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PD_manager: an mHealth platform for Parkinson's disease Management

Coordinator: Prof. Annalisa Angelini

Supervisor: Prof. Angelo Antonini

Ph.D. student : Dr. Andrea Marcante

SOMMARIO

ABSTRACT

Parkinson's disease (PD) current clinical management is mostly based on patient's subjective report about the effects of treatments and on medical examinations that unfortunately represent only a snapshot of a highly fluctuating clinical condition. This traditional approach requires time, it is biased by patient's judgment and is often not completely reliable, especially in moderate advanced stages. The main purpose of the EU funded project PD_manager (Horizon 2020, Grant Agreement n° 643706) is to build and evaluate an innovative, mHealth, patient-centric system for PD remote monitoring. After a first phase of research and development, a set of wearable devices has been selected and tested on 20 patients. The raw data recorded have been used to feed algorithms necessary to recognize motor symptoms. In parallel, other applications have been developed to test also the main non-motor symptoms. On a second phase, a case-control randomized multicentric study has been designed and performed to assess the acceptability and utility of the PD_manager system at patients' home, compared to the current gold standard for home monitoring, represented by symptoms diaries. 136 couples of patients and caregivers have been recruited, and at the end of the trial the system was found to be very well tolerated and easy to use, compared to diaries. The developed System is able to recognize motor and non-motor symptoms, helping healthcare professionals in taking decisions on therapeutic strategies. Moreover, PD_manager could represent a useful tool for patient's self-monitoring and self-care promotion.

INTRODUCTION

Parkinson's disease

Parkinson's disease (PD) is a degenerative disease of Central Nervous System that was first described in 1817 by James Parkinson (1) and is now recognized as the second most common neurodegenerative disease, second only to Alzheimer's disease. PD is rare before the age of 50 but the prevalence increases with age, affecting approximately 1% of the population over 60 years (2) . According to the Global Declaration for Parkinson's disease (3), 6.3 million people are affected by Parkinson's worldwide, with no differences between all races and cultures, with slightly more men than women affected. Possibly the disease prevalence will increase in the future, because of the general population ageing.

PD pathophysiology, from a neuropathological point of view, is characterized by the inclusions of Lewy bodies and Lewy neurites containing α-synuclein (α-syn) (4). These pathological intra neuronal inclusions lead to synaptic dysfunction, interfere with axonal transport and lead to neuronal damage, in particular of neuromelanin rich neurons in the dopaminergic substantia nigra pars compacta's (SNc) caudal and ventrolateral regions. The degeneration of the SNc leads to further degeneration of the nigrostriatal system with dopaminergic loss in the striatum and causing the core motor features of PD (4). These neuropathological features, however, can be early observed also in non-nigral sites such as the olfactory bulb and the enteral nervous system. Possibly, during the progression of the disease, the inclusions tend to spread in a cranial direction, affecting the cerebral cortex and causing cognitive deficits typical of the late stage (5). The etiology of PD is idiopathic in most of cases, in fact less than 3% late onset PD patients have a monogenetic etiology, while genetic causes of the disease are more frequent (about 20%) in early onset PD (6). Many genes mutations have been associated with PD, both with autosomal dominant inheritance (SNCA, LRRK2, VPS35 and CHCHD2) or autosomal recessive inheritance (PARK2, PINK1, DJ-1, ATP13A2, PLA2G6 and FBX07) (6) (7).

From a clinical point of view, PD is a life-altering but not life-threatening disease. It is predominantly characterized by difficulties with body movements, known as "motor symptoms". The classical description of PD symptoms includes an asymmetric presentation of resting tremor, rigidity and bradykinesia.

Resting tremor is the typical symptom of PD in fact up to 70-80% of PD patients have resting tremor in the early disease stages (8). Tremor is frequently observed in the distal parts of the limbs at a frequency of 3-5 Hz. Usually

