REAL-PD trial – protocol amendment

a home-based validation protocol to capture movement patterns and Parkinson's symptoms based on sensor-derived data

(Version 3, 06-JUN-2018)

ABR dossier-number NL53034.091.15

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
AE	**Adverse Event**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CRCN	**Clinical Research Center Nijmegen**
GCP	**Good Clinical Practice**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
PD	**Parkinson's disease**
PPMI	**Parkinson's Progression Markers Initiative**
(S)AE	**(Serious) Adverse Event**
SMM	**Senior Mobility Monitor**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Title: REAL-PD trial, a home-based validation protocol to capture movement patterns and Parkinson's symptoms based on sensor-derived data.

Rationale: Today's monitoring of patients with a chronic disorder like Parkinson's disease (PD) is imperfect and mainly dependent on short clinical observations and patient self-reports. Wearable sensors have the potential to provide objective and continuous measurement of symptoms. In the fast advancing field of wearable sensors and Parkinson's Disease, algorithms that are capable of producing relevant, valid and reliable measures during continuous free-living monitoring, have the highest potential to be useful for clinical practice and research purposes. However, the vast majority of algorithms developed for monitoring of Parkinson's Disease, are based on controlled lab studies. To fully benefit from the opportunities of wearable sensors, algorithms should be trained and validated on datasets that are collected in naturalistic, ecologically valid surroundings such as the private home.

Objective: The primary goal of this study is to assess the feasibility of a protocol for the creation of an ecologic dataset that can be used for the development and validation of novel algorithms aimed at capturing relevant PD features (i.e. motor fluctuations, falls and fall risk, gait quantification and freezing of gait) during continuous free-living monitoring using unobtrusive wearable sensors.

Study design: Observational study.

Study population: The study sample will consist of 50 participants in total: 25 PD patients (known with motor fluctuations and Parkinson-related gait disturbances) and 25 age-matched healthy controls.

Intervention: The protocol consists of two parts. In the first part (home visit), participants will be visited at their homes by two researchers. The aim is to capture as natural behaviour as possible while the participants wear several wearable sensor devices (smartwatch, smartphone, Empatica E4, Philips MobilityMonitor and multiple Physilog devices). As references, a series of standardized assessments will be performed and a video camera will be used to record the whole visit. After this, part 2 starts (home-based follow-up) during which the patient will continue wearing a selection of the sensors (smartwatch, smartphone and one MobilityMonitor) for 2 weeks and complete self-reports during this follow-up period (consisting of reports on medication intake, falls, symptoms and activities).

Main study parameters/endpoints: The primary outcome measures consist of several feasibility aspects of the protocol, including practical aspects of the protocol, user experiences and the quality of obtained data (from both sensors and references). Secondary study endpoints include all collected data that can be used to pilot with the development of novel algorithms, consisting of the obtained wearable sensor data and the references including videos, standardized assessments and self-reports.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In the current study, no invasive measurements will be performed. In part 1 of this study, participants receive a maximum 4,5-hour visit at their homes in the morning, which, for PD patients taking levodopa/dopamine medication, includes a delay of their first dose for assessment during an OFF period. The whole visit will be video-recorded and sensor devices will be worn on several body locations (wrists, shanks, lower back, necklace, trouser pocket). In the 2-week home-based follow-up (part 2), participants are asked to wear a smartwatch as much as possible, wear a necklace during the day (that can be hidden under their clothes), and regularly charge both the smartwatch, smartphone and necklace. In addition, participants are supposed to, if applicable, regularly complete self-reports regarding their medication use, falls and motor fluctuations. All these measurements will have a negligible physical, psychological and social risk for the patients.

Extensive safety measures will be applied regarding the management of (potentially) personally identifying research data that is being collected. Researchers can receive permission provided by The Michael J. Fox Foundation for Parkinson's Research to access to de-identified data for research purposes. Participation in the study warrants that patients have provided informed consent for this.

Subjects are expected to benefit personally from participating in this study, as they can use the devices for free during the study.

1. INTRODUCTION AND RATIONALE

Parkinson's disease (PD) is the most common degenerative movement disorder, affecting over 1% of the population over the age of 65 years and more than 500,000 US residents. The characteristic motor features are rest tremor, bradykinesia, rigidity, and impairment of posture and balance. The primary biochemical abnormality in PD is deficiency of dopamine due to degeneration of neurons in the substantia nigra pars compacta. Current therapy is based on a dopamine replacement strategy primarily involving the dopamine precursor, levodopa. However, PD patients eventually develop disability as a consequence of non-dopaminergic features such as freezing, falling and dementia which are not adequately controlled with levodopa.[1,2,3]

The most common form of clinical evaluation involves short observation during simple motor tasks such as getting up from chair and walk a short distance[4]. Assessment of response to the use of long-term medication is usually provided through a self-report of the patient, who evaluates the periods 'on' and 'off'. However, self-reports can be unreliable. Considering the complexity of determining optimal levodopa dosing schedule, a more objective way to assess motor fluctuations over longer periods, during normal daily life, can significantly improve the management of PD.

