Title: **Utilization of Target Ranges to Treat Patients with Parkinson's Disease by Objective Measurement Using the Personal KinetiGraph® (PKG®) compared to Standard of Care Assessment (TARGET-PD)- A Randomized Controlled Trial**

Sponsor:	**Global Kinetics Pty Ltd (GKC)**
National Principal investigator:	**Raja Mehanna, MD** **University of Texas Health Science Center at Houston-McGovern medical school** **6410 Fannin St., Houston, TX 77030, USA**
Date of protocol:	**June 06, 2019**
Protocol number:	**Study 003**
Version of protocol:	**Version 1.0**
Planned Study Dates:	**July 2019 to Dec 2023**
Data Coordinating Center:	**genae Americas, Inc.**

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PROTOCOL SIGNATURE PAGE

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I have reviewed this protocol and agree to adhere to the requirements and responsibilities listed herein. I am trained to the contents of this protocol, treating Parkinson's Disease, and the specific use of the devices listed in this protocol. I will ensure that the study is conducted in compliance with the protocol, Good Clinical Practices, Declaration of Helsinki, and all applicable regulatory requirements.

_____ _____

Site Principal Investigator Signature Date (DD/MMM/YYY)

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Site Principal Investigator Printed Name

SUMMARY OF CHANGES

Revision Level	Description of Changes	Date
1.0	**Initial Release**	**June 11, 2019**

Protocol Summary

<table>
<tr><td>Device</td><td>Personal KinetiGraph® (PKG®) System</td></tr>
<tr><td>Control</td><td>Clinic Standard of Care</td></tr>
<tr><td>Study Objective</td><td>This is a randomized controlled trial (RCT) to evaluate treating uncontrolled patients with Parkinson’s Disease (PwP) to a target range established by a published expert opinion manuscript. The study aims to evaluate clinical patient outcomes, quality of life measures and health care utilization of those patients specifically treated to a target range when using the PKG data in the clinical management of Parkinson’s disease (PD) in routine clinical care (treatment group) compared to those managed with medical history and clinical evaluation alone (control group) performed by a neurologist experienced in PD management. Both groups will be recommended to undergo medication changes until they reach a “controlled state” that is determined by either the clinician using standard of care (SOC) (PKG- Group) or using PKG based targets and SOC assessments (PKG+ Group). For subjects in the treatment arm (PKG+ Group) the references will be according to the following table using PKG scores*:
<table>
<tr><td></td><td>Target Range</td></tr>
<tr><td>Bradykinesia Score (BKS)</td><td>Median BKS 23-25 and/or FDS > 7.5</td></tr>
<tr><td>Dyskinesia Score (DKS)</td><td>Median DKS 7-9 and FDS < 13</td></tr>
</table>
The main objective of this study is to evaluate whether PwP who are managed with the aid of objective measurement and use of target ranges have improved PD symptoms and outcomes as compared to individuals treated using only standard of care (medical history, neurological examination).</td></tr>
<tr><td>Study Design</td><td>Prospective, multi-center, single-blind randomized (1:1) controlled, longitudinal follow-up study (1, 2, 3 years)</td></tr>
<tr><td>Number of Subjects</td><td>Up to 350 randomized subjects total (approximately 175 in each arm)</td></tr>
<tr><td>Number of Sites</td><td>Up to 40 Centers in the U.S. comprised of Movement Disorder Specialists (MDS) and General Neurologists (GN) experienced in PD management.</td></tr>
<tr><td>Primary Endpoint</td><td>The change in MDS-UPDRS Total score at 4 months from baseline defined as sections I, II, III and IV in PwP. The endpoint will be compared between those who</td></tr>
</table>

	are treated with standard of care and PKG data (PKG+ Group) and those who are treated per standard of care alone (PKG- Group). Subjects will be assessed in the ON state.

Secondary Endpoints	Secondary endpoints will include measurements as indicated below:
	
	• Percent "responders" for MDS-UPDRS Total score (based on a minimum clinically important change of >4 points)**
	• Change in motor endpoints at 4 months, 1, 2, 3, years including:
	  ○ MDS-UPDRS Part III;
	  ○ PKG Bradykinesia score (BKS),
	  ○ PKG Dyskinesia score (DKS) and measurement of OFF time
	• Change in PDQ-39 from baseline to 4 months, 1, 2, 3 years
	• Change in MDS-UPDRS Total score from baseline to 1, 2, 3 years
	• Change in MDS-UPDRS Parts I from baseline to 4 months, 1, 2, 3, years
	• Change in MDS-UPDRS Parts II from baseline to 4 months, 1, 2, 3, years
	• Change in MDS-UPDRS Part IV from baseline to 4 months, 1, 2, 3, years
	• Change in PKG Scores including BKS, DKS, PTT, FDS and PTI from baseline to 4 months, 1, 2, 3 years
	• Change in Levodopa Equivalent Dose (LED) from baseline to each interim visit and 4 months, 1, 2, 3 years
	• PKG Patient Survey at 4 months, 1, 2, 3, years
	
	Subjects will be assessed in the ON state as applicable.

Ancillary Endpoints	Ancillary endpoints will include measurements as indicated below: • Rate of protocol defined adverse events affecting health care utilization including: hospitalizations, emergency department, urgent care or unanticipated clinic visits from baseline to 4 months, 1, 2, 3 years follow-up • Rate of protocol defined adverse events and potential contraindications for increasing dopaminergic therapy including: falls, orthostatic hypotension, bothersome hallucinations, delirium, and impairment that prohibits interaction with the PKG watch from baseline to 4 months, 1, 2, 3 years follow up • Rate of enrolled subjects in PKG+ Group who are unable to be brought into Target Range throughout follow-up period
Study Population	Patients with Parkinson's Disease
Inclusion Criteria	**Study subjects must fulfill the following criteria:** • Able and willing to sign a written informed consent for study participation • Presumed to have Levodopa responsive idiopathic Parkinson's Disease • Age inclusive at the time of consent per PKG Indications for Use (46-83 years old)