tremor on PD disappears in action as well as in sleep (9) and is exacerbated by emotional stress. Rigidity is described as an increase in muscle tone related to a lack of relaxation of the antagonist muscle to a muscle actively being contracted in a motion. Extrapyramidal rigidity does not change during the whole range of motion, is not dependent on the speed of the movement and is not associated with increased muscle reflexes. In PD, extrapyramidal rigidity can be objectified with the presence of cogwheel phenomena during passive mobilization of joints. Bradykinesia is another hallmark of PD and is characterized slowness of movement. Bradykinesia can cause walking problems with decreased arm swing and postural instability, reduces fine motor skills especially of the hands (particularly evident during handwriting) and is also related to hypomimia, another classical feature of PD, represented by loss of facial expression. Even when patients are still able to ambulate without assistance, limited motor ability due to marked bradykinesia and inability to perform fine and alternate movements lead them to dependency in ADLs, being unable to provide for basic personal care like dressing, bathing, and often feeding. All these motor symptoms are usually Levodopa (LD) or Dopamino-Agonists (DA) responsive, so in the early stage (known as “Levodopa honeymoon period”) the disease is relatively easy to be managed by clinicians. However, within 3-5 years, the progressive and complete loss of dopaminergic neurons causes an abnormal response to LD with the appearance of motor complications: wearing-off, fluctuations of motor and non motor symptoms and dyskinesias. Wearing –off can be defined as the progressive reduction of LD effects before the next dose of LD, with re-appearance of tremors, bradykinesia or rigidity. This usually leads to increase the frequency of LD daily administrations. Motor fluctuations are changes of motor performances that became progressively synchronous with oral LD intake and plasma bioavailability (10) . Motor fluctuations occur in approximately 50 percent of patients after 5 years of levodopa therapy (at this time they usually affect patients for less than 25 percent of their waking hours), and the proportion of patients affected increases to 70 percent among those treated for more than 15 years (11). Dyskinesia is defined as an involuntary abnormal choreiform movement of limbs, head or trunk that is induced by LD assumption, especially in long term treated patients. Dyskinesia can be observed when blood levels of LD are maximal (peak of dose dyskinesia) or during the onset and end of a LD dose (diphasic dyskinesia). In milder forms of motor complications, the symptoms can be controlled with modifications of LD doses or with introduction of other drugs such as cathecol-O-methyl transferase inhibitors, monoamine oxidase B inhibitors and dopamine agonists including apomorphine. When also these strategies are not sufficient, advanced therapies such as LD gastrointestinal infusion, subcutaneous

apomorphine infusion or Deep Brain Stimulation can be adopted (12). Unfortunately, PD patients could also be affected by motor symptoms that have poor or no response to dopaminergic treatment. These include axial motor involvement causing posture abnormalities, postural instability, gait difficulties, freezing of gait (FOG) and falls that can be possibly managed with non-pharmacological interventions such as motor rehabilitation, movement strategy training and technology-based interventions (13).

The incidence of falls in advanced PD is high (40–70%), even if the drug therapy is well balanced. Falls in advanced PD are caused by postural instability, dynamic imbalance, orthostatic hypotension, FOG, side effects of medications, or postural abnormalities like camptocormia or Pisa Syndrome. Falls lead to injuries and fracture that further reduce patient independence and increase the risk of nursing home admission. Patients with previous falls often develop fear of falling which further limits their mobility, contributing to increased weakness and deterioration (14).

Another important clinical feature of PD is represented by non-motor symptoms. Non-motor symptoms were initially neglected in the classic description of the disease but they have gained attention during the last decade (15). For many patients, non-motor symptoms are an important cause of decreased quality of life (16) and include psychiatric manifestations such as anxiety and depression, compulsive behavior, dysautonomia (with orthostatic hypotension, urinary symptoms and constipation) as well as cognitive impairment, fatigue, REM sleep behavior disorder (RBD), excessive daytime sleepiness, restless legs, pain and anosmia. Some non-motor symptoms can precede motor symptoms by several years, during the prodromal phase. Especially RBD and anosmia have therefore been suggested for screening to identify prodromal or very early PD (17).

