to join a Zoom meeting. They must also have a smartphone to participate in using the Speech vitals app. It has become clinically acceptable to perform many components of neuropsychological evaluation via telehealth. Cognitive tests requiring

paper forms for the participant to write on will be mailed to participants, with each test enclosed in a separate enveloped marked "do not open until study visit" to avoid practice opportunities. The virtual study participants will only perform the picture description task from the speech protocol. This portion of the virtual visit alone will be recorded for subsequent transcription and analysis. Virtual participants will not perform the majority of the speech protocol, the language laptop task, the dual-tasking drawing/writing task, or the blood draw for genetic markers on the virutal visit day. They will be enrolled in the smartphone sub-study for 4-8 weeks. They will be asked to come in person to UMMS within 6 months to complete the remainder of the study activities. They will not need to repeat cognitive testing done previously, but will need to repeat the speech recording of the picture description. They will receive compensation only at the in person visit. The virtual opportunity will be offered at time of study enrollment, and participants may choose a one-time in person study visit, or a virtual visit followed by in person study visit. The rationale is that not all participants are comfortable with in person contact and this situation remains variable and evolving. Our new structure will allow recruitment to proceed more flexibility, bearing in mind the concerns of our older patient population. If a participant completes the virtual visit but not the in person visit due to any reason, their data will be included but they will not be counted toward the overall enrollment targets and will not receive financial compensation.

There will not be long-term follow-up data collected. The participant will be reminded at study completion that they may be contacted in the future for follow-up or related studies (as indicated in the consent form) unless they contact the study team to decline this option. The PI's contact information will be provided at this time for this purpose. Documentation of those who decline will be kept by the PI to ensure these patients are not contacted.

All relevant assessment tools and questionnaires are attached.

We will be processing blood samples for later analysis at VA Puget Sound Healthcare System. This will include spinning the blood in a centrifuge and aliquoting plasma and buffy coat with a pipette. No analysis will be taking place at UMass, only the centrifuging and aliquoting. Aliquoted samples will be stored in a freezer in the Clinical Research Center. Aliquoting will take place under a ventilated hood. Waste will be disposed of in the proper biohazard containers. We will be working in the Clinical Research Center under IBC I-631-15.

Smartphone and tablet procedures

Speech Vitals smartphone application (Aural Analytics): Speech Vitals is HIPAA- and GDPR-compliant mobile application and system developed

by Aural Analytics to collect and analyze speech in clinical studies. It's available for use on iOS and Android devices through the Apple Store and Google Play Store, respectively. The app is downloaded onto the participant's personal phone. Participants sign in using a study-provided user ID and password. The ID and password don't contain any personal information. Techical support questions should be directed to the UMass study team, who will work with Aural Analytics to resolve the issue. A Microsoft Surface tablet will be configured with specialized software for the dual-task procedures. Participants will be asked to perform various speaking tasks while copying shapes and drawing. Voice, facial expression, and manual kinematics will be automatically recorded with time stamp. The UMass study team members will be trainied by MIT Lincoln Lab (MIT LL) collaborators in the proper and safe use of audio/video recording.

11) **Data and Specimen Banking***

Blood/plasma samples will be taken and shared with VA Puget Sound Health Care System in the bank of Dr. Cyrus Zabetian. It will be plasma sent and analyzed for LRRK2, GBA and ApoE4 genes. All samples will be de-identified before being sent. They will be stored indefinitely. Blood will be stored in locked freezers on a locked floor in the lab at VA Pugent Sound. Only laboratory personnel on the protocol will have access to the samples via possession of a key. For future use of the specimen, Dr. Zabetian's research group and local collaborators at the VA Puget Sound Health Care System and University of Washington will be granted access. Specimen may be provided to other collaborators but this will be discussed with Dr. Smith first.

The lab will also share coded genotype and linked clinical data with the NIH Database of Genotype and Phenotype (dbGaP). All information shared will be de-identified. Information may also be shared with National Institute on Aging Genetics of Alzheimer's Disease Data Storage Site.