Wearables sensors provide the opportunity to measure symptoms and patient functioning in a continuous and objective way. In the fast advancing field of wearable sensors and Parkinson's Disease, algorithms that are capable of producing relevant, valid and reliable measures during continuous free-living monitoring, have the highest potential to be useful for clinical practice and research purposes. However, the vast majority of algorithms developed for monitoring of Parkinson's Disease are based on controlled lab studies. When applied on data collected during free-living monitoring, the performance of these algorithms is often disappointing. To fully benefit from the opportunities of wearable sensors, algorithms should be trained and validated on datasets that are collected in naturalistic, ecologically valid surroundings such as the private home.

Several aspects are challenging regarding the collection and application of data in these naturalistic environments, as summarized by Hammerla et al. (2015)[21]:

1. The main source of variance in the collected signals, is not disease-specific, but merely stems from variance in (largely unknown) activities that patient engage in. An assessment system has to generalize across this "noise" to obtain an impression of clinical features in PD;
2. For many clinical features, available references for the wearable sensor data are confined to expert ratings and patient self-reports. The use of these references is challenging because of two reasons; first of all, there is a significant disparity between the frequency at which data is

collected from body worn sensors (e.g. 100Hz) and the labeling from traditional clinical assessments (e.g. one per 30 minutes). Secondly, both expert ratings (e.g. MDS-UPDRS) and patient self-reports (e.g. Hauser diary) are far from fully objective ratings and subject to multiple reliability issues (e.g. inter-rater variability, recall bias).

Despite these challenges, some studies have already shown that it is possible to obtain promising results using deep learning techniques and other methods that are capable of coping with noise in both the sensor signal and references in naturalistic data sets[21].

Maetzler et al. (2016)[22] have proposed a selection of outcome domains that deserve attention because of their clinical relevance and promising results regarding the application of wearable sensors, most importantly motor fluctuations, gait impairments and physical (in)activity. Del Din et al. (2016)[23] have summarized the state-of-the-art of wearable sensor systems aiming at free-living monitoring of Parkinson's Disease. Although currently there are no fully validated and reliable systems available, promising progression has been made regarding the assessment of motor fluctuations, falls and fall risk, sleep, physical activity and the quantification of functional mobility (gait, turning, postural transitions). However, not all studies have addressed usability concerns or have used a sensor set-up that can be deployed in an unobtrusive way in the daily life of PD patients.

Therefore, this study will primarily focus on collecting data from wearable sensors that have proven to be usable for deployment in continuous free-living monitoring, and are suited for use in large-scale cohort studies. In this way, algorithms that are developed using the dataset obtained in this study, can be implemented in the study "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial", registered as ABR dossier-number NL53034.091.41 and CMO dossiernummer 2015-1776. Modern smartphones and smartwatches are examples of wearable devices that show excellent usability. Because many patients already use such a device for other purposes (currently at least a smartphone), valuable research data can be collected in an unobtrusive way without asking patients to wear "another" system. The extensive sensor complement of modern smartphones and smartwatches is another benefit; these devices not only contain sensors to measure movements itself (accelerometer, gyroscope, magnetometer), but also many other sensors (e.g. ambient light, GPS, proximity, WiFi scan) that can provide valuable context information when trying to obtain reliable outcomes in uncontrolled environments[24]. In Table 1, an overview is presented of the different outcome domains and an estimation of the feasibility to measure them with a 2-location approach (combination of a wrist-worn and a waist-worn device, considering the smartphone as a

waist sensor) based on the current literature. Because the wearable devices market is developing fast, the sensor selection in a part of this study will be extended to also include other key body locations (e.g. shanks, lower back, necklace) and promising new sensor types (e.g. galvanic skin response, PPG). Although feasibility of implementing these sensor types and locations in the study "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial" is currently limited, the knowledge of working with these devices will become increasingly relevant when more user-friendly alternative devices become available.

Table 1. An overview of the different outcome domains relevant in Parkinson's disease and an estimation of the feasibility to measure these with only a smartwatch and smartphone.

Relevant domains	**Free-living monitoring feasible with unobtrusive set-up?** ***(smartwatch & smartphone only)***
Motor symptoms	
Motor fluctuations	Some evidence[15,20,21,23]
Freezing of gait	Limited evidence[16,23]
Functional mobility	
Falls and fall risk	Some evidence[19,23]
Gait	Some evidence[20,23]
Turning	Limited evidence[23]
Behavior	
Physical (in)activity	Strong evidence[18,23]
Non-motor symptoms	
Sleep	Some evidence[17,23]

2. OBJECTIVES

The aim of the study described in this amendment, which is part of the REAL_PD trial (NL53034.091.41), is two-fold:

1) to test and where needed improve the feasibility of the data collection protocol; and
2) to establish an ecologic dataset that can be used for the development and validation of novel algorithms aimed at capturing relevant PD features (i.e. motor fluctuations, falls and fall risk, gait quantification and freezing of gait) during continuous free-living monitoring using unobtrusive wearable sensors.