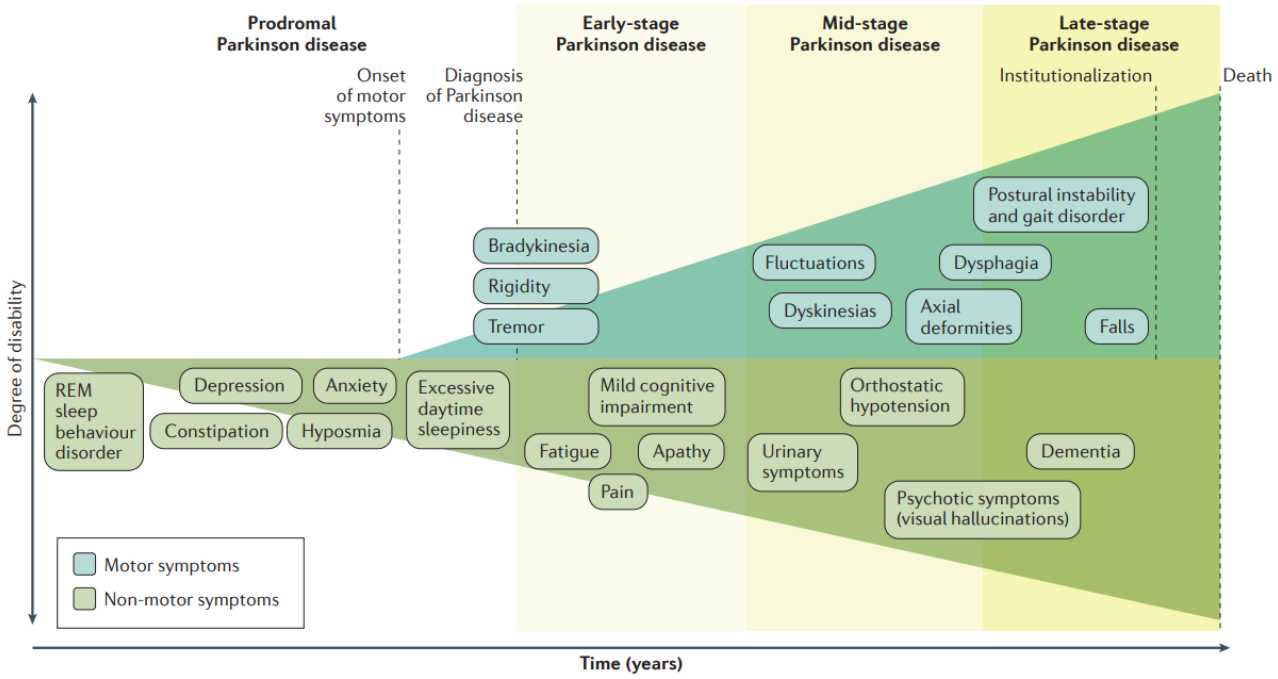


Figure 1 Clinical symptoms associated with PD progression from Poewe W, Seppi K, Tanner CM, et al. Parkinson disease **(18)**

Parkinson's disease monitoring systems

All the symptoms described above show how complex the clinical spectrum of PD can be, especially in the moderate-advanced stages, when patients experience an enhanced sensitivity to small changes in plasma L-dopa levels, that narrow the therapeutic window and negatively impact motor function (19). The complexity is also increased because of the high variability of symptoms between different patients and even within the same patient in different moments of the same day. Given the different levels of functional disability, what matters most for one patient about disease's symptoms may not be as important for another (20), so the management of motor and non-motor complications should be tailored to the individual subject. This implies a careful evaluation to assess for example whether the symptom is a side effect of the medications or is related to the progression of the disease. In current clinical practice this is a time-consuming process because fluctuations of symptoms are difficult to evaluate accurately (21). There are also symptoms that are rare or episodic (e.g. falls or freezing of gait), or behaviors that by definition, take place over long time periods outside the ambulatory room (e.g. aerobic and physical activity) and thus difficult to be evaluated by clinicians. Another important point is that many patients that live in rural areas or are affected by severe mobility impairments have limited access to proper expert care and when delivered, that care is institution based, rather that patient centered. It is mainly to

overcome these problems that clinicians and engineers started thinking and developing new management solutions.

Emerging care home-based models are combining remote monitoring, self-monitoring, and multidisciplinary care to enable the provision of patient-centered care at home, decreasing the need for in-clinic assessments (22) and giving the opportunity to reduce healthcare costs (23). Moreover, these systems are useful to generate real-time ecologically-valid, accurate, sensitive, and rich datasets not only regarding motor or non motor symptoms, but also including contextual information and data such as the time of medication, food intake, sleep quality or physical activity, that could be helpful for optimizing multidisciplinary care. The importance of colleting objective measurements in PD has been recently analyzed by a panel of experts of Movement Disorders Society (24). This is a growing need since currently available clinical evaluation scales suffer from being retrospective, subjective and affected by recall bias. Also, PD patients often have difficulty in recognize and correctly report their symptoms, for example differentiating dyskinesia from tremor or motor fluctuations from non-motor fluctuations. Patients' diaries of symptoms, even if specifically designed for annotating only PD main symptoms, have problems with recall and "diary fatigue" (25), and fail to detect early fluctuations. From a clinical point of view, the most useful data coming from home monitoring should be those related to symptoms and features that can be measured to reflect therapy effects, including bradykinesia, dyskinesia, fluctuations of symptoms, gait parameters and physical inactivity (26), but potentially the applications in diagnosis and treatment are various. For example, the discovery of occult disease symptoms, the correct quantification of fluctuations after the prescription of a treatment directed at reducing their severity, the precise timing of fluctuation relating to meals (e.g. suggesting LD absorption problems), or the more accurate assessment of response to advanced therapies, helping in reducing hospitalization after their initiation (24). Personalized strategies are also important to support patients' engagement in their care path, making them active in their own health (27), by giving a meaningful and comprehensible feedback about the disease's status.