	• Has not been previously managed with the PKG
Exclusion Criteria	**Subject with <u>any</u> of the following clinical criteria should be excluded:** • Contraindication to increasing levodopa (e.g. orthostatic hypotension, hallucinations/psychosis or any other medical condition in the last year that would preclude increasing levodopa or other appropriate Parkinson's Disease medications) • MoCA score <23 at screening visit • Diagnosis of Essential Tremor • Wheelchair bound or bedridden • Currently utilizing or planning in the next 6 months advanced PD therapies (DBS, infusion, etc.) • In the investigator's or sponsor's opinion, subject has any unstable or clinically significant condition that would impair the participant's ability to comply with study requirements or interfere with interpretation of the study endpoints (e.g., subject unable to complete PKG watch wear instructions per Patient Instruction Manual) Subjects will be assessed in the ON state where applicable.
Statistical Methods	The primary endpoint of change in total MDS-UPDRS will be compared between the treatment group (PKG+ Group) and the control group (PKG- Group) based on a two-sample t-test. In the event normality assumptions are violated, a non-parametric analog will be used. A difference between groups of 5 points is assumed for the change in total MDS-UPDRS as well as a standard deviation of 13 based on historical data. With these assumptions, a sample size of 280 evaluable subjects will provide approximately 83% power for the statistical hypothesis test for the primary endpoint. To account for attrition of up to 20%, a total enrollment of 350 subjects is planned. The primary analysis will be based on the intent-to-treat (ITT) population defined as all randomized subjects analyzed according to the treatment group assigned. Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analyses will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required. Continuous variables will be summarized with mean, standard deviation, median, max, min, and number of evaluable observations. Categorical variables will be summarized with frequency and percentages. Confidence intervals may be presented where appropriate using the t-distribution for continuous variables and Clopper-Pearson Exact method for categorical variables. Unless otherwise specified, statistical analyses will be performed using a one-sided 0.025 alpha level.

Study Visits	• Screening • Baseline (28 days +/- 7 days) • Interim Visits (within approximately 21-35 days of previous visit)– investigators will be recommended to change medications until the patient is within the defined target range (PKG+ Group) or per investigator SOC assessments (PKG- Group); up to 3 interim visits allowed • 4 months follow-up (120 days +/- 30 days) • 1 year follow-up (12 months +/- 2 months) • 2 year follow-up (24 months +/- 2 months) • 3 year follow-up (36 months +/- 2 months)

***** Pahwa R, Isaacson SH, Torres-Russotto D, Nahab F, Lynch PM, Kotschet KE. Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's disease: recommendations from an expert panel. Expert Rev Neurother. 2018 Jul 26; 1-12.
** Shulman LM, Gruber-Baldini AL, Anderson KE, et al. The Clinically Important Difference on the Unified Parkinson's Disease Rating Scale. Arch Neurol 2010: 67(1):64-70.

1.0 Introduction

Importance of motor management in Parkinson's Disease

Parkinson's disease is a progressive disease of the nervous system marked by tremor, muscular rigidity, and slow, imprecise movement, chiefly affecting middle-aged and elderly people. These symptoms are associated with degeneration of the basal ganglia in the brain and a deficiency of the neurotransmitter dopamine. Parkinsonism refers to the collective clinical symptoms of bradykinesia, rigidity, resting tremor, and postural and gait impairments. Accumulation of alpha-synuclein in the brain is a typical neuropathological hallmark of Parkinson's disease occurring early in the course of the disease and may predate the appearance of clinical features of the disease. Manifestations in the autonomic system controlling certain functions like heart rate, digestion, etc. may also precede motor deficits of the disease. Disease progression has been shown to be attributed to alpha-synuclein spreading from diseased to healthy cells. [1] Individuals with Parkinson's may exhibit diverse symptoms including behavioral, autonomic, somatic, and cognitive deficits however motor impairment, specifically bradykinesia or slowed movement, is required for diagnosis.

Motor symptoms are secondary to the continued loss of dopaminergic neurons in the par compacta of the substantia nigra.[2] Upon treatment with dopaminergic therapies, individuals may develop iatrogenic motor complications that may be controlled through adjustment of medications. Approximately 40% of patients develop fluctuations and dyskinesia within 4-6 years of treatment and 70% after long-term treatment (>9 years). Patients with fluctuations tend to have greater disease severity and disability, and those that fail to derive adequate benefit from medications report poorer quality of life.[3,4] Signs and symptoms of fluctuations vary, and it is thought that they may be under-recognized by clinicians as direct observation is often impractical and patient symptom recall can be incomplete and unreliable.[5]

Other symptoms may impact PD patients through the disease progression. Tremor is present in about 60-70% of subjects with the typical resting tremor being helpful in differentiating PD from other forms of parkinsonism. Additionally, approximately 90% of patients with PD will develop at least one nonmotor symptom, and nonmotor symptoms can be the presenting feature in PD.[2]

Justification for use of objective targets in the management of Parkinson's disease

Treating Parkinson's disease is challenging because of fluctuations in symptoms from day to day and throughout the course of a day. Other symptoms can also impact the variability of PD on an ongoing basis. Currently, in routine practice, most clinicians rely on clinical evaluation, a patient's self-reporting of symptoms and response to medication, to guide therapy. Clinical evaluations may be in the form of an unstructured interview or semi-structured questionnaires, that vary from provider to provider in terms of content, depth, and scope, or formal clinical assessment tools such as the Unified Parkinson's Disease Rating System (UPDRS). Some clinicians employ the use of subject symptom diaries. There are well-known limitations with

these assessment methods including: no assessment during activities of daily living, poor visibility of compliance with medications, inadequate recall and/or reporting of symptoms, no or poor data quality control and inter-rater variability.[6]

Wearable technologies have been developed in response to the lack of objective measurement tools for movement disorders symptoms and are being used in the clinical care of Parkinson's patients.[7,8] Recent studies have suggested that the use of wearable sensors can inform medication choices in a clinical trial setting and correlate with relevant clinical assessment scales.[9]

A recent study by Farzanehfar, *et al*.[10] demonstrated that the use of objective targets and measurement with the PKG® system significantly improved clinical care and quality of life for people with PD. For the first time, this study provided clinicians with objective and continuous information to help calibrate their treatment recommendations in a timely method. The study included 103 PD patients from the Northern part of Tasmania, Australia, with low levels of access to specialist care.

Key findings of this study included:

- Most people with PD (78%) were living with excessive symptoms that were out of target, including high levels of bradykinesia (slowness and freezing), dyskinesia (involuntary movements) and tremor (constant shaking).
- With the use of objective measurements and targets reported with the PKG® system, management was improved in more than half (58%) of the 77 participants who completed the study.
- Most significantly, PKG monitoring and use of targets led to changes in oral medication, which improved quality of life and clinical outcomes of 43% of patients who completed the study (33 patients):
    - 10-point improvement in quality of life as assessed by the PD Questionnaire (PDQ-39) ($p<0.08$).
    - 8-point improvement in clinical symptoms as measured by Total UPDRS clinical scale ($p<0.0009$).