We will primarily focus on measuring motor symptoms and functional mobility. Physical (in)activity and sleep also deserve attention but do not fit within the scope of the protocol of this study.

The outcomes of this study will be used to change the clinical assessment procedure included in the study protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, registered as ABR dossier-number NL53034.091.15 and CMO dossiernummer 2015-1776, and the novel algorithms will be applied to the data collected in this study.

3. STUDY DESIGN

This study is an observational study, including 25 patients diagnosed with PD and 25 age-matched healthy controls. The home-based validation protocol consists of two parts. In the first part (home visit), participants will be visited at their homes by two researchers. The aim is to capture as natural behaviour as possible according to the procedures defined in chapter 8.3. As references to the data from wearable sensors (see paragraph 6.1), a series of standardized assessments will be performed and a video camera will be used to record the whole visit. After this, part 2 starts (home-based follow-up) during which the patient will continue wearing a selection of the sensors for 2 weeks and complete self-reports during this follow-up period. The strength of part 1 lies in the detailed reference, while part 2 will capture more natural behavior albeit with less contextualization.

STUDY POPULATION

3.1 Population (base)

The study sample will consist of 30 participants in total: 25 PD patients (known with motor fluctuations and Parkinson-related gait disturbances) and 25 age-matched non-PD controls. The PD patients will be recruited from the applications of the REAL_PD trial. The non-PD group will be recruited by inviting the partners from the participating PD patients to also join this study.

3.2 Inclusion criteria

The inclusion criteria consist of:

- Male or female age 30 or older;
- Currently own and use a smartphone device with access to WiFi, Android 4.4 or higher, and featuring an accelerometer;
- Ability to provide written informed consent in accordance with Good Clinical Practice (GCP), International Conference on Harmonization (ICH), and local regulations;

PD group only:

- Subjects must have a diagnosis of Parkinson's Disease, confirmed by a neurologist;
- Subjects must be on levodopa or dopamine agonist medication;
- Subjects must be known with motor fluctuations (wearing off and/or unpredictable off phases) (screening based on MDS-UPDRS part IV item 4.3 ≥ 1);
- Subjects must be known with Parkinson-related gait disturbances (bradykinetic gait and/or freezing of gait) (screening based MDS-UPDRS part II item 2.12 ≥ 1 AND/OR item 2.13 ≥ 1)

3.3 Exclusion criteria

- Patient group only: patients receiving advanced therapy for their Parkinson's disease (deep brain stimulation, duodopa pump, apomorphine pump)
- Subjects known with psychiatric comorbidity or cognitive impairments that may hinder successful completion of study protocol.

3.4 Sample size calculation

This study is an observational descriptive study and therefore does not have power calculations based on hypothesis testing. We have selected a sample size of 25 patients and 25 healthy subjects

for the consideration that it would provide a dataset with sufficient amount and diversity in movement patterns.

4. TREATMENT OF SUBJECTS

NOT APPLICABLE

5. INVESTIGATIONAL PRODUCT

NOT APPLICABLE

6. NON-INVESTIGATIONAL PRODUCT

6.1 Name and description of non-investigational product(s)

First of all, a video camera will be used to record part 1 (home visit). The core selection of wearable sensor devices was based on their usability for deployment in continuous free-living monitoring and the feasibility for use in large-scale cohort studies. 4 non-investigational products will be used in *both* part 1 and part 2; an Android smartphone owned by the participants, an Android Wear smartwatch provided by us and a Philips Mobility Monitor (MM), which is worn as a necklace. To create a robust reference dataset for algorithm training, the sensor set-up will be extended only during part 1, by adding other key body locations and promising new sensor types. In this light, the Physilog 4 will be added to both shanks, lower back, and both wrists, and the Empatica E4 will be added to one wrist. All devices used in this study have a CE-marking.

Because of their limited usability for continuous daily life monitoring, we will not ask participants to continue wearing these additional devices during part 2 of the study. However, the data from these devices will become increasingly relevant for large-scale cohort studies when feasible alternative devices become available in the fast developing market of wearable devices. See table 2 for an overview of the sensor locations and devices that are used.

Table 2. Overview of the different wearable sensor devices used in the current study.

Location	Device	Collected sensor data
Wrist	Android Wear smartwatch (PD group: most affected side, if comfortable)	Accelerometer, gyroscope, magnetometer, barometer, light, photoplethysmogram (PPG), GPS, proximity, WiFi networks.
	Part 1 only: Empatica E4 (other side than Android Wear smartwatch)	Galvanic skin response (GSR), PPG, skin temperature.
	Part 1 only: Physilog 4 (both sides)	Accelerometer, gyroscope, barometer.
Smartphone (part 1: trouser pocket only)	Own smartphone (Android 5.0 or higher)	Accelerometer, gyroscope, magnetometer, barometer, light, GPS, proximity, WiFi networks, cellular networks.
Necklace	Philips Mobility Monitor	Accelerometer, gyroscope, barometer.
Lower back	***Part 1 only****:* Physilog 4	Accelerometer, gyroscope, barometer.
Shank	***Part 1 only:*** Physilog 4 (both sides)	Accelerometer, gyroscope, barometer.