Another important aspect that could benefit from home monitoring systems is caregiver burden, a well known problem in PD that is defined as "the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical and spiritual functioning" (28). The caregiver of PD patient has many responsibilities, for example medication administration, care coordination and self-care promotion, communication on behalf of the patient, falls prevention, emotional support. Caregiver also plays an important

role in directly assisting the person with activities of daily living, especially in the late stages of the disease. Identifying and responding to caregiver burden is crucial because informal caregivers make a central personal and societal contribution to the support of people with PD. Burden is strongly connected to PD psychiatric symptoms, which appear to be highly prevalent (29). A personalized help to caregivers by an adequate and objective feedback about the patient's clinical condition and a detailed education on all PD symptoms and complications is a solution that can be provided directly by supporting systems or through clinicians, on the basis of data gathered by remote monitoring systems. For example, to reduce the burden of caretakers, a study performed by Megalingam and colleagues proposes a wearable health monitoring system that can measure heart rate, temperature, electrocardiogram (ECG), tilt, and fall of the homebound patients and can send a notification via smartphone to the caregivers if a critical situation is occurring (30).

From a technical point of view, PD monitoring systems are essentially based on wearable devices that can be equipped with wide range (31) of different sensors such as inertial sensors, surface EMG, force sensors, portable EEG, heart rate sensors. The most studied and used are the inertial sensors. Inertial sensors include accelerometers and gyroscopes that can measure respectively the acceleration of a body on the three axis of space and its angular acceleration during rotation movements. These sensors are assembled on patented devices specifically designed for medical purposes and intended to detect one or more PD symptoms, or can be already built-in existing smart-things (such as smartphones, fitness bands, smart watches or tablets). This hardware is usually completed by companion software applications (e.g., mobile apps and web-based applications) to capture contextual data.

Wearable devices can be positioned in various body parts, depending on the purpose. Many studies have used different combinations of devices placed on wrists, ankles, shoes, hips, lower back. They are secured to patient's body with straps or in some cases integrated in proper clothes (32). Usually inertial sensors on limbs are used to detect tremor or dyskinesia, while those placed on foot or lower back are used for gait analysis or FOG detection. However, is still not clear which sensor fixed to which body part is best in detecting the various motor symptoms and there are no conclusive data on how many sensors are needed (33). In the last 10 years there is growing interest on use of these wearable devices in many medical fields, thanks to their objective advantages in terms of low power consumption, unobtrusiveness, light weight, reasonable costs and ease of use (34). In the

specific area of PD, wearable sensors have demonstrated for example their potential power for diagnosis (35), management (36) or to monitor pharmacological trials (37). In fact, specific algorithms and machine learning procedures can translate raw data coming from the sensors to quantify main motor symptoms of PD, in terms of severity, duration or constancy. For diagnostic purposes, many studies focused on detection of tremor, for example in distinguish parkinsonian tremor from essential tremor (38), however, currently reported misdiagnosis between resting and essential tremor may occur in 20–30% of the cases (39). Many researches focused their work on recognize different types of tremors (resting, action or postural tremor), analyzing the various frequency bands properly, and correctly distinguishing tremor from other movements and disorders (e.g. dyskinesia or bradikinesia) (40) (41) (42) (43). Several studies used wearable sensors also to detect dyskinesia. Tsipouras and colleagues used signals from several accelerometers and gyroscopes, asking patients to perform standardised motor tasks or spontaneous movements, to measure levodopa-induced dyskinesia (44). The recordings were compared to clinical annotation of the signals and, as a result, they found a sensitivity and positive predictive values of approximately 80 %. In another study, the authors used KinetiSense motion sensor units (Great Lakes NeuroTechnologies, Cleveland, OH) containing a triaxial gyroscope and triaxial accelerometer on three body parts and compared the results with clinical rating of dyskinesia with specific scale (45). The authors found that dyskinesia scores predicted by the model using all sensors were highly correlated with clinician scores (correlation coefficient of 0.86) and accurate predictions were maintained when two sensors on the most affected side of the body were used. Current approaches to detect bradykinesia use various wearable inertial sensors (accelerometer with or without gyroscopes) integrated in shoes, watch-like devices or sensors placed on different body parts, recording body motions and gait, mainly during specific tasks (for example Timed Up and Go test) (46). Various studies showed that several gait parameters recorded by wearable sensor-based devices strongly correlate not only with the disease state, but also with bradykinesia scores (47). Gait has been extensively studied with non-wearable systems like force plates or optoelectronic gait analysis, that represent the gold standard to record many gait parameters (31). However recent studies showed that also wearable devices equipped with inertial sensors are able to detect the cardinal characteristics of PD gait. (48) (49) (47). Statistical (e.g., mean, variance, skewness, kurtosis), frequency (e.g., energy, power spectral density, fundamental frequency), and spatiotemporal/kinematic (e.g., stride length, TUG time, stride velocity) features

were extracted and analyzed. Step or stride segmentation were key points for the gait analysis to recognize heel-strike and toe-off times characterizing the gait cycle and the complete walk (31).