Additionally, in 2018, two panels of movement disorder specialists published expert opinion manuscripts that serve as a basis for objective measurement to be incorporated into clinical practice guidelines. Both expert groups developed treatment targets for the management of bradykinesia, dyskinesia and motor fluctuations.[11,12] These therapeutic targets will be evaluated in this study.

Personal KinetiGraph (PKG®) Movement Recording System

The Personal KinetiGraph (PKG®) Movement Recording System was developed by neurologists at the Melbourne-based Florey Institute of Neuroscience and Mental Health. The product is manufactured and marketed by GKC.

The Personal KinetiGraph (PKG®) Movement Recording System consists of the following:

- A wrist-worn data logger (PKG Watch) designed to acquire data on the kinematics of movement disorder symptoms over a 6-10 day period.
- An application to configure the data logger and transfer the acquired data at the end of a recording.
- A series of algorithms that analyze the uploaded data, producing a PDF that is delivered to the clinician. The PDF contains objective data distinguishing the movement patterns consistent with tremor, bradykinesia, dyskinesia and immobility.
- Supporting device accessories.

2.0 PKG System

PKG Watch

The PKG Watch is a wrist worn medical device that looks like a wristwatch. It is worn on the wrist of the most severely affected side and contains a rechargeable battery, a triaxial accelerometer, memory, an optional vibration and indicator light-based reminder to the subject when PD medications are due and a means for recording when Parkinson's disease (PD) medications were taken, as well as a capacitive sensor to detect removal from the wrist.

Subjects wear the device for 6-10 consecutive days. During this wear time the PKG Watch automatically collects data on the type of movement experienced by the patient 24 hours per day, can remind the patient to register when they have taken their PD medication as prescribed by their clinician, and the patient can indicate when he/she has taken each prescribed dose of PD medication.

At the end of the recording period, data are downloaded and analyzed using a proprietary algorithm to translate raw movement data collected by the PKG Watch into a multi-page, printable output of the patient's movement over the wear period. This output is called a "PKG." The maximum acceleration in each 2-minute epoch is identified and the mean spectral power surrounding this peak is calculated. Algorithms produce Bradykinesia Scores (BKS) and Dyskinesia Scores (DKS) every two minutes. The PKG includes:

- a scaled record of a dyskinesia score (DKS) representative of dyskinesia plotted against time of day for individual days over the full recording period (Figure 2).
- a scaled record of a bradykinesia score (BKS) representative of bradykinesia plotted against time of day for individual days over the full recording period (Figure 2).
- a record of periods of immobility, which may be indicative of periods of daytime sleep and somnolence, plotted against time of day.

- a record of periods when the patient was not wearing the PKG Watch or when it was 'off-wrist'.
- a record of the patient's self-reported compliance with their prescribed program of Parkinson's disease medication.
- a record of periods of tremor for each day and a tremor summary.

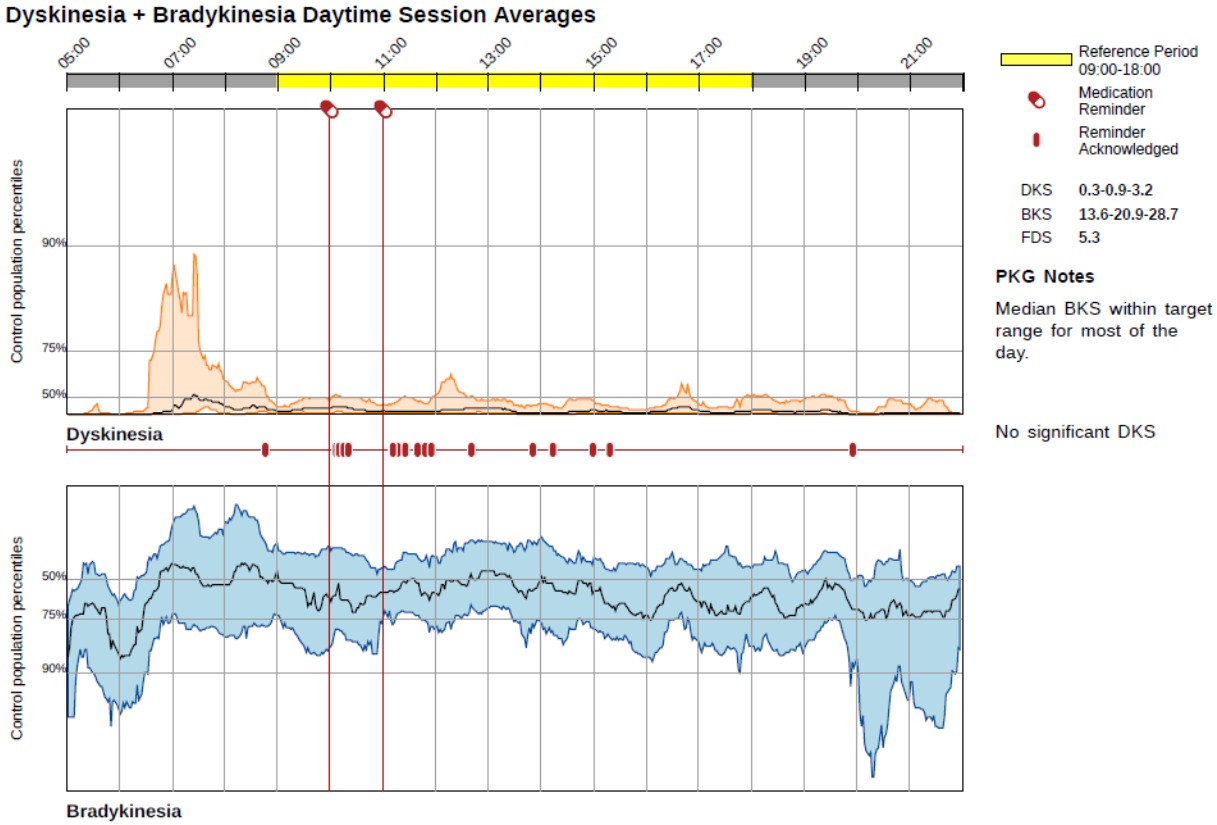

Figure 1: PKG Main Plot

2.1 Clinical Interpretation

Bradykinesia Scores (BKS) and Dyskinesia Scores (DKS) are continuous variables. In the case of the BKS, the scores can range from movements that are made with normal acceleration to those that have very low or no acceleration. There is a correlation between the median BKS and DKS between 0900-1800 hour and clinical rating scales.[12]

