The Accuracy of Digital Assessment of Performance Trial (ADAPT): Walk Test Study

PROTOCOL TITLE 'The Accuracy of Digital Assessment of Performance Trial (ADAPT): Walk Test Study'

Protocol ID	**NL78292.091.21**
Short title	**ADAPT**
EudraCT number	**Not applicable**
Version	**V4_15-02-2024**
Date	**February 15, 2024**
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Revision History

Version	***Date***	***Comments***
V1.1	***06 AUG 2021***	***Original Release***
V1.2	***07 OCT 2021***	***Added a new exclusion criteria; Added additional AE definitions; Added Device Deficiency section; Updated sample size calculation***
V2	***14 March 2022***	***Added an optional home measurement with the StepWatch for 2 weeks, added one questionnaire/ assessment, specified an exclusion criterion, changed assessment of medical history from visit one to visit one + visit two.***
V3	***20 July 2022***	***Added validation of free living passively recorded data as a secondary endpoint, added at home StepWatch measurement as obligatory, increased number of PD patients to be included***

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

6MWT	**6 Minute Walking Test**
ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
ADE	**Adverse Device Effect**
AR	**Adverse Reaction**
ARDS	**Access Restricted Data Store**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CIP	**Clinical Investigation Plan**
COPD	**Chronic Obstructive Pulmonary Disease**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MCID	**Minimally Clinically Important Difference**
PD	**Parkinson's Disease**
SAE	**Serious Adverse Event**
SADE	**Serious Adverse Device Effect**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**

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**
TUG	**Timed Up & Go Test**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Physical functioning is an important determinant of quality of life and therefore, a relevant issue in people with chronic conditions such as chronic obstructive pulmonary disease (COPD) and Parkinson's disease (PD). Physical capacity and physical activity are distinct and relatively independent aspects of physical functioning. With the rise of innovative technology, both aspects have become measurable in the free-living environment of people with chronic conditions. However, so far, physical capacity and physical activity have mainly been assessed in in-clinic settings using standardized performance tests (i.e. Six-Minute Walk Test (6MWT)) and questionnaires (i.e. LASA Physical Activity Questionnaire), respectively. Here we will examine the validity of a digital solution to remotely measure physical capacity and physical activity in two groups of participants: participants with PD and participants with COPD.

We aim to develop and validate algorithms to quantify and track physical capacity and physical activity to be used as clinical trial endpoints for the development of pharmacological and non-pharmacological interventions for participants with COPD and PD. The algorithms will be developed from sensor data collected on wrist worn devices (Verily Study Watch and, for a subset of participants, the Fitbit Sense). For analytical validation of the step counting algorithm, which is the basis of many other algorithms for walking activity and capacity, an ankle worn accelerometer (Modus StepWatch) will be used, as a reference device, simultaneously with Verily Study Watch at home for all participants. There will be two contexts for sensor data collection: 1) during the Virtual Walk Test, which is administered via application on a wrist worn device in the home setting, and 2) during the free-living context where participants simply wear the device(s) and the sensor data is passively recorded. In addition to the sensor data, each participant's relevant clinical outcomes, patient-reported outcomes, general demographics and medical history information will also be collected. The resulting data will be used to develop and/or validate algorithms to estimate participant's physical capacity as well as to quantify physical activity of the participant. By utilizing sensor data from wearable devices and their associated algorithms, we will be able to obtain frequent assessments of the participant's functional physical capacity and granular measurements of physical activity. Moreover, capturing comprehensive walking behavior through passive, continuous monitoring of participants in their own environment provides an opportunity for evaluating the possibility of using passive monitoring based measurements to be an indicator of one's functional capacity in the real world. If these digital tools are validated, these will support an improved ability to measure a participant's physical functioning at baseline and during treatment, and have the potential to capture the treatment-related change from baseline, more accurately. Ultimately, we expect that this effort will contribute to more effective and efficient development of pharmacological and non-pharmacological interventions for people with COPD and PD.

Objectives: The **primary objectives** for participants **with COPD** are: 1) to analytically validate algorithms that utilize free living data to estimate the in-clinic 6-

Minute-Walk-Test (6MWT) distance (free-living data based 6MWT distance estimator); 2) to analytically validate algorithms that utilize virtual 6MWT context-known data to estimate the in-clinic 6MWT distance (virtual 6MWT distance estimator). A subset of pre-selected data will be used to refine algorithms that are developed using data from other sources, and 3) to evaluate analytical validity of walking measurements based on passively recorded data. Test-retest reliability of four types of estimators (two (2) 6MWT distance and two (2) TUG time estimators) and walking measurements will be obtained as well. The primary objectives for participants **with PD** are: 1) to develop algorithms that utilize free living data to estimate the in-clinic 6MWT distance;2) to develop algorithms that utilize virtual 6MWT context-known data to estimate the in-clinic 6MWT distance; and 3) to evaluate analytical validity of walking measurements based on passively recorded data.

The secondary objectives for participants **with COPD** are: 1) to analytically validate algorithms that utilize free living data to estimate the outcome of in-clinic Timed-Up-and-Go test (TUG; free-living data based TUG time estimator) and 2) to analytically validate algorithms that utilize virtual TUG to estimate the in-clinic TUG (Virtual TUG time estimator). A subset of pre-selected data will be used to refine algorithms that are developed using data from other sources. Test-retest reliability of four types of estimators (two (2) 6MWT distance and two (2) TUG time estimators) will be obtained as well. The secondary objectives f**or participants with PD** are, 1) to develop algorithms that utilize free living data to estimate the outcome of in-clinic TUG and 2) to develop algorithms that utilize virtual TUG to estimate the in-clinic TUG.

The **exploratory objectives** is to obtain datasets that describe clinical and functional characteristics of people with COPD and PD for the development of additional digital biomarkers based on sensor collected data. The dataset will be used to develop prototype algorithms related to disease status or symptoms and test their relationship to clinical outcomes of interest.

Study design: We will perform a decentralized, prospective, observational study with a 15 week follow-up.

In-Clinic Portion: Participants will come to their assigned local physiotherapy practice four times (once every five weeks) for in-clinic assessments of walking capacity, and will be instrumented with up to three sensor wearable devices (Verily Study Watch, Modus StepWatch 4, and the Fitbit Sense) during the assessments. Participants will undergo a 10-week high intensity exercise training program supervised by a specialized physiotherapist as an intervention.

Remote Portion: Participants will be instructed to wear the Verily Study Watch for up to 23 hours per day for the entire study duration (15 weeks), to enable continuous free-living data collection, and will be asked to perform the Six-Minute Walk Test (6MWT) and Timed Up and Go test (TUG) once a week using the Verily Study Watch. Verily Study Watch will send out notification to perform 6MWT and TUG and guide participants through the remote assessments. A subset of participants may also wear the Fitbit Sense concurrently with the

Study Watch and will be asked to wear them for the first 5 weeks between first and second visits. All COPD and PD participants will also wear the Modus StepWatch 4 concurrently with the Study Watch for 14 days between week 5 and week 15. During these 14 days, participants are asked to wear the StepWatch for at least 10 days, which can fall on any random day with a minimum of two weekend days. Wear time of four to six hours on these days is intended.

Patients who are on a physiotherapist-supervised maintenance program with only low-frequency sessions (maximum 1 session per week) prior to study entry may continue during the first 5 weeks of the study (the baseline period). Newly referred patients will be asked to start intensive physiotherapy after the 5 week baseline period. However, if the participant and the physiotherapist think it is necessary or needed, it is allowed to start physiotherapy with a low frequency (maximum 1 session per week) during the baseline period. Five weeks of baseline period will allow to capture variability/fluctuation in symptoms, functional physical capacity, and other characteristics in participants activities of daily living based on sensor recorded data. Ten weeks of high intensity physiotherapy intervention is expected to induce changes in functional physical capacity and we will assess whether we can capture these changes using sensor data.

Study populations: 200 participants with COPD and up to 130 with PD (100 complete cases with both Study Watch and StepWatch at home) who are referred to a physiotherapist will be enrolled at up to 25-30 sites. Both patient groups should have sufficient cognitive capacity to understand and follow study procedures and be able to walk independently (with or without an assistive device). People who, in the estimation of their treating physician, are not able to perform walking tests safely at home will be excluded as well as those with more than one fall in the last three months, or unstable cardiovascular conditions.

Intervention: During this observational study, participants will be treated by a physiotherapist for their specific condition and resulting symptoms by undergoing a supervised physiotherapy program starting 5th week into the study for 10 weeks. Treatment will consist of a personalized approach based on the current clinical guidelines for physiotherapy for COPD[1] and PD, respectively. This personalized approach will consist of multiple treatment modalities, at least one of which has a component of aerobic exercise, which is hypothesized to impact walking test scores.[2,3]

Main study parameters/endpoints: For the analytical validation of algorithms developed based on data from people with COPD, the following endpoints will be used.
Co-Primary Endpoints are 1) Difference between in-clinic 6MWT distance and free-living data based 6MWT distance estimate, and 2) Difference between in-clinic 6MWT distance and Virtual 6MWT distance estimate.
Secondary Endpoints are 1) Difference between in-clinic TUG time and free-living data based TUG time estimate, 2) Difference between in-clinical TUG time and Virtual TUG time estimate, and 3) Difference between Study Watch based at-home walking measurements and reference device (StepWatch) based walking measurements, and 4) Test-retest agreement across various estimates from each algorithm that is validated.
Exploratory Endpoints are 1) ICC between free-living data based walking behavior measurements by StepWatch and Study Watch obtained from a subset of COPD participants

who consented to wear StepWatch as well as Study Watch at home 2) For the PD cohort, we will use the entire dataset to develop algorithms to estimate 6MWT distance, and ICC between free-living data based walking measurements by StepWatch and Study Watch obtained from a subset of PD participants who consented to wear StepWatch as well as Study Watch at home, and 3) For both groups, the entire dataset will be also used to develop exploratory digital biomarkers related to disease or other functional status and their relation with clinical outcomes of interest.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden of participating in this study consists of 4 visits to the local physiotherapy practice for in-clinic assessments of disease status and walking tests. These visits are scheduled in addition to the usual care physiotherapy assessments and therefore, can be considered an additional burden. Every in-clinic visit will take approximately 120 minutes in total. In addition, participants are asked to wear the Study Watch and StepWatch devices at home during waking hours for a minimum of 10 days over the 14 day period between second and last visits. The Study Watch will be worn continuously for 15 weeks and perform two walking tests once a week. The walking tests are guided and prompted by the Study Watch, making it easier to comply with these procedures. Simultaneous wear of the StepWatch along with Study Watch on the ankle and wrist, respectively, for at least 2 weeks during the study, will be an additional burden. However, the StepWatch does not require any form of interaction (i.e., no charging / syncing) The Verily Study Watch is being used in another study in participants with PD and the participants showed excellent compliance,[4] therefore it is expected that this will be a realistic approach. Participants will wear three different wearable devices in the clinic and max two devices at home. In the clinic, participants will wear the Study Watch on one wrist, Fitbit Sense on the other wrist, and the Modus StepWatch on the ankle for the duration of clinic visits for all four visits. For those who are willing to wear the optional FitBit device at home (minimum 50 people with COPD and 30 people with PD), simultaneous wear of the devices on each wrist, for at least the first five weeks of the study duration, will be an additional burden. However, participants will only wear a maximum of two devices at home simultaneously, even when the participant chooses to wear optional Fitbit device, because the timing of each device wear during study is different (i.e., Fitbit will be given for the first five weeks, and StepWatch will be given after the first five weeks). It is expected that this would be feasible based on prior studies where multiple devices were required to be worn for prolonged periods of time for the people with COPD[4] and PD.[5-7] In addition, wearing FitBit is not an obligatory part of the study, and participants can decline wearing multiple devices at the same time at home.