However, the use of wearable devices is not free from limitations. For some authors (50), data collected in home environment still not able to provide sufficient information about motor symptoms and, for instance, is still difficult to infer if detected slowness of movement is real bradikinesia or just fatigue, fear of falling or simply slower gait speed due to contextual factors. Moreover, the monitoring systems are mainly focused on motor symptoms, while patients often report large part of disability be originate from non-motor symptoms. Unfortunately, only few studies were focused on the complex and highly variable clinical manifestations (51) (52). Another aspect is that only few systems most wearable systems are not compatible with each other, so it might be difficult or even impossible to combine data gathered developed from different manufacturers, with deducible limitations in terms of applicability and usefulness of the data. Finally, especially for home monitoring system are crucial the usability and the wearability of the devices, to avoid a low rate of engagement among patients: as shown by a recent study demonstrating that 32% of users stop using wearables after 6 months, and 50% after just over a year (53). Lack of motivation to use wearables/self-monitoring systems should not be underestimated, particularly in the absence of meaningful feedback provided to their users. Preliminary evidence suggests that patient empowerment and their inclusion as active players in the development of research activities may favorably impact compliance (54), and the future development of monitoring systems should consider this aspect. In Table 1 un-meets needs in PD monitoring technologies are summarized, together with already achieved goals and future perspectives of development.

Clinical problem	Available/needed technologies	Clinical objective
Improving diagnosis	Needed – Sensors for prodromal features (e.g., constipation, REM sleep behavior, anosmia); blood sensors for biomarkers (α-synuclein, proteinomics, etc)	Enable population screening for PD, including the earliest possible (prodromal) stages
Monitoring response to therapy and motor complications (motor fluctuations, dyskinesia)	Available – Accelerometers, gyroscopes, magnetometers, electrogoniometers, surface EMG sensors Needed: small patches onto the skin or other sensors that improve patient adherence	Collect ecologically valid data of motor fluctuations, falls, freezing of gait episodes Implement sensor-based closed-loop technologies capable of delivering treatments (e.g., infusion pump)
Monitoring non-motor symptoms and progression	Available (but requiring improvements) – Sweat sensors, skin conductance sensors, heart rate sensors, blood pressure sensors	Collect ecologically valid data of non-motor symptoms and progression
Improving medical treatment	Available (but requiring improvements) – Oral capsules, subcutaneous and gastrointestinal infusion pumps	Implement adjustable extended-release drug formulations, smart (self-adjusting) levodopa delivery infusion systems
Enhancing surgical treatment	Available (but requiring improvements) – STN DBS, GPi DBS, Vim thalamus DBS	Implement closed-loop STN and GPi DBS (variable stimulation based on local field potentials)
Improving rehabilitation interventions	Available – Accelerometers, gyroscopes, magnetometers, electrogoniometers, surface EMG sensors, pulse oximetry sensors, respiratory rate sensors, blood pressure sensors	Implement closed-loop cueing and feedback systems validated for home use

Table 1 Examples of available and needed technologies relevant to the diagnosis and clinical management of patients with Parkinson disease **(50)** DBS: deep brain stimulation; EMG: electromyography; GPi: globus pallidus pars interna; PD: Parkinson disease; REM: rapid eye movement; STN: subthalamic nucleus; Vim: Ventrointermedial nucleus

PD_manager Project

The PD_manager Project is a European Project, founded by The EU Framework Program for Research and Innovation (Horizon 2020, Grant Agreement number 643706), that has the aim to build and evaluate an innovative, m-health, patient-centric system for Parkinson's disease management. Ten different partners from all over Europe are involved in the Project, including Universities, Research Hospitals and Private Companies, each one with different tasks and goals, but working all together to develop a new solution for home monitoring and care. The System is designed to use unobtrusive wearable devices for motor symptoms detection and quantification, but also a series of applications to monitor also non motor symptoms. The selection of features, tools and output of PD_manager is based on a user needs analysis (patients, caregivers, neurologists and other health-care providers). It examines current practices around every-day and specialist management of Parkinson's disease, and identify where these practices may be enhanced or complemented by technological and/or process support. On the basis of a needs analysis, a detailed specification of the tasks entailed in supporting and managing the disease will inform design specifications of technological support tools as well as providing educators and policy-makers with a clear and comprehensive view of the current and future nature of

Parkinson's disease management. From this task analysis, the information requirements necessary to support each task faced by each kind of user can be specified, which serves as a detailed specification for designing the PD_manager user-system interface.

