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Title:	Three Site <u>A</u>ssessment of the <u>P</u>otential for Home Dexterity Monitoring in a <u>PD</u> Biomarker Study (TAP-PD), A Parkinson's Progression Markers Initiative (PPMI) Sub-study
Clinical Phase:	Observational Study
Sponsor:	The Michael J. Fox Foundation for Parkinson's Research (MJFF), New York, New York, Kinetics Foundation, Palo Alto, CA; liaison officer: James McNames, Ph.D.
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PROTOCOL APPROVAL
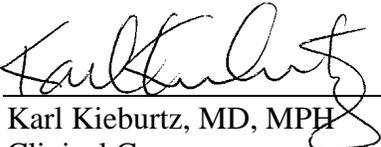
Three Site Assessment of the Potential for Home Dexterity Monitoring in a PD Biomarker Study (TAP-PD)

June 21, 2011

Kenneth Marek, MD   Date
Principal Investigator

6/22/11

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22 June 11

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Michael J Fox Foundation (Sponsor)

INVESTIGATOR AGREEMENT

Three Site Assessment of the Potential for Home Dexterity Monitoring in a PD
Biomarker Study (TAP-PD)

I have carefully read this protocol and agree that it contains all the necessary information for conducting the study safely.

I will conduct this study in strict accordance with this protocol and according to the current Good Clinical Practice (GCP) regulations and International Conference on Harmonization (ICH) guidelines, and local regulatory requirements.   Any changes in procedure will only be made if necessary to eliminate immediate hazards and/or to protect the safety, rights or welfare of subjects.

I will provide copies of the protocol and all other information relating to this project, which were furnished to me, to all physicians and other study personnel responsible to me who participate in this study.   I will discuss this information with them to assure that they are adequately informed regarding the conduct of the study.

I agree to keep records on all subject information (case report forms, informed consent statements and all other information collected during the study) in accordance with the current GCP, ICH, local, national and European regulations.

_____   _____
Site Number   Printed Site Name

_____
Printed Site Investigator Name

_____   _____
Site Investigator Signature   Date

TAP-PD PROTOCOL SYNOPSIS

Study Population	Subjects with recently-diagnosed PD who have consented to participate in the PPMI study.
Study Design	Longitudinal, observational cohort study

Eligibility Criteria	Inclusion criteria:
	  a) PD subject who is otherwise eligible for enrollment into PPMI.
	
	  b) Enrolled at one of three participating sites:
	    Oregon Health & Science University, Portland, OR
	    Institute for Neurodegenerative Disorders, New Haven, CT
	    University of Pennsylvania Movement Disorders Center, Philadelphia, PA
	
	  c) Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.
	
	  d) Willing and able to complete additional study procedures.
	
	Exclusion criteria:
	  a) Evidence of "atypical" parkinsonian syndromes (e.g. Progressive supranuclear palsy, Multiple system atrophy, drug-induced parkinsonism, Lewy body dementia).
	
	  b) Any medical condition other than PD that would interfere with the subject's ability to perform study procedures as determined by the investigator.

STUDY PROCEDURES	Baseline • Informed Consent for sub-study • Instructions on use of OPDM device and directly observed use of dexterity device in clinic • PPMI assessments including MDS-UPDRS • Provide OPDM device to subject to take home At home between baseline and 3 month PPMI visits • Perform dexterity devise tasks one time per week at the same time of the week and time of the day (13 sessions)

	PPMI 3, 6 and 12 month visits • Return dexterity device (month 3) • Complete subject survey of satisfaction with device (month 3) • PPMI assessments including MDS-Unified Parkinson Disease Rating Scale • Perform OPDM device task at study visit • Export data from device to Kinetics

ANALYSIS PLAN	Feasibility will be measured as the proportion of subjects who complete at least 3 valid sessions per month for all of the first 3 months of the study. Validity is defined as completing all three sections of the task.
	
	Reliability will be measured as the agreement between data collected during each session for a given month.
	
