1. Protocol Title

Effect of GOCOVRI on Quantity and Quality of Gait in Parkinson's disease

2. Objectives

Aim I: Investigate the effect of GOCOVRI™ on activity levels in people with Parkinson's disease (PD) and Levodopa induced dyskinesia (LID)

Hypothesis I: We hypothesize that GOCOVRI™ will result in an increase of daily activity due to improvement in LID symptoms.

Primary outcome measures: Total number of steps and turns per day

Aim II: Investigate the effect of GOCOVRI™ on comprehensive measures of gait and balance quality in people with PD with LID

Hypothesis II: We hypothesize GOCOVRI™ may improve discrete characteristics of gait and balance that is evident even within the first hour of the day walking.

3. Background

Levodopa induced dyskinesia (LID) is a symptom of Parkinson's disease for which there are limited treatment options. LID leads to reduced quality of life, increased caregiver burden and an increased risk of falls (Rascol et al., 2015, Chapuis et al., 2005). GOCOVRI™ is an extended release capsule prescription medication shown to reduce LID in people with PD (Pahwa et al., 2017, Pahwa et al., 2018). However, a number of studies have identified an increase in falls in those on the active medication study arm but not the placebo arm (13% increase in active and 7% in placebo) (Pahwa et al., 2017). In order to understand this increase in falls, comprehensive measurements of quantity of activity (gait measured in the home environment) and quality of activity (comprehensive gait characteristics that may increase risk of falls) need to be assessed in participants taking GOCOVRI™. In addition, the evidence for the effect of GOCOVRI™ on gait and balance in PD is limited (Smulders et al., 2016).

4. Study Design

This is an open label study in which the participants with PD will know they are taking medication and the experimenters will know which study visits and 7 days of monitoring are baseline, prior to taking GOCOVRI, and which study visits and 7 days of monitoring are after taking maximum dose of GOCOVRI after 5 weeks. Subjects will be given Amantadine extended release for purposes of this study.

5. Study Population

a. Number of Subjects

A total of 12 people with PD and LID will be recruited to the study. Primarily, participants are to be recruited from the OHSU Movement Disorders Clinic by Dr. Hiller. In addition to this, we have a laboratory database of PD volunteers for which we have information on LID from previous studies and for which Dr. Hiller will assist in reviewing. Finally, neurologists in the OHSU Movement Disorders Clinics will be alerted to the study by Dr. Hiller so they can refer suitable participants.

b. Inclusion and Exclusion Criteria

*Subjects will be **included** in the study if they have:*

1) a confirmed diagnosis of idiopathic Parkinson's disease by a movement disorders specialist and in accordance with the UK Brain Bank Criteria, 2) Hoehn & Yahr scores of II-IV, 3) aged between 50-85 years

old, 4) subjective report of experiencing at least 1h/day (two, half-hour periods) of ON time with troublesome LID, 5) ambulation with or without aids (e.g., walker or cane), 6) ≥30 days of a stable regimen of anti-Parkinson medications that includes a levodopa dose administered ≥3 times daily 7) a stable dose of levodopa throughout the study and 8) no amantadine for a minimum of 30 days prior to enrollment in to the study.

*Subjects will be **excluded** from the study if they have*: 1) other medical conditions which significantly affect mobility e.g., neurological/musculoskeletal disorders, 2) orthostatic hypotension at screening (defined as a drop of ≥20mm HG systolic and ≥10mm HG diastolic at 2 or 5 minutes of quiet standing after 5 minutes of supine rest), 3) a major psychotic disorder, 4) contraindication to GOCOVRI™ at time of screening, especially renal impairment estimated by glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2) as impaired renal function can increase the chances of adverse reactions to the study drug, 5) mild to severe cognitive impairment as measured by Montreal Cognitive Assessment (MoCA) score ≤ 23, 6) concurrent use of immediate release amantadine, and 7) are pregnant or plan to become pregnant.

c. Vulnerable Populations

None. Gender, ethnic origin, and minority status are neither inclusion nor exclusion criteria. Women and minorities will be included in this study. Children under the age of 18 will be excluded from this study. Subjects will not have mild to severe cognitive impairment.

