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Feasibility Of Objective Measures and Outpatient Washout  
in Disease Modifying Trials for Parkinson's Disease

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**Feasibility of Objective Measures and Outpatient Washout in  
Disease Modifying Trials For Parkinson's Disease**

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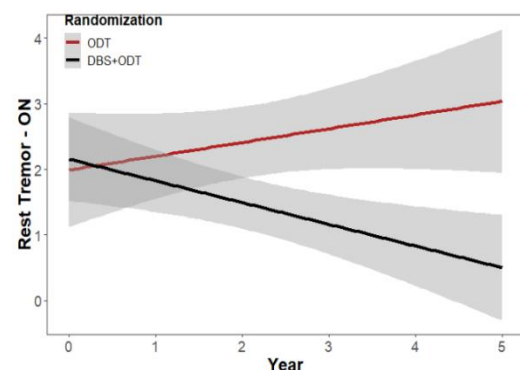
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## 1.0 Background and Rationale

**There is no therapy that slows or stops the progression of any Parkinson's disease symptom.** Parkinson's disease (PD) is the second most common neurodegenerative disorder of aging, affecting more than one million Americans (Reeve et al., 2014). People with PD are typically diagnosed around age 60 and can live with the disease for more than 20 years. Dopamine replacement strategies are the current standard of care for early-stage treatment. Deep brain stimulation (DBS) is an effective adjunctive therapy currently indicated after the emergence of side effects associated with medical therapy (i.e., dyskinesia or other motor fluctuations). Despite numerous medical and surgical options available, all current PD therapies are purely symptomatic.

**Early DBS is disease-modifying in preclinical models of Parkinson's disease.** DBS is currently relegated to mid- to late-stage PD after medications become problematic, but preclinical studies in rat and non-human primate models consistently demonstrate that subthalamic nucleus (STN) DBS protects against nigral neuron death only when applied in early-stage PD (Musacchio et al., 2017; Spieles-Engemann et al., 2010; Wallace et al., 2007). These animal studies and post-mortem reports (Kordower et al., 2013) offer strong support for applying any disease-modifying intervention at the earliest possible stage, where there is the greatest opportunity to influence existing neural network integrity. Based on compelling evidence from animal models, the DBS in early-stage PD pilot clinical trial was conducted at Vanderbilt to provide preliminary data to evaluate the safety and tolerability of early DBS therapy (IDEG050016, NCT0282152, IRB040797) (Camalier et al., 2014; D. Charles et al., 2012, 2014b; P. D. Charles et al., 2012; Finder et al., 2012; Gill et al., 2011; Kahn et al., 2011; Remple et al., 2011). That randomized clinical trial met its primary safety endpoint (D. Charles et al., 2014b), and the FDA has approved Vanderbilt to lead a multicenter, phase 3, randomized clinical trial to evaluate DBS in early-stage PD (IDEG050016).

**There is now class II evidence that early DBS slows the progression of Parkinson's rest tremor.** DBS in early-stage PD was recently shown to potentially slow the progression of rest tremor (Hacker et al., 2018). This finding is significant, not only because it is the first class II evidence of any therapy slowing the progression of any feature of PD, but also because tremor is a highly visible and very common feature of PD (up to 75% of patients) that early-stage PD patients often consider very distressing (Heusinkveld et al., 2018). Additionally, preliminary data through five years of follow-up indicates that subjects randomized to early DBS retain significant control of rest tremor compared to subjects who were randomized to early ODT alone (Fig. 1) (Hacker et al., 2020). These data indicate not only that early DBS may slow the underlying progression of rest tremor but also that it may provide long-term benefit compared to the standard of care. This result must now be prospectively tested in a phase 3 trial that is designed to provide class I evidence



**Figure 1:** Early DBS subjects had less rest tremor after 5 years (n=29;  $P=0.005$ ,  $\beta = -2.0$ , 95% CI: -3.4 to -0.7).

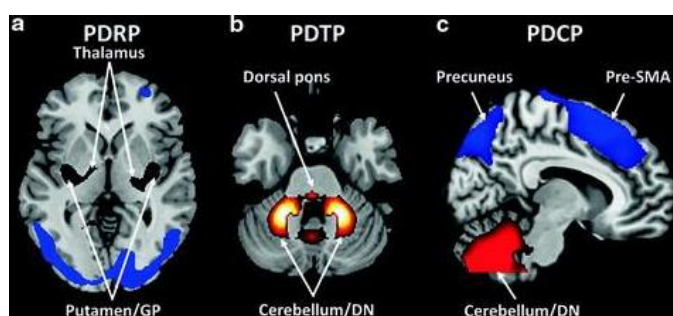
whether early DBS is the first treatment to slow the progression of any feature of any neurodegenerative disorder of aging (Faraji & Richardson, 2019; Karceski, 2018).

**There are no data available regarding objective Parkinson's disease measures during a week-long therapeutic washout.** The pilot trial demonstrated feasibility for key areas for a surgical trial in early-stage PD patients, such as recruitment and retention (Kahn et al., 2011) and accurate lead placement in subjects with mild symptoms (D. Charles et al., 2014b). The study also importantly demonstrated that early-stage PD patients tolerate repeated week-long therapeutic washout assessments. Those washouts, coupled with single-blind assessment of the Unified Parkinson's Disease Rating Scale Part III motor examination (UPDRS-III), were used to measure progression of underlying motor symptoms. That robust inpatient washout protocol allowed subjects to be evaluated in an untreated state, but ultimately, assessment of underlying symptom severity relied solely on subjective clinician rating. The placebo effect is well-known to strongly influence PD trials, particularly for surgical interventions (Mestre et al., 2014), but at the time of study start in 2006, there were no accepted, objective measures available to test in the pilot trial. As a result, there are no preliminary data regarding any objective assessment of PD severity during a week-long washout. Given the significant surgical risks associated with DBS and the prominent placebo effect, it is imperative that the phase 3 trial include the most rigorous and unbiased methods available to evaluate motor symptom progression alongside standard clinical rating scales.

**Parkinson's disease-specific metabolic networks correlate with disease severity.** Resting state FDG-PET imaging is used to evaluate system-level brain changes associated with PD progression and response to treatment. This neuroimaging technique coupled with spatial covariance mapping methods have identified three distinct PD-related metabolic brain networks, characterized by covarying metabolic changes in spatially distributed, functionally interconnected brain regions (Fig. 2) (Huang, Mattis, et al., 2007; Ma et al., 2007; Spetsieris et al., 2013). The Parkinson's Disease Related Pattern (PDRP) is a highly reproducible brain network that correlates with dopamine deficiency, disease severity, and clinical ratings for bradykinesia and rigidity (Eidelberg et al., 1994; Ma et al., 2007). Conversely, the PD Tremor-Related Pattern (PDTP) is a separate metabolic network that correlates with clinical tremor ratings but not with other cardinal motor features (bradykinesia or rigidity) (Mure et al., 2011). A third, separate and reproducible network is the PD-related cognitive pattern (PDCP) which strongly correlates with progressive cognitive dysfunction (executive dysfunction, memory, visuospatial performance) (Huang, Mattis, et al., 2007; Meles et al., 2015).

The PDRP network is modulated by PD medications (Asanuma et al., 2006), and DBS reduces levels of both PDRP and PDTP (Mure et al., 2011), but neither treatment modifies the PDCP network (Huang, Mattis, et al., 2007).

Importantly, it is not known how DBS influences brain networks associated with



**Figure 2: Distinct PD-related metabolic networks. (a) PDRP (bradykinesia, rigidity). (b) PDTP (tremor). (c) PDCP (cognition) [52]**

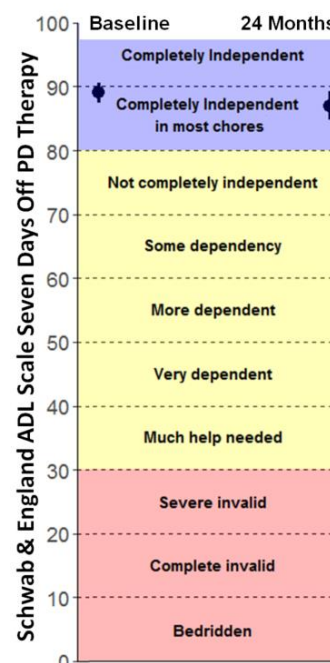
more intact dopaminergic systems (*i.e.*, *early-stage PD*), because all previous studies were conducted in patients who received DBS in advanced stage PD (Huang C, Mattis P, Perrine K, Brown N, Dhawan V, 2008; Lin et al., 2008). Evaluating changes in these metabolic networks in the untreated state from a randomized clinical trial of DBS in early-stage PD will generate insights into PD pathogenesis and underlying mechanisms of early DBS (planned R01 application).

**Wearable biosensors objectively measure Parkinson's disease motor symptoms.** Recent technological advances have introduced wearable biosensors that are affordable and FDA-cleared for safe and efficacious assessment in PD (Odin et al., 2018). These devices objectively detect motor symptoms (bradykinesia, tremor) as well as complications of medical therapy (dyskinesia). PD symptoms are highly variable, with notable variances, not only day-to-day, but also within the same day. Wearable technologies offer the opportunity to objectively evaluate symptom severity at study visits and also to provide real-world continuous monitoring outside of the research setting, representing a more realistic patient condition. The original early DBS trial launched before these devices were available, and therefore, the feasibility of integrating wearable technologies into a week-long washout of an aging PD population is currently unknown. Since results of the phase 3 trial could result in a major shift in clinical practice, rigorous assessment of Parkinson's symptom progression is needed to evaluate effectiveness of early DBS intervention.

**There were no safety issues during 147 washout experiences completed in the pilot trial, and independence in activities of daily living (ADL) was preserved in early-stage PD patients after washout.** One of the main objectives of the pilot trial was to evaluate the preliminary safety of early DBS and associated study procedures.