	Validity will be measured as the correlation between finger tapping scores obtained at home and:
	      Directly observed dexterity scores obtained in clinic
	      Clinical measures (MDS-UPDRS)
	
	Sensitivity to change will be measured as the change from mean score for month 1 to mean score for month 12 divided by the standard deviation of scores obtained in month 1.

Introduction

Over the past 25 years, there has been growing interest in strategies aimed at slowing, halting, or reversing the progression of Parkinson's disease (PD). However, assessing the efficacy of so-called "neuroprotective" and "neuro-restorative" strategies has been problematic due to the lack of reliable measures of disease progression. Over this same period of time the "gold standard" for assessing the severity and progression of PD has been a clinical rating scale, the Unified Parkinson's Disease Rating Scale (UPDRS). (Fahn et al, 1987) Ratings of PD disability using this scale have been based on the judgment of individual raters; thus, this scale is not truly quantitative and lacks sensitivity to subtle changes in disease state. A more quantitative and sensitive measure of the specific motor impairments characteristic of PD not requiring observational rating could provide a more reliable measure of PD severity, shorten the time of assessment, and reduce the cost of clinical trials. The Objective Parkinson's Disease Measurement system (OPDM), a computer-based device, has been developed that quantitatively measures finger-tapping speed, reaction time, hand movement time, foot tapping, and speech. The goals of this study are: 1) to assess the test-retest and rater reliability of this computer-based module that quantifies several movement parameters measuring bradykinesia, and 2) to assess which metrics correlate most closely with the motor section of the UPDRS, as rated by expert movement disorders specialists.

Background

On May 26, 2004, the Kinetics Foundation sponsored a workshop on "Tools for Objective Measurement of Signs of Parkinsonism." The primary goals of this project were two-fold: 1) Select practical objective measures of motor function in early PD and 2) Develop a computer-based device that could be used by patients in the home environment. Dr. Christopher G. Goetz [Rush Presbyterian Medical Center] chaired the meeting and the faculty who participated were: Drs. Rodger Elble, [University of Southern Illinois] (Tremor), Mark Hallett [National Institutes of Health] (Bradykinesia), Terrance Sanger [Stanford University] (Rigidity), Helen Bronte-Stewart [Stanford University] (Balance impairments), John Nutt [Oregon Health & Science University] (Gait), Lorraine Ramig [University of Colorado](Speech) and Glenn Stebbins (Clinimetric issues). The faculty selected six domains of parkinsonism that could potentially be assessed with objective measures— Tremor, Bradykinesia, Rigidity, Gait, Balance and Speech. Five of six (all except Rigidity) were considered pertinent in the context of available tools and clinical interest. Three of the domains (Tremor, Bradykinesia, and Speech) were regarded as having tools suitably portable to allow patients to provide data at home as well as in the physician's office. However, for Gait and Posture, available tools were considered restricted to an office setting only. It was also felt that Reaction time/Movement time could be incorporated as a behavioral-motor integrative test. **Bradykinesia** was the domain of greatest overall interest for objective assessment of parkinsonism. Three tools were identified that could be potentially utilized in home and office settings: 1) a Purdue Pegboard modified to detect start and stop time for the entire task and for individual peg insertions; 2) a musical key-board apparatus developed and standardized by Dr. Helen Bronte-Stewart that measures the rate of

alternating finger tapping with two fingers and 3) a computer-based device designed to measure Reaction Time and Movement Time.

Based on these concepts a transportable computer-based device that incorporated tasks that assessed seven domains of parkinsonian motor function was developed by Intel health and designed to be self administered by patients in their home. This "at home" device was then used in a 6 month longitudinal pilot study of patients with early stage PD (Goetz et al, 2008).