Data will not be banked. See #26 Confidentiality

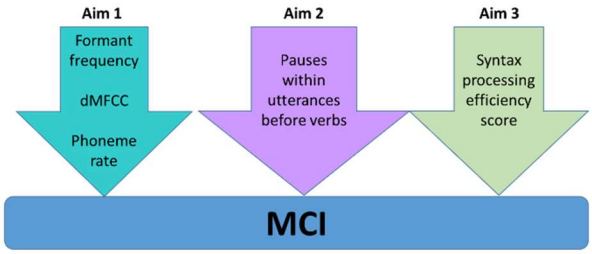
12) **Data Management***

Data Analysis Plan:

Aim 1. Statistical analysis- To use speech acoustic markers to estimate cognitive status, we will employ two co-primary outcomes; cognitive diagnosis and MoCA. Gaussian staircase (GS) regression will be used to predict these outcomes. Individual models will be developed to distinguish PD from controls and determine cognitive status. For MoCA, 3-4 cut points will be determined empirically. ROC curves will be used to quantify detection of these groups for each outcome and performance will be summarized using the area under the curve (AUC) statistic. We will assess for interactions by sex and age

Sample size/power- Our prior work used MoCA as the primary outcome with 35 mostly cognitively intact subjects. Enrolling subjects with a wider range of cognitive function will increase power to detect more granular MoCA cut points. We estimate that 50 PD-MCI will be sufficient to classify by MCI status and estimate 3-4 MoCA cut points as a measure of severity and clinically meaningful change for future clinical trials.

Figure 5.2 Primary outcomes to be used to classify PD-MCI



Aim 2. Statistical analysis- To use linguistic markers to detect PD-MCI, the primary outcome is the number of pauses before verbs/100 verbs and, as secondary outcomes, total within-utterance pause duration, number of pauses before nouns/100 nouns, modified words per minute, and percentage well-formed sentences. The primary analysis of these outcomes will be a non-linear mixed model with the three-level predictor of group membership (control, PD-MCI, PD with normal cognition) as the parameter of interest in the model. Standard ANOVA will be used as the global test of differences followed by pairwise t-tests.

Aim 3. Statistical analysis- To identify the syntax processing signature of PD-MCI, the primary outcome will be the timed efficiency of syntax processing. The total response time to complete each self-paced sentence will be calculated. Response times will be segregated by correct vs. incorrect response to the comprehension question. Syntax processing efficiency score will be calculated by dividing the percentage of correct responses by processing time for object-relative and subject-relative categories. We will create multilevel models and test for effect of group (PD-MCI, PD normal cognition, control), sentence type, and interaction. We will create linear regressions for individual subjects using the listening times for all words and calculate residuals for the critical word in objective-relative clauses. We will assess correlations between the averaged residuals and global cognition (MoCA) and other neuropsychological tests to determine the relationship between online processing and cognitive measures.

13) Provisions to Monitor the Data to Ensure the Safety of Subjects*

This research does not involve more than minimal risk to subjects.

There is a risk of research data being lost or exposed. We will take all reasonable measures to ensure this does not occur (see #15 and 26), including use of secure databases and data-sharing mechanisms with collaborators.

There is also a risk of information being lost or exposed through Amazon cloud.

The Geriatric Depression Scale will be examined at the time of the first encounter with the study subject, and if the subject screens positive for depression (>5 points), the patient will be advised to speak with their treating physician.

A color blindness test will be performed before the Stroop task. If a participant fails and is not previously known to be color-blind, they will be referred to ophthalmology.

14) Withdrawal of Subjects*

The study investigators do not foresee any potential causes to withdraw subjects. It is not expected that a participant may become cognitively impaired within the study period, given that the natural course of PD is very slowly progressive with cognitive changes over years not months.

15) Risks to Subjects*

This research does not involve more than minimal risk to subjects.

The risks are low, which would be time burden, possible frustration and there is a small risk that this study could increase stress.

Breach of confidentiality: One of the risks of being in this study is that the subject's personal information could be lost or exposed. This is very unlikely to happen, and we will do everything we can to make sure that the subject's personal information is protected.