Philips Mobility Monitor

For more information on the device, see paragraph 7.1, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776. In the current study the MM will be used as a necklace in part 1 and 2.

Android-based smartphone

The smartphone will be used to run the HopkinsPD app, to collect sensor data from the smartphone itself. The HopkinsPD app is developed by researchers of the John Hopkins University for better monitoring of Parkinson’s disease. It enables the collection of relevant sensor data, including accelerometer, gyroscope, magnetometer, barometer, light, proximity, GPS, WiFi networks and cellular networks (the latter 3 are used to measure location indoors and outdoors, which provides important context for algorithms designed for free-living monitoring). Because it collects potentially personally identifiable data (GPS, WiFi networks and cellular networks), data will not be streamed to any server but logged on the internal memory of the smartphone during data collection in both part 1 and 2. For more details about the data management, see paragraph 11.1.

In part 1, participants will be encouraged to carry their smartphone with them (in the location where participants usually carry their smartphone), to ensure the collection of useful data during the limited timeframe. In part 2, with the emphasis on naturalistic data collection, participants will not receive any specific instruction regarding the use of their smartphone.

Android Wear smartwatch

On the Android Wear smartwatch, an application (highly similar to the HopkinsPD app) will be installed that enables the collection of relevant sensor data, including accelerometer, gyroscope, magnetometer, barometer, light, photoplethysmogram (PPG), GPS, proximity, WiFi networks. During data collection in both part 1 and part 2, data will be logged on the internal memory of the device. For more details about the data management, see paragraph 11.1.

Empatica E4

The Empatica E4 is a wrist-worn monitoring device with a CE-marking. It contains a GSR, PPG and skin temperature sensor. Full specifications can be found at https://support.empatica.com/hc/en-us/articles/202581999-E4-wristband-technical-specifications. The obtained data will be streamed in a de-identified form to servers managed by Empatica. No personal data will be streamed to servers from Empatica.

Physilog 4

The Physilog 4 is a small monitoring device with a CE-marking manufactured by Gait-Up. It contains a accelerometer, gyroscope and barometer sensor. Full specification can be found at http://www.gaitup.com/wp-content/uploads/Brochure_Datasheet_Physilog_RA_V2.6.pdf. During data collection, data will be logged on the internal memory of the devices.

Video camera

During part 1, the whole visit will be videotaped using one high definition hand-held camera. The raw video data will be stored on the memory of the device, and subsequently transferred to the internal servers of the Radboudumc. The video data will not be stored on any other location. For more details about the data management, see paragraph 11.1.

Synchronization between multiple sensor devices & video recordings

To ensure proper synchronization in part 1 between the different sensors, video reference and assessments, a 2-way approach will be used; (1) the internal clock of each device will be kept aligned with the internal clock of the smartphone (which is connected to internet), the smartphone time will be noted for each assessment, and (2) all sensor devices will be triggered (shaken hard for 10 seconds) at the same time in front of the camera at the beginning and at the end of the recordings. In part 2, the data collection software for both smartwatch, pendant and smartphone will ensure that the timestamps are synchronized with the internal clock of the smartphone, and participants will be instructed to use the smartphone time for the paper-based self-reports.

6.2 Summary of findings from non-clinical studies

See paragraph 7.2, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

6.3 Summary of findings from clinical studies

Not applicable.

6.4 Summary of known and potential risks and benefits

See paragraph 7.4, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

6.5 Description and justification of route of administration and dosage

Not applicable.

6.6 Dosages, dosage modifications and method of administration

Not applicable.

6.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

6.8 Drug accountability

Not applicable.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The main analysis in the current study consists of an assessment of the feasibility of the protocol, addressing practical aspects of the protocol, user experiences and the quality of obtained data; all feasibility parameters are summarized in table 3.

Table 3. Summary of feasibility parameters, including an explanation and a brief description how they will be assessed.