In this study, 50 patients not treated with symptomatic PD medication underwent training on the device and were tested weekly in their home. Electronically encrypted data was transmitted via the internet to a central repository. Subjects also underwent rating using the UPDRS at baseline, 3 and 6 months. Although the UPDRS scores showed a significant worsening over a 6 month period (p = 0.009), no statistically significant worsening occurred in the seven tasks assessed by the "at home" device. However, there appeared to be a trend of worsening in certain tasks such as the "keyboard", speech and tremor tasks. It was concluded that the home testing can detect changes in parkinsonian motor function. However, it is hypothesized that this device may provide better sensitivity in the controlled environment of a physician's clinic. Thus, we have proposed a sub-study involving a cohort of PD subjects enrolled in the PPMI study, to evaluate the feasibility of incorporating home dexterity testing (using the OPDM) and to assess the validity of home dexterity testing relative to examiner-based measures (e.g. UPDRS).

Study Objectives

Primary Objective

To assess the feasibility of incorporating home dexterity testing using the OPDM-Dexterity measure into a longitudinal observational study of progression of Parkinson's disease (PPMI).

Secondary Objectives

1) To assess the reliability of home dexterity testing over repeated short-term administrations.

2) To assess the validity of home dexterity testing relative to examiner-based measures (e.g. UPDRS).

3) To assess the sensitivity to change of dexterity testing by comparing scores at baseline and year 1.

OPDM Study Protocol

1. Study Population

Subjects with recently-diagnosed Parkinson disease (PD) who have consented to participate in the PPMI study. Control subjects will not be included in this study.

PD Subjects Eligibility Criteria

Inclusion criteria:
   a) PD subject who is otherwise eligible for enrollment into PPMI.

   b) Enrolled at one of three participating sites:
       Oregon Health & Science University, Portland, OR
       Institute for Neurodegenerative Disorders, New Haven, CT
       University of Pennsylvania Movement Disorders Center, Philadelphia, PA

   c) Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations.

   d) Willing and able to complete additional study procedures.

Exclusion criteria:
   a) Evidence of "atypical" parkinsonian syndromes (e.g. Progressive supranuclear palsy, Multiple system atrophy, drug-induced parkinsonism, Lewy body dementia).

   b) Any medical condition other than PD that would interfere with the subject's ability to perform study procedures as determined by the investigator.

2. Subject Enrollment

The subject will be asked to provide written informed consent prior to study procedures. OPDM testing will be performed as part of the PPMI Baseline visit activities (as outlined in the PPMI protocol). After a subject signs informed consent to participate in the TAP-PD sub-study they will receive instructions and training by the clinical staff on how to use the OPDM device and when and how to perform the at home testing. It is estimated that the time required per subject will be approximately 2 hours. Subjects who withdraw from TAP-PD may continue participation in PPMI; however, if a subject withdraws from the parent PPMI study, the subject must also be withdrawn from TAP-PD.

3. Assessments

Screening and Baseline data:
Subject information such as demographic, clinical data, concomitant medications, MDS-UPDRS (part I, II & III) and additional assessments will be collected as described in the PPMI protocol.

Disability assessment:
The following assessments completed as part of the PPMI protocol will be used as part of the data set for TAP-PD participants.
    A. Modified Hoehn and Yahr stage
    B. MDS-UPDRS parts I, II and III
    C. Other assessments and evaluations preformed as part of the PPMI protocol.

4. Objective Parkinson's Disease Measurement (OPDM) Setup

An illustration of the OPDM is illustrated in Figure 1 showing the pegs, buttons and keys that will be used by the subjects during the test procedure.