The eight-day washout was well-tolerated by early-stage PD patients in the pilot, and most participants remained very active even with increased motor symptoms experienced off therapy (Fig. 3) (D. Charles et al., 2014b). Daily autonomic testing was conducted during the inpatient washout, and there were no adverse events (AEs) related to therapy withdrawal in any of the 147 washout experiences completed. While essential for that initial investigation, inpatient admission to a dedicated clinical research center for 24/7 evaluation is likely not necessary and may be overly burdensome to participants. The Vanderbilt CRC provides outpatient space and nursing care, which, in combination with nearby hotel lodging and transportation services, could provide a more cost-effective alternative to conduct the therapeutic washout assessments that are needed to evaluate underlying motor symptom progression. The feasibility of conducting an outpatient therapeutic washout in an aging population of early-stage PD patients, however, has not been tested.

**Public Health Relevance.** The World Health Organization estimates that the number of people aged  $\geq 65$  years will reach 1.5



**Figure 3: ADL Independence was Preserved after 7-Day Washout in the DBS in Early PD Pilot (n=29, means and 95% CIs shown) [10].**

billion by 2050. This rapid aging population growth underscores the urgent clinical need to identify therapies that slow progression of age-related neurodegenerative diseases and ultimately improve quality of life (QoL). This line of research aligns with the Aging Well in 21<sup>st</sup> Century Strategic Directions for Research on Aging by enhancing our understanding of the aging brain in PD, the second most common neurodegenerative disorder of aging. The robust improvement in QoL, ADL, and motor function provided by DBS in mid- and advanced-stage PD, paired with the disease-modifying potential of early intervention (Hacker et al., 2018), strongly warrant a future multicenter trial, testing its efficacy in early-stage PD patients.

**Summary.** A phase 3 trial is planned which will test the hypothesis that early DBS slows the progression of PD motor symptoms. The proposed study seeks to quickly fill a critical gap in study design knowledge by piloting new unbiased measures alongside standard clinical assessments and patient-reported outcomes during a therapeutic washout conducted for the first time in the outpatient setting (Fig. 4). It is imperative to first pilot these changes to the washout protocol in a prospective early-stage PD cohort to determine if and how they should be included in a future trial. This feasibility study will set the stage for focused investigation into potential mechanisms of disease-modification with early DBS in Parkinson's disease.

## 2.0 Specific Aims

**Specific Aim 1:** To determine the feasibility of including off-therapy FDG-PET scans into the week-long washout protocol in early-stage PD patients.

**Aim 1a:** To describe changes in metabolic network expression levels (PDRP, PDCP, PDTP) after a 7-day washout in early-stage PD patients.

**Aim 1b:** To provide point estimates with confidence intervals for expression of PD-related metabolic networks (PDRP, PDCP, PDTP; on and off therapy).

**Aim 1c:** To describe relationships between metabolic network scores and respective study assessments.

**Aim 1d:** To test feasibility of collecting FDG-PET scans in early-stage PD patients washed out for 7 days.

**Specific Aim 2:** To test feasibility of including wearable biosensors into a week-long washout in early PD patients.

**Aim 2a:** To test the acceptability of including two wearable biosensors into the study protocol.

**Aim 2b:** To provide point estimates with confidence intervals for assessments of bradykinesia, tremor and dyskinesia from two wearable biosensors.

**Aim 2c:** To describe relationships between scores from wearable biosensors and standard clinical assessments.

**Aim 2d:** To describe relationships between scores from wearable biosensors and PD-related metabolic networks (PDRP, PDTP; on and off therapy)

**Specific Aim 3:** To determine the feasibility of conducting outpatient therapeutic washouts in early-stage PD.

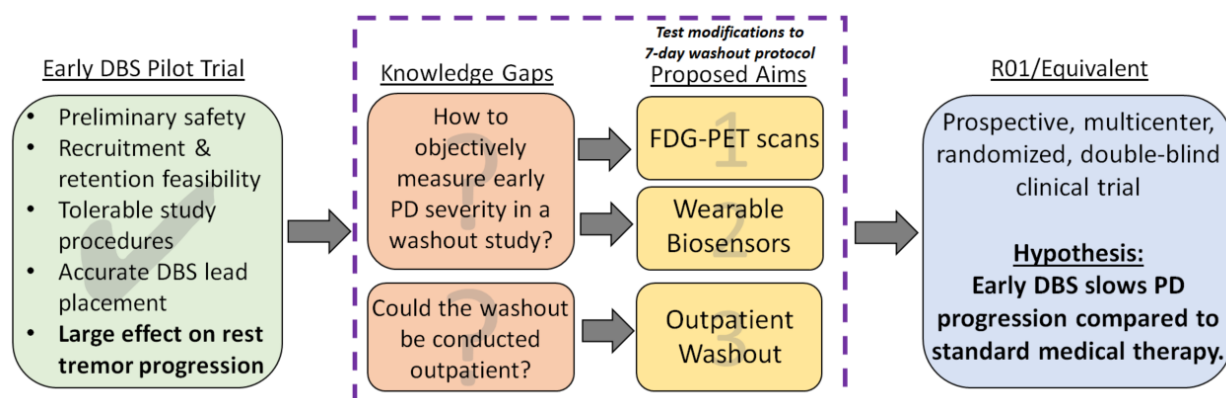
**Aim 3a:** To evaluate the preliminary safety of outpatient therapeutic washouts in early-stage Parkinson's disease.

**Aim 3b:** To evaluate the feasibility of conducting outpatient therapeutic washouts in early-stage Parkinson's disease.

### 3.0 Study Overview

To establish feasibility of conducting a Phase 3 study, Vanderbilt completed the first prospective, randomized, single-blind clinical trial of DBS in early PD in 2012 (IDE #G050016). Prior to this pilot, DBS had not been studied in early PD before the onset of motor fluctuations or dyskinesias. The pilot results demonstrate the feasibility to recruit, obtain meaningful informed consent, randomize, treat, and retain subjects with early PD in a Phase 3 clinical trial involving surgical risks and repeated week-long inpatient stays (Camalier et al., 2014; D. Charles et al., 2012, 2014b; P. D. Charles et al., 2012; Finder et al., 2012; Gill et al., 2011; Kahn et al., 2011; Remple et al., 2011). The pilot study met its primary safety endpoint, finding that subjects receiving stimulation did not experience PD *worsening* that differed from the control group (D. Charles et al., 2014b). Based on these results, the FDA has approved the conduct of a prospective, double-blind, placebo-controlled, phase 3, multicenter safety and efficacy trial of DBS in early-stage PD (IDE G050016) in 280 participants across 18 US centers.

This study will directly bridge information learned from the first investigation to inform the phase 3 trial by testing necessary protocol modifications to add objective, unbiased measures of PD severity (Fig. 4).



**Figure 4: Knowledge gaps to fill before adding objective measures to the washout protocol.**

### 4.0 Inclusion/Exclusion Criteria

Enrollment criteria for this study are identical to the inclusion/exclusion criteria for the planned phase 3 trial of DBS in early-stage PD. These criteria reflect the most recent

guidelines from the Movement Disorders Society to reduce the likelihood of enrolling a participant who later proves not to have idiopathic PD (Postuma et al., 2015).

\*Screened by study neurologist.

#### 4.1 Inclusion Criteria

Subjects will be eligible to participate in the study if all of the following conditions exist:

1. \*A clinical diagnosis of idiopathic PD. The diagnosis will be based upon the presence of at least two of the three cardinal motor signs of this disorder (akinesia/bradykinesia, rest tremor, and rigidity) with at least one of the signs being rest tremor or bradykinesia.
2. Clear and dramatic beneficial response to dopaminergic therapy (defined as demonstrating at least 30% improvement in parkinsonian motor signs based upon the UPDRS-III motor examination subscore, following the administration of their dopaminergic medications during the screening neurological examination)
3. \*Hoehn and Yahr (H&Y) stage II when OFF medication.
4. Aged 50 to 75 years.
5. Subjects must be on dopaminergic therapy for at least one year prior to the screening visit and less than four years prior to the completion of the washout period.
6. Subjects must have a stable response to dopaminergic medication.
7. Available for follow-up for the entire duration of the study.
8. Subjects receiving antidepressant medication used specifically for the treatment of depression must be on stable doses for at least eight weeks prior to enrolling in the study.
9. Subjects must agree to maintain a stable regimen, if deemed medically appropriate by the treating physician, of any psychotropic medications throughout the study.

#### 4.2 Exclusion Criteria

Subjects will be excluded from participation in the study if any of the following conditions exist:

1. \*Evidence of an alternative diagnosis or secondary parkinsonism, as suggested by:
  - a. Features unusual early in the clinical course (e.g., prominent postural instability, freezing phenomena, or hallucinations unrelated to medications in the first 3 years after symptom onset)
  - b. Dementia preceding motor symptoms
  - c. Neurologic signs of upper motor neuron or cerebellar involvement
  - d. Significant orthostatic hypotension unrelated to medications
  - e. Unequivocal cortical sensory loss (i.e., graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia
  - f. Vertical supranuclear gaze palsy, or selective slowing of vertical saccades

- g. Unequivocal cerebellar abnormalities on examination, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (e.g., sustained gaze-evoked nystagmus, macro square wave jerks, hypermetric saccades)
  - h. Documentation of a condition known to produce parkinsonism and plausibly connected to the subject's symptoms (e.g., history of stroke, exposure to toxins, or encephalitis; or neuroleptic use within the past 6 months)
- 2. \*The expert evaluating physician, based on the full diagnostic assessment, believes that an alternative syndrome is more likely than PD.
- 3. \*Uncontrolled medical condition or clinically significant medical disease that would increase the risk of developing pre- or postoperative complications (e.g., significant cardiac or pulmonary disease, uncontrolled hypertension).
- 4. \*Evidence of existing dyskinesias.
- 5. \*Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia.
- 6. \*Currently active diagnosis of a major psychiatric disorder
- 7. Previous brain operation or injury.
- 8. Active participation in another clinical trial for the treatment of PD.
- 9. \*Any current substance use disorder.
- 10. Any history of recurrent or unprovoked seizures.
- 11. Any prior movement disorder treatments that involved intracranial surgery or device implantation.
- 12. Any active implanted intracranial device (e.g., cochlear implant) or implanted device to treat movement disorders (e.g., duodopa pump) whether turned on or off.
- 13. History of suicide attempt.
- 14. A female who is breastfeeding or of child-bearing potential with a positive urine pregnancy test or not using adequate contraception.
- 15. Inability or unwillingness of subject to give written informed consent.
- 16. \*Parkinsonian features restricted to the lower limbs for more than three years.
- 17. \*Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and timecourse consistent with drug-induced parkinsonism.
- 18. Evidence of an alternative diagnosis or secondary parkinsonism (in the opinion of the study neurologist), as suggested by a collection of findings from the following Red Flags defined by the Movement Disorders Society (Postuma et al., 2015):
  - a. Rapid progression of gait impairment requiring regular use of a wheelchair.
  - b. \*Early bulbar dysfunction, defined as one of severe dysphonia, dysarthria (speech unintelligible most of the time), or dysphagia [requiring soft food, nasogastric (NG) tube, or gastrostomy feeding].
  - c. \*Inspiratory respiratory dysfunction defined as either diurnal or nocturnal inspiratory stridor or frequent inspiratory sighs.
  - d. \*Recurrent (>1/year) falls because of impaired balance within 3 years of onset.
  - e. \*Otherwise unexplained pyramidal tract signs, defined as pyramidal weakness or clear pathologic hyperreflexia (excluding mild reflex asymmetry in the more affected limb and isolated extensor plantar response).