Study parameter	Description	Endpoint
Practical aspects		
Recruitment	• Willingness of PD patients and healthy controls to participate in trial with home-based measurements (including video).	• Number of inclusions, number of refused consents.
Execution part 1	• Realistic estimations of time needed for assessments and free living parts • Division of tasks between assessors • Usefulness of checklist for behaviors in part 1	• Feedback from assessors.
Execution part 2	• Amount of support needed	• Number of calls, number of e-mails during the follow-up period.
Experiences of participants		
Experienced burden	• Part 1: duration of visit, OFF phase assessment, etc. • Part 2: usability aspects of different sensors, amount of effort required for self-reports, etc.	• Evaluation visit.
Data collection		
Captured behavior (part 1)	• Feasibility to detect “naturalistic” behavior during home visit.	• Experiences of assessors and

Study parameter	Description	Endpoint
	• Feasibility to detect PD-related symptoms (e.g. tremor, FOG) during home visit.	researchers labeling the videos.
Video (part 1)	• Quality of video recordings	• Evaluation by researchers labeling the videos.
Self-reports (part 2)	• Compliance of self-reports (on medication intake, falls, symptoms and activities)	• Number of completed vs. missing registrations.
Sensor data (both parts)	• Streaming compliance (part 2) • Data quality aspects (including comparison between research devices and commercial devices in part 1)	• Number of hours of collected data • Data quality evaluation by researchers analyzing the data.
Synchronization (both parts)	• Synchronization between different sensor and reference measurements	• Evaluation by researchers analyzing the data.

7.1.2 Secondary study parameters/endpoints

This study also involves piloting with using the obtained dataset for the training of novel algorithms aimed at the detection of motor fluctuations, falls, fall risk, the quantification of gait and freezing of gait. The following data will be used by specialized data scientist for this goal:

Domain	Source
Sensor data	• Android Wear smartwatch: accelerometer, gyroscope, magnetometer, barometer, light, PPG, GPS, proximity, WiFi networks. • Smartphone: accelerometer, gyroscope, magnetometer, barometer, light, GPS, proximity, WiFi networks, cellular networks. • Mobility Monitor: accelerometer, gyroscope, barometer. • Physilog 4: accelerometer, gyroscope, barometer. • Empatica E4: Galvanic skin response (GSR), PPG, skin temperature.
References	• Standardized assessments (part 1): MDS-UPDRS, AIMS, disease state

Domain	Source
	• Labeled video (part 1) • Self-reports (part 2): medication intake, Hauser diary, fall diary
Participant characteristics	• Obtained from screening call: age, gender, weight, height, hand dominance, occupational status, smartphone brand, model and Android version, PD medication use, disease duration, quality of life (PDQ-39). • Obtained from evaluation visit: information about general activities participants engaged in during the trial period (work, sports, etc.), relevant comorbidities affecting movements

7.2 Randomization, blinding and treatment allocation

This study does not involve a specific treatment and does not make an evaluation about an intervention. In view of this, randomization, blinding and treatment allocation are not applicable.

7.3 Study procedures

Before inclusion, every applicant will receive a screening call to collect baseline characteristics (age, gender, weight, height, hand dominance, occupational status, smartphone brand, model and Android version, PD medication use, disease duration and MDS-UPDRS questions related to motor fluctuations and gait disturbances (last 3 items: PD patients only)). During this call, more information about the study will also be offered. If the patient is eligible and willing to participate, the information letter (see E1 documents) together with the consent form (see E2) will be send out by e-mail or post. The information letter is slightly adapted depending on whether the participant is part of the PD or non-PD group (see E1 documents); the informed consent is equal for all groups. The research team and an independent physician can be approached for questions and verbal explanation. The applicant has one week to consider final participation and to sign the consent form and send it to the research team by e-mail or post. After receiving the signed consent form, the research team will contact, by phone, in order to schedule the home-visit and provide further practical explanations.

Participants in the PD group will receive an additional informed consent form (see E1 documents), asking for their permission to verify the diagnosis of Parkinson's disease with their general practitioner and inform him/her about their participation in the study. Only after receiving the

participant's consent, a letter will be sent to his/her general practitioner, asking to send the confirmation and year of diagnosis by mail to the research team.

Part 1: home visit

The participants will be visited by two researchers in the morning. Participants in the PD group will be instructed to delay their first dose on the day of the visit. Aim of the visit is two-fold: (1) collect sensor data from the participant's home environment of (close to) natural behavior (PD patients taking medication: in both ON and OFF state) and (2) provide references to this data, consisting of both a continuous video recording of the whole visit and standardized assessments. One researcher will be responsible for doing the assessments and communicating with the patient, while the other researcher will take care of the video recordings. See table 4 and 5 for an overview of the planning of the home visit, both for the PD patients (table 4) and the age-matched healthy controls (table 5).

Table 4. Timelines of the home visit for PD patients.

0:00-0:15	Introduction and installation of sensors (including synchronization)	
0:15-0:45	MDS-UPDRS part III and AIMS (OFF)	
0:45-1:45	Free living part 1 (OFF)	Every 30 minutes: Disease state (Hauser diary by both participant and assessor)
1:45-2:00	Participant takes his medication	
2:00-3:00	Complete MDS-UPDRS and AIMS (ON)	
3:00-4:00	Free living part 2 (ON)	
4:00-4:30	Completion and preparations for 2-week follow-up	

Table 5. Timelines of the home visit for the healthy controls.