A set of unobtrusive, simple-in-use, co-operative, mobile devices has been selected for symptoms monitoring and collection of adherence data. The set will consist of an Android Smartphone (with accelerometer and dedicated apps installed), a wristband (with sensors for heart rate and accelerometer and gyroscopes), and a pair of sensor insoles (with capacitive pressure sensors as well as a 3D acceleration sensor for the measurement of motion sequences). This combination of devices will be tested to verify the system's capability to correctly assess motor symptoms (initially with data from 20 inpatients with motor complications, then in home monitoring regimen). Patients are commonly assessed in physician office with the Movement Disorders Society UPDRS (55) to evaluate general severity of motor disability. Nonetheless obtaining long-term, objective information on motor status using an unobtrusive approach, that minimizes visits to the clinicians' office, is very important for the assessment of disease progression from the treating clinician with emphasis in the management of the wearing-off. Specifically, the patient, with the possible support of his caregiver, will be able to monitor occurrence of motor symptoms such as tremor, dyskinesia, bradykinesia, gait, posture, balance, with the sensor insole, as well as the accelerometers of the wristband and of the smartphone will provide the necessary raw data needed for that purpose. Also, detailed studies of the analytical strategies and knowledge sets used by expert health-care providers (e.g., neurologists undertaking diagnosis activities) will inform the design of a decision-support system (DSS) embedded within PD_manager. The DSS is potentially a very useful instrument for clinicians, because it will be able to suggest if and how modify drug therapy, based on symptoms detection and analysis. Medication, nutrition and physical activity and physiotherapy plans will be proposed by the system and will be approved and adjusted by the neurologist, the nutritionist or the physiotherapist respectively and will be available for the patient and the caregiver through a mobile app. The definition of factors and signs just before wearing off, that could constitute a sort of premonitory index of ON/OFFstatus, will also be studied during the data mining studies. The System will also propose and validate strategies to help physicians and healthcare professionals to search and evaluate the most diagnostic information (i.e., the information that is most relevant to help PD patients to cope with their symptoms, relief from them and make the best of their resources). Usually consultations are very short, so the feedback needs to be short and

integrated into the daily working routine of the health professional. Moreover, medical staff and patients usually decide the treatment plan and its modifications together – shared decision making. This decision-making is on the basis of subjective experiences by the patient / carer (self-report), and on the basis of objective assessment (available thanks to PD_manager) of motor, cognitive, and non-cognitive symptoms, as well as the level of adherence to the suggested management plan. Furthermore, objective data ought to be combined with subjective symptoms (e.g., depression, impulse control disorders, and cognitive dysfunction) referred by the patients to gain a holistic view on the patient's state. This holds true especially at the stage in which PD patients' response to medications becomes unpredictable and clinicians have to make decisions about whether and what changes in the disease management should be made. This will allow to better understand experts' use of the available information that will in turn inform and guide the development of models and the setup and the revision of the mobile devices. In this way, there will be a feedback loop between the design of technologies and the knowledge acquired about the procedures routinely adopted by clinicians. At the same time, the policy and ethical framework under which Parkinson's disease is managed will be assessed. These outcomes of behavioural modelling will be validated within a computational modelling framework, which will establish the viability of, and constraints on, the PD_manager support environment.

Regarding non-motor symptoms monitoring, PD_manager will focus on the emotional state of the patient, his cognitive problems, his speech disturbances and any sleep disorders he may be experiencing. All this information will reinforce the collected dataset about the patient and enable clinicians adopt a more complete approach for the management of the disease. Caregivers will greatly contribute to the collection of correct information for non-motor symptoms. Specifically, the project will support the evaluation of the overall non-motor symptom frequency and severity, impulsiveness, depression and compulsive behaviour with neuropsicological scales and using a brand-new smartphone application with dedicated games and tests. An objective evaluation of speech disturbances will be also implemented: vocal impairment relevant to PD is described as hypophonia (inability to produce normal voice pitch) and dysarthria (difficulty in articulating words). The research effort will be to classify patients and the progress of the disease based on their speech problems.

Specific Project partners will conduct a dedicated nutritional study for Parkinson's. The resulting mobile application will support each patient to set nutritional priorities based on the issues they face. The nutritional issues faced by patients with PD are complex and diverse. For example, PD patient needs to eat regularly, eat a