With blood draw comes the risk of slight pain due to the needle puncture. The point of blood draw may become black and blue but this is harmless. The arm drawn from may be sore. Infection, light-headedness and fainting are also possible but unlikely.

16) Potential Benefits to Subjects*

We do not expect individual participants to benefit from participating in this studyThe knowledge gained from this research study may be of benefit to future PD patients.

17) Vulnerable Populations*

No children, pregnant women or prisoners will be enrolled. Minorities will be recruited/enrolled in the same manner as other study participants, but will be required to speak English. This is because the pilot version of the app will be available only in English. Based on the success of the pilot and resources available, the company hopes to expand the app to other languages. The study will not involve cognitively impaired adults. The cognitive ability of each candidate will be assessed using the Montreal Cognitive Assessment and persons with dementia will be excluded.

18) Multi-Site Research*

N/A

19) Community-Based Participatory Research*

N/A

20) Sharing of Results with Subjects*

Study participants may request to have any final published manuscript(s) shared with them.

21) Setting

Physical Setting: All study visits and assessments will take place in the Clinical Trials Unit or the offices of the research team at UMass Memorial University campus or via videoconferencing from participants' homes to the offices of the research team at UMass. Recruiting will take place in the UMass Memorial Neurology clinic, and through recruitment flyers available at local rehabilitation centers, foundations and support groups. This trial is posted on clinicaltrials.gov and the Michael J Fox Foundation Trial Finder. If necessary, to increase recruitment, we will ask Movement disorders centers in Boston to post and circulate our flyer. To minimize selection bias, consecutive subjects who meet all eligibility criteria will be considered for enrollment.

Intervention Setting: There is no intervention. In some participants smartphone-based assessments will be performed independently in the participant's home environment.

22) Resources Available

This study will take about 75% effort to train, screen, enroll, complete required tests and procedures, data enter, maintain equipment and supplies, and work with the IRB.

All study staff have current CITI certification and training on the security issues of maintaining confidential information. There will be training on all aspects of the trial.

The roles of the study staff:

PRINCIPAL INVESTIGATOR (PI) is responsible for all aspects of the study and will have overall responsibility to lead the site study team. The PI will oversee the accrual of appropriate subjects, the conduct of the study according to the protocol, and the collection of required data. The PI will consent subjects, take medical history, conduct physical exam and study assessments, maintain regulatory documents, evaluate eligibility, data completion, query resolution, adverse event monitoring/reporting, IRB communications, IRB continuing reviews, and all study evaluations.

The PI has 10 years of experience in clinical research in PD. She has been PI on investigator-iniated, collaborative, and industy-sponsored clinical studies. She has also served on the University of Pennsylvania IRB.

CO-INVESTIGATORS are other providers in the Movement Disorders Center at UMass who treat patients with PD. They will assist with recruitment, screening of potential subjects, and performing MDS-UPDRS.

RESEARCH ASSISTANTS will assist with recruitment, screening of potential subjects, scheduling study visits, obtaining informed consent, taking medical history and medication lists, performing the cognitive, speech and language assessments, performing certain parts of the physical examination (including MDS-UPDRS rating if appropriate for level of experience deteremined by PI), and instructing participants on usage of the smartphone app. Research assistants also maintain regulatory documents and paper study documents, assist with creation and maintanence of a Redcap database, manage IRB communications, IRB continuing reviews, and all study evaluations.

External Collaborators: The PI has informed collaborators from the following places that they do not fall under the jurisdiction of the UMMS IRB, and collaborators will obtain any necessary IRB approvals that they require.

Aural Analytics: Responsible for providing the Speech Vitals smartphone application customized to our study protocol, assisting with IRB, task and

protocol support related to the app portion of the study. Responsible for overseeing the transfer, storage, data quality assurance, analysis of data collected from the app. In working with the UMMS PI, they will have access to additional deidentified clinical and demographic data in order to provide subgroup analyses. Interaction with participants will be limited to technical support.