0:00-0:15	Introduction and installation of sensors (including synchronization)
0:15-1:15	Free living part 1
1:15-2:15	Complete MDS-UPDRS and AIMS
2:15-2:45	Completion and preparations for 2-week follow-up

Participants will wear the sensor devices as described in chapter 7.1, which will be fully charged before the start of the experiments. The full MDS-UPDRS assessment, as described in paragraph 8.1, of protocol "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial", version 7, registered with CMO dossiernummer 2015-1776, will be part of the assessment in both groups, with the addition of the AIMS. For the PD patients, part III of the MDS-UPDRS and the AIMS will be performed both in OFF and ON phase.

In order to capture as natural behavior as possible, there will be no fixed script for the "free living" parts of the visit. This will involve some improvisation on the part of the visitors to encourage the participants to perform habitual activities, for example to do their normal morning routines. To make sure all essential behavior is covered, a checklist (Table 6) will be used. In this checklist, special attention will be given to behavior during which clinical features of interest are measurable (for example gait for measuring response fluctuations) and for behavior that is likely to give false positive results for clinical features of interest (for example sitting down regarding fall detection). Missed elements from the checklist will be marked by the assessor including the corresponding reason why this behaviour could not be captured. During the free living parts, every 30 minutes the visitors will assess the disease state (Hauser diary). Participants will also assess their own disease state every 30 minutes (using the Hauser diary). For the PD patients, the free living part will be conducted in both OFF and ON, and the checklist for behavior applies to both free living parts separately. Regarding the medication intake, exact timing, dose and medication type will be tracked for this group.

Table 6. Example of a checklist for essential behaviors to be captured with sensors and video-recording. Items may be added or removed during the testing process.

Take-off-put-on sensors	
Postural transitions	
Sit-stand (normal chair)	Sit-stand (low chair/couch)
Stand-sit (normal chair)	Stand-sit (low chair/couch)
Stand-lie	Lie-stand
Gait	
Walking inside	Making turns
Walk stairs up and down	Walking while carrying a light object
10 minute walk outside	Walking while carrying heavy object
Standard ADL routines	
Tidy bed sheet	Writing on paper
Preparing breakfast/lunch	Typing on a computer
Brush teeth	Typing on a smartphone

Washing hands	Putting on a coat

The whole visit will be video-recorded. The acquired video's will be labeled by a movement disorder expert, who will rate the disease status and assessments as well, and mark any fall incidents, near falls or freezing of gait episodes during the visit.

Part 2: home-based follow-up

After the home visit (part 1) the participants will continue wearing the wearable sensors during their everyday life as much as possible for 2 weeks (except for the part 1 only sensors, see table 2). During this period, reference data will consist of self-reports on Parkinson medication intake (PD patients only), motor fluctuations (PD patients only), falls (all participants) and activities (all participants). For this, a paper-based diary will be provided which participants will use to (1) complete daily reports on medication intake, falls and when applicable circumstances around the fall during the full 2-week follow-up period, and (2) keep track of motor fluctuations using the Hauser diary and custom questions about gait, freezing of gait, tremor and activities on selected days (2 days in trial period: one weekday, one during weekend). After the follow-up period, a researcher of the Radboudumc will visit the participant again to collect the Android Wear watch, MobilityMonitor and completed diaries, and to transfer the data from the participant's own smartphone using a USB connection to a computer that runs on the hospital's server. During this visit, an evaluation of the subject's experience will take place. This evaluation will include questions about the usability of the technologies employed, questions about general activities participants engaged in during the trial period (work, sports, etc.), and relevant comorbidities affecting the participant's movements.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

7.5 Replacement of individual subjects after withdrawal

Successful participation is defined as having at least completed part 1 of the study and in part 2 at least 7 days of data streaming from the sensors. Patients who fail this criterion, will be replaced.

7.6 Follow-up of subjects withdrawn from treatment

Giving the aim of the study, the subjects who withdrawn, do not need a follow-up.

7.7 Premature termination of the study

We cannot guarantee that patients will comply with prolonged use of wearable sensors or data transmissions will work. In these cases, this study will be put on hold and adjustments will be made before continuation.

8. SAFETY REPORTING

See chapter 9 of protocol "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial", version 7, registered with CMO dossiernummer 2015-1776.

9. STATISTICAL ANALYSIS

9.1 Primary study parameter(s)

The results from the feasibility assessment will be presented using descriptive statistics.

9.2 Secondary study parameter(s)

The obtained dataset will be used by specialized data scientist for the development of novel algorithms aimed at the detection of motor fluctuations, falls, fall risk and the quantification of gait.

9.3 Interim analysis (if applicable)

In view of the objective of this study, we will not to use an interim analysis.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

See paragraph 11.1, of protocol "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial", version 7, registered with CMO dossiernummer 2015-1776.

10.2 Recruitment and consent

See paragraph 11.2, of protocol "REAL_PD: development of clinical prognostic models for Parkinson's disease from large-scale wearable sensor deployment and clinical data – a population-based trial", version 7, registered with CMO dossiernummer 2015-1776.