The main risks related to the safety of performing an unsupervised (submaximal) aerobic exercise test at home are related to falls and cardiovascular events. Falls may be more frequent in the PD population, while cardiovascular risk is higher in COPD because of (potentially undiagnosed) cardiovascular comorbidity. Risks associated with home measurement will be minimized by excluding participants that have fallen more than once in the last three months and by asking the treating physician (i.e. general practitioner, pulmonologist or neurologist) to assess a person's ability to participate in this study. Finally,

participants will receive 10 weeks of personalized physiotherapy, which they would also receive if they would not participate in this study.

1. INTRODUCTION AND RATIONALE

Physical functioning is an important determinant of quality of life and therefore a relevant issue in people with chronic conditions such as chronic obstructive pulmonary disease (COPD) and Parkinson's disease (PD).[3] Physical capacity and physical activity are distinct and relatively independent aspects of physical functioning.[8] With the rise of innovative technology, both aspects have become measurable in the free-living environment of people with chronic conditions.[9-13] However, so far, in clinical practice, applying wearable technology in at home settings is not part of usual care. Physical capacity and physical activity are, for example assessed in in-clinic settings using standardized performance tests (i.e. Six-Minute Walk Test (6MWT)) and questionnaires (i.e. LASA Physical Activity Questionnaire), respectively.

Relying only on in-clinic standardized tests and surveys is suboptimal for several reasons. First, in-clinic tests give limited, or potentially distorted information on how a patient is functioning in daily life. For example, patients with PD, experience a phenomenon called "kinesia paradoxa,"in which they function unexpectedly well under stressful circumstances, including in-clinic observations.[14] This problem is compounded by the fact that many patients take extra medication prior to the consultation (hoping to make a good impression), and some even practice the clinical tests while sitting in the waiting room. Second, the brief in-clinic evaluations cannot reliably capture the common and disabling fluctuations in response to Parkinson medication (the so-called ON-OFF fluctuations).[15] Finally, episodic visits are not well suited to detect changes in important lifestyle issues,[16,17] such as gradual declines in physical activity that can have a devastating impact on both COPD and PD.[18] Moreover, measuring physical activity with a questionnaire has been shown to be highly unreliable, because of their retrospective and subjective nature. Consequently, it is currently impossible to accurately assess physical capacity and physical activity in order to tailor treatment decisions to the actual needs of patients and to evaluate treatment effects, leading to unnecessary disability, poor quality of life, and avoidable medical costs.

Wearable technology, such as inertial sensors (i.e. accelerometers and gyroscopes) may offer a solution for the above mentioned challenges. By deploying wearable devices, we are able to evaluate how people actually function, for long periods of time (allowing repeated measurement), in real-life. Both remote assessments and passive monitoring of mobility allow data collection without relying on the patient's memory or in-clinic functioning. Remote assessment will allow us to perform (validated) tests on mobility and physical capacity more often and in the person's own home environment. Passive monitoring data will allow us to test the feasibility of developing walking measurements in the real world that reflect a comprehensive picture of one's walking behavior in a real life setting. These are hypothesized to be clinically meaningful aspects of health for both PD and COPD. Although free-living walking measures may not mimic in-clinic walking capacity measured by in-clinic clinical outcome assessments (e.g., 6MWT) in the same manner, some aspects of walking behavior in the real world may provide insights in walking capacity (e.g., high end walking speed, high end duration of walking during routine activities) and other aspects of functionality. Finally, free-living walking measures based on passively recorded data offer a few advantages over remote assessment. First, current in-clinic clinical outcome assessments of walking capacity require patients to come to the clinic which can be

burdensome to patients and their caregivers. Therefore, if sensor based digital tools can measure one's walking capacity at home, that would reduce patient burden. Second, even when a test is performed at home, it is still a test, which is not part of the usual daily activities. Third, a patient's functioning can fluctuate day-by-day, and even within a day. Passively collecting walking measures from sensor data, will provide patients and clinicians a fuller picture of these fluctuations. These fluctuations are potentially critical indicators for functional status (e.g., variability of walking behavior over days is known to have clinical relevance).[19,20]

Here we will develop digital solutions to remotely measure physical capacity and physical activity in two groups of participants-people with COPD and people with PD. Specifically, for COPD, we will use the subset of data to refine existing algorithms, and use the majority of the data to evaluate the analytical validity for estimation of 6MWT distance and free-living walking measurements. For PD, we will use the entire dataset to develop algorithms to estimate 6MWT distance. For both groups, the entire dataset will be also used to develop exploratory digital biomarkers related to disease or other functional status and their relation with clinical outcomes of interest.

2. OBJECTIVES

2.1 Primary Objectives

We aim to develop digital biomarkers for functional physical capacity and physical activity based on data collected both during a virtual walk test, administered on the Verily Study Watch, and by using free-living, passively recorded sensor data collected by the watch. More specifically, we aim:

For COPD:
1) To analytically validate algorithms that utilize free living data to estimate the in-clinic 6-minute-walk-test (6MWT) distance and obtain analytical validation of the algorithms; and
2) To analytically validate algorithms that utilize virtual 6MWT context-known data to estimate the in-clinic 6MWT distance and obtain analytical validation of the algorithms.

A small set of pre-selected data will be used to refine the algorithms that are mainly developed using data from other sources.

For PD:
1) To develop algorithms that utilize free living data to estimate the in-clinic 6-minute-walk-test (6MWT) distance; and
2) To develop algorithms that utilize virtual 6MWT context-known data to estimate the in-clinic 6MWT distance.

2.2 Secondary objectives

For COPD:
1) To analytically validate algorithms that utilize free living data to estimate the outcome of in-clinic Timed-up-and-go test (TUG) and obtain analytical validation of the algorithms;
2) To analytically validate algorithms that utilize virtual TUG to estimate the outcome of in-clinic TUG and obtain analytical validation of the algorithms;
3) To evaluate analytical validity of algorithms capturing various aspects of walking that utilize passively recorded sensor data; and
4) To obtain test-retest reliability of the following algorithms based on weekly Virtual 6MWT between first and second visits:

- Free-living data based 6MWT distance estimator
- Virtual 6MWT distance estimator
- Free-living data based TUG time estimator
- Virtual TUG time estimator.
- Free-living walking measurements

A small set of pre-selected data will be used to refine the algorithms that are mainly developed using data from other sources.

For PD:
1) To obtain the dataset to develop algorithms that utilize free living data to estimate the outcome of in-clinic Timed-up-and-go test (TUG); and

2) To obtain the dataset to develop algorithms that utilize virtual 6MWT context-known data to estimate the outcome of in-clinic Timed-Up-and-Go test (TUG).
3) To obtain the dataset to evaluate analytical validity of free-living walking measurements utilize passively recorded sensor data.

COPD and PD participants will wear StepWatch and Study Watch at home over two weeks. This will provide a dataset to compare free-living data based walking measurements by the two devices. StepWatch will be used as a reference device to evaluate the performance of Study Watch walking measurements to quantify waking activity and walking capacity in at home settings.

2.3 Exploratory objectives

We aim to obtain datasets to describe clinical and functional characteristics of people with COPD and PD for the development of digital biomarkers based on sensor collected data. The dataset will be used to develop prototype algorithms related to disease status or symptoms and test their relationship to clinical outcomes of interest.

We aim to relate both the virtual 6MWT clinical assessment and free-living based metrics to physical capacity and physical activity to patient-centered outcomes (i.e., measures something of relevance and importance to the patients, i.e. meaningful aspects of health in activities of daily living). To do that, we will collect Patient Reported Outcomes via well established, relevant questionnaires on motor symptoms, non-motor symptoms, activities of daily living, physical activity, quality of life and fatigue.
Additionally, this study aims to assess whether developed algorithms can be used/generalized for multiple sensor devices to derive metrics capturing physical capacity of patients. To do that Fitbit Sense will be worn in addition to Verily Study Watch to a subset of study participants. While being worn in the same individuals simultaneously, common types of sensors (i.e., accelerometer and photoplethysmography sensor) in both devices will record time-series data with matching timestamps and will be used to derive metrics using the same algorithms for assessing the feasibility of device agnostic algorithm development.