Female participants of childbearing age will need to have a urine pregnancy test to screen for pregnancy before being given study drug, and will be asked to commit to contraception for the duration of the study. If a participant inadvertently becomes pregnant during the study, the study drug will be stopped immediately and they will be removed from the study.

d. Setting

Prior to the first study visit, participants will go to the OHSU outpatient Laboratory or a local laboratory for an assessment of renal function (unless this test has previously been completed with in the 30 days prior to the first study visit). If renal impairment (estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2) is found, subjects will be excluded from the study as impaired renal function can increase the chances of adverse reactions to the study drug.

Participants will have virtual study visits remotely using Zoom: at baseline (week 1; 4 visits) and the other after 4 weeks of GOCOVRI™ (week 6, after 2 weeks at their maximum dose; 4 visits). During the baseline period (week 1) and the last week of maximum dose GOCOVRI (week 5), the participants will wear a SmartSocks sensor system for up to 10 hours of their total waking time, and a Phillips Actiwatch 24 hours/day for 7 consecutive days. All visits will occur remotely using Zoom and will last approximately 1 hour. All participants will be tested in their 'ON' medication state.

e. Recruitment Methods

Primarily, participants are to be recruited from the OHSU Movement Disorders Clinic by Dr. Hiller. In addition to this, we have a laboratory database of PD volunteers for which we have information on LID from previous studies (IRB# 7797) and for which Dr. Hiller will assist in reviewing. Finally, neurologists in the OHSU Movement Disorders Clinics will be alerted to the study by Dr. Hiller so they can refer suitable participants.

Compensation. Participants will receive $25 for baseline assessments and also after final assessments, and $75 for each full week of wearing the SmartSocks sensor system and Actiwatch monitor ($150 for two full weeks) in-home, and an additional $25 incentive for completing study in full. Payment will be pro-rated for each day completed ($11 per day for wearing the sensors). In total: $225 per subject. For ease of payment to the subjects after completing the week of wearing the sensors, we will give each subject a debit card (called a ClinCard) during the study. We will load the appropriate amount of money on the card after each study visit and completion of in-home mobility monitoring.

f. Consent Process

For subjects who wish to participate, an informed consent will be presented and explained to the subjects through a remote meeting and will sign a hard copy consent form. The consent form will be dropped off or mailed to the study subject. A study team member will review the consent form with the subject via Zoom or a phone call and sign a hard copy.The informed consent explains the nature of the study and the possible risks and benefit of the experiment, as well as HIPAA privacy information. This form also informs the subjects that they may withdraw from testing at any time without penalty. Subjects will be given ample opportunity to read, ask questions, and when satisfied, document their consent to participate by signing the informed consent form.

Non-English Speaking Subjects

We plan to recruit non-English speaking subjects. We will include a short form in the person's native language and have an interpreter present during recruitment and the test session translate and ensure the person fully understand the study and their role in the study. We have included the Spanish short-consent form in our study documents, as this is the most likely foreign language. However, we can add other languages if there is the potential of recruiting someone with a different primary language.

6. Procedures Involved

Subjects will provide informed consent during a screening visit, and then will be screened for orthostatic hypotension (by blood pressure test listed in exclusions above), renal function (if not already available) and a urinary pregnancy test (female participants of childbearing age ONLY). To rule out potential participants with orthostatic hypotension for people who don't already know they have this condition, we will send an automatic blood-pressure cuff to participant and blood pressure will be checked during start of first virtual visit. We will explain how to place the cuff on arm and do the test themselves or with assistance of caregiver. Participants will take blood pressure while lying down after 5 minutes and then stand and repeat measurements at 2 and 5 minutes of standing. Orthostatic hypotension is defined as a drop of ≥20mm HG systolic and ≥10mm HG diastolic at 2 or 5 minutes of quiet standing after 5 minutes of supine rest. After confirming eligibility for study, the virtual visit will completed during which, subjects will be taught how to wear and charge the inertial sensors at home (SmartSocks sensor system) on the feet and belt for 7 days, as well as an activity watch (Phillips Actiwatch) worn on one wrist. They will be instructed on how to return the sensors by mail in a prepaid postal service box provided by the study. At the first study visit, subjects will then have a neurological exam to assess LID and PD severity and exclusion/inclusion criteria, followed by balance assessments using body-worn inertial sensors. After a total of 4 weeks on medication, subjects will repeat clinical, orthostatic hypotension test, and gait testing during the second study visit, followed by another week of daily-life monitoring (**Figure 1**).