10.3 Benefits and risks assessment, group relatedness

In the current study, no invasive measurements will be performed. In part 1 of this study, participants receive a maximum 4,5-hour visit at their homes in the morning, which, for PD patients, includes a delay of their first dose for assessment during an OFF period. The whole visit will be video-recorded and sensor devices will be worn on several body locations (wrists, shanks, lower back, necklace). In the 2-week home-based follow-up (part 2), participants are asked to wear a smartwatch as much as

possible, wear a necklace during the day (that can be hidden under their clothes), and regularly charge both the smartwatch, smartphone and necklace. In addition, participants are supposed to, if applicable, regularly complete self-reports regarding their medication use, falls and motor fluctuations. All these measurements will have a negligible physical, psychological and social risk for the patients.

Extensive safety measures will be applied regarding the management of (potentially) personally identifying research data that is being collected (video data, GPS, WiFi networks and cellular networks); this type of data will only be stored on the secured internal servers of the Radboudumc in an encrypted form (see paragraph 11.1). In addition, a de-identification step will be conducted before this data is included in the data repository. To access the de-identified data repository, researchers can receive permission for research purposes, provided by the Michael J. Fox Foundation. Besides the Radboudumc and the Michael J. Fox Foundation, designated researchers from Philips Research, Aston University, Intel Corporation and UCB have already been granted access by the Michael J. Fox Foundation to use the data repository for development of algorithms to capture PD characteristics based on wearable sensor data. In addition, the executive researcher of the Radboudumc can grant researchers from Philips Research, Aston University, Intel and UCB permission to view the raw video data for purposes that fit within the scope of this protocol. Researcher that have been granted permission, will be able to view the raw video data by using a secured digital research environment (DRE), in which the data will remain on the Radboudumc internal servers, but can be viewed via a virtual remote desktop client through a secured internet connection. Participation in the study warrants that patients have provided informed consent for this.

Subjects are expected to benefit personally from participating in this study, as they can use the devices for free during the study.

10.4 Compensation for injury

According to the local IRB Arnhem-Nijmegen the current study is free of risk and subjects do not need to apply for an additional subject Insurance.

10.5 Incentives

The patients will receive €20 for their participation upon completion of the minimal follow-up period (7 days of data streaming in part 2) and completion of part 1. Moreover, they can use the devices for free during the study period.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

The goal of this study is to create a data repository of valuable research data that does not contain personally identifiable information. The Michael J. Fox Foundation for Parkinson's Research can grant researchers permission to access this dataset for research purposes. However, some of the research data that is collected does contain (potentially) personally identifiable information. On this topic, we consulted the privacy and security officers (Léon Haszing and Gideon Teerenstra) of our hospital for their advice. The policy of this study is that this type of data will only be stored on the secured internal servers of the Radboudumc. Extra measures will be implemented to ensure secure management of (potentially) personally identifiable information. In addition, a de-identification step will be conducted before this data is included in the data repository. In this paragraph, we will describe the data storage, merging and sharing in more detail.

Data collection

Collected data will never be stored together with directly personally identifiable data (such as name, address, e-mail and phone number). Instead, all participants in this study will receive a unique identification code (e.g. thuisa1a, thuisa1b, thuisa1c, etc.). The executive researcher of the Radboudumc owns the list of names and corresponding identification codes and will be able to track back data to individual patients. For support purposes, this list will also be stored in our dedicated support system, ZenDesk (see further in this paragraph). Depending on whether the collected research data itself was labeled as potentially personally identifiable information by the security and privacy officers of our hospital, a different level of security measures will be implemented. See table 7 for a detailed description of all research data that is being collected in this study and its data collection and storing procedures.

Table 7: overview of all the research data that is being collected in this study and where it is stored.

Device/source	Collected data	Data collection and storage
Potentially personally identifiable information is collected* (in bold)		
Android smartphone	**GPS, WiFi networks, cellular networks,** meta-data (phone ID, Android OS version, brand, model, battery level, screen on/off), accelerometer, gyroscope, magnetometer, barometer, light, proximity.	Data is stored on the internal memory of the device during data collection. At the end of participation, researchers from the Radboudumc will extract the data by connecting the smartphone with a USB cable to a computer running on the hospital's network, and store the data in encrypted