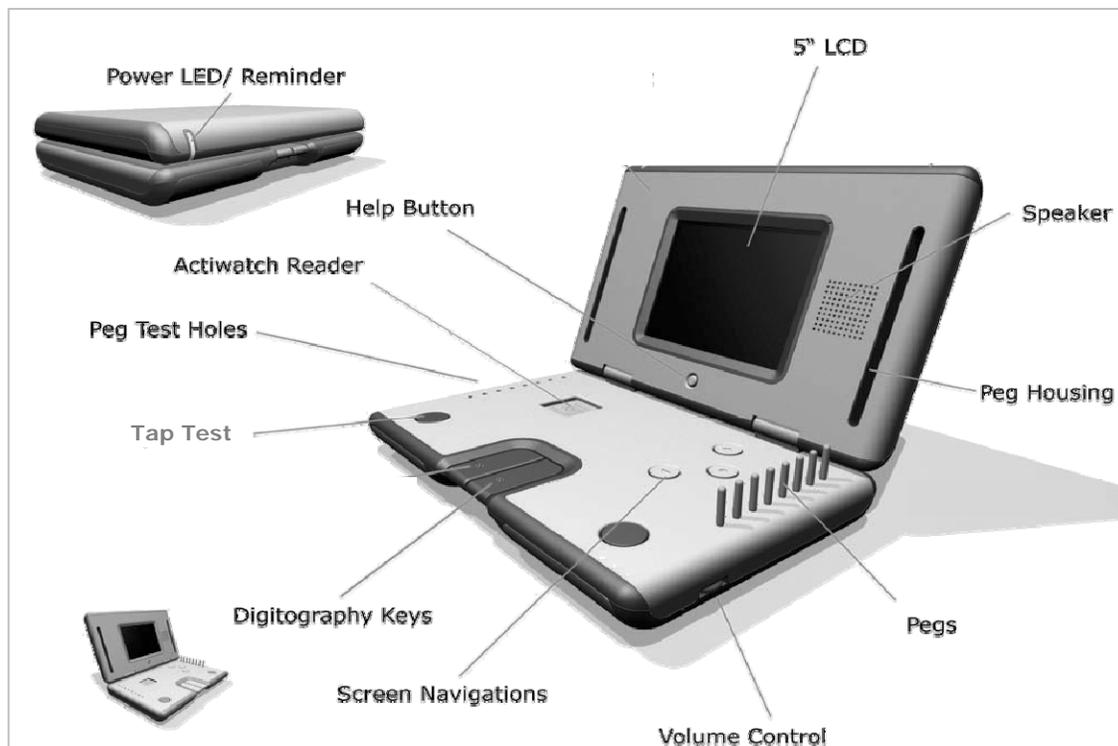Figure 1. Objective Parkinson's Disease Measurement (OPDM) Tool

Each subject will undergo a brief period of training on the operation of the OPDM device by the study coordinator prior to the start of the tasks. In this study, the OPDM will be administered 4 times at the study site, as well as self-administration over a 3 month period at home. The OPDM is designed to be self-administered and the subject will be

guided through the various tasks by auditory and visual instructions and cues. The OPDM script is appended. The estimated time required for completion of the OPDM protocol is 15-20 minutes. The subject will be informed to call the coordinator should they need assistance with the device or how to complete the at home portion of the assessment.

5. **OPDM Task protocol**

Digitography (Keyboard test): The subject is instructed to use the index and middle fingers of the right hand to alternately tap two side-by-side keys (Digitography keys, fig. 1) as fast as they can. An auditory and visual signal indicates the start of the test. The subject continues to tap until instructed to stop. The test is repeated with the left hand. The subject will rest the wrist on a pad in front of the device during this test.

Paced Keyboard Test: The subject is instructed to use the index and middle fingers of the right hand to alternately tap the two side-by-side keys (Digitography keys, fig. 1) in time with a metronome. The pace will start slow and increase. The subject is instructed to continue alternate tapping in rhythm with the metronome until instructed to stop. The subject will repeat the task with the index and middle finger of the left hand.

Pegboard: Each subject will be presented with 8 pegs inserted into holes on one side of the OPDM (fig. 1). The subject is instructed to transfer the pegs one at a time into a hole on the opposite side of the device as quickly as possible, starting when an auditory and visual signal appears. Subjects will then repeat the task with the opposite hand.