- f. \*Bilateral symmetric parkinsonism throughout the disease course. The patient or caregiver reports bilateral symptom onset with no side predominance, and no side predominance is observed on objective examination.
- 19. Received radiation exposure as part of other recent research studies and individuals who work around radiation will be excluded from the study
- 20. Subjects who do not pass the neuropsychological screening battery.
- 21. \*Subjects who, in the opinion of the study neurologist or principal investigator, should not participate in the study

## **5.0 Recruitment and Retention**

### **5.1 Recruitment Feasibility**

The early DBS pilot easily filled enrollment (37 patients in 31 months). The majority were existing patients from the Vanderbilt Movement Disorders Clinic. Currently, Vanderbilt treats 1,924 PD patients annually, which is more than twice the number than when the original trial recruitment was ongoing (IRB040797).

### **5.2 Recruitment Plan**

Subjects will be recruited from regional movement disorder clinics, by patient handouts and recruitment cards (Appendices A, L, and N), by personal communication with treating neurologists, and through Parkinson's disease support groups. In addition, subjects will be recruited using the MyResearch at Vanderbilt and ResearchMatch online platforms and email notification systems.

Potential participants will be contacted by phone and then sent the informed consent forms and a letter describing this study, including contact information for study staff and investigators who will be available to answer questions.

#### **5.2.1 RedCap Screening Survey**

Recruitment materials will include a hyperlink and QR code that directs potential participants to a brief RedCap screening survey (Appendix B).

#### **5.2.2 Research Match**

ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch Network to use ResearchMatch for the purposes of conducting recruitment feasibility analysis or participant recruitment. The Vanderbilt IRB provides oversight for ResearchMatch as a recruitment tool, and this has been documented within the ResearchMatch IRB

Letter of Understanding (available upon request). However, individual requests to use ResearchMatch as a recruitment tool are required to be approved by the participating institution's IRB.

IRB approval is requested to send the following study recruitment message to potential study volunteers through ResearchMatch.org. ResearchMatch requires confirmation that this language has been IRB approved and that my direct study contact information has been removed (email/phone) before sending my study announcement through ResearchMatch to volunteers that appear to be a good match for my study.

**Contact Message Content Description:**

*Below is the study-specific announcement that will be inserted into the ResearchMatch notification regarding this study (Appendix C):*

Researchers at Vanderbilt are looking for individuals with early-stage Parkinson's disease to participate in a study on ways to measure disease progression. Results from this study will be used to plan a phase 3 Parkinson's disease clinical trial.

To participate, you must be:

- 50 to 75 years old
- Diagnosed with Parkinson's disease
- Taking medications to treat your Parkinson's disease symptoms for at least 1 year and no more than 4 years

Participants in this study will be asked to:

- Receive 2 brain scans
- Wear a movement tracking wristwatch for 6 days before coming to Vanderbilt

Compensation for participation in this study includes:

- 8 nights lodging at a hotel near Vanderbilt
- Meals paid for throughout the 8-day study
- Up to \$485 additional compensation for time, travel, and participation

Thank you for your consideration!

*ResearchMatch provides standard notification language (in grey) that will be received by all ResearchMatch volunteers who may be a match for a given study. My specific message for which I am seeking approval will be inserted accordingly:*

A research team with **VANDERBILT UNIVERSITY in NASHVILLE, TENNESSEE**, believes you might be good match for the following study:

*<Researcher's IRB approved study-specific  
recruitment announcement is inserted here>*

If you are interested in this study and having the research team contact you directly, please select the "Yes, I'm interested" link below. By clicking the "Yes, I'm interested" link, your contact information will be released to the research team. If you select the "No, thanks." link or do not respond to this study message, your contact information will not be released to the research team.

QUICK LINK OPTION: YES

QUICK LINK OPTION: NO

### 5.2.3 MyResearch at Vanderbilt

MyResearch is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users that have previously confirmed they would like to be contacted directly for research. This repository provides investigators a forum for advertising for volunteers for a specific study. Email notifications are limited to IRB approved language, describe study specifics and provide contact information. To utilize this initiative, investigators complete a MyResearch Access Request that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate.

IRB approval is requested to send the following study recruitment message to potential study volunteers through MyResearch at Vanderbilt. MyResearch asks for confirmation that this language has been IRB approved before sending my study announcement through MyResearch to volunteers.

#### Contact Message Content Description:

*Below is the study-specific announcement that will be inserted into the MyResearch notification regarding this study (Appendix D):*

Researchers at Vanderbilt are looking for individuals with early-stage Parkinson's disease to participate in a study on ways to measure disease progression. Results from this study will be used to plan a phase 3 Parkinson's disease clinical trial.

To participate, you must be:

- 50 to 75 years old
- Diagnosed with Parkinson's disease
- Taking medications to treat your Parkinson's disease symptoms for at least 1 year and no more than 4 years

Participants in this study will be asked to:

- Receive 2 brain scans
- Wear a movement tracking wristwatch for 6 days before coming to Vanderbilt

Compensation for participation in this study includes:

- 8 nights lodging at a hotel near Vanderbilt
- Meals paid for throughout the 8-day study
- Up to \$485 additional compensation for time, travel, and participation

If you are interested in learning more about participating in this study, please complete the brief screening survey at the link below:

[REDACTED]

Thank you for your consideration!

*MyResearch provides standard notification language (in grey) that will be received by all volunteers who are contacted for the study. My specific message for which I am seeking approval will be inserted accordingly:*

Hello,

In a survey sent to My Health at Vanderbilt users you agreed to be contacted directly to receive information about research studies. Below is a description of a research study at Vanderbilt that could possibly match your health profile.

*<Researcher's IRB approved study-specific recruitment announcement is inserted here>*

Please feel free to contact us anytime with questions or comments at

[REDACTED].

Thank you,  
The MyResearch Team  
Vanderbilt Institute for Clinical and Translational Research

### 5.2.4 Parkinson's Disease Support Groups

Parkinson's Disease Support Groups are great resources for finding potential participants. With many members, an announcement in these groups will be another helpful tool for recruitment. IRB approval is requested to send the following study recruitment message to potential study volunteers in Parkinson's Disease support groups.

#### Contact Message Content Description:

*Below is the study-specific announcement that will be forwarded to Parkinson's Disease support groups (Appendix M):*

Researchers at Vanderbilt are looking for individuals with early-stage Parkinson's disease to participate in a study on ways to measure disease progression. Results from this study will be used to plan a phase 3 Parkinson's disease clinical trial.

To participate, you must be:

- 50 to 75 years old
- Diagnosed with Parkinson's disease
- Taking medications to treat your Parkinson's disease symptoms for at least 1 year and no more than 4 years

Participants in this study will be asked to:

- Receive 2 brain scans
- Wear a movement tracking wristwatch for 6 days before coming to Vanderbilt

Compensation for participation in this study includes:

- 8 nights lodging at a hotel near Vanderbilt
- Meals paid for throughout the 8-day study
- Up to \$485 additional compensation for time, travel, and participation

If you are interested in learning more about participating in this study, please complete the brief screening survey at the link below:

[REDACTED]

If you are having difficulty with the survey or have questions/concerns, please contact the study coordinator, [REDACTED]

[REDACTED]

### 5.2.5 Radio Advertisements

### 5.3 Retention Plan

During the daily ambulatory clinic visit, the study neurologist will assess the subject's functional ability for activities of daily living to continue the outpatient washout and use the provided transportation between the hotel and VUMC. At any point during the washout, if the subject or study neurologist have concern that the additional assistance is needed, the study coordinator will accompany the subject during transportation from the hotel to the ambulatory clinic and the return trip to the hotel. Assistance beyond transportation needs between the hotel and VUMC is not expected based on the preservation of independence in activities of daily living observed during the washouts in the pilot trial (Fig. 3). However, if the study neurologist determines that inpatient care is required, the subject will be admitted to the CRC as an inpatient and study procedures will be continued and performed as was done in the pilot trial. With these additional steps, it is expected that every subject will complete the week-long therapeutic washout, as was achieved in the pilot trial.

## 6.1 Overview

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washout in the outpatient setting. This study will evaluate the feasibility of incorporating metabolic PET scans (Aim 1) and wearable biosensors (Aim 2) into a week-long washout visit conducted in the outpatient setting (Aim 3). These results will address uncertainties surrounding including these changes in the FDA-approved phase 3 protocol, including acceptability among patients and research staff, as well as providing baseline point and variance estimates.

## **6.2 Participant Lodging and Transportation**

The pilot trial completed 147 week-long washouts of all PD medications and DBS without any safety issues, and early-stage PD subjects preserved independence in ADL throughout the washout (Fig. 3) (D. Charles et al., 2014b). To potentially reduce patient burden, this study will test the feasibility of conducting therapeutic washouts in the outpatient setting. Lodging for PD participants will be provided at a nearby hotel (< 1 mile from VUMC). PD subjects will be asked to check into the hotel the afternoon/evening prior to day 1 of the week-long outpatient study visit. PD subjects will be instructed to use the hotel's free shuttle service for transportation to/from the CRC daily for safety evaluations (including autonomic testing), neurological examinations, and study assessments.