MIT/Lincoln Labs: Responsible for collaborating with PI in analysis and interpretation of speech samples and data from the dual-task protocol using the Surface tablet. They will have access to speech samples with basic, deidentified clinical information such as disease status, motor and cognitive test scores. They will provide the technology for the tablet interface and will have access to the video, audio and kinematic data from study participants. MIT/LL employees will not have any interaction with study participants and will not have access to any PHI (including email address). There will be collaboration in abstract and manuscript preparation and future funding proposals based from the current work.

Stepp Lab (Boston University): Responsible for mentoring the PI in acoustic processing, analysis and interpretation. Dr. Cara Stepp and her approved delegates may have access to speech samples and associated acoustic data, de-identified clinical information such as disease status, motor and cognitive test scores. There will be collaboration in abstract and manuscript preparation and future funding proposals based from the current work.

VA Puget Sound Health Care System and Dr. Cyrus Zabetian: Responsible for receiving and processing the blood and plasma samples for genetic information. Dr. Zabetian also runs the bank which the samples will be stored in. Some information will be shared will the NIH Database of Genotype and Phenotype.

Douglas Martini, PhD (UMass Amherst): Responsible for designing and implementing inertrial sensor portion of the protocol. Will provide and maintain the sensors and associated software required to obtain sensor data, analyze and interpret sensor data, and participate in manuscript preparation.

Resources for participants: Participants are not anticipated to require any medical or psychological services related to their participation in the study. They will continue to access their regular medical and/or psychological care providers independently of the study.

23) **Prior Approvals**

Neurology Department Interim Chair, Brian Silver, MD

24) **Recruitment Methods**

The recruitment goals are realistic and feasible based on the volume of PD patients seen at the UMass Neurology Movement Disorders Clinic. There are approximately 800 PD patients being actively followed in the clinic. Based on known prevalence of dementia in PD, we expect approximately 75% of these patients will not have dementia and will be eligible for the study. Out of the approximately 600 eligible patients, we then expect to be able to enroll 20% (120 patients). In addition, we expect an additional 20-30 patient referrals from outside sources and word-of-mouth within the local PD community. These sources combined should allow us to achieve our target of 100 patients within 12-24 months. We expect the recruitment of healthy controls through word-of-mouth and other methods to be more than adequate to meet our target goal of 50 age-matched healthy controls.

Potential subjects will be identified and recruited by several methods:

- Flyers placed in the UMass Neurology Clinic waiting room and clinic rooms (flyer attached)
- Direct discussion and referral from the patient's neurologist at UMass during routine clinic visits such that (a) the PI might recruit her own patients or (b) other providers might ask patients if they are willing to talk with a member of the study team. In the latter case, providers will either pass along a flyer and patients will contact the study team directly, or providers will contact the study team and ask them if they are available to talk with an interested patient. The providers will not share protected health information with the study team.

The study team will advertise to the UMass community via UMMS newsletters and social media, outreach to local PD rehabilitation, and group exercisecenters (including but not limited to: Fairlawn Rehabilitation Center, Whittier Rehabilitation Center), DopaFit, support groups and charitable organizations (including but not limited to: Ashland Senior Center, Framingham Callahan Center, Westborough Good Shepherd Lutheran Center, Worcester St. Vincent Hospital, and foundations such as the American Parkinson Disease Association about the study via discussion with the organizers of these groups and mailing of flyers. The Conquering Diseases Volunteer Registry will be informed through emails to this list. These sites have eagerly participated in referring PD patients to UMass trials in the past. They will direct interested individuals to the PI for additional information. The PI has informal working relationships with these sites as a leader in PD education and research outreach in the community. These sites will receive copies of the study flyer and will inform their PD populations about the study using the language on the flyer. Interested individuals will be directed to the PI's contact information. No data will be shared between these sites and UMass.