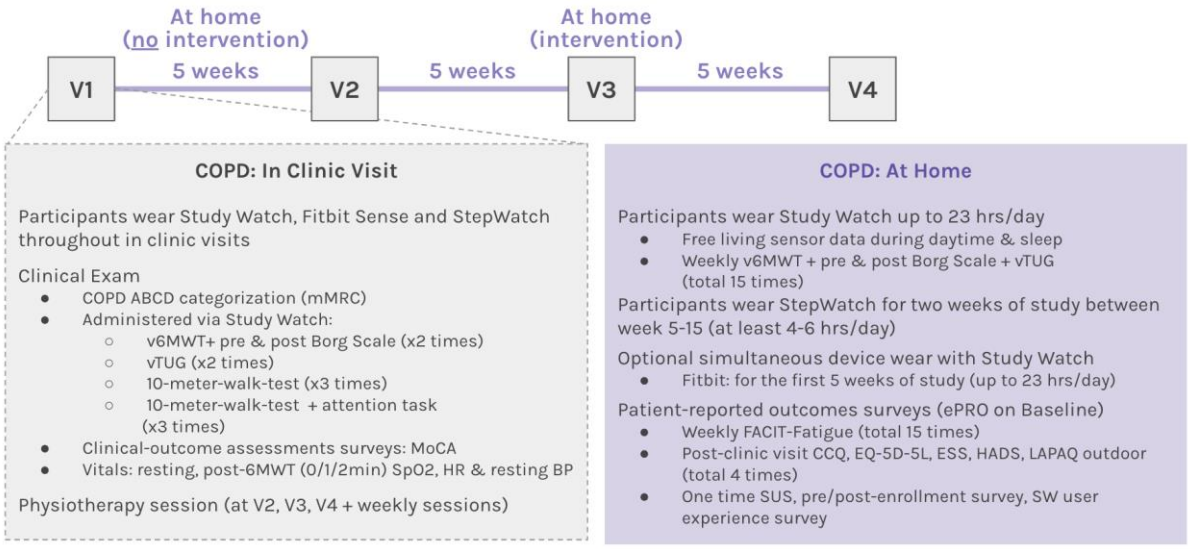
3. STUDY DESIGN

This study is a decentralized, prospective, observational study with 15 weeks follow-up (Figure 1). The study will be performed in two different populations-participants with COPD and participants with PD. Participants will go to their assigned local physiotherapy practice 4 times (once every 5 weeks) for in-clinic assessments of walking capacity and disease symptoms (specific to COPD and PD cohorts), while wearing three (3) different wearable sensor devices-the Verily Study Watch on one wrist, Fitbit Sense on another wrist and Modus StepWatch on the ankle. After each visit, participants will also fill out questionnaires on motor symptoms, cognition, quality of life, activities of daily living, and fatigue. In addition to wearing the Verily Study Watch for 23 hours per day and StepWatch device for two weeks of the study, at least 4-6 hours per day, between Visits 2 and 4 (and a Fitbit device for the participants who agree to do so, for the first 5 weeks, 23 hours per day of the study participation,), participants will be instructed to perform weekly home assessments (i.e. 6MWT and TUG tests). These assessments will be guided by the graphic user interface on the Verily Study Watch. Between week 5, and the end of the study (week 15), participants will participate in 10 weeks of physiotherapy treatment including a high-intensity aerobic exercise component. The intervention is hypothesized to impact walking capacity and induce variation in walking test scores. In the first 5 weeks of the trial, physiotherapy is allowed, only when deemed necessary by the patient and physiotherapist. Patients will not receive high-intensity aerobic exercise training during this period.

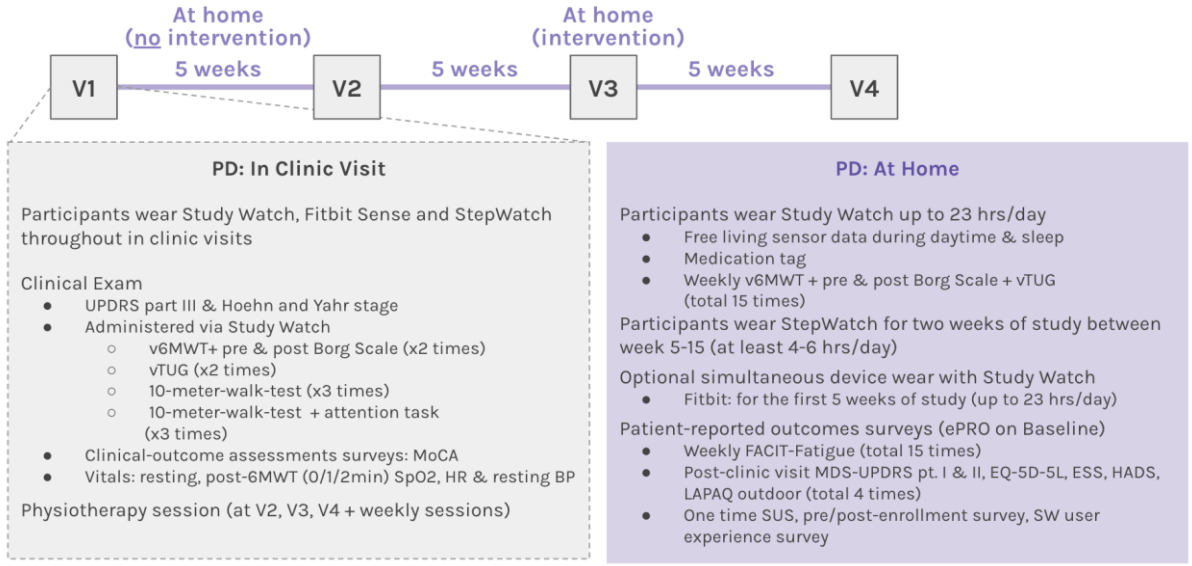
Estimated study timelines:
First Participant enrolled: December , 2021
Enrolment Period: 18 months
Follow-up duration: 15 weeks per participant
Total study duration: 30 months
Data cleaning/closeout: 3 months
End of study: July 2024

Figure 1. Study Design

COPD arm



PD arm



4. STUDY POPULATION

4.1 Population (base)

Two hundred (200) participants with COPD and up to 130 participants with PD who have been referred to a physiotherapist will be enrolled. Both cohorts of participants (COPD and PD) are expected to have reduced 6MWT distance outcomes that correlate with disease severity. However, due to the different underlying mechanisms of the diseases, the reasons for changes to the 6MWT distance may be different (i.e., pulmonary obstruction and overall limitation of the cardiovascular for people with COPD vs. reduced walking capacity and mobility for the people with PD due primarily to neurological impairment). In order to develop algorithms that will work across multiple root causes for functional capacity reduction, two different populations, COPD and PD, are selected. Different sets of features will be identified from each group to assist in developing algorithms with suitable performance for both conditions. These conditions are expected to be exemplary for other pulmonary, cardiovascular or neurological conditions as we look to expand the usage of developed algorithms across more indications.

4.2 Inclusion criteria

To be eligible to participate in this study, a potential participant must meet all of the following criteria:

- Participant is an adult, at least 18 years of age;
- Participant can read and understand Dutch;
- Participant is willing, competent, and able to comply with all aspects of the protocol, including follow-up schedule;
- Participant is willing and able to complete patient-reported outcomes via internet through their own devices at home or provided device at assigned physiotherapist's office after each visit;
- Participant can walk (with or without assistive equipment/oxygen therapy, and the circumstances do not completely prevent arm swings for the arm where watch is worn);
- (PD-specific) Participant has PD with Hoehn and Yahr stage 1-2;
- (COPD-specific) Participant has COPD irrespective of airway obstruction severity and has a limited exercise capacity as judged by the physiotherapist
- (For those who consent to wear optional Fitbit Sense at-home) Participant has a smartphone, and is willing to download Fitbit application in the phone to sync Fitbit Sense to set up and transfer data from Fitbit Sense to Fitbit database.

4.3 Exclusion criteria

A potential participant who meets any of the following criteria will be excluded from participation in this study:

- Participant is allergic to nickel used in Study Watch;
- Participant cannot make an arm swing at all or is in a situation that prevents arm swing completely (e.g., rollator);
- Comorbidity (co-occurrence) of COPD and PD;
- Participants with cognitive impairment that would prevent them from understanding and performing tasks in the study;

- Participant is pregnant or plans to become pregnant during the course of the study;
- Participant is participating in another investigational drug or device study that may conflict with the objectives, follow-up, or testing of this study;
- Participant has recently (within 3 months prior to the start of the study) completed or is currently participating in a supervised high-intensity aerobic exercise program. We define high-intensity as ≥ 3 sessions per week, for ≥30 minutes at ≥70% of the maximum exercise capacity;
- Participants with high fall risk or cardiovascular risk profile impacting the safety of performing at-home walk tests without supervision (as judged by referring physician's decision, record of unstable cardiac disease, Hoehn and Yahr stage 3 or greater (PD-specific), >1 fall in the last 3 months);
- Any disease or condition that prevents understanding or communication of informed consent, study demands, and testing protocols, including:
    - cognitive decline including diagnosed forms of dementia,
    - psychiatric disease including diagnosed forms of depression.

4.4 Sample size calculation

The study plans to enroll 200 participants for COPD and 100 for PD. For the COPD cohort, the objective is to conduct analytical validation of algorithms that estimate in-clinic 6MWT distance based on free-living based data and virtual 6MWT context-known data. The algorithms are being developed based on the prior dataset from community-dwelling individuals in their usual state of health, including people with COPD.

<u>For COPD</u>

Sample size calculations were based on our co-primary endpoints of Intra-class correlation coefficient (ICC)[21] between estimated 6MWT distance from free-living data and virtual 6MWT context-known data with in-clinic 6MWT distance. However, since free-living data is known to be less structured and may not involve walking for 6 minutes or any prolonged period, we expect to see lower performance from the free-living data based model compared to virtual context-known data based model. Previous literature[22] shows a minimum ICC of 0.75 from virtual walk tests. Thus the minimum success criteria for virtual context-known algorithm was ICC >0.75. For the IRL model the threshold was lowered to an ICC of >0.70.

All sample size calculations were based on a preliminary COPD and healthy cohorts obtained from BHS (NCT03154346) data that predicts 6MWT distance from in-clinic context-known data and free-living data.

Based on the preliminary data collected, the following assumptions are made for sample size calculations:

- Each participant will have 2 pairs of data available (a pair consists of one algorithm estimated 6MWT distance and one clinician measured 6MWT distance)
- Model performance based on virtual context-known data will be higher than model based on free-living data
- Minimum target performance based on IRL data is ICC>0.70. Minimum target performance based on virtual walk test data is ICC>0.75
- Since both free-living data based estimate and context-known data based estimate algorithms will be validated separately, no multiplicity is being considered, and each hypothesis test will be conducted with tolerance of 5% Type I error.

- About 75% of participants will have sufficient data for the final algorithm assessment. (This takes into consideration participants' drop outs, sensor data of insufficient quality to generate reliable algorithm outputs, and failure to obtain the ground truth labels (e.g. clinician evaluation of 6MWT distance))
- The table below illustrates the power achieved for a given algorithm performance assuming N=200 (including 25% drop-out) and a type I error of 0.05.

Table 1: Power Analysis with Various Modeling Assumptions

Success criteria	Current Performance	Power achieved(%)
ICC from free-living data based model		
>0.70	0.74	0.27
	0.76	0.50
	0.78	0.72
	0.79	0.82
ICC from virtual context-known data based model		
>0.75	0.78	0.23
	0.80	0.48
	0.82	0.75
	0.83	0.85

For PD

.

For our secondary endpoint, we performed a sample size calculation specifically for our PD cohort. This is an additional calculation to our primary sample size calculation which aims at the analytical validation of 6MWT distance measured with StudyWatch in clinic versus free living for COPD patients. This secondary sample size calculation was based on Intra-class correlation coefficient (ICC)[19] between estimated walking measurements obtained from Study Watch data and StepWatch data in a free-living setting. Sample size calculations were derived from a total of 48 walking measurements estimating different aspects of walking behavior in an individual such as bouts of walking, bout speed, bout cadence, number of bouts, bout durations, and daily step counts.