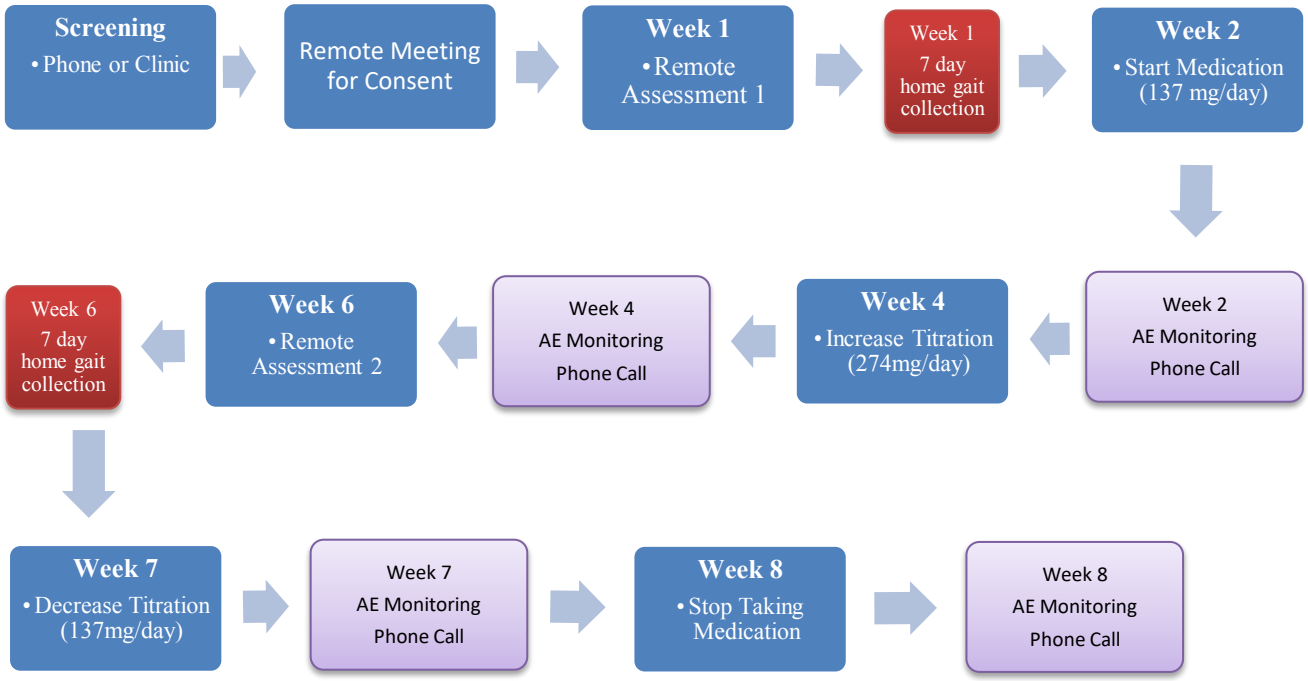

Figure 1. Study protocol. Participants will initially be screened followed by a balance laboratory visit and 7-day gait assessment in the home. Following a 4-week titration to maximum dose, participants will take GOCOVRI™ at the maximum dose for 2 weeks before a second assessment and set of daily-life gait collection (week 6). A two-week titration to reduce medication intake will then follow until week 8.

Drug dosage

We will use an open-label trial design in which 12 participants will be given GOCOVRI™ provided by Adamas Pharmaceuticals, Inc. Dr. Amie Hiller (PI) will sign the medication order and prescribe the doses and the medication will be administered by the OHSU research pharmacy. A research coordinator will pick up the medication from the pharmacy prior to the baseline study visit to give to the subject with instructions about when to start taking the medication and how to increase dose over time. The drug will be administered orally once daily before bedtime. A forced four-week titration will be prescribed with the active treatment arm receiving 137mg/day (2 pills) during weeks 2 and 3 which will be increased to 274mg/day (4 pills; unless dyskinesia is relieved by the lower dose; then will stay at initial dose – increase will be based on clinical response to the lower dose) for weeks 4, 5 and 6 (see Figure 1). Participants will be contacted by a research assistant after the dosage is increased to ensure there are no issues, which if reported will be followed up by Dr. Hiller. In addition, participants will be encouraged to call a study team member if they are having difficulty tolerating the medication at any point during the study. If the subjects experience side-effects at higher dose, then they will be asked to continue at the 137mg/day until after the second assessment, then tapered off in a single week. If patients wished to continue on GOCOVRI we will reach out to their provider and share their interest in wanting to remain on the medication. It will be explained to patients that they will only be guaranteed to receive GOCOVRI during the course of the study and future use will be at their and their provider's discretion with cost as determined by their individual insurance and pharmacy providers.