variety of foods from all of the food groups and eat prudently to maintain a healthy weight. Although this sounds like simple advice, its implementation can be a challenge, particularly when the symptoms of Parkinson's are affecting the patient's ability to shop, prepare food, and eat. Moreover, constipation is common in Parkinson's disease. Although the constipation observed in Parkinson's is due in large part to the disease itself, lifestyle measures can be useful for managing it. Finally, the medications used for Parkinson's can themselves cause nutrition-related side-effects, such as nausea and poor appetite, which can lead to undesired weight loss. Typically, these side-effects are most severe when a medication is first prescribed but some individuals have continuing problems with them. Amino acids (from dietary protein) can interfere with the uptake of levodopa into the brain. The PD_manager mobile app designed for nutrition support will be linked to the Open Platform for Clinical Nutrition (OPEN) (56), which is a freely accessible web-based application (developed by one of the Project partners) that supports food and physical activity recording and diet planning. It enables online interaction between a dietician and his patient. To support its use in different countries and languages, OPEN allows translation of the user interface into any language as well as the use of any food composition dataset that complies with Food data structure and format standard (BS EN 16104:2012). By default, OPEN refers to international dietary recommendations, which can be modified by the dietician to suit the needs of individuals. With PD_manager nutrition app, the patient will be able to build a personalized nutritional strategy. In early Parkinson's, the PD_manager will serve as online consultant educating patients and their caregivers. When the disease progresses, and new symptoms emerge (such as swallowing difficulties, medication side-effects, bowel issues, and eating challenges), the PD_manager will recommend dietary changes to manage and reduce such symptoms. As the goal of thoughtful nutrition is not just to ease PD symptoms, but also to allow the patient to continue to use food as a source of pleasure in his life, the PD_manager will motivate patients to enjoy in cooking and eating.

Another task of the Project is dedicated to empowering of game-based physiotherapy at home. Various serious games will be developed for that purpose, on different platforms: one tablet and two different optoelectronic infrared sensors. These games will provide specific scenarios that will encourage and motivate the patient on making selected exercises as prescribed by physiotherapists. Each game will collect data on patient's movements and progression that will then be available to doctors and physiotherapists for overview and tracking of patient's progress.

Finally, one last important part of the project is the educational module for patients, caregivers and healthcare providers. The focus will be on occupational and speech therapies in order to provide access to these services particularly for people with limited financial capabilities, since in most countries such services are provided only by private sector. An educational video gallery will be built for that purpose.

An open architecture based on Fi-ware Generic enablers will support the use of any commercial set of sensors within the Internet of Things concept. A robust knowledge management platform (KMP) will be designed and developed that can be used for different purposes from health professionals and public health monitoring authorities. In PD_manager, the KMP will be used for informing a DSS that will suggest disease management modifications to the clinician, who can then approve these modifications and send them to patients and caregivers.

Other Projects have been developed to test similar approaches to PD monitoring. For example, SENSE-PARK (57) seem similar to PD_manager in terms of measurements and patient monitoring, but to a closer look they are very different: PD_manager proposes a holistic mobile approach that includes education and gives emphasis in adherence to the medical recommendations. Moreover, the open, based on the Internet of Things concept, knowledge management platform that will be developed as well as the studies of experts' behaviour and patients nutrition and physiotherapy and the effort to build a DSS that suggests modifications in the medication plan take the PD management a step beyond the concept developed in SENSE-PARK. Actually, the SENSE-PARK sensor system could be a way to test the open nature of the PD_manager knowledge management platform and the features extracted from this sensor system could feed the PD_manager DSS instead of the data captured with the mobile devices proposed in PD_manager. Providing disease state-defining parameters and constantly giving feedback to patients, that are main objectives of the SENSE-PARK project, will be core features of the PD_manager system too and thus clustering will be needed in order to better address these two issues. Another Project on PD monitoring is REMPARK (58) - Personal Health Device for the Remote and Autonomous Management of Parkinson's Disease, that focuses only in the motor status of the patients without a more holistic approach. There are no duplicated efforts in gait analysis since the sensor insoles approach adopted in PD_manager is innovative and studied for the first time. Moreover, postural gait analysis is just a sub-task in PD_manager since the objective is to have data that will be evaluated by the clinician and the DSS, while REMPARK is developing an autonomous gait guidance system as a core activity. In CUPID (59) Project the goal

was to implement a closed-loop system for personalized and at-home rehabilitation of people with Parkinson's disease, using sensors, audio biofeedback, exergaming and external cueing to provide intensive motivating training, monitored remotely by experts, for at home rehabilitation. The scope of PD_manager is to suggest medication modifications based on the evolution of symptoms, and the patient's adherence to the prescribed management plan that of course includes rehabilitation in most patients. Adherence to physiotherapy through video games will be just an aspect of PD_manager since it is necessary in order to provide a holistic approach for the management of the disease, but the study will not go as deep as CUPID does in this field. Thus the 2 projects actually complement each other. The feedback from CUPID could be integrated as input for the PD_manager DSS and thus clustering should be sought.