Previous literature shows a range of minimum ICC values for walking related metrics in free living context.[23-25] Not all metrics had known ICC. Generally an ICC ≥0.75 is considered excellent, 0.60–0.74 good, 0.40–0.59 fair, and <0.40 poor.[26] Minimum success criteria for the metrics, based on the literature, are listed in the following table.

All sample size calculations were based on a preliminary healthy cohort obtained from a

prior pilot study data that compared walking measurements obtained from Study watch compared with StepWatch in a free-living setting.

Based on the preliminary data collected, the following assumptions are made for sample size calculations:

- Each participant will have 2 pairs of data available (a pair consists of one algorithm estimated free living walking measurements from Study Watch and one from StepWatch)
- Minimum target performance based on free living data is different for each metric and thus are specified in the table below
- Since each of the free living metrics will be validated separately, no multiplicity is being considered, and each hypothesis test will be conducted with tolerance of 5% Type I error
- About 80% of participants will have sufficient data for the final algorithm assessment. (This takes into consideration participants' drop outs (20%), sensor data of insufficient quality to generate reliable algorithm outputs, and failure to obtain the ground truth labels (e.g. step watch errors).

The table below illustrates the power achieved by the algorithm for the best performing metrics assuming N=100 (including 20% drop-out) and a type I error of 0.05. This suggests that N=100 participants with StepWatch at home data will provide moderate power with given success criteria and current performance for some metrics to assess the analytical validity of these metrics as secondary endpoints.

Table 2: Power Analysis with Various success criteria, for n=100

Walking Suite Measures	Success criteria (from literature)	Current Performance	Power achieved(%)
Cadence 95 percentile	>0.82	0.88	0.64
Bout cadence 75 percentile	> 0.75	0.82	0.51
Cadence 75 percentile	>0.7	0.77	0.4
Number of Bouts	>0.66	0.7	0.17

For the optional part of the study (i.e. wearing the Fitbit at home) we only defined minimum numbers (for Fitbit, 50 COPD and 30 PD) and have not defined a maximum number of participants and aim to include as many participants as possible beyond the minimum numbers.

5. TREATMENT OF SUBJECTS

Participants will be given physiotherapy treatment for 10 weeks, as part of usual care. Both participant populations will receive personalized treatment determined by the treating physiotherapist according to the most recent physiotherapy guidelines for both COPD and PD.[27,28] Treatment modalities can vary between participants, but all participants will at least have 2 times of aerobic exercise training per week, as part of a multi-modality and personalized treatment.

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

6.1.1 Verily Study Watch

The Verily Study Watch is an investigational medical device manufactured by Verily Life Sciences LLC. It is a wrist-worn wearable device with sensors, band, USB syncing/charging hub, and cradle that continuously records physiological, movement, and environmental data. The Verily Study Watch is intended to be used for clinical research applications only. As such, the device is not CE marked.

As shown in Figure 2, the Study Watch collects physiological and/or environmental information through sensors. The sensors collect data that may include movement and activity, pulse rate, and electrodermal activity (EDA). The wristband is made of fluoro elastomer (similar to other wristwatches). Data from the device is encrypted and securely sent to the cloud using a USB syncing/charging cradle and wireless connectivity bridge. The USB syncing/charging cradle connects to the Study Watch through 4 contacts on the underside of the device. The Study Watch is worn externally on the wrist and does not come into contact with any body fluids.

Figure 2. Verily Study Watch

The Study Watch is a miniaturized data monitoring and data collection device for continuous recording of physiological activity and environmental data. The device consists of a wrist watch containing sensors, a USB syncing/charging cradle, and a connectivity bridge (Study Hub).

The Study Watch is used as a general participant monitor intended for data collection only. As a general participant monitor, it provides physiological and environmental information for general research and performance measurement purposes. No treatment decisions are made with the data collected from the device.

The Study Watch is able to collect data during a set of two Virtual Walk tests (the 6MWT and TUG; see sections 8.4, 8.5 *and Figure 3*) performed weekly and labels for events (e.g. medication intake for the PD cohort) provided by the participant. At the beginning and at the end of each test, the participant will press a button on the Study Watch to tag and record the

exact time of the test. Participants with PD will also press a button to tag the time when they take their medication.
Except in the case of the Virtual Walk tests, and performance and event tagging, the device requires no other user intervention to capture or analyze physiological data and collects data passively with minimal information communicated to the user via the device (i.e., date and time, charge status, sync status when connected for data transfer). Participants' button press inputs marking the beginning and end of each walk test will be used to determine the onset and offset of the test in the sensor data. Medication tagging will be used to understand manifestation of medication on and off states in the sensor measurements for PD patients.

The Study Watch has been carefully designed to use current technologies (e.g.virtually continuous data collection)) to investigate physiological and environmental variables that may shed light on the evaluated disease, its progression, and response to therapy when combined with other clinical variables collected during the study.. Since it is intended for research only and it is not CE marked, approval from a competent authority in the Netherlands will be obtained for use of this investigational device for this Accuracy of Digital Assessment of Performance Trial. We have previously obtained approval for using the Study Watch in the context of the Personalized Parkinson Project (registered under file VGF2002688).

6.2 Summary of findings from non-clinical studies

A summary of findings from non-clinical studies and clinical studies is provided in the Investigator's Brochure (IB).

6.3 Summary of known and potential risks and benefits

There are limited risks to the participant during the data collection. Potential risks relate to the in-clinic assessments and the unsupervised home assessments. Identified risks include risk of falls or cardiovascular events which have been mitigated by design (exclusion criteria and approval from treating physician). A structured risk and benefit analysis is available in section 12.

Potential benefits of use of the Study Watch compared to other monitoring systems may include, but are not limited to:

- The device is portable and easy to use even by participants with tremor or dexterity problems;
- The device is non-invasive and poses no significant safety issues;
- Data transfer does not require connection to a mobile phone or computer, and simply fitting the watch in a cradle / plugging USB is sufficient for both charging and data streaming;
- Device can be used in every situation of daily living (e.g. at home, at the gym, or at the office);
- Faster and more effective data capture than other similar devices;
- Combines existing sensor and ECG technology for multiparametric assessment;
- Physiological context (motion parameters) associated with detected events;
- High sampling frequencies (up to 200 Hz), which permits accurate

measurements;
- Long battery life, allowing for continuous data assessment for up to 7 days before charging is necessary (in the present study, we ask the participants to charge the Study Watch once a day); and
- Repeated measurements of physical functioning in patients' natural environment is permitted.

The following documents are available for detailed information on the device and operating instructions:
- Verily Study Watch and Study Hub Investigator Brochure;
- Verily Study Watch Instructions for Use;
- Verily Study Hub User Manual; and
- Verily Study Watch Virtual Walk Test Instruction Manual.

Participants will be trained by physiotherapists on proper use of devices and will be provided Study Watch Instructions for use and Virtual Walk Test participant training guide.

6.4 Investigational Product Accountability

The Principal Investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigational devices, which shall include: the date of receipt, identification of each investigational device (batch number/serial number or unique code), the version and date of the Study Watch firmware, the expiration date (if applicable), the date(s) of use, subject identification, and date on which the investigational device was returned (if applicable).

The Investigator or authorized designee will record the receipt and disposition of the investigational device on the appropriate form. At the end of the clinical investigation, the original logs will be returned to the sponsor and copies of the logs kept in the Regulatory Binder at the investigational site.

The investigational site, Radboud university medical center, (Radboudumc) is responsible for maintaining control over any associated investigational devices that are received and used and ensuring all investigational devices are inventoried, and provided only to study staff who have been appropriately trained.

7. NON-INVESTIGATIONAL PRODUCT

7.1 Fitbit Sense and Fitabase

Fitbit Sense is a wrist-worn wearable consumer electronics device (CE marked in EU, made by Fitbit). Fitabase is a third party software that allows access to fitbit data for clinical research purposes masking sensitive information, and providing de-identification (pseudonymization). Fitbit’s on-board sensors collect data that may include movement and activity, pulse rate, electrodermal activity (EDA), electrocardiogram (ECG), and on-skin temperature. The device also provides a variety of wellness metrics related to activity level, pulse rate, heart rate, heart rate variability, oxygen saturation and sleep on the device and through mobile application. Fitbit Sense may collect geolocation data if users turn on activity labeling features outdoors (like manually selecting a jogging activity on the watch activity labeling menu) but this data will not be accessible by site staff nor researchers. The entire

data types that are collected and accessible from Fitbit are listed in Appendix A. The Fitbit sense device in this investigation is being used within the intended purpose for which CE marking was issued.

Data from the device is transferred to Fitbit's database through Fitbit's mobile application (from the device to the mobile application via bluetooth connectivity and from the mobile application to Fitbit's database via WiFi or cellular connectivity). Researchers and site staff at Radboud may access the aggregated data using Fitabase (a third party provider that allows access to de-identified Fitbit Data for research purposes) , but to ensure strict adherence to current regulations, no data transfer will be made from Radboud to Verily. Verily must set up an appropriate Access Restricted Data Store (ARDS). Verily will be able to access the data only through an Access Restricted Data Store (ARDS) that will receive data from Radboud via the Fitabase platform.

For the current study, access will be limited to aggregated data and derived metrics (e.g., step counts, sleep duration, etc.) based on raw data recorded using Fitbit's accelerometer, gyroscope, and photoplethysmography sensors. These metrics will be used for algorithm development and comparison with metrics derived from Study Watch sensor data. Verily will not have access to other types of sensor data or participant location data, as these will be masked by Fitabase.

7.2 Modus StepWatch 4

StepWatch 4 is an ankle-worn wearable medical device (CE Class 1 medical marked in EU), and will be used as a reference device for measuring participants' ambulation in the physiotherapy practice and at-home for a subset of participants who consent to do so. On-board accelerometer collects motion data, and a companion application installed on an iPad at the physiotherapist's office will be used to transfer the data from the StepWatch to Modus StepWatch Cloud and to obtain derived metrics (e.g. step counts). The sensor data and derived metrics will be transferred from the Modus StepWatch Cloud to Verily Cloud for data analysis and algorithm development. The Modus StepWatch 4 device in this investigation is being used within the intended purpose for which CE marking was issued.

Both COPD and PD participants will wear StepWatch at home. Data transfer will occur at the physiotherapist's office when they return the device after two weeks of wear. No at-home iPad or data transfers are expected from the participants.