Data collection

Prior to the first study visit, participants will go to the OHSU outpatient Laboratory or a local laboratory who will assess renal function (unless this test has previously been completed with in the 30 days prior

to the first study visit). If renal impairment (estimated glomerular filtration rate (eGFR) < 50 ml/min/1.73 m^2) is found, subjects will be excluded from the study, and the subjects will be informed of the results and the results will be sent to their primary care physician. Subjects will complete a blood pressure test for orthostatic hypotension (OH). If OH is found, the person will be excluded from the study.

Participants will attend three study assessments remotely using Zoom at baseline (week 1) and after 4 weeks of GOCOVRI™ (week 6, after 2 weeks at their maximum dose). All participants will be tested in their 'ON' medication state.

Clinical characteristics

PD subjective and objective disease severity will be assessed using the MDS-UPDRS parts I-III. LID severity will be assessed using the MDS-UPDRS part IV, and the Unified Dyskinesia Rating Scale (UDysRS). The mAIMS testing will occur during 60 seconds of standing with feet together while doing serial subtraction by 3s, and without the dual task. During this mAIMS and UDysRS motor testing subjects will wear 3 Opal inertial sensors (sternum and feet) to explore whether it is possible to measure dyskinesia quantitatively in a way that correlates with the mAIMS and UDysRS assessments. Levels of physical activity will be assessed with the International Physical Activity Questionnaire. The Weighted Functional Comorbidity Index is a patient-reported assessment to relate comorbilities to physical function. The PDQ-39 Questionnaire will be given before and after GOCOVRI as a patient-reported outcome of quality of life. Orthostatic hypotension will be measured at the first study visit both objectively (blood pressure taken while lying supine for 5 minutes, followed by standing at 1, 3 and 5 minutes) and subjectively using the patient-oriented, Orthostatic Hypotension Questionnaire (Kaufmann et al., 2012).

Balance assessment

Balance characteristics will be collected using three inertial sensors (Opal, APDM, Inc.) during sixty-second quiet stance trials (with and without a cognitive dual-task).

Videos/photographs. During the clinical assessment and balance testing the participant will be videoed (with audio) using Zoom. We will use the videos to aid in data analysis, for educational materials, research presentations, and publications. The participant will not be able to view the images before use and they may be recognizable in the images.

Daily-life data collection

In order to collect physical activity and gait data in the home environment, data collection will take place for 7 days following the baseline remote assessments at week 1 and the second remote asssessments at week 6. Overall activity levels for the 7 days will be continuously collected (24h/day) via a single, wrist-worn monitor (**Figure 2A, Phillips Actiwatch**). The wrist monitor will aid in evaluating early morning activity levels, in case subjects do not immediately put on the sock sensors.

To determine gait quantity and quality during the day, patients will be asked to wear a SmartSocks sensor system (**Figures 2B & 2C**) for 7 consecutive days. The SmartSocks system consists of one SmartSock sensor on each foot, and a single Opal sensor around the waist. The SmartSocks and the waist Opal will be worn for at least 8 hours/day. At night, the sensors will be removed and placed in a docking station to charge. At the baseline visit, participants will learn how to wear and charge the SmartSocks system. Subjects will be asked to charge the sensors in the bedroom and to put them on within 10 minutes of waking in order to collect gait data from the first hour of their day, prior to taking their first dose of

levodopa. After finishing the 7 days, subjects will mail back the sensors and docking station using pre-paid US mailing boxes or the sensors will be picked up by a research assistant. When participants have reached the maximum dose of GOCOVRI at week 4, a SmartSocks sensor system will be sent back to the participant by US mail or dropped off by a research assistant for a second week of daily-life mobility monitoring. Participants will be asked to repeat the same procedures for this second week (**Figure 1**). Data will be uploaded to an OHSU approved secure server upon return of the devices. After return of the sensors the integrity of the data will be assessment and if there is less than 5h/day an 5 days of data, then subjects will be asked to repeat the 1 week of wearing the sensors.