A very high bradykinesia score represents compete immobility of the logger for that 2-minute period.[13] These periods of immobility had a 85.2% concordance with the detection of sleep by ambulatory daytime polysomnography, ($p < 0.0001$ Chi Squared)[13]. High Epworth Sleepiness Scores (ESS) were associated with a high proportion of time immobile (PTI) throughout the day ($p > 0.01$ Mann-Whitney). The median PTI between 0900 -1800 hours in 30 age matched control subjects was 2%, representing 10 min. PD patients had higher PTI (median 4.8%) than controls ($p < 0.0001$, Mann-Whitney). PD subjects with a PTI above the 75th percentile (5% or 27 min) of controls had more bradykinesia, less dyskinesia and higher PDQ-39 scores than those with PTI below this level. There was no relationship between PTI and dose or type of PD

medications. However, in 53% of subjects, PTI increased in the 30-60 min after levodopa confirming that in some subject's levodopa results in increased sleepiness.[14]

The PKG Watch can deliver a reminder to take PD medication by delivering a vibratory cue to the wrist. Consumption of medications is acknowledged by the subject. Some patients performed this acknowledgement repeatedly and unconsciously and this behavior is a risk marker for Impulse Control Disorder.[15] A Response Ratio (RR) represents the number of acknowledgements/ number of doses and is expressed as a percentage. In ~75% of people with PD who had high Impulsive-Compulsive Behavior (ICB) Scores, the RR was tightly correlated with ratings of Impulsive-Compulsive Behaviors (r^2=0.79). These patients had dyskinesia, particularly when making extraneous responses. In the other 25% who had high Impulsive-Compulsive Behavior Scores according to rating scales, the RR was low and these subjects had higher Apathy scores and low levels of dyskinesia. It was concluded that the elevated Response Ratio is a specific measure of a type of Impulse Control behavior where increased incentive salience is attributed to cues by the presence of high striatal dopamine levels, manifest by high levels of dyskinesia and that there is a second form of ICBs which occur in the absence of dyskinesia, has normal Response Ratios and higher Apathy scores and may represent prefrontal pathology.[15]

A Fluctuation Dyskinesia Score (FDS) was produced from the PKG data by summing the interquartile range of bradykinesia scores and dyskinesia scores and expressing it as an algorithm.[16] This FDS can distinguish between fluctuating and non-fluctuating patients with high sensitivity and selectivity and was significantly lower following activation of deep brain stimulators. The FDS following deep brain stimulation lay in a band just above the score separating fluctuators from non-fluctuators, suggesting a range representing adequate motor control. When compared with control subjects the FDS of newly diagnosed patients show a loss of fluctuation with onset of PD. The FDS was calculated in subjects whose duration of disease was known and this showed that newly diagnosed patients soon develop higher scores which either fall under or within the range representing adequate motor control or instead go on to develop more severe fluctuations. It was concluded that the FDS promises to be a useful tool for identifying patients whose fluctuations are progressing and may require therapeutic changes.[16]

2.2 PKG and PKG Report

The investigator will be provided a summary report of the PKG that includes key findings by an independent neurologist, registered nurse and/or neuro diagnostic technologist trained specifically in interpreting the PKG for the PKG+ Group only. It is intended that the investigator then reviews and assesses the PKG information and additionally reviews findings with the patient, concluding the likely impact of the disease on the movement of the patient. This PKG and PKG report may lead the clinician to prescribe a change in medication amount/frequency or recommend a new therapy until the patient becomes controlled.

2.3 Regulatory Status in the United States

The PKG Movement Recording System was first FDA cleared on August 22, 2014 (K140086) and is intended to quantify kinematics of movement disorder symptoms in conditions such as Parkinson's disease, including tremor, bradykinesia and dyskinesia. Generation 2 PKG system 510(k) clearance was issued on September 20, 2016 (K161717) for Model: GKC-2000 (Gen 2) in which internal hardware to the logger was modified. Future generations of the PKG Movement Recording System will be cleared by the FDA through the regulatory approval process prior to being utilized in this clinical study. All commercially available versions of the PKG System and associated product instructions for use may be used in this study. The study is a post-market study and the system will be used within its FDA-cleared indication for use.

3.0 Subject Population

Approximately 350 subjects with Parkinson's Disease will be consented to provide 280 subjects followed through the initial 4-month follow-up period, which includes up to 20% attrition during this phase.

Subject selection criteria will include patients with PD who meet the following criteria. Subjects will be assessed in the ON state where applicable.

3.1 Inclusion Criteria

Study subjects must fulfill the following criteria:

- Able and willing to sign a written informed consent for study participation
- Presumed levodopa responsive idiopathic Parkinson's Disease
- Age inclusive at the time of consent per PKG Indications for Use (46-83 years old)
- Has not been previously managed with the PKG

3.2 Exclusion Criteria

Subject with <u>any</u> of the following clinical criteria should be excluded:

- Contraindication to increasing levodopa (e.g. orthostatic hypotension, hallucinations/psychosis or any other medical condition in the last year that would preclude increasing levodopa or other appropriate Parkinson's Disease medications)
- MoCA score <23 at screening visit
- Diagnosis of Essential Tremor
- Wheelchair bound or bedridden
- Currently utilizing or planning in the next 6 months advanced PD therapies (DBS, infusion, etc.)
- In the investigator's or sponsor's opinion, subject has any unstable or clinically significant condition that would impair the participant's ability to comply with study

requirements or interfere with interpretation of the study endpoints (e.g., subject unable to complete PKG watch wear instructions per Patient Instruction Manual)

Subjects will be assessed in the ON state where applicable.

4.0 Methods

4.1 Study Design Overview

The TARGET-PD RCT investigates the use of the PKG and standard of care in treating towards a target range compared to standard of care alone in the treatment of patients with uncontrolled Parkinson's disease. This is a prospective, multi-center, single-blind, randomized controlled study.

Each subject will be followed for 4 months after the baseline visit. All subjects in either group will have interim visits until they are considered to be controlled by the clinician per SOC (PKG-Group) or in the PKG based target range (i.e., controlled per expert review paper guidance in Pahwa et al., 2018)[11] for the PKG+ Group. Interim visits may be conducted via telephone or in-office.

4.2 General Methods

Protocol-Required Data Collection

Protocol-required data collection at a given visit interval may be completed on one or multiple visit dates, if preferred by the institution as long as the testing is performed in compliance with protocol requirements and occurs within the corresponding visit window.

Data will be collected on study-specific case report forms (CRFs).

In the event inaccurate and/or incomplete PKG data collection occurs (e.g., subject wore PKG successfully but for less than the required duration, subject PKG Watch wrist band was not sufficiently secured creating PKG artifacts precluding interpretation, subject performed activities, such as the use of power tools, for a sufficient duration that interfered with PKG data collection, data collection completed when subject was OFF), data collection may be repeated one time. A note will be made in the case report form (CRF) that documents the reason for the repeated data collection and the initial and final test results will be recorded in the medical record. Only the final results will be recorded on the CRF.

