Clinical Outcome Assessments (COA) Qualification Program
DDT COA #000142: Virtual Motor Exam for Parkinson's Disease, Part III Estimator (VME Part III)
Letter of Intent

Section 1. Administrative Structure
Description of the submitter including, but not limited to, principal investigator(s), working group member(s), institutions, and contact information.

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Section 2. Concepts of interest for meaningful treatment benefit

a. A description of the meaningful aspect of patient experience that will represent the intended benefit of treatment (e.g., presence/severity of disease-related symptoms, limitations in performance of daily activities)

The burden of Parkinson's disease in the United States has increased substantially in the last two decades, with incident cases up 98% and prevalence increasing by 90% [1]. This is largely due to an aging population, and it is

estimated the number of people with Parkinson's disease will double by 2040 [2]. While symptomatic treatments have been used for decades, there are currently no disease modifying therapies available.

Today, drug development clinical studies rely largely on subjective in-clinic neurological exams, typically captured in a clinical rating scale such as the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), to measure disease severity and progression. To demonstrate that a potential treatment alters the course of disease progression requires a sensitive measurement of disease state. However, our ability to detect signals of effectiveness is hindered by the weak inter- and intra-rater reliability and limitations on the frequency of assessment of the current "gold-standard" primary endpoint of Parkinson's disease severity, specifically the MDS-UPDRS Part III motor exam.

b. Provide a conceptual framework for the COA(s)

To address these challenges, we have built the Virtual Motor Exam for Parkinson's disease, Part III Estimator (VME Part III) for adults with Parkinson's disease, which is administered on a wrist-worn wearable device, the Verily Study Watch. The VME Part III provides an estimate of the MDS-UPDRS Part III Total motor score, as rated by a panel of clinicians. It guides participants wearing the Study Watch through a series of up to 8 simple motor tasks. Overall, the exam takes less than 20 minutes, and can be performed in the comfort of a person's home, without the guidance of a clinician [3, 4].

Participants are able to enter a self-assessment of performance after each task. The self-assessment ratings are not used in either the training or validation of the VME Part III Estimator algorithm. These data are exploratory and will inform potential development of future algorithms.

The VME Part III allows for more frequent and at-home assessment of motor symptom severity in a real-world setting. The intention is for clinical investigators to be able to use it as an efficacy endpoint in drug development clinical studies. We recognize the importance of going beyond the UPDRS Part III to capture non-motor symptoms of Parkinson's disease, as well as the need to move from subjective to objective measurements. The VME Part III Estimate is the first in a suite of tools we plan to submit as Drug Development Tools, and it was chosen as the first step because the clinical meaningfulness of the MDS-UPDRS Part III is already well established. We look forward to the Agency's feedback as we plan our more comprehensive approach.

Section 3. Context of use for COA qualification

a. Targeted study population including a definition of the disease and anticipated selection criteria for clinical trials (e.g., baseline symptom severity, patient demographics, comorbidities, language/culture groups)

Our targeted study population is adults who have been diagnosed with Parkinson's disease. It is our intention that this tool be used to estimate the MDS-UPDRS Part III rating for adults with Parkinson's disease across the full range of disease progression. As such, we are collecting data from people who have de novo Parkinson's disease (newly diagnosed, not on symptomatic treatment yet), people with mild to moderate Parkinson's disease (diagnosed within the last five years), and people whose Parkinson's is more severe, defined as experiencing motor fluctuations, with at least one troubling motor "off" period each day (Table 1).

Table 1: Demographics, Baseline Symptom Severity and Language / Culture Groups

Study	Total N (Currently Enrolled)	Mean Age (SD), (% male)	Inclusion Criteria at Enrollment	Mean (SD) Symptom Severity at Enrollment	Location, Language
Study A	144 (1)	TBD	*De novo* Parkinson's: Adults less than 2 years since PD diagnosis. Not on symptomatic treatment at baseline.	Data not yet available	Netherlands, Dutch
Study B	500 (497)	61.7 (8.9), 59.8% M	Mild to Moderate Parkinson's: Adults with diagnosis of PD within last 5 years	UPDRS Part III: Off: 33.3 (12.9)	Netherlands, Dutch
Study C	105 (61)	61.7 (7.93), 42.6% M	Moderate to Severe Parkinson's: Adults at least 5 years since PD diagnosis. Taking levodopa and experiencing motor fluctuations.	UPDRS Part III: On: 20.8 (9.78) Off: 32.3 (11.20)	Japan, Japanese

b. Targeted study design and statistical analysis plan (includes the role of the planned clinical outcome assessment in future drug development clinical trials, including the planned set of primary and secondary endpoints with hierarchy, if appropriate)

Our goal is to demonstrate that VME Part III Estimate is a good proxy for the MDS-UPDRS Part III Total Score as rated by a panel of clinicians (Consensus Clinician Rating). We plan to conduct the assessments below.

- Primary assessment:

Assessing construct validity by demonstrating the degree of agreement between VME Part III Estimate and the Consensus Clinician Rating for the MDS-UPDRS Part III Total Score is non-inferior to the degree of agreement between Single Rater Clinical Rating and the Consensus Clinician Rating for the MDS-UPDRS Part III Total Score.

- Secondary assessment:
  Assessing construct validity by demonstrating that the difference between the VME Part III Estimate and the MDS-UPDRS Part III Total Consensus Clinician Rating is less than a predefined threshold. The threshold will be defined in consultation of what is clinically meaningful.

Further details to evaluate the algorithm's performance will be included in the qualification plan.

c. Applicable study settings for future clinical trials

i. Geographic location with language/culture groups

To date, the Verily Study Watch with Virtual Motor Exam for Parkinson's disease has been deployed in 2 countries (the Netherlands and Japan). The Study Watch user manual and graphical user interface (GUI) both have validated translations in Dutch and Japanese, and have been used in 3 different study protocols across a range of disease severity (UPDRS Part III Total range: 7 - 88, off state).

In addition, by the end of 2021, the Study Watch with the Virtual Motor Exam will be deployed in the United States, the United Kingdom, Spain, France, Poland, Germany, Italy, and Canada to collect digital measurements that will be used as exploratory endpoints in upcoming clinical trials. The tool has language settings that allow for Graphical User Interface (GUI) localization to each of these countries. We have designed this tool to be used by people in various countries, and while the interface is mostly graphical, language prompts have been customized for deployment in the relevant populations. Further discussion is also ongoing with several sponsors to include VME to collect data for development of exploratory outcome measures in additional upcoming trials, with possible expansion into additional countries.

ii. Other study setting specifics (e.g., inpatient versus outpatient)

Data have been collected in both the in-clinic and at-home settings. The Virtual Motor Exam for Parkinson’s disease has been deployed in observational studies and will be deployed in interventional studies in 2021.

Section 4. COA type [Patient-reported outcome (PRO), Clinician-reported outcome (ClinRO), Observer-reported outcome (ObsRO), performance outcome (PerfO) measure, or Other]

Other - Digital Health Technology

Verily Study Watch is a sensor-based wearable device for non-invasive, continuous monitoring. The Investigational Study Watch is used in research and clinical studies, and the FDA-cleared Study Watch for ECG (K182456) and Irregular Pulse Monitor (K192415) is used in care collaborations with partners.