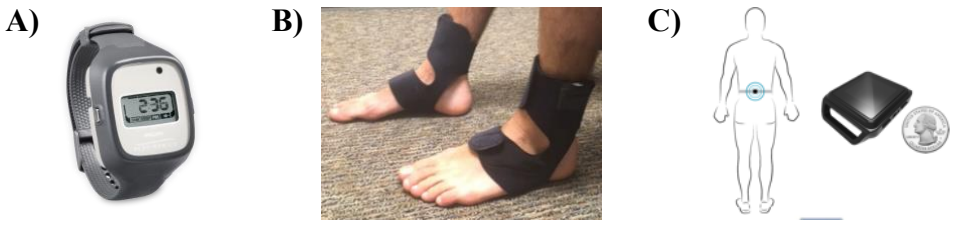

Figure 2. Sensors for daily-life data collection**: A)** Phillips Actiwatch 2 for activity levels and **B)** SmartSocks for daily-life data collection / **C)** Lumbar Opal for activity quality.

In addition to wearing the sensors for a week, subjects will also complete two diaries. First, the Hauser diary to document motor fluctuations. The Hauser diary asks patients to document their motor status every 30 minutes (either ON, ON with troublesome dyskinesia's, OFF or asleep). In order to ensure validity of Hauser diary entries, participants will be asked to complete ratings of the diary alongside a clinician or researcher during the baseline study visit. This will make sure the participants know how to correctly enter scores in the diary. Second, participants will be asked to complete a medication diary in which they document which Parkinson's medications have been taken, dosage and time of day administered. Participants will be asked to return their diaries with the sensors following the home gait seven-day assessments. Participants will also complete a technology use survey about ease of use of the sensors. Lastly, the participant and clinician will evaluate the participant's improvement post intervention by using the Patient Global Impression of Change Scale (PGIC) and Clinician Global Impression of Change Scale (CGIC).

Study Timeline

A timeline of the study is shown in **Table 1**. The study is expected to be completed within one year, including data collection, data processing and data analysis.

	Q1			Q2			Q3			Q4		
	1	2	3	4	5	6	7	8	9	10	11	12
IRB Approval	■											
Enrollment		■	■	■	■	■						
Baseline Assessment		■	■	■	■	■	■					
Home Assessment 1		■	■	■	■	■	■	■				
Final Assessment 2			■	■	■	■	■	■	■			
Home Assessment 2			■	■	■	■	■	■	■			
Data Processing					■	■	■	■	■	■		
Data Analysis										■	■	■
Manuscript Submission												■

Table 1. Study timeline.

7. Data and Specimens

a. Handling of Data and Specimens

All paper and electronic data collection forms, videos from the balance sessions, and output of Mobility Lab system and Actiwatch will be coded and not use the subject's name or other PHI in the subject ID. All subject-identifying information will be uploaded immediately after test session (Mobility Lab system) or when returned after wearing sensors/Actiwatch at home, to be stored and managed securely on our laboratory database, located on an OHSU-approved secure server. Subject confidentiality will be maintained in accordance with HIPAA regulations. Only individuals who are specifically authorized to view PHI by the investigator will have access to information that could be used to identify the subjects. Data will be stored at minimum for five years after the final publication related this project, and at maximum, indefinitely, if subjects also sign our Balance Disorders Laboratory Data Repository consent form (eIRB# 7997).

b. Sharing of Results with Subjects

There is no plan to share results with the subjects, aside from availability of final published manuscripts.

c. Data and Specimen Banking

If subjects also sign our Balance Disorders Laboratory Data Repository consent form (eIRB# 7997), then their data will be stored indefinitely in the repository (located on secure OHSU server).