Parkinson's Disease Medication Use

All subjects in the study will be asked to continue taking Parkinson's disease medication(s) as prescribed by their Parkinson's clinician throughout the duration of this study. Any modifications to medicines made during this study will be based on the clinician's judgment. Changes to medications will be recommended until the patient is considered to be controlled

unless contraindications are identified by the investigator. All PD medications and subsequent changes will be recorded in the medication log CRF. In addition, non-PD prescription medications of anti-depressants, anti-psychotics and blood pressure lowering agents will be tracked in the other medication log CRF.

Timing of Clinical Visits

Subjects will be asked to plan administration of Parkinson's medications to coincide with the time of each study-required clinic visit to ensure that in-clinic study evaluations occur when the subject is "ON" or believes they are achieving benefit from prescribed medications to standardize data collection for each patient and within the overall study cohort.

PKG Watch Administration

Study staff will be trained on the deployment and use of the PKG Watch to answer any patient questions and on the GKC ordering portal. The PKG Watch request will be entered into the GKC clinical portal. GKC will receive the order for the PKG Watch and send the PKG Watch to the patient for wear prior to the next study visit. The patient will return the PKG Watch to GKC and GKC will then upload the PKG including a summary of key findings for the study staff to download.

For both PKG+ Group and PKG- Group subjects, the PKG Watch will be programmed per standard commercial practices with the PD medication alert feature enabled (see Technical Instructions Manual). Subjects will be instructed to provide acknowledgement of PD medications taken by swiping the PKG Watch as described in the Patient Instruction Manual. The Patient Instruction Manual instructs patients to take PD medications as prescribed by their doctor.

The study staff will provide each subject with training on the use of the PKG Watch, a copy of the Patient Instruction Manual and complete the patient demonstration. Study staff will place the PKG Watch order in the Portal to allow GKC to deliver the PKG Watch to the subject. Once the subject has completed 6 full days of wear, the subject will return the PKG Watch to GKC. GKC will then download data from the PKG Watch per the instructions for use prior to the baseline visit. If, for any reason, the subject is unable to provide at least 6 full days of PKG data, the subject may have another PKG Watch programmed and dispensed for an additional wear period.

If at any time during the study, the subject is unable to successfully wear the PKG Watch or comply with study requirements, the subject may be exited from the study per Principal Investigator discretion.

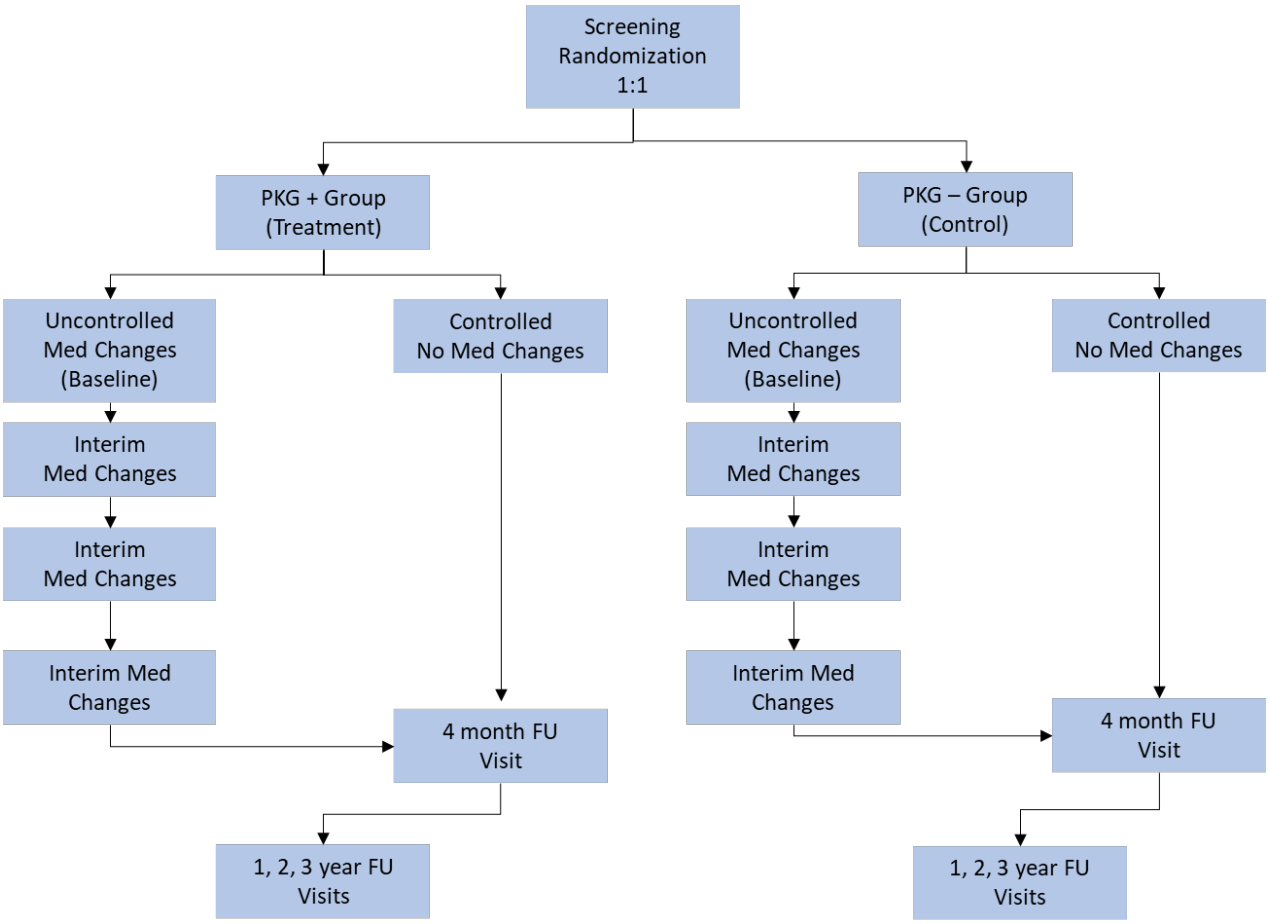

Figure 2. Study Flow Chart

4.3 Screening Visit

Subjects that have not been treated previously with the PKG (i.e. PKG naïve) will be identified from routine clinical care, offered study participation, and provided a study informed consent document. Study goals and expectations will be discussed with subjects and all subject questions will be answered by a study Investigator and/or delegated designee. Subjects willing to participate will provide written informed consent.