## **6.3 Study Visits**

To accurately characterize the severity of subjects' PD, in a manner similar to the pilot trial, PD participants will undergo a week-long washout of all PD medications (Vanderbilt IRB 040797, 180766) (D. Charles et al., 2014a). During the eight-day study visit, subjects will be assessed in two conditions: an ON condition and an OFF condition. "OFF" is operationally defined as the condition when a subject has received no antiparkinsonian medications. "ON" is operationally defined as the condition when both the subject and physician agree that the patient experiences maximal therapeutic benefit from medication.

After ON therapy measures are collected on Day 1, subjects will discontinue medications and stimulation for a seven day "washout". The OFF assessments will be conducted daily during a one-week washout period. Subjects will then resume all medications and exit the study.

## **6.4 Clinical Assessments**

### **6.4.1 Screening Visit**

After informed consent is obtained, subjects will undergo a detailed half-day screening visit to ensure only those that have idiopathic PD and meet the inclusion and exclusion criteria are selected for the study.

Subjects will come to the morning visit off medications to evaluate levodopa response during the screening visit. Subjects will follow the same testing protocol used for standard of care pre-operative evaluation at Vanderbilt (Table 1).

<b>Table 1: Medication Instructions for Testing</b>	
<b>Stop Taking XX Hours Prior to Evaluation</b>	<b>Medication</b>
<b>72 Hours</b>	<ul style="list-style-type: none"> <li>• Ropinirole XL (Requip XL)</li> <li>• Pramipexole ER (Mirapex ER)</li> <li>• Neupro Patch</li> </ul>
<b>48 Hours</b>	<p><b>All Dopamine Agonists</b></p> <ul style="list-style-type: none"> <li>• Requip IM (immediate release)</li> <li>• Pramipexole (Mirapex)</li> <li>• Bromocriptine (Parlodel)</li> <li>• Pergolide (Permax)</li> <li>• Apomorphine (Apokyn)</li> </ul> <p><b>Anticholinergic Medications</b></p> <ul style="list-style-type: none"> <li>• Trihexyphenidyl (Artane)</li> <li>• Benztropine (Cogentin)</li> </ul>
<b>24 Hours</b>	<p><b>All Levodopa/Carbidopa Preparations</b></p> <ul style="list-style-type: none"> <li>• Levodopa/Carbidopa</li> <li>• Sinemet</li> <li>• Sinemet CR</li> <li>• Stalevo</li> <li>• Rytary</li> </ul> <p><b>COMT Inhibitors</b></p> <ul style="list-style-type: none"> <li>• Entacapone (Comtan)</li> <li>• Tolcapone (Tasmar)</li> </ul> <p><b>MAO-B Inhibitors</b></p> <ul style="list-style-type: none"> <li>• Selegiline (Eldepryl, Zelapar)</li> <li>• Rasagiline (Azilect)</li> <li>• Amantadine</li> </ul>

Subjects will complete the following during the screening visit:

- Arrive off PD medication
- UPDRS-III off evaluation (study neurologist)
- Take first morning dose of PD medication
- UPDRS-III on evaluation (study neurologist)
- Neurological examination (study neurologist)
- Inclusion/exclusion criteria review (study neurologist; study coordinator)
- Neuropsychological screening assessment (trained research assistant)

### 1. Physical and Neurological Examination

This will be performed by a neurologist with special training in PD and movement disorders. Subjects will come to the morning visit off medications (having only taken the last dose the previous evening and only withholding the first morning dose) to evaluate levodopa response during the screening visit. Subjects will perform the UPDRS-III motor examination off therapy and be rated by the study neurologist. Subjects will then take 100-150% of their usual first levodopa-equivalent morning dose of PD medications and then perform the UPDRS-III motor examination on therapy (approximately 1 hour later, when the subject indicates their PD medication is working) and be rated again by the study neurologist. If the subject's scores improve by 30% from off to on therapy, that inclusion criterion will have been met.

### 2. Inclusion/Exclusion Criteria Review

The study coordinator will review the inclusion/exclusion criteria with the subject during the screening visit. Some inclusion/exclusion criteria will be evaluated by the study neurologist (noted with \* in Sections 4.1 & 4.2).

### 3. Neuropsychological Screening Assessment

If the subject meets all the other inclusion/exclusion criteria, they will proceed to the neuropsychological screening assessment. This assessment is estimated to take 30 minutes to complete and will be performed by a trained research assistant. The screening assessment will include:

1. **Montreal Cognitive Assessment (MoCA):** a quick test to screen for dysfunction in several cognitive domains; the 30-question assessment evaluates orientation, short-term memory, executive function, language skills, abstraction, animal recognition, attention and clock drawing; scores of  $\geq 26/30$  are normal (Nasreddine et al., 2005).
2. **Scales for Outcomes in Parkinson's Disease – Cognition (SCOPA-Cog):** assesses cognitive function in PD; the 10-question assessment, scored from 0–43, evaluates memory, attention, executive function, and visuospatial function; scores of  $< 22$  is considered the cutoff for dementia (Marinus et al., 2003; Verbaan et al., 2011).
3. **Adjusted Barona Equation:** demographically assesses premorbid intelligence under the index scores of the Wechsler Adult Intelligence Scale-Revised; the 7-item test estimates premorbid intelligence functioning by age,

sex, race, region, occupation, urban-rural residence, and education; adjusted for the Flynn effect (Kirton et al., 2020).

4. **Patient-Reported Outcomes Measurement Information System (PROMIS)-Emotional Distress-Depression and Anxiety short forms:** a short, electronic assessment subjectively measuring a patient's emotional distress; the depression short form contains 8 items, and the anxiety short form contains 7 items; the depression short form focuses on negative mood, decrease in positive affect, information-processing deficits, negative views of the self, and negative social cognition; the anxiety short form focuses on fear, anxious misery, hyperarousal, and somatic symptoms related to arousal; higher PROMIS scores indicate more of that domain (depression/anxiety) (Cella et al., 2010).
5. **Suicide Assessment Five-Step Evaluation and Triage with Columbia Suicide Severity Rating Scale (SAFE-T with C-SSRS):** assesses suicide risk through a series of simple questions, helping to identify whether someone is at risk for suicide, the severity and immediacy of that risk, and gauge the level of support that the person needs; the 7-question assessment evaluates suicidal ideation severity and suicidal behavior; any question answered with "yes" indicates that someone should seek a behavioral health referral; if any of questions 4-7 are answered with "yes," immediate help should be sought (*Triage and Risk Identification The Columbia Lighthouse Project*, 2016).
  - If a potential subject endorses any suicidal ideation on the SAFE-T with C-SSRS (i.e., "yes" to any of the 7 questions), the following actions will be taken:
    1. The research protocol will be discontinued.
    2. The study coordinator will notify the study neurologist (Dr. David Charles or his designee, to be selected prior to participant study visit) immediately in-person or by phone, and the study neurologist will manage and be responsible for the disposition of the participant.
    3. The study coordinator will also notify the neuropsychologist (Dr. Ciaran Considine) and the PI (Dr. Mallory Hacker) by email.
6. **Parkinson's Disease Specific Psychosis Scale (PD-SPSS):** measures symptoms of psychosis induced by levodopa in PD patients; the 10-question assessment asks patient/family/both about the presence, severity, frequency, and consequences of the hallucinations (visual, auditory, olfactory) and delusions (Ondo et al., 2015).

7. **Questionnaire for Impulse Control Disorders in PD (QUIP-Rating Scale):** assesses severity of symptoms relating to impulse control disorders in PD patients; the 28-item scale, scored from 0-112, assesses four domains: sexual, gambling, buying, and eating behaviors; while also assessing the frequency of compulsive hobbyism, punting, and medication use; the cutoff to diagnose individual impulsive-compulsive disorders (ICDs) is a score of  $\geq 6$  for gambling,  $\geq 8$  for sexual, and  $\geq 7$  for eating; the cutoff for combined ICDs is a score of  $\geq 10$ ; the cutoff for hobbyism-punting is a score of  $\geq 7$  (Evans et al., 2019).
4. **Pregnancy Screening Test** – Female subjects of child-bearing potential will be given a urine pregnancy screening test. Subjects with a positive urine pregnancy test will be excluded from the study.

#### **6.4.2 Medication Optimization Visit**

Within two weeks of completing the screening assessment, all subjects will be seen by the treating neurologist to optimize Parkinson's disease medications so that the ratings obtained at study visits reflect true ON medication states. This visit may be conducted in-person or via telehealth. Medication adjustments will be performed as necessary up to two weeks prior to the baseline assessment, after which no further adjustments will be made. Parkinson's medication doses will be monitored and recorded by the study physician during all routine office visits in addition to all official study visits. The washout assessment should begin within 90 days of successfully passing all screening criteria.

#### **6.4.3 Parkinson's Kinetigraph (PKG) at Home**

Subjects will be asked to wear a wristwatch (the Parkinson's KinetiGraph/PKG) for 7 days prior to their week-long outpatient study visit (within two weeks before their scheduled study visit). After passing the screening visit, the study coordinator will contact subjects to provide information about using the PKG wristwatch (Appendix G). The PKG measures PD symptoms of bradykinesia, dyskinesia, tremor, immobility, and sleep.

After passing the screening visit and scheduling the 8-day study visit, the study coordinator will order the PKG system, which will be mailed directly to the subject's home. Subjects will follow the instructions provided and be instructed to contact the study coordinator if there are any issues with beginning the watch recording. After the 7-day recording is complete, subjects will be asked to follow the instructions for returning the PKG watch by mail using the provided postage/packaging.

#### **6.4.4 Study Visit**

Subjects will be evaluated daily at the CRC in outpatient rooms following a similar protocol to what was implemented in the pilot (D. Charles et al., 2014b), which includes the following clinical assessments: MDS-UPDRS (I-IV), UPDRS (I-IV), PDQ-39 (quality of life), Hohen & Yahr scale, and Schwab & England ADL scale (D. Charles et al., 2014b; Tramontana et al., 2015).