Data from the Fitbit Sense and StepWatch 4 are with timestamps which allow the exact synchronization of sensor data from the devices with data from Study Watch for analysis to achieve study objectives.

The following documents are available for detailed information on the device and operating instructions:

- Fitbit Sense Instructions for Use; and
- Modus StepWatch Instruction for Use (physiotherapists' in-clinic use.
- Modus StepWatch 1 pager for participant's at home wear

8. METHODS

8.1 Study endpoints

8.1.1. Primary study endpoint

For COPD:
1) Measurement agreement/Intra-class correlation between in-clinic 6MWT distance and free-living data based 6MWT distance estimate; and
2) Measurement agreement/Intra-class correlation (ICC) between in-clinical 6MWT distance and Virtual 6MWT distance estimate
For PD: not applicable.

8.1.2 Secondary study endpoints (if applicable)

For COPD:
1) ICC between in-clinic TUG time and free-living data based TUG time estimate;
2) ICC between in-clinical TUG time and Virtual TUG time estimate; and
3) Test-retest agreement across various estimates from each algorithm that is validated.

This is not applicable for PD.

8.2 Study procedures

This study will be coordinated by Radboudumc, but executed in 25 - 30 physiotherapy practices throughout the Netherlands. In each practice 2 physiotherapists will participate (up to 50 in total)- one specializing in COPD, and one specializing in PD. We will recruit physiotherapy practices using the nationwide ParkinsonNet infrastructure. Physiotherapists, who are part of the national ParkinsonNet, are experts in PD, and in general, have a high (>10 participants a year) patient load. Because physiotherapists usually work in a practice with more specialized physiotherapists, we aim to recruit physiotherapists with expertise in COPD within the same physiotherapy practice as the ParkinsonNet physiotherapists. We will select physiotherapists who have completed an additional course that specializes in providing physiotherapy in COPD participants. Throughout the study, the Radboudumc Helpdesk (already operational as part of the PPP study[29]) will proactively assist participants, physiotherapists, address problems and questions, and solve/communicate issues related to the execution of the trial.

8.3 Participant recruitment and procedures

The physiotherapist will identify potentially eligible patients and ask if they would be interested in the study and if a researcher from Radboudumc can contact them. Further information about the study is provided by the research team. When the patient agrees, a researcher from Radboudumc will call the potential participant soon after. During this contact moment, potential participants can ask questions and the researcher informs the participant about the study. When willing to participate, the potential participant is directed to the Baseline Platform where he/she is invited to create an account and to electronically sign the

screening consent. The researcher subsequently asks the allocated physiotherapist to schedule an appointment for the first visit. ,

Before the first visit, potential participants will review and submit a screening consent to provide his/her personal information, information for eligibility, and to give permission to contact their treating physician to ask for permission to participate in this study. At the first visit, once the potential participant is screened as eligible, a study consent is signed on paper by the participant, and physiotherapist. The participant will receive a copy of the signed informed consent form. Before signing, participants will review information associated with the specific research they are participating in, including objectives, types of data collected, study sponsor, study principal investigators, contact method, schedule of visits, and contact information for the participant to report issues. After the study consent is signed, participants will be asked to wear the Study Watch, Fitbit Sense, and StepWatch during the first visit and following visits. Study Watch will be asked to be worn on the non-dominant hand unless there are particular reasons preventing the wear. StepWatch will be worn on the ankle that is the same side of Study Watch. Optional Fitbit will be asked to be worn on the dominant hand for those who choose to wear it. Participants will be asked to keep wearing the device(s) on the same hand(s) and ankle throughout the study duration/wear duration and the information on wearing hand for each device will be tracked in eCRF.

At the first, and subsequent visits to the clinic, required assessments and measurements are performed as described in Table 2. In-clinic assessments are repeated every 5 weeks. After each visit, participants are asked to fill out the following questionnaires: FACIT-Fatigue, EQ-5D-5L, Epworth Sleepiness Scale, HADS, LAPAQ outdoor, MDS-UPDRS part I (PD-only), MDS-UPDRS part II (PD-only), PDQ-39 (PD-only), CCQ (COPD-only). All questionnaires will be completed once within 14 days after each visit (either digitally in the Baseline platform or on paper) except for the FACIT-Fatigue and System Usability Survey, which will be completed weekly and only once after Visit 3, respectively. Unless specified as PD-only or COPD-only, questionnaires are for both PD and COPD cohorts. Participants will perform the virtual 6MWT and TUG at home using the Study Watch one time per week. The day and time of the week on which the tests are performed are standardized (i.e. same day + time of the week) while they are wearing the watch for up to 23 hours a day. For StepWatch device at home, the device will be provided, and participants will be asked to wear it simultaneously with the Study Watch for two weeks, between Visits 2 and 4.For those who are willing and consented to wearing a Fitbit device, the device will be provided, and participants will be asked to wear it simultaneously with the Study Watch on the opposite wrist for the first five weeks between the first and second visits.

Table 2. Overview of study consents, assessments for COPD and PD cohorts

Exams, Tests and Data Collection	**Pre Visit**	**Visit 1 (Baseline)**	**Visit 2 (5th wk)**	**Visit 3 (10th wk)**	**Visit 4 (15th wk)**	**After each visit**	**Weekly at home**
Visit Window		Day 0	In the 5th week	In the 10th week	In the 15th week	Within 7 days after each visit	
Screening consent	X						
Demographic information	X	X					
Pre-visit platform survey	X						
Inclusion/Exclusion criteria		X					
Study consent		X					
Medical history*		X	x				
Change in health status between visits			X	X	X		
User experience survey						X (at home, post visit 3 only)	
Post-visit platform survey					X		

User feedback on Study Watch					X		
Skin tone (Fitzpatrick Scale)		X					
Arm Hair Index		X					
Concomitant Medications		X	X	X	X		
Physiotherapy			X	X	X		X (self-training at home)
Adverse Events			X	X	X		
Exams, Tests and Data Collection	**Pre Visit**	**Visit 1 (Baseline)**	**Visit 2 (5th wk)**	**Visit 3 (10th wk)**	**Visit 4 (15th wk)**	**After each visit**	**Weekly at home**
In Clinic Assessments & Surveys							
6MWT with pre & post Borg Scale (two times per clinic visit)		X	X	X	X		
TUG		X	X	X	X		
10MWT with single context (three times per clinic visit)		X	X	X	X		
10MWT with dual context (three times per clinic visit)		X	X	X	X		

Montreal Cognitive Assessment (MoCA)		X			X		
MDS-UPDRS Part I Rater Questionnaire (*PD only*)		X	X	X	X		
MDS-UPDRS Part III (*PD only*)		X	X	X	X		
MDS-UPDRS Part IV (PD only)		X	X	X	X		
Hoehn and Yahr Scale (*PD only*)		X	X	X	X		
COPD ABCD categorization (mMRC, *COPD only*)		X	X	X	X		
In Clinic Vitals & Measurements							
Pre-6MWT (#1&2) Resting blood pressure, SpO2, heart rate		X	X	X	X		
Post 0 minute -6MWT (#1&2) SpO2, heart rate		X	X	X	X		
Post 1 minute -6MWT (#1&2) SpO2, heart rate		X	X	X	X		
Post 2 minute -6MWT (#1&2) SpO2, heart rate		X	X	X	X		
Height, weight, leg length		X					

Exams, Tests and Data Collection	**Pre Visit**	**Visit 1 (Baseline)**	**Visit 2 (5th wk)**	**Visit 3 (10th wk)**	**Visit 4 (15th wk)**	**After each visit**	**Weekly at home**
At-home Clinical Assessments & Surveys**							
Virtual Walk Tests on the Study Watch (virtual 6MWT & TUG)							X
FACIT-Fatigue (13-item)							X
EQ-5D-5L						X	
Epworth Sleepiness Scale (ESS)						X	
Hospital Anxiety and Depression Scale (HADS)						X	
LASA Physical Activity Questionnaire (LAPAQ)						X	
MDS-UPDRS Part I & Part II Patient Questionnaires (*PD only*)						X	
Parkinson's Disease Quality of Life Questionnaire (PDQ-39, *PD only*)						X	
Clinical COPD Questionnaire (CCQ, *COPD only*)						X	

Optional Fitbit at home use		X (first 5 weeks, at home, 23 hours per day between visit 1 and visit 2)					
StepWatch at home use		X (for two weeks, at home; within the two weeks wearing the device at least 10 days, which can fall on any random day with a minimum of two weekend days. Wear time of four to six hours on these days).					

**Medical history will be collected during both visit 1 and visit 2*

** These can be done in-clinic or at-home based on participant's preference.

8.4 Assessments – in-clinic

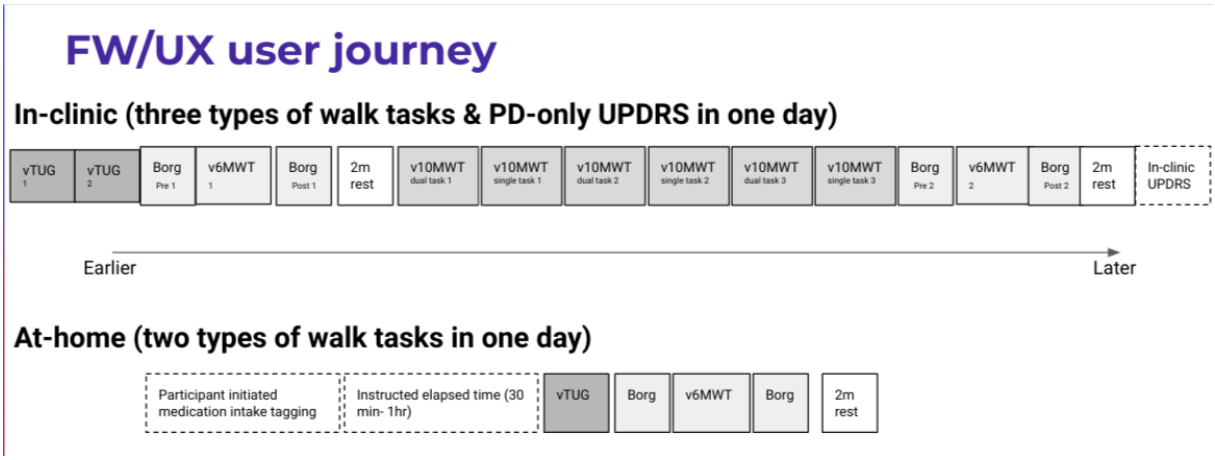
All study procedures will be performed at the local physiotherapy practices, by the treating physiotherapist, with coordination with Radboudumc. Physiotherapists will be extensively trained in performing all assessments as part of the study protocol in a highly standardized manner. They will also be guided and coached by the research team at Radboudumc to increase engagement and data quality. Participants are invited to come to the study site four times over a 15 week duration. The in-clinic assessments consist of a number of walking tests: 6MWT (twice), TUG (twice), and 10MWT with and without cognitive load (three times for each context). In addition, demographics are taken during the first visit and participants are asked to fill out some questionnaires on disease symptoms and quality of life after each study visit. Questionnaires can be filled out digitally at home or at the physiotherapy practice if the participant does not own a computer. The exact assessments are described in Table 2 (in-clinic and at-home assessments).