8. Data Analysis

Aim I: We will collect a number of metrics related to activity level (such as, percentage of the day spent active, number of steps per day/hour, number of turns per day/hour). In addition, we will collect metrics related to the quality of gait and balance (such as mean and variability of: stride length, percentage of time spent in double support, foot strike angle, turn angle, turn velocity). We will undertake analyses to determine which of our metrics are significantly different between Week 1 (before GOCOVRI) and Week 6 (after GOCOVRI) groups with paired t-tests (if data appear normally distributed) or nonparametric Wilcoxon signed-rank test (data not normally distributesd). We expect to see the significant change in some of our metrics (e.g., number of turns per day, percentage of the day active, stride time variability) due to improvement in LID symptoms. This result would indicate that GOCOVRI helps increase the overall activity level in addition to improving LID symptoms.

Aim II: We will also separately examine the first hour of sensor data recording each day to see the overnight effect of GOCOVRI™ on activity and balance/gait. We will undertake analyses to determine which of our metrics are significantly different during the first hour of the day between Week 1 (before GOCOVRI) and Week 6 (after GOCOVRI) groups with paired t-tests (if data appear normally distributed) or nonparametric Wilcoxon signed-rank (data not normally distributesd). We expect to see a significant change in metrics related to activity level especially during the first hour of the day before the levodopa intake as some subject with PD may have difficulty in initiating walking during the first hour of the day. This result would indicate that GOCOVRI is also helping patients to overcome the difficulty in initially walking during the first hour of the day before the levodopa intake.

Finally, we will explore the opportunity to identify which metrics of gait and balance best relate to LID and the medication fluctuations throughout the day to further understand how LID affects mobility.

9. Privacy, Confidentiality, and Data Security

Subject privacy. Recruitment will take place over the telephone with the researcher in a private office. Consenting will occur during a remote meeting prior to the first study visit with only study team member(s) present. Likewise, during the remote visits only study team members will be present.

Data privacy. Upon consent, a subject ID# will be assigned for a subject and all data files will only have this number on it – the ID number will not contain any of the 18 HIPAA identifiers. The file containing the link between subject name and ID# will be maintained on an encrypted lab computer, in an electronic-access office, and file will only be accessible by study team members who need it. After test session, electronic data will be uploaded to our laboratory database and in a web-accessible REDCap database that is located on a secure OHSU server. Any paper files will be kept in electronic-access only lab offices.

10. Provisions to Monitor the Data to Ensure the Safety of Subjects

Unanticipated events (UPs), protocol deviations/non-compliance, and adverse event (AE) data will be collected from the time the consent form is signed until the participant completes their study participation. AEs may be volunteered spontaneously by the participant, during telephone follow-ups, or be discovered as a result of general questioning during study visits. All study team members are responsible for recording UP, AE, and SAE information.

Unanticipated events (UPs): A unanticipated event is an unexpected (in frequency or severity) occurrence that is related or possibly related to the research project and places the subject at greater risk of harm than was previously known or recognized. All study team members are responsible for monitoring for UPs and reporting to the PI in a timely fashion (3 business days). The investigator will evaluate all UPs and take appropriate action as a result. UPs that place the subject at greater risk of harm will be reported to the OHSU eIRB within 5 business days of occurrence.

Protocol Deviations and non-compliance (PVs). All study team members are responsible for conducting the study according to the protocol and periodic evaluations will be conducted by the investigator to ensure protocol adherence. Major protocol deviations/non-compliance will be reported to the OHSU eIRB within 5 business days. All other protocol deviations/non-compliance will be reported in aggregate at continuing review/check-in. Modifications to the protocol will be approved by the institutional review board prior to implementation by the study staff.

Adverse Events: An adverse event (AE) is any untoward medical occurrence in a participant occurs during a clinical trial which does not necessarily have a causal relationship with the treatment. An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the administration of treatment, whether or not related to the treatment (study drug or placebo). An AE could be absent at baseline, or if present, appears to worsen during the study treatment. Mild/moderate AEs that are not serious will be reported in aggregate at time of continuing review/check-in.

Serious Adverse Events (SAE). A serious adverse event is (SAE) defined as any untoward medical occurrence that at any dose results in one of the following outcomes:

- Death

- A life-threatening adverse drug experience
- Results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug event when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The PI will real-time monitor AEs/SAEs with SAEs reporting to the OHSU IRB within 5 days of the study staff learning of the event. The AE form will be used to record events.

All events will be evaluated for:

(1). Date(s) of Occurrence.