UPDRS and MDS-UPDRS assessments will be videotaped during the initial ON period (day 1) and at the end of the seven-day washout period when subjects are OFF medication (day 8). All scores will be assigned by the same blinded, independent reviewer who evaluated videos during the pilot trial, Dr. Kevin Cannard, M.D., Walter Reed Army Medical Center.

A week-long therapeutic washout will be conducted to characterize the underlying severity of subjects' PD. In a manner similar to the visits conducted in the pilot trial at baseline and 6, 12, 18, and 24 months (D. Charles et al., 2014b), all subjects will be evaluated in two conditions: ON therapy (day 1) and OFF therapy after a seven-day washout (day 8). A battery of tests will assess subjects in the ON state, and an abbreviated battery will be administered in the OFF state (Table 2).

<b>Table 2: Washout Assessment Procedures</b>										
<b>Evaluation/Procedure</b>	<b>Day of Assessment</b>									
	<b>SV</b>	<b>0/1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>Early Exit</b>
Informed Consent	X									
History and*, Medication Review*	X	X								
Physical and Neurologic Examination*	X	X							X	X
Investigator Wellness Check*			X	X	X	X	X	X		X
Neuropsychological Screening~	X									
Inclusion/Exclusion Criteria Review*, ^	X									
Adverse Event Review^		X	X	X	X	X	X	X	X	X
Autonomic Testing <sup>#</sup>		X	X	X	X	X	X	X	X	X
Neuropsychological Test Battery~		X						X		
PDQ-39+		X								

MDS-UPDRS & UPDRS Parts I^, II^, IV^		X								
MDS-UPDRS & UPDRS Part III (videotaped)^		X							X	X
Kinesia ONE Motor tasks^		X	X	X	X	X	X	X	X	X
Hoehn & Yahr*		X							X	X
Schwab & England^		X							X	X
Timed Tests (stand/walk/sit, finger taps)^		X							X	X
Unified Dyskinesia Rating Scale (videotaped)^		X								
Clinician Global Impression of Severity (CGI-S)*		X							X	X
Clinician Global Impression of Change (CGI-C)*									X	X
Patient Global Impression of Severity (PGI-S)+		X							X	X
Patient Global Impression of Change (PGI-C)+									X	X
Quality of Life in Essential Tremor (QUEST)+		X							X	
EQ-5D-5L+		X							X	
Pain Assessment+	X	X	X	X	X	X	X	X	X	X
King's PD Pain Scale+		X							X	
Columbia Suicide Severity Rating Scale~	X	X								
PET/CT Scan		X							X	
SV = Screening Visit *Performed by the study neurologist. ~Performed by a research assistant trained by neuropsychologist to complete the neuropsychological assessments. + Completed by patient via self-report (guided by the study coordinator) ^Collected by the study coordinator #Collected by CRC staff										

- i. **Physical and Neurological Examination:** completed by a neurologist with specialized training in PD and movement disorders.
- ii. **UPDRS:** a validated standardized rating scale for PD subjects with good interrater reliability, and universally accepted as a rating scale for PD subjects. The UPDRS consists of four sections: ADL, mentation behavior and mood, motor examination, and drug-related complications of therapy. Our primary assessment of each subject will be based on the UPDRS, Part III. Assessments

- will be recorded in both the ON and OFF medication (and stimulation if present) states.
- iii. **MDS-UPDRS:** a revision of the UPDRS; evaluates various aspects of PD including non-motor and motor experiences of daily living and motor complications. The MDS-UPDRS consists of four sections: Part I (Non-Motor Aspects of Experiences of Daily Living), Part II (Motor Aspects of Experiences of Daily Living), Part III (Motor Examination), Part IV (Motor Complications)
  - iv. **Kinesia ONE Motor Tasks:** the task-based motor assessment, Kinesia ONE, will be administered daily while subjects are at the CRC for the outpatient visit. Kinesia ONE will be performed twice on days 1 (on therapy) and 8 (off therapy), with mean scores used for data analysis. Kinesia ONE will be performed once on days 2-7 to provide interim motor data during the washout assessment.
  - v. **Modified Hoehn and Yahr Staging:** a standard scale used for describing the stage or severity of PD.
  - vi. **Modified Schwab and England ADL Scale:** assesses subjects' degree of functional independence and provides useful adjunctive information regarding changes in quality of life.
  - vii. **Clinician Global Impression of Severity (CGI-S):** On day 1 and day 8 (or the day of study exit), the study neurologist will be asked to rate their global impression of the severity of the subject's disease. This severity is rated on a scale that includes four response options from 1 "normal" to 4 "severe".
  - viii. **Clinical Global Impression of Change (CGI-C):** On day 8 (or the day of study exit), the study neurologist will be asked to rate their global impression of the change in the subject's state relative to the baseline state from the beginning of the study. This change is rated on a 7-point rating scale, ranging from very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Subjects with 'improvement' are those rated as very much improved, much improved, or minimally improved (*Terms Used in This Evidence Summary | Parkinson's Disease with End-of-Dose Motor Fluctuations*, 2017).
  - ix. **Patient Global Impression of Severity (PGI-S):** On day 1 and day 8 (or the day of study exit), the subjects will be asked to rate their global impression of their disease severity. This severity is rated on a scale that goes from 1 "normal" to 4 "severe".
  - x. **The Patient Global Impression of Change (PGI-C):** On day 8 (or the day of study exit), subjects will be asked to rate their global impression on the change of their state relative to the baseline state from the beginning of the study. This change is rated on a 7-point rating scale, ranging from very much improved, much improved, minimally improved, no change, minimally worse, much worse, or very much worse. Subjects with 'improvement' are those rated as very much improved, much improved, or minimally improved (*Terms Used in This Evidence Summary | Parkinson's Disease with End-of-Dose Motor Fluctuations*, 2017).

- xi. **Quality of Life in Essential Tremor (QUEST):** patient-reported quality of life assessment related to tremor
- xii. **EQ-5D-5L:** a brief, patient-reported health related quality of life questionnaire
- xiii. **Pain Assessment (Numerical Rating Scale):** patient-reported pain intensity on a scale of 0 (no pain at all) to 10 (the worst pain ever possible); this pain scale will be used daily to evaluate pain as subject's PD medications wear off
- xiv. **King's PD Pain Scale:** a patient-reported pain scale that evaluates the burden (global and bedside) and characterizes various types of pain in PD
- xv. **Medication review:** recorded upon admission and then optimized and recorded prior to discharge from CRC
- xvi. **Adverse events:** recorded upon admission, discharge, and at any other time during the study that the subject or investigator becomes aware of an event.
- xvii. **Autonomic testing:** blood pressure and heart rate measured sitting and at one and three minutes standing will be measured daily in the CRC
- xviii. **The Parkinson's Disease Quality of Life Questionnaire (PDQ-39): a questionnaire that** will be used to assess patient quality of life
- xix. **Unified Dyskinesia Rating Scale:** evaluates involuntary movements often associated with Parkinson's disease treatment
- xx. **Timed Tests:** subjects will be evaluated on how long it takes to stand/walk/sit and the speed of finger taps
  - a. Stand Walk Sit Test: To assess gait, subjects will be asked to stand from a seated position, walk 20 feet, turn, and return to the start point. The subject will be timed, and the number of steps taken to walk the given distance will be counted.
  - b. Finger tap: To test for hand dexterity, subjects will be asked to alternately tap two mechanical counters as fast as they can for 30 seconds with their index finger. This will be performed with each hand and the total number of counts will be tabulated.

## 6.5 Neuropsychological Test Battery

The battery of neuropsychological assessments that were completed in the original pilot trial has been updated to improve efficiency. The full neuropsychological battery will be conducted both ON (day 1) and OFF therapy (day 7). The battery is estimated to take 90 minutes to complete and includes the following:

1. **Grooved Pegboard Test:** a dexterity test assessing motor function and the cognitive domains of attention and executive function; the pegboard contains 25 holes with randomly positioned slots and pegs; pegs must be rotated to match the hole before being inserted; the test measures performance and speed; higher raw scores indicated difficulty with the task (Hovik et al., 2017).
2. **Benton Judgement of Line Orientation (JLO) – Short Form**  
Administration: a measure of visuospatial ability, determined by ability to

match presented lines to target lines of the same orientation; the 30-item test is presented in flip-book style where two lines appear at the top page and 11 lines at different angles appear at the bottom page; subjects identify the two lines on the bottom page that match with 2 lines on the top page; the two standard versions of the JLO, forms H and V, contain the same test items but are presented in different sequences; higher scores demonstrate better visuospatial ability (Spencer et al., 2013).

3. **Neuropsychological Assessment Battery – Naming (NAB – Naming):** measures visual confrontation naming and can identify aphasia; the 31-item test contains 31 color photographs of common objects; subjects have a 10-second time limit to name each object; it has two alternate forms to minimize likelihood of practice effects (Sachs et al., 2016).
4. **Delis-Kaplan Executive Function System (DKEFS) – Tower:** evaluates executive function through the spatial planning subdomain; in this task, subjects must rearrange a set of disks placed on rods to match a predetermined arrangement; there are nine different towers to be completed that range in difficulty, beginning with simple towers that require only 1–3 moves and becoming gradually more difficult, with towers requiring up to 26 moves (Yochim et al., 2009).
5. **Hopkins Verbal Learning Test – Revised (HVL-T-R):** a well-tolerated test for all levels of impairments that measures verbal learning and memory, the learning test consists of 12 nouns within three semantic groups which is used to assess acquisition and delayed recall; lower raw scores indicate difficulties with the task (Hovik et al., 2017).
6. **Delis-Kaplan Executive Function System (DKEFS)– Letter Fluency, Category Fluency, Category-switching:** tests key components of verbal fluency and semantic search strategies; Letter Fluency has three trials that each require generation of words that start with a specific letter (A, F, and S); Category Fluency has two trials that each require generation of words that belong to a specific semantic category (boys’ and animals names); Category Switching has a single trial that requires the examinee to continuously alternate between two different semantic categories (fruits and furniture) (Strong et al., 2010).
7. **Delis-Kaplan Executive Function System (DKEFS) – Color, Word, Color-Word, Color-Word Switching, Interference, Interference-Switching:** tests executive function with basic skills—such as reading—in addition to inhibition and the process of switching; there are 4 trials in this test; the color naming trial has a series of red, green, and blue squares where the subject says the names of the colors as quickly as he/she can without making mistakes; the word reading trial has a page containing the words “red,” “green,” and “blue” printed in black ink where the subject reads the words aloud as quickly as he/she can without making mistakes; the interference trial has the words “red,” “green,” and “blue” printed incongruently in red, green, or blue ink where the subject says the color of the ink in which each word is printed as quickly as he/she can without

making mistakes; the interference-switching trial has the words “red,” “green,” and “blue” written in red, green, or blue ink where half of these words are enclosed within boxes; the subject in the interference-switching trial says the color of the ink in which each word is printed (as in the interference trial), but to read the word aloud (and not name the ink color) when a word appears inside a box, as quickly as he/she can without making mistakes (Lippa & Davis, 2010).