Subject selection criteria will be documented. A Montreal Cognitive Assessment (MoCA) will be performed as part of selection criteria at the screening visit to exclude patients with dementia who are unlikely to be able to use the PKG independently. Only versions 7 or 8 of the MoCA will be used. Version and subform will be recorded in the screening visit CRF. Subjects who do not meet the study selection criteria will be documented as a screen failure on Subject Enrollment Logs in the Site Regulatory Binder and in the Electronic Data Capture system (EDC), as required Eligible subjects will be assigned a Subject ID number and randomized using the EDC system in a 1:1 ratio to the PKG- Group (standard of care clinical assessments without use of PKG data) or the PKG+ Group (standard of care clinical assessments plus use of PKG data). Medical history and demographics will be collected on all patients after randomized into the study. The point of

enrollment into this study is when all selection criteria are met, an informed consent form is completed, and the randomization assignment has been completed.

A PKG Watch will be ordered through the GKC Portal and dispensed to the all subjects as previously described.

Screening and enrollment activities may be done remotely by phone or secure video conferencing (per existing site practices), as part of a routine clinic visit, as per local clinic and/or IRB requirements.

4.4 Baseline Visit

At 28 days +/- 7 days (21-35 days) after the screening visit, subjects will return to the clinic for the Baseline Visit. For the PKG+ Group, the site staff will ensure the PKG Report is available prior to the Baseline Visit. A subject unable to wear a PKG Watch for at least 6 full days may be exited from the study (complete Study Completion Form) if they are unable to complete a repeat wear of the PKG Watch.

Subjects in both groups will undergo the routine clinical evaluation per standard of care. For all subjects, a medical history update, medication history, and an "ON" state neurological assessment will be completed. Protocol defined adverse events including falls, orthostatic hypotension, bothersome hallucinations, delirium, impairment that prohibits interaction with the PKG watch will be recorded. All subjects will also complete the PDQ-39 questionnaire and MDS-UPDRS. If the MDS-UPDRS is not considered part of the routine clinic visit, the MDS-UPDRS will be conducted for all visits by an independent certified rater.

For subjects in the PKG- Group (SOC control group), protocol required data collection will occur at the baseline visit. A Subject "ON" State Assessment will be completed and changes in medical history and medications will be recorded. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures. The study investigator will be blinded to the PKG information. In this group, the investigator will use clinical history and examination to determine if the subject is "controlled" or "uncontrolled" based on standard of care.

For subjects in the PKG+ Group, the study investigator will review and report on the PKG prior to the visit and use the information to guide the discussion with the subject during the clinical assessment. Subjects will remain blinded to their treatment group so direct reference to the PKG is to be avoided. The PKG will be used to determine if the subject is "controlled" or "uncontrolled" using the consensus-derived target ranges.[12] PKG results will be recorded in the PKG Reporting CRF. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures along with the PKG information.

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25 and/or FDS > 7.5
Dyskinesia Score (DKS)	Median DKS 7-9 and FDS < 13

4.5 Interim Follow-Up Visits

Interim follow-ups will be completed for subjects who are not considered to be controlled. For PKG- group subjects, controlled means per clinician standard of care assessment and for PKG+ group subjects, this is per the Acceptable Target Range[12]:

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25 and/or FDS > 7.5
Dyskinesia Score (DKS)	Median DKS 7-9 and FDS < 13

Interim visits can be completed in-clinic or remotely via telephone per institutional requirements. This timeframe may vary depending on a variety of factors such as physician care practices, amount of total medication change needed, subject medication regimen compliance and subject tolerance to medication changes.

Approximately 28 days prior to each planned subject follow-up visit, a PKG Watch will be ordered through the GKC Portal and dispensed to each subject as previously described and PKG report obtained prior to the visit of PKG+ group subjects for investigator review.

For subjects in the PKG+ Group, the site staff will ensure the PKG is available prior to the Interim Follow-up Visit. Protocol required data collection will occur at each follow-up interim visit. A Subject "ON" State Assessment will be completed and changes in medical history and medications will be recorded. Any protocol defined AEs that have occurred will be captured on the AE Reporting CRF (see Section 8). The study investigator will review the PKG provided by GKC prior to the visit and use the information to guide the discussion with the subject during the clinical assessment. PKG results will be recorded in the PKG Reporting CRF. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures along with the PKG information.

For subjects in the PKG- Group, protocol required data collection will occur at each follow-up interim visit. A Subject "ON" State Assessment will be completed and changes in medical history and medications will be recorded. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures. The study investigator will be blinded to the PKG information during interim visits.

These steps will be repeated for each interim follow-up until the study subject is determined to be controlled or a maximum of the 4-month follow-up visit.

Up to 4 medication changes including at the Baseline visit and up to 3 interim visits will be allowed to get each subject into a "controlled" state. Interim follow-up visits end when PD symptoms have become optimized (considered controlled on oral therapies) per standard of care assessments for PKG- group subjects and per the Acceptable Target Range as published in Pahwa et al., 2018 and no further treatment changes are indicated as assessed by the study investigator and the subject will proceed to the next required study visit at 4-months Follow-Up.

4.6 4-Month Follow-Up Visit

All subjects will complete a follow-up visit approximately 4-months +/- 30 days (90-150 days) from the Baseline Visit.

Approximately 28 days prior to each planned subject follow-up, a PKG Watch will be ordered through the GKC Portal and dispensed to each subject as previously described. The site staff will ensure the PKG is available prior to the visit for the PKG+ Group.

Subjects in both groups will undergo the routine clinical work-up per standard of care. Protocol required data collection will occur at the visit. A Subject "ON" State Assessment will be completed and changes in medical history and medications will be recorded. Any protocol defined AEs that have occurred will be captured on the AE Reporting CRF (see Section 8). Subject surveys will be administered and include the PKG Patient Survey, PDQ-39, MDS-UPDRS, and MoCA. Medication changes (PD and other) will be updated in the corresponding medication log in the CRF.

For subjects in the PKG- Group (control group), the study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures. The study investigator will be blinded to the PKG information. In this group, the investigator will use clinical history and examination to determine if the subject is "controlled" or "uncontrolled."

For the PKG+ Group, the site staff will ensure the PKG Report is available prior to the 4-Month Follow-Up Visit. A subject unable to wear a PKG Watch for at least 6 full days may be exited from the study (complete Study Completion Form) if they are unable to complete a repeat wear of the PKG Watch. The study investigator will review and report on the PKG prior to the visit and use the information to guide the discussion with the subject during the clinical assessment. The PKG will be used to determine if the subject is "controlled" or "uncontrolled."[12] PKG results will be recorded in the PKG Reporting CRF. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical

management planning based on his/her routine clinical assessment procedures along with the PKG information.