Start Date – "Start Date" is the day the AE began. If a previously recorded AE worsens, a new record should be created with a new start date. There should be no AE start date prior to the date of the informed consent. Any AE that started prior to the informed consent date belongs instead in the medical history. If an item recorded on the medical history worsens during the study, the date of the worsening is entered as an AE with the start date as the date the condition worsened. The start date is recorded to determine an AE's temporal relationship to the study intervention. For example, if an aggregate listing of AEs indicate a high number of reported fainting incidents in a study of treatment for epilepsy, the study statistician is likely to investigate the relationship between the reported events and the administration of the study treatment.

End Date – "End Date" is the day the AE resolved or the day the AE worsened. If an AE worsens, record an end date and create a new AE record with a new start date and severity.

(2). Temporality. new event or existing event

(3). Expected. anticipated or unanticipated

(4). Severity. Mild, Moderate, Severe, Life-Threatening/disabling, Death

Severity – The severity of an event is the investigator's assessment of the intensity of the AE. Severe events interrupt the participant's/subject's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating. Consequently, a change in severity may constitute a new reportable AE. Severity is not synonymous with seriousness (see full definition of SAE, above). A severe rash is not likely to be an SAE. Likewise, a severe headache is not necessarily an SAE. However, mild chest pain may result in a day's hospitalization and thus is an SAE.

(5). Relatedness to study. Unrelated, Unlikely, Probable, Possible, Definite.

Relatedness – The relationship to the study intervention is the investigator's assessment of the degree of "relatedness" of the AE to the study intervention. Before beginning a study, definitions for each of the relatedness responses should be supplied.

(6). Action taken.

With study intervention– None, study intervention interrupted, study intervention discontinued, study intervention modified.

Other actions taken– None, Non-Study Treatment Required. If treatment was required, then the corresponding treatment needs to be recorded on the Prior and Concomitant Medications CRF.

(7). Outcome. Not Recovered/Not Resolved, Recovered/Resolved, Recovered/Resolved with sequelae, . Recovering/resolving, Fatal, (f) Unknown.

The outcome of an AE may not be captured at the visit during which it was first reported, but must be captured to provide a complete picture of the event. Entering the outcome of an AE may be deferred until the AE is resolved, or the participant/subject completes the study. For AEs that have not resolved at the time of a study visit, the outcome should be marked as "unresolved" on the AE case report form.

(8). Serious Adverse Event (SAE): Yes, No

This question should only be answered YES if the AE meets at least one of the criteria listed in the General Instructions under the Serious Adverse Event heading. If an AE is serious, this provides a trigger that additional information must be provided by the investigator. The investigator then completes a serious AE form and follows reporting procedures.

Interim safety review will only take place if 3 or more Serious Adverse Events occur within six months. Otherwise, there are no other interim safety reviews planned and there are no predetermined stopping rules.

If the PI has any concern that adverse event is related to the study drug she will have a discuss with patient and study team and if event is of a significant or serious nature the study drug will be stopped. If further medical evaluation or care if needed the PI will direct this.

Conflict of Interest: A co-investigator (Fay Horak PhD) has a conflict of interest with this study. She has a financial interest in the APDM company that makes the Opal sensors utilized in this protocol. The principle investigator will ensure that Dr. Horak is not involved in determining subject eligibility, consenting or enrolling subjects, evaluating or reporting UPs, AEs, SAEs, and protocol deviations or non-compliance. Dr. Horak will not be involved in the statistical analysis of this project. The nature of this financial interest and the design of the study will be reviewed by committees at OHSU. They will put in place a plan to help ensure that this research study is not affected by the financial interest. We will disclose this conflict of interest to the participants in the informed consent form.

11. Risks and Benefits

a. Risks to Subjects

Falls. Subjects who have neurological condition that can affect gait and balance (*e.g.,* Parkinson's disease) may be at a risk of falling. During the remote test sessions, the study staff will advise that the subject have a family member available to assist them, and the balance assessments will consist of only a few standing tests.

Loss of Confidentiality. There is a minimal risk of the loss of confidentiality, however this risk will be minimized by the measures mentioned in section 9, above, to restrict access to data and keep it stored safely.