6. **Study Visit Procedures**

Baseline
- Obtain Informed Consent for TAP-PD
- Instruct and train subject on the use of finger-dexterity tasks including observation by study staff that training has been adequate
- Directly observed use of dexterity device in clinic
- PPMI assessments as described by PPMI protocol including MDS-Unified Parkinson Disease Rating Scale
- Provide OPDM device to subject to take home

At home between baseline and 3 month PPMI visits
- Perform dexterity device tasks one time per week (+/- 2 hours), at the same time of the week and time of the day, for about a 12 week time period (until subject returns for Month 3 PPMI study visit)

PPMI 3 month visit (V01)
- PPMI assessments including MDS-Unified Parkinson Disease Rating Scale
- Perform OPDM device task at study visit

- PPMI study staff to review home dexterity data and confirm that participant is correctly performing task
- Study staff to provide feedback to participants on performance
- Export data from device to Kinetics from at home and in clinic OPDM tasks
- Subject will return OPDM dexterity device to the site
- Complete survey of satisfaction with device

PPMI 6 month visit (V02)
- PPMI assessments including MDS-Unified Parkinson Disease Rating Scale
- Perform OPDM device task at study visit
- Export data from device to Kinetics

PPMI 12 month visit (V04)
- PPMI assessments including MDS-Unified Parkinson Disease Rating Scale
- Perform OPDM device task at study visit
- Export data from device to Kinetics

7. Adverse Events

Any adverse event, defined as any untoward medical event that the subject experiences during the visit will be recorded, including severity of the event, and causal relationship with the testing procedures as determined by the investigator.

Data recording, handling, transfer and storage:

A. Data collection

Subjects will retain the unique identification number assigned as part of the PPMI study. At the study visit, each subject's unique identification number will be recorded on all data collection forms. The date and time of each test portion will be recorded on the data collection forms. The clinical, demographic data and MDS-UPDRS scores will be recorded on source documents at the time of the study visit as outlined above. Some of the medical history and clinical information will be derived from source documents including prior medical records and recorded on the paper data forms.

The data from source documents and CRFs will be entered into a secure electronic database that will be accessible only by the investigators and research staff, secured with password protection. The patient name and identifying information will not be recorded on the case report forms (CRFs), but will be kept in a separate file at the site linking the patient name with the unique identification number. The CRFs will be transferred via a secure internet connection to a secure dedicated data server at Clinical Trials Coordination Center (CTCC) at the University of Rochester. Data entry and data transfers will follow the same process and security measures as those followed in the main PPMI study. There will be two types of data to be uploaded and integrated as described below.

1. **OPDM data.** This data will be saved during the testing period onto a portable data drive specific to the OPDM device, and transferred to the Kinetics server via a secured FTP link. This data will be encrypted.

2. **Meta data.** This data includes all of TAP-PD data such as the date of test and the subject questionnaire. These data will be entered by the site through a web form directly into the data server from the source document worksheets used during the study. This will be accomplished using standard internet secure encryption techniques (SSL) that comply with HIPAA.

B. Integrating data

When the data is uploaded, each data session will include the start and end time of the objective motor test battery and an ID for the machine with which the test was administered. OPDM data will be transferred from Kinetics to the CTCC for verification and quality control. After completing QC, the data will be transferred as part of the PPMI data set to the Laboratory of Neuro Imaging (LONI) at the University of California (UCLA) School of Medicine to be stored indefinitely for research purposes. PPMI research data (including the TAP-PD data) will be made available to researchers to conduct analyses related to PD and other disorders.

C. Data Analysis and objective motor score construction

Sensitivity to change will be measured as the change from mean score for month 1 to mean score for month 12 divided by the standard deviation of scores obtained in month 1.

Feasibility will be measured as the proportion of subjects who complete at least 3 valid sessions per month for all of the first 3 months of the study. Validity is defined as completing all three sections of the task.

Reliability will be measured as the agreement between data collected during each session for a given month.

Validity will be measured as the correlation between finger tapping scores obtained at home and:
Directly observed dexterity scores obtained in clinic
Clinical measures (MDS-UPDRS)

References

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