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25 and/or FDS > 7.5
Dyskinesia Score (DKS)	Median DKS 7-9 and FDS < 13

4.7 Annual Follow-Up Visits

All subjects will undergo annual follow-up clinic visits at 12 months (+/- 2 months), 24 months (+/- 2 months) and 36 months (+/- 2 months) following the Baseline Visit.

Approximately 28 days prior to each planned subject follow-up, a PKG Watch will be ordered through the GKC Portal and dispensed to each subject as previously described. The site staff will ensure the PKG is available prior to the Annual Follow-up Visit. Protocol required data collection will occur at each follow-up. A Subject "ON" State Assessment will be completed and changes in medical history and medications will be recorded. Any protocol defined AEs that have occurred will be captured on the AE Reporting CRF (see Section 8). All subjects will complete a PKG Patient Survey, PDQ-39, MDS-UPDRS and MoCA.

For subjects in the PKG+ Group, the study investigator will review the PKG prior to the visit and use the information to guide the discussion with the subject during the clinical assessment. Treatment decisions based on the PKG results will be recorded in the PKG Reporting CRF. The study investigator will complete the Clinician Assessment CRF to denote patient-reported symptoms, treatable findings, and clinical management planning based on his/her routine clinical assessment procedures along with the PKG information.

If a subject requires medication changes in between annual follow-up visits, interim visits will be conducted per clinic standard of care. If medication changes are made, these will be documented in the Medication log and on the Clinician Assessment CRF.

Table 1. Schedule of Events

Study Activity	**Screening**	**Baseline (28 days; +/- 7 days)**	**Interims (Up to 3 visits)**	**Follow-Up (4 month +/- 30 days)**	**Annual follow-ups (1, 2, 3 year +/-2 months)**
Visit Type	**In-clinic or phone per standard of care**	**In-clinic 21-35 days**	**In-clinic or phone per standard of care**	**In-clinic 90-150 days**	**In-clinic**
Medical History	X				

ICF	X				
Subject Selection Criteria	X				
Randomization	X				
Clinical Management Plans		X	X	X	X
PD and Other Medications	X	X	X	X	X
AE collection (protocol defined only)		X	X	X	X
PKG Scores (provided for PKG + Group)		X	X	X	X
MDS-UPDRS I, II, III, IV and Total Score		X		X	X
MoCA	X			X	X
PDQ-39		X		X	X
PKG Patient Survey				X	X

5.0 Endpoints

5.1 Primary Endpoint

The change in MDS-UPDRS Total score at 4 months from baseline defined as sections I, II, III and IV in PwP. The endpoint will be compared between those who are treated with standard of care and PKG data (PKG+ Group) and those who are treated per standard of care alone (PKG- Group).

Subjects will be assessed in the ON state.

5.2 Secondary Endpoints

Secondary endpoints will include measurements as indicated below:

- Percent "responders" for MDS-UPDRS Total score (based on a minimum clinically important change of >4 points)[17]
- Change in motor endpoints at 4 months, 1, 2, 3, years including:
    - MDS-UPDRS Part III;
    - PKG Bradykinesia score (BKS),

  - PKG Dyskinesia score (DKS) and measurement of OFF time
- Change in PDQ-39 from baseline to 4 months, 1, 2, 3 years
- Change in MDS-UPDRS Total score from baseline to 1, 2, 3 years
- Change in MDS-UPDRS Part I from baseline to 4 months, 1, 2, 3, years
- Change in MDS-UPDRS Part II from baseline to 4 months, 1, 2, 3, years
- Change in MDS-UPDRS Part IV from baseline to 4 months, 1, 2, 3, years
- Change in PKG Scores including BKS, DKS, PTT, FDS and PTI from baseline to 4 months, 1, 2, 3 years
- Change in LED from baseline to each interim visit and 4 months, 1, 2, 3 years
- PKG Patient Survey at 4 months, 1, 2, 3, years

Subjects will be assessed in the ON state as applicable.

5.3 Ancillary Endpoints

Ancillary endpoints will include measurements as indicated below:

- Rate of protocol defined adverse events affecting health care utilization including: hospitalizations, emergency department, urgent care or unanticipated clinic visits from baseline to 4 months, 1, 2, 3 years follow-up
- Rate of protocol defined adverse events and potential contraindications for increasing dopaminergic therapy including: falls, orthostatic hypotension, bothersome hallucinations, delirium, and impairment that prohibits interaction with the PKG watch from baseline to 4 months, 1, 2 3 years follow up
- Rate of enrolled subjects in PKG + group who are unable to be brought into Target Range through follow-up visits

6.0 Statistical Methods

6.1 Hypothesis

The primary endpoint of change in total MDS-UPDRS will be compared between the treatment group (PKG+ Group) and the control group (PKG- Group) based on a two-sample t-test. In the event normality assumptions are violated, a non-parametric analog will be used. A difference between groups of 5 points is assumed for the change in total MDS-UPDRS as well as a standard deviation of 13 based on historical data. With these assumptions, a sample size of 280 evaluable subjects will provide approximately 83% power for the statistical hypothesis test for the primary endpoint. To account for attrition of up to 20%, a total enrollment of 350 subjects is planned.

The difference in the primary endpoint between randomized groups will be compared with a two-sample t-test of means at the 1-sided alpha of 0.025 (equivalent to a two-sided 0.05 alpha level). In the event normality assumptions are violated, a non-parametric analog will be used.

6.2 Total Sample Size

Approximately 350 subjects will be consented to provide an estimated 280 subjects followed through the 4-Month follow-up period (assuming 20% attrition).

Initial sample size has been generated on currently available information and may be revised mid-study as new information external to the trial becomes available. As noted by FDA guidance (https://www.fda.gov/downloads/drugs/guidances/ucm201790.pdf), this approach does not raise issues of bias or concern if the interim comparative trial data is blinded and the sole source of changes to the sample size is external information. The independent Clinical Trial Steering Committee will be responsible for reviewing the data, recommending a go-forward decision and ensuring minimization of bias.

6.3 Statistical Analysis

Analysis Populations

The primary analysis will be based on the intent-to-treat (ITT) population defined as all randomized subjects analyzed according to the treatment group assigned.

In addition, analyses based on the per-protocol (PP) population and the modified intent-to-treat (mITT) population will be performed for the primary and secondary endpoints. The PP population is defined as all subjects who are randomized and adhere to the study protocol requirements, including: meeting all of the subject selection criteria, completion of the PKG Watch wear period, inability for investigator to further make treatment changes due to known contraindication, completion of subject surveys and completion of follow-up visits. The mITT population is defined as all study subjects who are randomized, meet all subject selection criteria throughout the study, and complete the 3-year final study visit.