Study Drug (GOCOVRI®).
GOCOVRI may interact with other anticholinergic drugs, carbonic anhydrase inhibitors, sodium bicarbonate, alcohol, and "live" vaccines. GOCOVRI is not recommended for use during pregnancy; it may harm a fetus. GOCOVRI passes into breast milk but its effect on nursing infants is unknown. GOCOVRI may alter breast milk production or excretion.

We will be using GOCOVRI for its FDA approved indication of dyskinesias in Parkinson's disease. With a gradual withdraw of the drug there should be minimal risk for significant side effects. If after the withdraw dyskinesias are bothersome to the patient and they wish to restart GOCOVRI we will reach out to their provider and share their interest in wanting to remain on the medication. It will be explained to patients that they will only be guaranteed to receive GOCOVRI during the course of the study and future use will be at their and their provider's discretion with cost as determined by their individual insurance and pharmacy providers. Immediate release amantadine is the same active compound in a different formulation and is a very commonly used, very affordable, and usually readily accessible to most patients. Dyskinesias are generally treated for patient comfort and lack of treatment is not felt to be of short-term, serious medical risk as long as medications are not abruptly stopped.

Common side effects: The most commonly observed adverse reactions occurring at a frequency of >10% and greater than placebo in prior studies were hallucinations, dizziness, dry mouth, peripheral edema (swelling of the extremities), constipation, falls, increase in impulse control/compulsive behaviors, and dizziness on standing (orthostatic hypotension).

Less common side effects: Anxiety, (7%) insomnia (10%), abnormal dreams (5%), confusion (5%), headache (6%), nausea (5%), vomiting (3%), gait disturbance(5%), bruising (6%), urinary tract infection, changes in skin pigmentation (6%), decrease appetite (6%), blurred vision(4%), cataracts (3%), dry eyes (3%), joint swelling (3%), muscle spasms (3%), noncancerous enlargement of the prostate gland (benign prostatic hyperplasia; 6%)), dry nose (5%), and cough (3%)

Rare but serious side effects: somnolence and fatigue (4%; daytime sleepiness or episodes of falling asleep during activities that require full attention), suicidality (≤2%) and depression (6%), apathy (2 %), confusion (3%).

Neuroleptic Malignant Syndrome. Rapid withdrawal of GOCOVRI® could result in a symptom complex called neuroleptic malignant syndrome. This syndrome is a life-threatening neurological disorder. Symptoms include: high fever, sweating, unstable blood pressure, stupor, muscular rigidity, and autonomic dysfunction. Adverse event phone calls post-titration down will occur each week by a medical professional.

Alcohol. Alcohol consumption may increase the potential for central nervous system effects such as dizziness, confusion, lightheadedness, and orthostatic hypotension. The participant will be warned that alcohol consumption may increase the potential for central nervous system effects such as dizziness, confusion, lightheadedness, or a drop in blood pressure when standing. Participants will

be advised to limit alcohol use to a minimum and any participant consuming more than 2 drinks a day will be excluded from participation.

Pregnancy. Nursing an infant and pregnant women will be excluded from the study. This study may involve risks to an embryo, fetus, or nursing infant that are currently unknown. If you are sexually active and could become pregnant, you and your male partner(s) must use effective birth control or not have sex. If a participant becomes pregnant during the research study, they must tell the investigator and their PCP immediately. The study drug will be stopped immediately and subject will be removed from the study.

The drug in this study may damage sperm or be present in seminal fluid. Men should not father a child or donate sperm while in this study. If one is a sexually active male and could cause a pregnancy, one must be sure that effective birth control is used or not have sex. The study drug may involve risks to an embryo or fetus that are currently unknown. If a sexual partner becomes pregnant during the research study, they must tell the investigator and have their partner tell her PCP immediately.

b. Potential Benefits to Subjects

There is no expected direct benefit to subjects.

12. Drugs or Devices (delete if not applicable)

This is an investigator-initiated study funded through a grant from the drug manufacturer. The drug being studied is being studied for its FDA approved use for "The treatment of dyskinesias in patients with Parkinson's disease receiving levodopa-based therapy". We will follow all applicable Research Pharmacy policies and procedures and provide the research pharmacy with a manual for the study drug.

Also see the ICH-GCP guidance for a summary of investigator and sponsor responsibilities in clinical trials.

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