8. **Wechsler Adult Intelligence Scale-IV (WAIS-IV) Digit Span (Digits Forward & Backward):** a measure of working memory and attention span in adults, who are asked to repeat a sequence of numbers they are read; Digit Span includes three tasks: forward, backward, and sequencing; the forward task has subjects repeat numbers spoken by the examiner; the backward task has subjects repeat numbers in the reverse order of what is presented; the sequencing task has the subject sequence numbers from the lowest to highest number; the examiner reads each number out at the rate of one number per second, but subjects have no time limit to answer (Coalson et al., 2010, p. 1). \*\*this test is administered via tablet/Q-interactive software)
9. **Symbol Digit Modalities Test (SDMT) - Oral:** a quick test assessing processing speed and divided attention; for the SDMT test, subjects are provided a sheet with nine symbols, each paired with a number on top of the page; the remainder of the page consists of a randomized, sequential assortment of these symbols where subjects verbally respond with the number that corresponds with each symbol; subjects have 90 seconds to pair numbers with shapes (Strober et al., 2020).
10. **Patient-Reported Outcomes Measurement Information System (PROMIS)-Emotional Distress-Depression and Anxiety short forms:** a short, electronic assessment subjectively measuring a patient’s emotional distress; the depression short form contains 8 items, and the anxiety short form contains 7 items; the depression short form focuses on negative mood, decrease in positive affect, information-processing deficits, negative views of the self, and negative social cognition; the anxiety short form focuses on fear, anxious misery, hyperarousal, and somatic symptoms related to arousal; higher PROMIS scores indicate more of that domain (depression/anxiety) (Cella et al., 2010).
11. **Patient-Reported Outcomes Measurement Information System (PROMIS) – Sleep Disturbance (SD) and Sleep-Related Impairment (SRI) short forms:** self-reported assessments analyzing factors such as sleep quality, alertness, and tiredness; the two 8-item short forms assess the degree of general sleep impact regardless of the underlying etiology; each item of the PROMIS SD and SRI scales is rated on a five-point scale; items are summed giving a range in raw scores from 8 to 40, with higher scores indicating greater severity of SD or SRI (Lei et al., 2020).
12. **Cambridge Neuropsychological Test Automated Battery (CANTAB) – Pattern Recognition Memory (PRM):** a short test of visual pattern recognition measuring correctness and latency; the PRM tests visual pattern

recognition memory in a two-choice forced discrimination paradigm; the subject is presented with two series of 12 visual patterns, each presented individually; in the recognition phase, the subject is required to choose between a pattern they have already seen and a novel pattern; it is scored by the number of correct responses and speed of response (Juncos-Rabadán et al., 2014).

13. **Cambridge Neuropsychological Test Automated Battery (CANTAB) – One-touch Stockings of Cambridge (OTS):** assesses executive function through testing spatial planning and working memory; this test relies on working memory in addition to spatial planning; in this task, two arrays of colored balls are displayed where the subject is tasked to choose from a series of numbered boxes, the minimum number of moves required to achieve the upper display by rearranging the lower array (Wild & Musser, 2014).
14. **Suicide Assessment Five-Step Evaluation and Triage with Columbia Suicide Severity Rating Scale (SAFE-T with C-SSRS):** assesses suicide risk through a series of simple questions, helping to identify whether someone is at risk for suicide, the severity and immediacy of that risk, and gauge the level of support that the person needs; the 7-question assessment evaluates suicidal ideation severity and suicidal behavior; any question answered with “yes” indicates that someone should seek a behavioral health referral; if any of questions 4-7 are answered with “yes,” immediate help should be sought (*Triage and Risk Identification The Columbia Lighthouse Project*, 2016). *If a potential subject endorses any suicidal ideation on the SAFE-T with C-SSRS (i.e., “yes” to any of the questions), the following actions will be taken:*
  1. *The research protocol will be discontinued.*
  2. *The study coordinator will notify the study neurologist (Dr. David Charles or his designee, determined prior to the study visit) in-person or by phone immediately. The study coordinator will also notify the neuropsychologist (Dr. Ciaran Considine) and PI (Dr. Mallory Hacker) by email.*
15. **Parkinson’s Disease Specific Psychosis Scale (PD-SPSS):** measures symptoms of psychosis induced by levodopa in PD patients; the 10-question assessment asks patient/family/both about the presence, severity, frequency, and consequences of the hallucinations (visual, auditory, olfactory) and delusions (Ondo et al., 2015).
16. **Questionnaire for Impulse Control Disorders in PD (QUIP-Rating Scale):** assesses severity of symptoms relating to impulse control disorders in PD patients; the 28-item scale, scored from 0-112, assesses four domains: sexual, gambling, buying, and eating behaviors; while also assessing the frequency of compulsive hobbyism, punting, and medication use; the cutoff

to diagnose individual impulsive-compulsive disorders (ICDs) is a score of  $\geq 6$  for gambling,  $\geq 8$  for sexual, and  $\geq 7$  for eating; the cutoff for combined ICDs is a score of  $\geq 10$ ; the cutoff for hobbyism-punding is a score of  $\geq 7$  (Evans et al., 2019).

## 6.6 Neuroimaging Assessments

[REDACTED]

Patients will be asked to fast overnight (no food or drink except for water beginning at midnight) prior to coming for the ON therapy FDG-PET scan. Parameters similar to the Alzheimer's Disease Neuroimaging Initiative (ADNI) project will be used.

### 6.6.1 PET Scanning Procedures

Subjects will be injected with 5mCi of FDG administered as a bolus in a quiet darkened room and scanned beginning 30 minutes after injection with 6 frames of 5 minutes each on a Phillips Vereos, Digital PET/CT camera which utilizes a digital photon detector element allowing for fully digital photon counting and fast time-of-flight technology, with spatial resolution of 3.99mm FWHM transverse, 4.36mm FWHM tangential (at 10cm), and 4.64mm FWHM radial (at 10cm).

During the FDG uptake period, participants will be asked to rest quietly in a dimly lit room, eyes closed, no reading or talking.

During the scan, participants will be asked to keep their eyes open (without any visual stimulation).

After fasting overnight (no food or drink except for water beginning at midnight), Day 8 (off therapy) UPDRS-III assessments will be videotaped, and subjects will subsequently (within 2 hours) be scanned with FDG-PET under the same conditions as was performed for the Day 1 scan.

### 6.6.2 PET Image Processing

Images will be reconstructed with a 256x256 FOV, 2mm in plane and corrected for attenuation using low dose CT scan. Images of FDG metabolism will be processed using SPM V.12 software (<http://www.fil.ion.ucl.ac.uk/spm/>). All images will be spatially normalized to an age appropriate FDG-PET template in Montreal Neurological Institute space (Collins et al., 1994), and smoothed with an

8 mm full width half maximum Gaussian kernel to improve the signal-to-noise ratio.

### **6.6.3 Metabolic Expression Analysis**

Spatial covariance analysis will be performed on scans using a fully automated voxel-based algorithm (<http://feinsteinneuroscience.org>) (Huang, Tang, et al., 2007; Ma et al., 2007; Mure et al., 2011; Tang et al., 2010). PDRP, PDCP, and PDTP quantification will be performed blind to on versus off medication status. Subject scores for the patterns will be Z-transformed using mean and SD of an age and gender-matched healthy control group such that the mean Z-score in controls is 0 with an SD of 1.

## **6.7 Subject Interviews**

In collaboration with the Vanderbilt Qualitative Research Core (VU-QRS), semi-structured interviews were developed to query patients about the acceptability and operational considerations of adding objective measures to the washout (Aims 1d, 2a) and conducting washouts in the outpatient setting (Aim 3b). Patient interview questions cover burden, satisfaction, practicability judgment, suggestions for improvement, and whether he/she would recommend other patients to participate in a study with similar procedures (Appendix E). Members of the QRS research team will call patients approximately 1 week after the study visit to conduct the interviews (~60 minutes).

## **6.8 Research Personnel Surveys**

A survey was developed to query research personnel on operational considerations, barriers, suggestions for improvement, recommendations for protocol modifications, additional time needed to complete objective measures, and comments made by patients during assessments (Appendix F). All research personnel involved with a subject's study visit will be emailed hyperlinks to the Redcap survey after each study visit.

## **7.0 Healthy Controls**

### **7.1 Overview**

This study will enroll 20 age-matched healthy control participants to complete the FDG-PET scan and neuropsychological test battery. Data from these healthy controls will be used to generate Z-scores for the PD-related metabolic networks that will be analyzed in the Parkinson's disease patients.

### **7.2 Inclusion Criteria**

- Aged 50-75 years

- Available to participate in the study visit and procedures.
- The subject is willing and able to provide written informed consent

### **7.3 Exclusion Criteria**

- Subjects for whom participation in the study may cause harm.
- Subjects with past brain surgery, injury, or illness that would alter brain structure or function.
- Subjects with neurological disorders (except headache).
- Subjects with significant prior exposure to radiation.
- Subjects with a history of cognitive impairment.

### **7.4 Recruitment Plan**

This study will recruit 20 healthy control subjects using the MyResearch at Vanderbilt and ResearchMatch online platforms and email notification systems. Additionally, flyers (Appendix H) will be distributed throughout the VUMC campus. All recruitment materials will provide contact information for the study coordinator and direct potential participants to an online screening survey. After completing the screening survey or discussing the study with the study coordinator, potential participants will be e-mailed a description of the study with a hyperlink to a healthy adult electronic consent form, or if preferred, participants will be mailed a paper copy of the consent form (both enclosed). The email communication will include contact information for study staff and investigators who will be available to answer questions.