		form on an internal server of the Radboudumc. Encryption keys will consist of 16 randomly assigned digits and stored on a different internal server of the Radboudumc.
Android Wear smartwatch	**GPS, WiFi networks,** meta-data (watch ID, OS version, brand, model, battery level), accelerometer, gyroscope, magnetometer, barometer, light, photoplethysmogram (PPG), proximity.	Data is stored on the internal memory of the device during data collection. At the end of participation, researchers from the Radboudumc will extract the data by connecting the smartphone with a USB cable to a computer running on the hospital's network, and store the data in encrypted form on an internal server of the Radboudumc. Encryption keys will consist of 16 randomly assigned digits and stored on a different internal server of the Radboudumc.
Hand-held high definition video camera	**Raw (unedited) video data** from home visit.	Data is stored on the internal memory of the device during data collection. Researchers from the Radboudumc will extract, encrypt and store the data on an internal server of the Radboudumc. Encryption keys will consist of 16 randomly assigned digits and stored on a different internal server of the Radboudumc.
No potentially personally identifiable information is collected*		
Empatica E4 watch	Galvanic skin response (GSR), PPG, skin temperature, accelerometer.	Data is streamed to secured servers managed by Empatica.
Philips Mobility Monitor	Accelerometer, gyroscope, barometer.	Data is stored on the internal memory of the device during data collection. Philips Research extracts and stores the data on their secured internal servers.
Physilog 4	Accelerometer, gyroscope, barometer.	Data is logged on the internal memory of the device and transferred to the internal servers of the Radboudumc.

Screening and evaluation phone call	Baseline characteristics (age, gender, weight, height, hand dominance, occupational status, smartphone brand, model and Android version, PD medication use, disease duration), results of evaluation, information about general activities participants engaged in during the trial period (work, sports, etc.), relevant comorbidities.	Data will be entered manually into a certified data management system (Castor), managed by the Radboudumc.
Paper-based assessments and self-reports	MDS-UPDRS, AIMS, Hauser diary, PDQ-39	Data from these paper-based forms will be entered manually into a certified data management system (Castor), managed by the Radboudumc.
Provided by general practitioners	Confirmation and year of diagnosis	All paper-based information provided by the general practitioners that may contain personal information, will be stored in a locked drawer at the Radboudumc. Only the pseudonymized information will be intered into Castor.

*after consultation with privacy and security officers (Léon Haszing and Gideon Teerenstra) of the Radboudumc

In addition to the research data, contact information of the participants (e.g. name, address, e-mail and phone number) will be stored for logistical and support purposes. All members of the Radboudumc research team have exclusive authorization rights to access this information. Personal data will be kept separately from the research data acquired, and stored in a dedicated support system, ZenDesk. ZenDesk will be used to support the logistics of the recruitment process and the technical support during part 2 of this study. ZenDesk is internet-based, governed by access right and authenticated by username and password. Moreover, ZenDesk has numerous measures in place to guarantee security: the servers are hosted at Tier III, SSAE-16, or ISO 27001 compliant facilities and have 24-hour manned security, biometric access control, video surveillance, and physical locks. The network is protected by redundant layer 7 firewalls, best-of-class router technology, regular audits and detection for network attacks. All communications with ZenDesk servers by default use industry standard SSL. The ZenDesk

servers are located on a different site than the servers used for research data in this study. Therefore, research data is never stored on the same server as patients identifying codes.

Contact information of the participating patients and physiotherapists, together with their personal identification code* will be deleted after the study has finished. A printed version of the codelist will be kept in the Radboudumc for 5 years, after which this document will be destroyed.

Merging and sharing of data

All research data that does not contain personally identifiable data will be merged into one research data repository by researchers from the Radboudumc. Regarding research data that includes potentially personally identifiable information, a de-identification step will be conducted before including this data in the data repository. For the raw video, this means that only the expert labels and corresponding timestamps will be part of the data repository. Concerning the obtained location data (GPS, WiFi and cellular networks), the absolute location coordinates will be transformed to relative data, in a way that the exact location cannot be derived, but that it can still be used as an indicator for displacement.

The Michael J. Fox Foundation can grant researchers permission to access the de-identified data repository for research purposes (including use in future publications) through an internet-based platform. Besides the Radboudumc and the Michael J. Fox Foundation, researchers from Philips Research, Aston University, Intel and UCB have already been granted permission by the Michael J. Fox Foundation to use the de-identified data repository for the development of algorithms. In addition, the executive researcher of the Radboudumc can grant researchers from Philips Research, Aston University, Intel and UCB permission to view the raw video data for purposes that fit within the scope of this protocol. Researcher who have been granted permission, will be able to view the raw video data by using a secured digital research environment (DRE), in which the data will remain on the Radboudumc internal servers, but can be viewed via a virtual remote desktop client through a secured internet connection. Participation in this study warrants that participants have provided consent for this.

11.2 Monitoring and Quality Assurance

During both part 1 and part 2, continuity and quality of the flow of sensor data from the smartwatches and smartphones will be regularly checked by researchers at the Radboudumc, to actively identify any problems with the equipment.

11.3 Amendments

See paragraph 12.3, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

11.4 Annual progress report

See paragraph 12.4, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

11.5 End of study report

See paragraph 12.5, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

11.6 Public disclosure and publication policy

See paragraph 12.6, of protocol “REAL_PD: development of clinical prognostic models for Parkinson’s disease from large-scale wearable sensor deployment and clinical data – a population-based trial”, version 7, registered with CMO dossiernummer 2015-1776.

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