- Once a potential subject is identified, they will be screened for eligibility by:
- Either by phone or in person in the Neurology clinic, study personnel will confirm that the participant has a diagnosis of PD (or that they are a healthy controland otherwise meets inclusion/exclusion criteria. Participants who score <21 on MoCA will be excluded.). If they remain eligible and are interested in participating, they will be scheduled for an initial visit. Subjects will be compensated for their time and parking for the study visit (not the screening session), $20 per participant for the approximately 3 hour study visit in the form of a gift card.

25) Local Number of Subjects

Our goal is to screen 150 PD and 75 control subjects at UMass Memorial University campus and other local sites over a 12 month period. We anticipate no more than 25% screen failures. Approximately 100 patients and 50 healthy controls will therefore complete the research protocol which will be sufficient for the exploratory nature of this study.

26) Confidentiality

The information collected as data for this study includes: age, sex, years of education, medical history, medication list, PD disease duration, scores of motor and cognitive assessments, questionnaire responses, speech samples, linguistic and non-linguistic data from analysis of speech samples and syntax task, and facial expression and manual kinematics data from the dual-task procedure.

Subject confidentiality will be strictly maintained by the use of study ID numbers.

Speech data recorded during the study visit will be saved in wav file format, using only study ID in file name, and stored on password-protected UMMS secured laptop with back-up on external hard drive kept in locked drawer in PI office. Speech samples, facial expression, and manual kinematics data (labled with study ID only) may be shared through UMMS-approved secure data-sharing mechanisms with MIT-LL and Stepp lab collaborators designated by the PI.

Inertial sensor data will be labeled only with study ID. Sensor data will be stored locally on the secure, password-protected UMMS laptop designated for study team use only and shared via UMMS-approved secure data-

sharing mechanisms with Douglas Martini, PhD. This de-identified data will be stored on a password-protected secure UMass Amherst computer.

Aural Analytics/smartphone app data: Speech recordings and metadata about the session are stored locally on the user's device until they are successfully uploaded to our HIPAA-compliant web servers, at which point they are deleted from the device. The data uploads anytime the app is open and device connected to internet. No demographic data that has meaning outside of the study context will be collected. IP addresses are not collected.

The data is encrypted in transit and at rest on our servers. All data is hosted on AWS in the US behind secure API gateways and is access-controlled so only trained and approved employees can access it. Meta-data includes non-identifying information, such as time and data for the session and information about the participant's device. Audio may be sent to a HIPAA-compliant transcription provider for transcription.

The system calculated speech metrics from the audio files and these metrics are provided to the study PI at the end of the study via secure web portal.

If a participant requires technical assistance or forgets their username/password for the app, they will contact the UMass study team who will act as the intermediary between the participant and Aural Analytics. Aural Analytics will not have direct contact with particiapnts in order to protect their privacy.

MIT LL: Speech, facial expression, and kinematics data will be stored in a secure location at MIT LL under control of and accessible to Dr. Thomas Quatieri and Dr. James Williamson. Data will be stored in a secure, password protected limited access section of MIT LL LLAN networked computer system. The file server and workstations are all beind the MIT LL Firewall. At the conclusion of the study, a de-identified digital data set will be retaine for future modeling and algorithm development efforts, stored in a network folder at MIT LL for 10 years pas the study completed that is locked-down to an acess control list. Only members of the project team will have access to these project folders.

The PI will collect the participants' Speech Vitals username in order to create a key that links the Speech Vitals ID to the UMass study ID. This key will be stored securely in Redcap. Only the PI and designated study team members will have access to the REDCap key linking subject ID number with identifiers. Access to this key will be at the discretion of the PI and will not include Aural Analytics or their collaborations.

The PI will store her electronic records in a secure Redcap database which undergoes frequent back-up and security updates to protect integrity and confidentially of the data. This secure database will be password-protected. The UMass study team will have access to the database (including identifying data) at the discretion of the PI. Data will be transferred out of Redcap only to an encrypted UMass network computer located in a locked office and files with de-identified clinical and demographic data will be shared with secure UMass file transfer site to collaborators (Aural Analytics, MIT LL, Dr. Cara Stepp). Speech files labeled with study ID only may be shared via UMass secure file transfer site with MIT LL and Dr. Stepp. All UMass study personnel will be able to enter data into the database.. The PI takes full responsibility for the secure storage, management and transmission of the data.