8.5 Assessments – at-home

After the first study visit to physiotherapists' clinics, participants will be asked to wear the Study Watch (up to 23 hours a day) for passive longitudinal measurements of physiologic activity and environmental data. In addition, all participants will be asked to complete the virtual 6MWT with pre- and post-6MWT Borg Scales and virtual TUG, once a week (every week on the same day) with guidance via graphical user interface on the Study Watch. The Verily Study Watch will provide an alert to the participant at 9 am of the preset day of the week (preset during the first visit by site coordinator) to remind them to perform the task. Participants with PD will be asked to perform the Walk Test 30 minutes to an hour after they intake medication and tag the event on the Study Watch. Participants with COPD are asked to perform the task any time they prefer during the day that they receive an alert on the Study Watch. Participants will have the ability to postpone the task until a later time point in the same day, should that suit their schedule better. If a prescribed task is not executed on a given day, the reminder alert will be prompted the next day at 9 am. Participants with PD are also asked to tag time of medication intake every time they intake PD medication. Participants with COPD are not asked to tag time of medication intake. Figure 3 describes the in-clinic and at-home sequences of assessments using the Study Watch Participants will also wear the Modus StepWatch 4 concurrently with the Study Watch over 14 days, which can fall on any random 10 days with a minimum of two weekend days. At least four to six hours of wear on these days is intended.

A subset of participants may also wear the Fitbit Sense concurrently with the Study Watch and will be asked to wear them for the first 5 weeks between first and second visits.

Figure 3. Study Watch Assessment Sequences in clinic and at home.



Each box is a task guided by the Study Watch graphical user interface. Different hues of gray represent three different types of walk tasks and 2-minute rest periods. Dotted boxes indicate activities required only for the participants with PD. In-clinic: dotted box indicates in-clinic MDS-UPDRS part III that we will indicate start and finish of the subtests using the Study Watch. At-home: during at-home periods, participants with PD will be asked to tag medication intake whenever they take medications. For the prescribed day of the week, participants will receive an alert from the watch. Participants with PD will be instructed to perform Virtual Walk Test within 30 min to an hour relative to a medication intake on that day. Participants with COPD will be instructed to perform the task any time they prefer during the prescribed, alerted day.

8.6 Timeline

We aim to include 300 participants within 18 months. We will include 25 – 30 physiotherapy practices with both a ParkinsonNet physiotherapist and a physiotherapist specializing in COPD (up to 50 physiotherapists). On average each ParkinsonNet physiotherapist[30-32] will need to include 4 PD participants and each therapist specializing in COPD should include 8 COPD participants. This breaks down into 1 participant with PD per physiotherapist per 2 months and 1 participant with COPD per physiotherapist per month. Based on our extensive experience in performing large clinical trials,[5,33-37] we expect this to be highly feasible. After 3 months of inclusion, if we find that enrollment rates are too low, we have an alternative, backup scenario in place in which we will recruit participants with COPD from hospitals that have a high case load of people with COPD or with PD (either pulmonologists or neurologists). In this case, outpatient clinics will refer people with COPD to selected COPD specialized physiotherapists and the study activities will be performed as planned. With 15 weeks follow-up, all data should be included 13 months after first enrollment.

8.7 Withdrawal of individual subjects

Participants 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. If a subject at any time discontinues involvement in the study for any reason (drops-out) without explicitly withdrawing consent , the subject will be considered to only have participated in the portion of the study with which he/she was eligible and present. The subject will be considered a “non-participant” for the portion of the study for which he/she was not eligible or not present. The scope of the information covered in the informed consent is limited only to the data collected while

the subject is actively participating in study.

8.8 Specific criteria for withdrawal (if applicable)

Participants will only be withdrawn from the study when a medical condition does not allow the participant to continue the study procedures, e.g. because of repeated falling or an unstable cardiovascular condition. In case of a (serious) adverse event, the sponsor will carefully evaluate whether the participant can continue to participate in the study (see section 9.2 on adverse events).

Participants that, during the study, turn out to not have either COPD or PD, but another related diagnosed (i.e. Parkinsonism) will be withdrawn from the study.

8.9 Replacement of individual subjects after withdrawal

We have taken into account 25% of data loss due to a drop-out or any other reasons in our sample size calculation of the COPD cohort. If the COPD cohort encounters higher than 25% drop-out rates, we will include new participants until we reach 150 complete COPD cases. For the PD cohort we have considered 10% drop-out. If the PD cohort exceeds the 10%, we will include new participants until we reach 90 complete PD cases.

8.9 Follow-up of subjects withdrawn from treatment

If a subject at any time chooses to withdraw from the study, further attempts to collect data will not be undertaken.

If a subject at any time discontinues involvement in the study for any reason (drops-out), the subject will be considered to only have participated in the portion of the study with which he/she was eligible and present. The subject will be considered a “non-participant” for the portion of the study for which he/she was not eligible or not present.

8.10 Lost-to- Follow-up

A subject will be considered lost-to-follow-up and terminated from the study when three unsuccessful attempts by the Investigator or his/her designee to contact the subject have been documented.

8.11 Premature termination of the study

If suspicion of an unacceptable risk to subjects arises during the clinical investigation, or when so instructed by the Ethics Committee (EC), the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk is confirmed. Moreover, the sponsor will consider terminating or suspending the participation of an Investigator if monitoring and/or auditing identifies major or repeated deviations on the part of an Investigator.

8.12 Potential factors impacting the data collected

We designed the study to mitigate potential factors affecting data quality and sources of bias.

The main factors considered were participant compliance (requirement to wear the Study Watch for the duration of the study), fatigue bias (when participants repeat tests during sessions), and learning bias (associated with surveys).

Study Watch wear compliance will be monitored and controlled. Physiotherapists will be notified if participants are not compliant and will discuss with participants at the following visit.

Fatigue bias will be monitored by surveys(Facit and Epworth) and assessed by the physiotherapists during clinic visits who may offer breaks.

Learning bias will be mitigated by analyzing the data controlling for the number of repetition of the survey.

Factors associated with participant compliance.

Wearing the Study Watch for the duration of the study is essential for data quality. We will be collecting the daily wear of the Study Watch by participants and control the collected data for compliance. Physiotherapists will be notified

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance with section 10, subsection 4, of the WMO (Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen), the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC (Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)) without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs, ADEs, SADEs, and device deficiencies

9.2.1 Adverse events (AEs) and Adverse device effect (ADE)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the investigational product or any trial procedures. All adverse events reported spontaneously by the subject or observed by the investigator or his/her staff will be recorded. Adverse events will be classified according to the definition in Table 3.

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. Note that this definition includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device. That also includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Table 3. Adverse event (AE) classification

ADVERSE EVENTS	**Non-device-related**	**Device- or procedure related**
Non-Serious	Adverse Events (AE)	Adverse Device Effect (ADE)
Serious	Serious Adverse Event (SAE)	Serious Adverse Device Effect (SADE) Unanticipated Serious Device Effect (USADE)

No AEs are expected from the clinical assessments of the self-reported questionnaires.

AEs that may be expected from the Verily Study Watch, include: pruritus, dryness, redness, rash, and swelling around the wrist from wearing of the Study Watch. Participants exhibiting anticipated adverse events related to Study Watch shall contact the Radboud study team and discuss whether they can continue to participate in the study.

Any pre-existing medical condition or symptom present in a subject will not be considered an AE in this study, unless it worsens as a result of this study. Any mild changes that occur will be monitored by the Investigator and data will be recorded appropriately.

9.2.2 Serious adverse events (SAEs) and serious adverse device effect (SADEs)

A serious adverse event is any untoward medical occurrence or effect that:

- Results in death;
- Is life threatening (at the time of the event);
- Requires hospitalization or prolongation of existing inpatients' hospitalization;
- Results in persistent or significant disability or incapacity;
- Is a congenital anomaly or birth defect; or
- Any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

In accordance with section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if the frequency and severity of adverse effect suggests that the disadvantages of participation may be significantly greater than what was foreseen in the protocol. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardize the subjects' health. The investigator will ensure that all subjects are kept informed.

The following hospitalizations are not considered to be an SAE:

- Hospitalizations due to PD or COPD; or
- Hospital admissions that already were scheduled at the moment of inclusion.

The sponsor will report the SAEs through the web portal, ToetsingOnline, to the accredited METC that approved the protocol, within seven (7) days of first knowledge for SAEs that result in death or are life threatening followed by a maximum period of 8 days to complete the initial preliminary report. All other SAEs will be reported within a maximum period of 15 days after the sponsor has first knowledge of the serious adverse events. SAEs will also be reported in the annual progress report to the accredited METC, until the end of the study in the Netherlands.

9.2.3 Device deficiencies, device failures and malfunctions

A device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use errors, or inadequacy in the information supplied by the manufacturer.

An incident is any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly,

might lead to or might have led to the death of a patient, or USER or of other persons or to a serious deterioration in their state of health.

Throughout the study, and in conformity with ISO 14155:2020, and Medical device Regulation Regulation (EU) 2017/745, all observed device deficiencies are to be documented by the Investigator and reported to the Manufacturer on Device Deficiency Forms that are included in the study documentation. The investigational device is returned to the Sponsor for analysis if necessary. Instructions for returning the investigational device will be provided by Verily.

The Investigator is responsible for notification of the sponsor within 5 working days.

Device deficiencies that meet the definition for incidents (i.e. any device deficiency or failures that might lead or might have led to a serious adverse event if suitable action had not been taken, or intervention had not been made, or if circumstances had been less fortunate) must be reported to the Verily immediately without delay.

9.3 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- A list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study; and
- A report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported until the end of the study within the Netherlands, as defined in the protocol

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

We will not install a DSMB as this study includes limited risks (see section 12).

10. STATISTICAL ANALYSIS

10.1 Analysis population

Full Analysis Set is defined as participants who have at least one available pair of algorithm generated output (either 6MWT distance estimator or TUG estimator) and in-clinic collection of ground truth (either 6MWT distance or TUG measured by clinicians). Participants from the Full Analysis Set will be used in analysis.