6.4 Analysis Plan Overview

Interim analyses will be performed after approximately 100 and 200 subjects have been randomized and followed through the 4-month follow-up period.

The primary endpoint will be compared between those who are treated with standard of care and access to the PKG (PKG+ Group) and those who are treated per standard of care alone (PKG- Group) via a two-sample t-test. Except where otherwise specified, the following general principles apply to the planned statistical analyses. All statistical analysis will be conducted using SAS version 9.4 or later (SAS Institute Inc., Cary, NC) or other widely-accepted statistical or graphical software as required. Continuous variables will be summarized with mean, standard deviation, median, max, min, and number of evaluable observations. Categorical variables will be summarized with frequency and percentages. Confidence intervals may be presented where appropriate using the t-distribution for continuous variables and Clopper -

Pearson Exact method for categorical variables. Unless otherwise specified, statistical analyses will be performed using a one-sided 0.025 alpha level.

Additional analyses will be conducted to adjust for key baseline characteristics associated with either outcome or group assignment. A subset analysis related to falls per the ancillary endpoint will be performed at selected sites. These analyses will be performed using linear regression with primary predictor of group assignment and outcome of change in Total MDS-UPDRS. and further detailed in the study Statistical Analysis Plan.

7.0 Investigator Qualifications

Movement Disorder Specialists and General Neurologists who treat PD participating in this study will be using the PKG in routine clinical care and have completed PKG product training provided by GKC and be trained on the use of target ranges prior to participating in this study.

8.0 Risk/Benefit Analysis

All aspects of clinical management will be made at the clinician's discretion and with the patient's safety in mind. This study represents a minimal risk as both groups are undergoing clinician-guided medication management. Furthermore, the PKG Movement Recording System within this study fulfills the following general criteria:

- **Not** intended as an implant or presents a potential for serious risk to the health, safety, or welfare of a subject;
- **Not** purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject, or
- **Not** for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject.

In the case of the PKG+ group, additional objective measures will also be used to help guide the clinician. The results of this study are expected to yield generalizable knowledge about the utility of using objective measures in the management of PD.

In this post-market clinical study, study sites and participants will use commercially available system components according to existing product labeling. The study includes non-invasive clinical assessments and patient surveys routinely used to characterize Parkinson's disease symptoms. The study includes study-specific clinician and patient surveys as well.

Adverse events and risks associated with this study are similar to those normally associated with standard clinical care of patients with Parkinson's disease; thus, additional adverse events are not anticipated.

However, only the list below of protocol defined adverse events will be collected starting at point of enrollment and analyzed for the ancillary endpoints:

- falls
- orthostatic hypotension
- bothersome hallucinations
- delirium
- impairment that prohibits interaction with the PKG watch
- hospitalizations
- emergency department visits
- urgent care visits
- unanticipated clinic visits

An independent review of protocol collected adverse and serious adverse events will be performed and assessed related to protocol, study eligibility and outcomes. Events will be reported to IRBs and regulatory authorities as applicable.

Current product safety information, including contraindications, warnings, and precautions, are located in the Patient Instructions Manual, Technical Instructions Manual, and Clinical Interpretation Guide. Any complaints regarding any component of the PKG Movement Recording System will be reported to GKC and processed per GKC's standard post-market surveillance processes and any adverse events associated with the use of the PKG Movement Recording System will be summarized in the final report for this study.

9.0 Study Monitoring and Oversight

Trained personnel appointed by GKC will conduct monitoring activities to ensure that the study is conducted in accordance with this study protocol, applicable regulatory requirements and clinical guidelines. Monitoring activities will include a combination of ongoing remote data review, risk-based monitoring and on-site source document verification. No formal Data Safety and Monitoring Committee will be established for this study as this is a minimal safety risk study. However, as previously outlined, the Clinical Trial Steering Committee will periodically review study parameters including interim analyses.

Each center will obtain Institutional Review Board (IRB) approval of this study protocol and informed consent prior to commencement of subject enrollment and remain under the administration of an IRB throughout the duration of the study.

10.0 Abbreviations and Definitions

AE	Adverse Event – Any untoward medical occurrence in a participant, which does not necessarily have a causal relationship with the trial intervention.
BKS	Bradykinesia Score – A score produced by PKG algorithms indicating symptoms of bradykinesia
DKS	Dyskinesia Score – A score produced by PKG algorithms indicating symptoms of dyskinesia.
FDS	Fluctuation Dyskinesia Score – A score produced by PKG algorithms indicating levels of fluctuation shown but interquartile ranges.
IQR	Interquartile Range - A measure of statistical dispersion, being equal to the difference between 75th and 25th percentiles.
LED	Levodopa Equivalent Dose – The comparison of levodopa with other medication regimes.
MoCA	Montreal Cognitive Assessment – A rapid screening instrument for mild cognitive dysfunction.
PD	Parkinson's Disease – A progressive disease of the nervous system marked by tremor, muscular rigidity, and slow, imprecise movement, chiefly affecting middle-aged and elderly people. It is associated with degeneration of the basal ganglia of the brain and a deficiency of the neurotransmitter dopamine.
PDQ-39	Parkinson's Disease Questionnaire – A 39 self-report questionnaire that assesses Parkinson's disease-specific health related quality over the previous month.
PKG	Personal KinetiGraph - The output (including graphs, values, and curation) generated from the data captured on the PKG watch
PTI	Percent Time Immobile – Overall percentage of time the PKG detects that the patient is motionless.
PTT	Percent Time Tremor – Overall percentage of time the PKG detects that the patient experiences tremors.
PwP	People with Parkinson's Disease
Target Ranges	Defined using Pahwa R, Isaacson SH, Torres-Russotto D, Nahab FB, Lynch PM, Kotschet KE. Role of the Personal KinetiGraph in the routine clinical assessment of Parkinson's disease: Recommendations from an expert panel. Expert Review of Neurotherapeutics. 2018. DOI: 10.1080/14737175.2018.1503948.

	Target Range
Bradykinesia Score (BKS)	Median BKS 23-25 and/or FDS > 7.5

Dyskinesia Score (DKS)	Median DKS 7-9 and FDS < 13

UPDRS-MDS Unified Parkinson's Disease Rating Scale, MDS version – A revision of the universally accepted UPDRS. (Goetz CG et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. Movement Disorders. Vol. 23, No. 15, 2008, pp. 2129-2170.)

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