All paper records will contain a study number rather than identifying information and will be stored in a locked cabinet in the PI's locked office.
The screening log, which necessarily contains identifiers, will be kept on a password-protected UMMS computer in the locked office of the PI.

In accordance with UMass and federal policy, research records will be maintained for 3 years after completion of the study, and the HIPAA documents will be kept for 6 years after completion of the study.

Videoconferencing will be completed through a secure, encrypted platform utilized routinely for telemedicine applications (doxy.me). In the case that doxy.me is not available or is not technically feasible for participants, alternatives will be used that contain equivalent privacy standards and are technically acceptable to the study investigators: VSee; Secure Video; TeleHealth365.

UMass investigators will destroy the identifiers linking to data 5 years after the end of the study. This will involve destroying the REDCap project housing identifiers. We have no plans to destroy the deidentified data, as they would be used for continual research and development. At all times, we will limit the information being collected to only the pre-specified data and questionnaires in the study protocol. We will follow privacy obligations to study subjects under the Health Insurance Portability and Accountability Act (HIPAA).

Only de-identified data will be used for dissemination of data outside the designated study team, and for publication of the data.

27) Provisions to Protect the Privacy Interests of Subjects (HIPAA)

Participant assessment will take place in the Neurology clinic in a private room or remotely via videoconferencing to the participant's home. If there is a need to leave a voicemail or message for a subject or potential subject, a message may be left that the call is in regards to a research study at UMass and a contact number for our study team will be provided, but no further details will be mentioned in the voicemail/message.

All participants will sign a HIPAA form when enrolled into the study. *Participation in the study will not affect their health or medical care.*

28) Compensation for Research-Related Injury

This research involves only minimal risk to subjects. No funds have been set aside for compensation for research-related injury.

29) Economic Burden to Subjects

Participants will be responsible for transportation to study visits and for all fees related to smartphone data usage, according to their smartphone carrier agreement and plan.

30) Consent Process

The consent process will be implemented following "SOP: Informed Consent Process for Research (HRP-802 INVESTIGATOR GUIDANCE: Informed Consent. and HRP-803 INVESTIGATOR GUIDANCE: Documentation of Informed Consent)."

In the UMass University Campus Neurology clinic, or via secure videoconference, the study personnel will educate potential study candidates on the purpose, procedures, possible risks and benefits, and subject responsibilities.

Written informed consent will be obtained from each participant. It will be ensured that participants have ample time to review the consent form and that their questions or concerns are addressed. Study staff will highlight the fact that participation in the study is voluntary, and assure subjects and their families that the subject will receive the standard-of-care treatment of their neurologic condition regardless of their decision of whether or not to participate in the study, to protect the subjects from coercion or undue influence. Subjects with dementia will be excluded, thereby minimizing the possibility of invalid informed consent. The principal investigator or research assistant will be responsible for ensuring that a signed and dated informed consent is obtained from each subject prior to conducting any study-related activities. A copy of the consent form will be provided to each participant.

31) Process to Document Consent in Writing

Consent will be achieved referencing SOP *"*HRP-803 INVESTIGATOR GUIDANCE:Documentation of Informed Consent *"*.

See #30 for consent process.

Potential study participants will undergo a screening procedure prior to signing of consent. The study team will obtain verbal agreement for all procedures performed prior to signing of consent (including MoCA) before administration.

Administration of the MoCA prior to written documentation of consent is not only a screening procedure for study eligibility, but will also determine whether a subject is capable of providing consent to participate.

32) Drugs or Devices

The app fits the following criteria for IDE exemption:

- The device is a diagnostic device
- The testing is noninvasive
- The testing does not require an invasive sampling procedure that presents significant risk
- The testing does not by design or intention introduce energy into a subject
- The testing is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure

The sponsor is responsible for labeling the device in accordance with 21 CFR 809.10(c): "For Research Use Only. Not for use in diagnostic procedures."

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