10.2 Primary Analysis

For COPD:
One of the primary objectives is to assess the validity of the free-living data based 6MWT distance estimator. The measurement agreement between the estimates from the free-living 6MWT distance Estimator and the in-clinic 6MWT distance measured by the test administrator will be assessed by Intra-class correlation (ICC) and is expected to be more than a clinically meaningful threshold. We define this clinically meaningful threshold with ICC success criteria and, for COPD population, ICC is 0.70. A test of equivalence, two one-sided test (TOST), will be used to assess the validity of the free-living data based 6MWT distance estimator. A Bland Altman plot will also be provided.

The other primary objective is to assess the validity of the virtual 6MWT distance estimator. We assume the model performance from virtual 6MWT will be higher than that of the free-living data based model, and the ICC threshold is >0.75. A TOST procedure and a Bland Altman plot will also be used to assess the validity of the Virtual 6MWT distance estimator.

Considering that two co-primary endpoints will be validated separately, each TOST will be conducted at 5.0 level, without correction for multiplicity.

The algorithms are mainly developed using data collected from other sources, however, a small set of pre-selected data will be used to refine these algorithms prior to validation. As such, algorithm performance on this subset of data will not be included in the final validation analysis.

For PD:
The primary objective is to use collected data for future algorithm development. No formal performance evaluation will be conducted.

10.3 Secondary Analysis

For COPD:

Intraclass correlation coefficent (ICC) and Bland Altman plots will be used to assess the validity of the free-living data based TUG time estimator and the Virtual TUG time estimator. ICC will be used to evaluate the agreement in free-living metrics between study watch and reference device (Step Watch). 41

The test-retest reliability of below algorithms will be assessed by looking at repeated estimates from the algorithm (e.g., week-over-week) and compared with the test-retest reliability of the in-clinic clinician measured 6MWT distance.

The algorithms are mainly developed using data collected from other sources, however, a small set of pre-selected data will be used to refine these algorithms.

For PD:
ICC will be used to evaluate the agreement in free-living metrics between study watch and reference device (Step Watch).

10.4 Other Statistical Considerations

Participants' disposition, device use compliance, and data availability will be summarized for participants enrolled in the study. Demographic and baseline characteristics will be summarized for participants in the Full Analysis Set.

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This clinical study involving human subjects are conducted pursuant to the following codes:

- The Declaration of Helsinki 2007-2008 and its subsequent amendments;
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001; on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice (GCP);
- The Medical Research Involving Human Subjects Act (WMO);
- ICH E6, International Conference of Harmonization (ICH) guideline for Good Clinical Practice; MDR(EU) 2017/745;
- EN ISO 14155:2020; and
- General Data Protection Regulation 2018 (GDPR), in Dutch the 'Algemene verordening gegevensbescherming' (AVG).

Any additional requirements imposed by the METC or regulatory authority shall be followed.

11.2 Recruitment and consent

The procedure for recruitment and consent is described in paragraph 7.2. Participants are recruited by participating physiotherapists; either newly referred people with COPD and PD or people who are already treated by the physiotherapist but haven't received aerobic exercise training in the last 6 months are potentially eligible. Potentially eligible participants are asked by the physiotherapist if they are interested in participating in this study. If so, they receive the information letter. One week after receiving this letter, a researcher from Radboudumc calls the person. During this call, the person can ask questions and the researcher checks if the person fulfills the inclusion criteria. When eligible and willing to participate, an appointment for the first in-clinic assessment is made. Before participants come to the first clinic visit, participants will receive an email to create an account in the Baseline Platform that they will use for completion of surveys and getting notifications for upcoming visits. After creating the account, they will review and sign an electronic screening consent form to provide contact information and to give permission to contact their treating physician.

At the start of the first in-clinic visit, the IRB approved informed consent form is signed by both the participant and the physiotherapist on paper. The participant l receives a copy of the form.

11.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable (study only includes adults able to provide informed consent).

11.4 Benefits and risks assessment, group relatedness

There are limited risks to the participant during the data collection. Potential risks relate to the in-clinic assessments and the unsupervised home assessments. A structured risk and benefit analysis is available in section 12. The participant will not directly benefit the study. However, they do receive 10 weeks of personalized physiotherapy as part of this protocol.

Because they have an indication for physiotherapy, they will also receive a physiotherapeutic intervention if they choose not to participate in this study.

Importantly, participants will indirectly benefit from the study. The remote measurement of physical capacity, physical activity and potentially disease status are novel insights being derived and measured by the data generated by the participants wearing the sensors. This may, in the future, have a positive impact on remote disease monitoring and more precise and personalized disease management. In turn, this potentially provides future benefits for all people affected by the disease. Prospectively, measurements from the Verily Study Watch could supplement and enhance the information available to the physician, providing continuous measurement and quantitative (rather than subjective) data. The device detects important physiologic parameters that are expected to change with disease conditions or behavioral patterns (e.g. electrodermal activity, physical movement of the body in three dimensions [acceleration], skin temperature, heart rhythm, etc.). In addition to collecting data, the device also functions as a wristwatch.

11.5 Compensation for injury

The sponsor/investigator has liability insurance in accordance with article 7 of the WMO. Additionally, the sponsor has insurance in accordance with the legal requirements in the Netherlands (see Article 7 WMO). This insurance provides coverage in the event of damage to research subjects as a result of the study.This coverage applies to damage that becomes apparent during the study, up to and within, 4 years after the end of the study.

11.6 Incentives (if applicable)

The only potential incentive that participants receive as part of this study is enhancement of the treatment already being provided as part of their physiotherapy that is covered by the participant's health insurance.

11.7 Handling and storage of data and documents

11.7.1 Data Protection

Radboudumc will use Verily's proprietary online platform (i.e. Baseline Platform) to collect clinical, behavioral, psychological, self-reported, other health-related data and demographic information. The Baseline Platform includes a proprietary Electronic Data Capture system, referred to as EDC, or eSource. Participants will be assigned a unique identifier (code) by the Baseline Platform.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. All data used in the analysis and reporting of this evaluation will be pseudonymized and used without identifiable reference to the study participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities. Sponsor may provide access to study data to its scientific collaborators to perform further explorative analysis.

11.7.2 Privacy of Personal Data

The collection and processing of personal data from participants enrolled in this study will be limited to the data that are necessary to fulfill the objectives of the study. This data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the personal data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration must be put in place. Study personnel whose responsibilities require access to personal data agree to keep the identity of participants confidential.

The informed consent obtained from the participant describes the legal basis for the processing of personal data, i.e. the legal basis for collecting and processing data for this study is for research purposes as the legitimate interest. This is the lawful basis for the Investigator/institution to have direct access to participant's original source data for study-related monitoring, audit, IRB review, and regulatory inspection. We must also describe the technical and organizational measures we are using to protect the privacy, security, and confidentiality of this data as part of processing this data for research purposes.

The informed consent also addresses the transfer of the data to other entities and to other countries, both within and outside of the EU.

The participant has the right to request through the Investigator access to his or her personal data and with some limitations related to research, the right to request rectification of any data that are not correct or complete. Reasonable steps will be taken to respond to such a request, taking into consideration the nature of the request, the conditions of the study, and the applicable laws and regulations.

11.7.3 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF or ePRO, unless transmitted to the sponsor or designee electronically (e.g., device data). Verily uses a proprietary online portal ("Baseline Platform") for collecting clinical, behavioral, psychological, self-reported, and other health-related data from participants. Additionally, Verily utilizes a proprietary Electronic Data Capture system, referred to as EDC, or eSource. Verily is responsible for the data management activities of this study, including data quality review. The sponsor assumes accountability for actions delegated to other individuals. The sponsor will review data to ensure key elements are collected, as it concerns the study. In case it should become necessary, additional monitoring instructions can apply.

11.7.4 Record Keeping

It is the responsibility of the Investigator and research staff to maintain a comprehensive and centralized filing system of all study-related documentation. This filing system must be suitable for inspection at any time by the sponsor, a CRO (Clinical Research Organization), an auditor, and/or the site EC. The study records should include:

- Participant Files, which include (but not limited to):

    - Signed and dated Informed Consent Form and supporting documentation of the Informed Consent process; and
    - Participant eCRFs and supporting source documentation/medical records.
- Regulatory Binder, which contains the following (but not limited to):
    - Clinical Investigation Plan/amendments/signature pages;
    - EC submissions/approvals/communications;
    - EC approved Informed Consent Forms (current and previous);
    - Clinical Study Agreement(s)/Investigator Agreements;
    - Investigator Brochure;
    - Instructions For Use, if required;
    - Electronic Case Report Forms;
    - Signature and Delegation of Authority Logs;
    - Site Screening and Enrolment Logs;
    - Device Accountability Logs;
    - CVs/Medical/Professional Licenses/Financial Disclosure Form;
    - Training Logs;
    - Laboratory documents (e.g., certification, norms/ ranges, etc.), if required; and
    - Correspondence between the Site and the sponsor.

The PI (Principal Investigator) will ensure that the records are maintained for a period of 15 years after the investigation is terminated or completed, according to “Medical Device Regulations (EU) 2017/745”.

11.7.5 Investigator Records and Reports

Records may be audited by regulatory authorities, and must be retained for the appropriate period (according to the regulatory requirements). The Investigator is responsible for the following:

- Records of all persons authorized to conduct the clinical study;
- Records of receipt, use or disposition of the devices, as applicable;
- Participant completed electronic Case Report Forms and any supporting documentation; and
- Informed Consent documentation (including copy of an approved, blank consent form).
- Records of all Adverse Events, Serious Adverse Events (SAE), Adverse Device Effects, Serious Adverse Device Effect (SADE) and Unanticipated Adverse Device Effects (UADE)
- Clinical Investigational Plan (including certification of approval) and reasons for deviations from the CIP;
- Signed Investigator Agreement and CVs for all Investigators participating in the study; and
- All correspondence which pertains to the clinical study.

11.7.6 Record Retention

In compliance with the ICH/GCP guidelines, the Investigator/institution will maintain all (e)CRFs/ source documents that support the data collected from each participant, as well as

all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s).

The participating physiotherapy practices will maintain records related to the study and excluding treatment records during the study. After the study, the records are archived at Radboudumc for an additional 13 years (total storage of 15 years, as required by law). The informed consents are stored at a different location than the investigator records and reports (separated locked cabinets at the Expertise Center for Parkinson and Movement disorders, route 914).

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigator agrees to retain study-related documents in a location that is secure and to which access can be gained if required. The following documents must be archived-the Regulatory Binder containing all regulatory required documents as well as the Participant Files, which include the signed participant Informed Consent Forms, eCRFs, and source documents, if necessary. Records must be retained for the 15 years (according to “Medical Device Regulations (EU) 2017/745”).