#### **7.4.1 RedCap Screening Survey**

Recruitment materials will include a hyperlink and QR code that directs potential participants to a brief RedCap screening survey (Appendix I).

#### **7.4.2 Research Match**

ResearchMatch.org is a national electronic, web-based recruitment tool that was created through the Clinical & Translational Science Awards Consortium in 2009 and is maintained at Vanderbilt University. There is no cost for researchers at participating institutions in the ResearchMatch Network to use ResearchMatch for the purposes of conducting recruitment feasibility analysis or participant recruitment. The Vanderbilt IRB provides oversight for ResearchMatch as a recruitment tool and this has been documented within the ResearchMatch IRB Letter of Understanding (available upon request). However, individual requests to use ResearchMatch as a recruitment tool are required to be approved by the participating institution's IRB.

IRB approval is requested to send the following study recruitment message to potential study volunteers through ResearchMatch.org. ResearchMatch requires confirmation that this language has been IRB approved and that my direct study contact information has been removed (email/phone) before sending my study announcement through ResearchMatch to volunteers that appear to be a good match for my study.

**Contact Message Content Description:**

*Below is the study-specific announcement that will be inserted into the ResearchMatch notification regarding this study (Appendix J):*

Parkinson's disease researchers at Vanderbilt University Medical Center are recruiting healthy volunteers to participate in a study testing brain function with brain scans and cognitive testing.

To participate, you must be:

- 50 to 75 years old
- Without a history of brain surgery, illness, injury, or cognitive impairment

Participants in this study will be asked to receive:

- 1 brain scan
- Cognitive testing

Compensation for participation in this study includes:

- Up to \$115

Thank you for your consideration!

*ResearchMatch provides standard notification language (in grey) that will be received by all ResearchMatch volunteers who may be a match for a given study. My specific message for which I am seeking approval will be inserted accordingly:*

---

A research team with **VANDERBILT UNIVERSITY in NASHVILLE, TENNESSEE**, believes you might be good match for the following study:

*<Researcher's IRB approved study-specific recruitment announcement is inserted here>*

If you are interested in this study and having the research team contact you directly, please select the "Yes, I'm interested" link below. By clicking the "Yes, I'm interested" link, your contact information will be released to the research team. If you select the "No, thanks." link or do not respond to this study message, your contact information will not be released to the research team.

QUICK LINK OPTION: YES

QUICK LINK OPTION: NO

### 7.4.3 MyResearch at Vanderbilt

MyResearch is a participant repository recruitment tool available to Vanderbilt researchers that reaches over 18,000 My Health at Vanderbilt users that have previously confirmed they would like to be contacted directly for research. This repository provides investigators a forum for advertising for volunteers for a specific study. Email notifications are limited to IRB approved language, describe study specifics and provide contact information. To utilize this initiative, investigators complete a MyResearch Access Request that is reviewed to ensure the recruitment tool and requested number of contacts are appropriate.

IRB approval is requested to send the following study recruitment message to potential study volunteers through MyResearch at Vanderbilt. MyResearch asks for confirmation that this language has been IRB approved before sending my study announcement through MyResearch to volunteers.

#### Contact Message Content Description:

*Below is the study-specific announcement that will be inserted into the MyResearch notification regarding this study (Appendix K):*

Parkinson's disease researchers at Vanderbilt University Medical Center are recruiting healthy volunteers to participate in a study testing brain function with brain scans and cognitive testing.

To participate, you must be:

- 50-75 years old
- Without a history of brain surgery, illness, injury, or cognitive impairment

Participants in this study will be asked to receive:

- 1 brain scan

- Cognitive testing

Compensation for participation in this study includes:

- Up to \$115

Thank you for your consideration!

If you are interested in learning more about participating in this study, please complete the brief screening survey at the link below:

[REDACTED]

Thank you for your consideration!

*MyResearch provides standard notification language (in grey) that will be received by all volunteers who are contacted for the study. My specific message for which I am seeking approval will be inserted accordingly:*

---

Hello,

In a survey sent to My Health at Vanderbilt users you agreed to be contacted directly to receive information about research studies. Below is a description of a research study at Vanderbilt that could possibly match your health profile.

*<Researcher's IRB approved study-specific  
recruitment announcement is inserted here>*

Please feel free to contact us anytime with questions or comments at [MyResearch@Vanderbilt.edu](mailto:MyResearch@Vanderbilt.edu), or call toll free at 855.514.7001.

Thank you,  
The MyResearch Team  
Vanderbilt Institute for Clinical and Translational Research

## 7.5 Study Procedures

After providing informed consent, control participants will complete a remote MoCA assessment via Zoom to screen out individuals with cognitive impairment (Full MoCA

via Audio-Visual Conference, <https://www.mocatest.org/remote-moca-testing/>). Control participants with remote MoCA scores of  $\leq 25$  will be excluded from the study.

Control participants will come in for a half-day study visit. They will be asked to fast overnight beginning at midnight (no food or drink except for water) the day before the study visit. An FDG-PET scan will be completed following the same procedures as described for the Parkinson's disease cohort (**6.6.1 PET Scanning Procedures**). The same neuropsychological test battery performed for the PD cohort (**6.5 Neuropsychological Test Battery**) will also be conducted for control participants.

<b>Table 3: Healthy Control Participant Procedures</b>		
<b>Evaluation/Procedure</b>	<b>Pre-Visit</b>	<b>Study Visit</b>
REDCap Screening Survey	X	
Informed Consent	X	
Remote MoCA Screening	X	
FDG-PET Scan		X
Demographics		X
Neuropsychological Test Battery		X
Participant Reimbursement Form		X

## 8.0 Data Management

Data will be collected and recorded electronically using REDCap case report forms (eCRFs). eCRFs will be filed by a de-identified subject ID. Each REDcap instrument includes a description of how the form is to be completed and scored as well as when and where it should be completed. The study coordinator will ensure that physicians have forms available at all times. After the physician has completed a subject evaluation, they will review forms for accuracy, legitimacy, and completeness of responses. Original forms will be maintained by study staff and filed by subject identification number. The Principal Investigator will directly oversee all data collection. Data from these CRFs will be entered into an online Research Electronic Data Capture (REDCap) database by the study coordinator and the database manager.

## 9.0 Risks

This project is a onetime clinical assessment of a cohort of early-stage Parkinson's disease patients. The study does not confer risks associated with an investigational drug or device and is not focused on vulnerable populations.

Subjects will be exposed to unique research-related risks:

This study requires a dopaminergic medication withdrawal, and, therefore, participants could be at risk of a dopaminergic withdrawal syndrome [similar to Neuroleptic

Malignant Syndrome (NMS) type reaction]. This is an extremely rare, potentially life-threatening condition characterized by altered mental status, fever, rigidity, and autonomic instability. Subject withdrawal from dopaminergic medication (i.e., washout) will occur at the outpatient study visit. Rapid reduction of dopaminergic drugs can induce an NMS type reaction in PD patients (Phibbs & David Charles, 2011). All participants will receive daily examination and autonomic testing to monitor for signs of the development of this rare reaction. There were no episodes of NMS type reactions in this cohort during our pilot study (there were 147 total week-long washout experiences without an episode).

This study will conduct two  $^{18}\text{F}$ -fluorodeoxyglucose-positron electron tomography/computerized tomography (FDG-PET/CT) scans per subject, with potential risks including the administration of  $^{18}\text{F}$ -FDG and the physical discomfort during PET scanning.

*Radiation exposure:* Participants are exposed to radiation from  $^{18}\text{F}$ -FDG and the attenuation CT scan. Subjects will receive an effective dose = 9.8 mSv, which is equal to 40 months (3.2 years) of the background radiation from natural surroundings. This is well below the FDA/NRC standard limits for annual or research-related exposure, and large-scale studies of the long-term risk of radiation exposure (within FDA limits) have shown no increase in cancer rates associated with this amount of exposure (Ernst et al., 1998). However, because radiation exposure is cumulative, potential subjects who have received radiation exposure as part of other recent research studies, and individuals who work around radiation will be excluded from the PET/CT sub-study. We note that because all female participants are post-menopausal, there will be no risk to a fetus as part of this study. To reduce patients' radiation exposure, frequent voiding will be encouraged after FDG administration. Specifically, a 90-minute voiding interval is anticipated and will be made feasible by asking the subjects to drink a 12-16 oz beverage each hour for three hours after FDG administration. Furthermore, subjects will be encouraged to drink water 10 minutes prior to injection of FDG in order to avoid dehydration and increase post-injection voiding.

*Discomforts associated with PET scanning:* Discomforts associated with PET studies include having to remain still for 30 minutes. During scanning, incidental findings could arise, which could cause psychological stress to the participants. Participants may also feel hungry because they are not allowed to eat overnight as part of the  $^{18}\text{F}$ -FDG PET protocol.

## **10.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others**

Adverse events will be collected and reported in full compliance with the law in order to protect the safety of subjects.

An **adverse event (AE)** is any untoward medical occurrence in a subject during participation in the clinical study or with use of the experimental agent being studied. An adverse finding can include a sign, symptom, abnormal assessment (laboratory test value, vital signs, electrocardiogram finding, etc.), or any combination of these.

A **serious adverse event (SAE)** is any adverse event that results in one or more of the following outcomes:

- Death
- A life-threatening event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- An important medical event based upon appropriate medical judgment

### **10.1 Adverse Event Classification**

AEs will be labeled according to severity, which is based on their impact on the patient. An AE will be termed “mild” if it does not have a major impact on the patient, “moderate” if it causes the patient some minor inconvenience, and “severe” if it causes a substantial disruption to the patient’s well-being.

### **10.2 Adverse Event Collection**

The investigators and study coordinator will routinely assess if any adverse events occur during the study period. Adverse events will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA).

### **10.3 Reporting of Adverse Effects**

The incidence of adverse events that occur in each study group will be captured and summarized. Serious adverse events will be reported to the IRB and FDA as required and also to the MSM within three working days for evaluation of the event.

### **10.4 Intervention in the Event of Adverse Effects**

At outpatient CRC visits, daily safety and neurological assessments will be conducted by the neurologist and study personnel. Nursing staff at Vanderbilt’s Clinical Research Center are well-versed in evaluating autonomic function and dysfunction and will monitor each participant’s autonomic function daily. Outside of the CRC setting, participants will stay at a hotel 0.7 mi from VUMC. All subjects will be provided with a computer tablet for a HIPAA-compliant telehealth visit with the study neurologist available 24/7. If additional medical care is needed, an in-person visit by a nurse practitioner who will work in conjunction with the study neurologist will be available to all participants (7 days/week; 7am-7pm). In the unlikely event that emergent care is needed, participants will be transported via ambulance to VUMC’s emergency department. AEs will be evaluated by the study Medical Safety Monitor

in real-time. Should subjects experience an adverse event as a result of this study, they will receive reasonable, immediate, and necessary medical care for this event at VUMC at no cost.

### **10.5 Independent Medical Safety Monitor**

This project is a onetime clinical assessment of a cohort of early-stage Parkinson's disease patients. The study does not confer risks associated with an investigational drug or device and is not focused on vulnerable populations. Therefore, according to NIH policy, a Data and Safety Monitoring Plan is not required.

However, due to the potential risk of a rare dopaminergic withdrawal reaction similar to neuroleptic malignant syndrome (Phibbs & David Charles, 2011), the study will have the following independent safety monitoring and reporting plan for unexpected adverse effects:

An independent, non-conflicted Medical Safety Monitor (MSM) will provide safety oversight for this study. Responsibilities for the MSM will include ongoing monitoring of reports of serious adverse events in real-time to ensure good clinical practice and to identify safety concerns quickly. The MSM may impart protocol modifications to lessen the occurrence of future serious adverse events. The MSM will prepare regular biannual reports concerning serious adverse events for submission to the PI. Additional reporting to the IRB will occur in compliance with their respective regulatory requirements, as appropriate. The MSM will also be responsible for making recommendations to the NIH, PI, and co-investigators with regards to study continuation, modification, or conclusion.

The MSM for this study will be Amy Brown, MD (Assistant Professor of Neurology, Vanderbilt University Medical Center). Dr. Brown does not have any potential conflicts of interests, is not associated with this research project, and thus works independently of the PI, Dr. Mallory Hacker. Dr. Brown is qualified to review the patient safety data generated by the study because of her extensive experience in the area of medical and surgical management of Parkinson's disease.

## **11.0 Study Withdrawal/Discontinuation**

Subjects may withdraw from the study at any time. Subjects may withdraw their consent to participate at any time. To do so, the subject should contact the study coordinator or principal investigator.

## **12.0 Statistical Considerations**

### **12.1 Sample Size Determination**

A sample size of 20 patients was selected to maximize available funds to enhance the value of information attained from this feasibility study. **Aim 1b, 2b:** N=20 will allow

constructing two-sided 90% confidence intervals (CIs) with a width of 0.39 assuming SD=1 (standardized effect size).

### **12.2 Statistical Analysis Plan, Aim 1**

To align with this feasibility study's scope, estimates of mean change in network expression (PDRP, PDCP, PDTP) from day 1 (on therapy) to day 8 (off therapy) and their CIs will be reported (Aim 1a). Aim 1b will be summarized with descriptive statistics including point estimates and measures of precision for each network in both on and off treatment conditions. Continuous clinical and demographic data of patients will be summarized with means, SDs, and ranges. Categorical data will be presented as percentages and frequencies. Before versus after washout expression level change will be analyzed with analysis of variance (ANOVA) or linear mixed-effects models (LMM) to quantify such effect sizes. Relationships between continuous metabolic network scores and respective motor (on & off therapy) and neuropsychological (executive function, attention, memory) assessments will be visualized with scatterplots (Aim 1c). Spearman's rho will report the direction and magnitude of correlation. Due to this study's exploratory nature, no correlation p-values or formal hypothesis testing will be reported. Missing data and drop-out will be descriptively reported (Aim 1d). Missing data will be analyzed using a hierarchical cluster analysis to measure the similarity patterns of missingness between the variables.

### **12.3 Statistical Analysis Plan, Aim 2**

Aim 2a will be reported similar to Aim 1c. Point estimates and CIs for measures of bradykinesia, tremor, and dyskinesia will be reported for both wearable biosensors (Aim 2b). Scatterplots will be used to visualize relationships between biosensor scores and respective clinical assessments collected during the washout (Aim 2c). Spearman's rho will be used to report the direction and magnitude of correlation. Due to the exploratory nature of this study, p-values for correlations will not be reported.

### **12.4 Statistical Analysis Plan, Aim 3**

Aim 3a will report adverse events. Aim 3b will be reported similar to Aims 1c and 2a.

### **12.5 Qualitative Analysis**

Patients will be qualitatively interviewed for Aims 1c, 2a, and 3b. VU-QRC will perform coding and analysis of the interview transcripts. Qualitative analysis will occur in three interrelated phases: 1) individual quotes will be isolated in the transcripts; 2) a hierarchical coding system will be developed to organize the quotations in relationship to the study questions and to capture the full range and depth of participant response; and 3) the structure, frequency, and interrelationships of the coded quotes will be used to develop an integrative theoretical framework of how well the FDG-PET scans (Aim 1c) and wearable devices (Aim 2a) were tolerated during the outpatient washout assessment (Aim 3b). The hierarchical coding system will be developed based on a preliminary

review of the transcripts to align with the feasibility objectives of the proposed study. Each major category will be subdivided, and the subcategories will be further expanded to describe the information related to the study question. Coding will be done by two trained research assistants. They will be trained to code on a selected transcript. After this, discrepancies in coding will be resolved by an additional team of trained coders. The analysis will begin by reviewing simple frequencies of codes and will proceed towards a theoretical framework. The process includes both inductive analysis (theory to fact) and deductive analysis (fact to theory). The resulting framework will be communicated using diagrammatic models supported by a narrative text. The text will incorporate direct quotation from patients and research personnel to illustrate and communicate important constructs and relationships. Management of transcripts, quotations, and codes will be done using Microsoft Excel 2016 and SPSS version 25.0.

### 13.0 Confidentiality and Record Retention

The privacy of study participants will be maintained in full compliance with the law. Case report forms will be identified by a unique subject code that does not contain identifiable information. Records will be kept in a locked box in a room that is kept locked when not in use. Following the six-year record retention period after conclusion of the study, records will be promptly and efficiently destroyed.

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## 15.0 Amendments

### 15.1 Amendment #1 Date of IRB Approval 03/16/2020

This amendment requests increasing the sample size from 12 to 15 participants to enhance the value of information gained from this feasibility study.

### 15.2 Amendment #2 Date of IRB Approval 07/22/2020

This amendment revises this consent form to include disclosure statements requested by the study sponsor (Department of Defense).

### 15.3 Amendment #3 Date of IRB Approval 07/30/2020

This amendment requests increasing the sample size from 15 to 20 participants to enhance the value of information gained from this feasibility study.

### 15.4 Amendment #4 Date of IRB Approval: 01/28/2021

This amendment added funding source 1K01AG066971-01A1.

### 15.5 Amendment #5 Date of IRB Approval: 03/10/2021

This amendment adds electronic informed consent, adds a new sub-aim, updates the neuropsychological assessments, removes language concerning contrast medium for the CT scan (previously included by error; CT is for attenuation only), provides the moderator guide and questions for the patient interviews (Appendix E), and provides the research personnel survey (Appendix F). The consent form has been updated to reflect the aforementioned protocol changes.

### 15.6 Amendment #6 Date of IRB Approval: 06/20/2021

This amendment updated recruitment flyers to include current study coordinator contact information.

### 15.7 Amendment #7 Date of IRB Approval: 09/21/2021

This amendment revised the protocol and ICD to enhance clarity of study procedures, added additional recruitment flyers, added a patient information document regarding the PKG watch (Appendix G), adds healthy controls (n=20) to the study, including recruitment flyers (Appendix H), REDCap Screening Survey (Appendix I), Research Match Announcement (Appendix J), and MRAV Announcement (Appendix K).

### 15.8 Amendment #8 Date of IRB Approval: 11/19/2021

This amendment adds recruitment cards (Appendix L) and revises the pre-screening form.

**15.9 Amendment #9****Date of IRB Approval: 02/22/2022**

This amendment revised the protocol, ICD, and eConsent to enhance clarity on the screening visit, medication instructions (corrected to align with Vanderbilt's current procedures), and the medication optimization visit. This amendment also includes a revised patient interview (Appendix E).

**15.10 Amendment #10****Date of IRB Approval: 04/22/2022**

This amendment updates questions in the research personnel survey (Appendix F) and the patient interview (Appendix E), added new recruitment announcement (Appendix M), and adjusts the CGI and PGI severity scales used.

**15.11 Amendment #11****Date of IRB Approval: 07/29/2022**

This amendment changes our Medical Safety Monitor (MSM), adds a backup neurologist, and revises the protocol, ICD, and eConsent to remove tasks that will not be performed, add a timeline between the screening visit and washout period, and add concise language to clear up confusion with enrollment inclusion/exclusion criteria. This amendment also includes new recruitment material.

**15.12 Amendment #12****Date of IRB Approval: 10/18/2023**

This amendment revised the Procedures Schedule allowing Coordinators to complete the MDS-UPDRS & UPDRS I, II, IV and the Schwab and England Evaluation. This amendment also revises the eligibility criteria to clarify ambiguity regarding stable response to dopaminergic medications.

**15.13 Amendment #13****Date of IRB Approval: 04/01/2024**

This amendment adds radio as a method of recruitment, and the 15-second radio script is included (Appendix O). This amendment also clarifies study instruments used, per the protocol. Lastly, this amendment revises the eligibility criteria to clarify ambiguity.

**15.14 Amendment #14****Date of IRB Approval: 04/10/2024**

This amendment revises the radio language to adhere to FCC requirements.

**15.15 Amendment #15****Date of IRB Approval: Pending**

This amendment adjusts the point of contact from [REDACTED]. It also clarifies the new version and date of changes in the footer to account for the updated contact information.