11.8 Monitoring and Quality Assurance

Monitoring of the clinical investigation will be a continuous process to ensure that high-quality data are obtained through compliance with the study protocol and will be conducted in accordance with Good Clinical Practice guidelines (ICH E6). Electronic Case Report Forms (eCRFs) will be reviewed for completeness, conformity with requirements, and safety monitoring of adverse events. A detailed monitoring plan will be submitted to the designated Authority at the Radboudumc for approval.

On-site monitoring will be frequent enough to assure continued acceptability of the data by assessing compliance of the center to the protocol, adherence to the data collection procedures, and maintenance of clinical investigation records. Accuracy of data reported on the forms will be verified by comparison to the subject’s source documents/medical records, when applicable. If necessary, appropriate corrective action will be taken to ensure adherence to the CIP.

The Investigator guarantees direct access to source documents/medical and hospital records by sponsor personnel or their designee and appropriate regulatory authorities. The clinical investigation may also be subject to a quality assurance audit by the sponsor or their designee, as well as inspection by appropriate regulatory authorities.

All monitors will be qualified to perform their assigned responsibilities. Monitors are qualified by training and experience to monitor the progress of clinical trials and will not be involved in the study beyond their activities required to ensure adherence to the protocol.

11.8.1 Deviations from clinical investigation plan

Investigators must follow the study protocol as defined in this document. Under emergency circumstances, deviations from the CIP to protect the rights, safety and well-being of human

subjects may proceed without prior approval of the principal investigator and the METC. Such deviations shall be documented and reported to the sponsor and the METC immediately.

Any other protocol deviations should be avoided and they should be first discussed with the principal investigator and, for medical issues, the Independent Expert may be consulted prior to implementation.

Any deviation from the protocol will be recorded together with an explanation for the deviation and reported within 30 working days to the principal investigator, who is responsible for analysing them and assessing their significance in terms of impact of the deviation on the scientific value of the trial as well as the impact on the subject's safety and rights. Deviations will be reviewed by the principal investigator and corrective actions taken. These may imply the need to amend the protocol or to terminate the investigation. In most cases, corrective actions will consist of additional training of investigators and support staff on the protocol and study procedures, and to conduct ongoing training with regard to protocol amendments, in order to prevent further deviations. In the event of repetitive, significant deviations at a particular study site, which jeopardize subject safety and/or quality of data, the principal investigator may consider to terminate the investigation at that particular site.

All amendments to the protocol shall be approved by the Principal Investigator(s) and be recorded with a justification for the Amendments. Protocol amendments shall be submitted to the METC as applicable.

11.8.2 Site Initiation Visit

Site Initiation Visits (SIV) will be conducted by the Radboudumc to train the Investigator and supporting clinical investigation staff on the CIP objectives, subject timelines, device operation, electronic Case Report Form completion, Informed Consent procedures, subject screening and enrollment, study documentation and administration, device accountability, record-keeping requirements, Investigator and sponsor responsibilities, role of the Ethics Committee (EC)/Competent Authority (CA), adverse event and protocol deviation reporting, monitoring requirements and any applicable regulatory documents prior to enrolling the first participant. The site may not enroll study subjects into the clinical investigation until all applicable EC and regulatory approvals have been received by the sponsor and the site initiation visit is completed. SIV training will be documented and the documentation filed at the investigational site and at the sponsor.

11.8.3 Interim Site Monitoring and/or Audits

On-site monitoring visits (performed by Radboudumc or designee) and/or audits (performed by an independent party, commonly a Regulatory Agency) will assess the progress of the clinical investigation and identify any concerns that result from device performance or review of the Investigator's study records, study management documents and subject Informed

Consent documentation. The study monitor will also ensure the Investigator adheres to the CIP and all applicable regulations.

To assure the integrity of key data collected in the clinical investigation, the study monitor will compare individual subject medical records/source documentation and reports prepared by the Investigator or designee to the electronic Case Report Forms (eCRFs).

In some instances, Site Monitoring Visits can be performed remotely as long as key data provided on eCRFs is properly monitored against source documents.
Investigators found not complying with the CIP and regulations will be terminated from the clinical investigation and shall be required to return all unused devices and/or associated clinical investigation materials and procedure manuals to the sponsor.

11.8.4 Site Close-out Visit

A Site Close-out Visit will be conducted at the completion of the clinical study. During the close-out visit, Radboudumc or designee will ensure that all eCRFs and data queries are signed and dated and have been transmitted to the sponsor, the device accountability log has been reconciled and any remaining study devices have been shipped back to Verily. Additionally, Radboudumc will review the Investigator's ongoing study responsibilities, including to report any unexpected or device related adverse events, to submit a final study report and a notification of study close to the EC and to maintain study files per regulations. In some instances, the Site Close-out Visit may be conducted over the phone.

Completed eCRFs will be verified against source data/medical records by the designated study monitor for completeness and consistency. If corrections/modifications are needed during the monitoring visit, the Investigator or designee will correct the data directly on the eCRF. Corrections will be listed in the audit trail of the eCRF/EDC system. All data corrections will comply with the International Conference of Harmonization (ICH) and Good Clinical Practice (GCP) guidelines.

11.9 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority. Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor.

11.12 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.13 Temporary halt and (prematurely) end of study report

The end of the study is defined as the last participant's last visit. The sponsor or the safety committee can decide to terminate the study at any time. While the study may be terminated early due to safety or adverse event concerns, there is no plan for early termination based on outcomes.

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 15 days. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason for such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.14 End of study report

The sponsor will notify the accredited EC and the Competent Authority of the end of the study within three (3) months of completion or termination of the study. Study completion is defined as the last participant's last visit.

Within one year after the end of the study, the sponsor will submit a final Clinical Report with the results of the study, including any publications/abstracts of the study, to the accredited EC and the Competent Authority.

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last participant's last visit.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.15 Public disclosure and publication policy

Any publication or presentation by the Investigator, Research Collaborators, or any other collaborative center(s) based on data or results resulting from this study shall only be done in strict accordance with the Publication Policy specified in the respective Collaboration Agreements with Radboudumc.

The Party proposing a Publication shall provide the other Party with a copy of the proposed Publication at least thirty (30) business days prior to its intended submission for publication. The non-publishing Party will review the Publication to: (1) determine whether any of such Party's Confidential Information is disclosed in the Publication; (2) identify potentially patentable inventions; and (3) with respect to Partner as the publishing Party, determine whether the Publication in any way may disclose details relating to the performance of the Verily Technology itself, its derivatives, or the methods or technology by which it was collected or generated. The non-publishing Party shall provide comments within thirty (30) days of receipt of any proposed Publication by the publishing Party. Upon the request of the non-publishing Party, the publishing Party will delete the non-publishing Party's Confidential Information (other than as expressly and mutually agreed by the Parties under the applicable Work Plan) from any form of Publication. If the non-publishing Party notifies the publishing Party that the Publication reveals a potentially patentable invention of the non-publishing Party, then the publishing Party will delay submission of the Publication for publication to enable the preparation and filing of a patent application with respect to such invention; provided, however, that such delay shall not exceed ninety (90) days. If Verily notifies Partner that the Publication is reasonably likely to disclose details relating to the performance of the Verily Technology itself, its derivatives, or the methods or technology by which it was collected or generated, Partner will delete that portion of the Publication so implicated.

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

There are limited risks to the participant during the data collection. Potential risks relate to the in-clinic assessments and the unsupervised home assessments with the TUG and 6MWT. Considering the in-clinic assessments, all tests are supervised by a trained physiotherapist who will monitor participant safety continuously. As these tests that are performed as part of this project are also part of usual care, we expect the risks during clinical assessment to be minimal. For the home assessments, there may be a risk of falling or cardiovascular events. We have tried to minimize these risks by including a population that is expected to perform these tests safely at home (i.e. exclusion criteria; not fallen more than once in the last 3 months, no unstable cardiovascular diseases, permission of treating physician to participate). Moreover, the first walking tests are performed under direct supervision of the physiotherapist who can judge and discuss potential safety issues with the participant.

12.1.1 Verily Study Watch

The structured risk analysis of the Verily Study Watch is included in the Investigator Brochure (D1. Investigator Brochure.2020-6969.v3.11-JUN-2019).

12.1.2 Participant burden and benefits

The burden of participating in this study consists of 4 visits to the local physiotherapy practice for in-clinic assessments of disease status and walking tests. Every in-clinic visit will take approximately 120 minutes. In addition, participants are asked to wear the Study Watch continuously for 15 weeks and perform two walking tests once a week. Participants may benefit directly from participating in this study because they will receive 10 weeks of physiotherapy by a specialized physiotherapist.

12.2 Synthesis

The risks associated with participation in this study can be considered negligible in terms of participants getting serious harm. Even though the potential damage is serious (i.e fractures after a fall incident or cardiovascular events), the chances of this to occur is minimal because we have taken a number of actions to minimize the risk. These actions include:

- Including a population with low fall risk (i.e. patients that have fallen more than once in the last six months will be excluded);
- Excluding participants with an unstable cardiovascular condition;
- Asking the treating physician permission for participation; and/or
- Performing the first walking tests in-clinic, and under direct supervision of the physiotherapist. The physiotherapist will be able to make a reliable judgement of the potential risk of performing the tests unsupervised at home.

Table 5. Risk classification schedule

Extent of additional risk/ Degree of damage	Minimal damage	Moderate damage	Serious damage
Minimal chance	Negligible risk	Negligible risk	Moderate risk
Moderate chance	Negligible risk	Moderate risk	High risk
High chance	Moderate risk	High risk	High risk

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APPENDIX A

Researchers and/or study staff at Radboud will access and download the following data gathered from your de-identified Fitbit account:

- Daily steps total
- Measured steps per minutes
- Estimated energy expenditure per minutes
- Distance moved per minutes
- Minutes of vigorous activity per minutes
- Minutes of moderate activity per minutes
- Minutes of light activity per minutes
- Minutes of sedentary time per minutes
- Sleep length, quality, and movement per minutes
- Heart rate per second
- Manually entered and automatically detected physical activities, such as walking or running
- Manually entered information in your Fitbit study account (such as height, weight, gender, and age; information that you elected to share with the Fitbit account (for example linking a smart scale), and information about other accounts that you may link with your Fitbit study account. *This information will be ignored by the study staff.*

Note that geolocation data collection is not accessible by researchers and study staff. No data will be transferred to Verily or available for Verily employees until Verily sets up appropriate Access Controlled Data Store (ARDS).