OBJECTIVES

The PhD candidate has developed his research and study in the context of PD_manager Project, working as medical doctor in Research Hospital San Camillo IRCCS (Alberoni, Venice Lido), clinical partner of the Project's Consortium. During the PhD course, the candidate has also worked together with other clinical and technical partners in a tight interplay to complete the tasks requested.

The main objectives were:

- The design and completion of a Pilot Study on 20 inpatients wearing a set of wearable devices. The Pilot Study aims to collect a well-organized set of raw motor data, that will be analyzed to test if the System, using the measurements coming from the devices, is able to recognize the main motor symptoms of the disease.
- The design and completion of a Multicenter Study to assess the acceptability and usability of the PD_manager System at patients' home, compared to currently used practices for home monitoring and, from clinician point of view, to test the utility in terms of providing useful information for medical decisions and practicality of the mHealth platform.

The secondary objectives were:

- The creation of an educational video gallery for patients and caregivers
- To contribute in the creation of an automated Decision Support System for clinical management optimization
- To contribute in the development of a Cognitive App for monitoring of cognitive status
- To collect clinical data and vocal recordings for Voice Recognition App implementation

MATERIALS AND METHODS

Pilot study

The Pilot Study is a key pillar of the PD_manager project since it provides the basis for the second phase of the project, the Multicentric study. The main purpose of the Pilot Study is to verify if the selected wearable devices are able to detect and quantify the main PD motor symptoms. To do that, a well defined set of raw motor data have been gathered and analyzed by signal processing and data mining procedures for detection and evaluation of motor symptoms and fluctuation of symptoms. Other important goal of the pilot study was the analysis of selected non motor symptoms: cognitive status and speech. The data gathering of these two aspects has been integrated with the recordings of motor symptoms in a comprehensive protocol, together with clinical and demographic data, user needs analysis and usability and wearability evaluations. The pilot study has been specifically designed to obtain data from all these aspects, both in on and in Off condition with a precise schedule.

Patients

A total number of 20 patients was required for this pilot study. The involved Clinical partners of the Project contributed as follow: 10 hospitalized patients have been recruited at IRCCS Fondazione Ospedale San Camillo (Venice, Italy), 5 outpatients at IRCCS Santa Lucia (Rome, Italy), 5 outpatients at University Hospital of Ioannina (Ioannina, Greece).

The inclusion criteria are specific requirements that have to be satisfied to enroll a patient. For this study, the selected requirements were a diagnosis of idiopathic Parkinson's Disease (according to the UK Brain Bank criteria) and a Hohen &Yahr (60) score between 3 and 4 (during the OFF state). This second criteria was chosen to select a cohort of patients representative for a moderate-advanced disease stage. In fact, in this stage the symptoms are less responsive to drug therapy and patients start to present motor complications or initial cognitive impairment, so this kind of patients are the optimal target population for home monitoring systems usage and evaluation. The exclusion criteria were: co-morbidities with stroke or other brain disease, severe cognitive impairment (or dementia) and inability to walk.

For each patient have been collected essential clinical information such as: age, initial diagnosis. side of onset (side of the body where the motor symptoms began), disease duration, current symptoms, current treatment (duration, current dosage: Levodopa Equivalent Daily Dosage, Dopamine Agonist Equivalent Daily Dosage), previous treatment (duration), years under levodopa, presence or history of psychiatric disease, psychiatric treatment, comorbidities, other medications (from comorbidities). Before each recording session, specific MDS-UPDRS subitems have been scored, in On and Off state (see below, Pag. 25 Motor recording protocol and MDS-UPDRS Subitems evaluation).

Devices and Applications

Moticon's sensor insoles

Sensor insoles, produced by Moticon, is an every-day, flexible and thin solution (Fig. 2a) to measure distribution of pressure, acceleration, weight-bearing, balance and motion sequences. This is achieved with 13 capacitive pressure sensors as well as a 3D acceleration sensor and a temperature sensor which are integrated in the insole for the collection of data. OpenGo science (61) (that is the technology used to program the sensor insoles) is a system for the measurement of plantar pressure distribution that is universally applicable and open for application developers. It is ideal for the use in clinical research and particularly in the fields of rehabilitation and training analysis. The patients will wear these insoles inside their shoes, during the recordings.

Beaker Software

The Beaker software, developed by Moticon, was necessary for the implementation of the recordings using the insoles, and was also used for the synchronization of data. Inherently Beaker allows importing other synchronized raw data (e.g. signals from wristband and smartphone). The user can decide which data can be visualized (Fig. 2c). Beaker also supports video importing and automatic synchronization through filming QR codes at the beginning of the recording. In this way the researcher can visualize at a single screen the detailed gait analysis, as many other available signals, the video of the patient for a visual analysis of the symptoms and their correlation with the signals from the patient. All data are synchronized and ready for further analysis (Fig. 3).

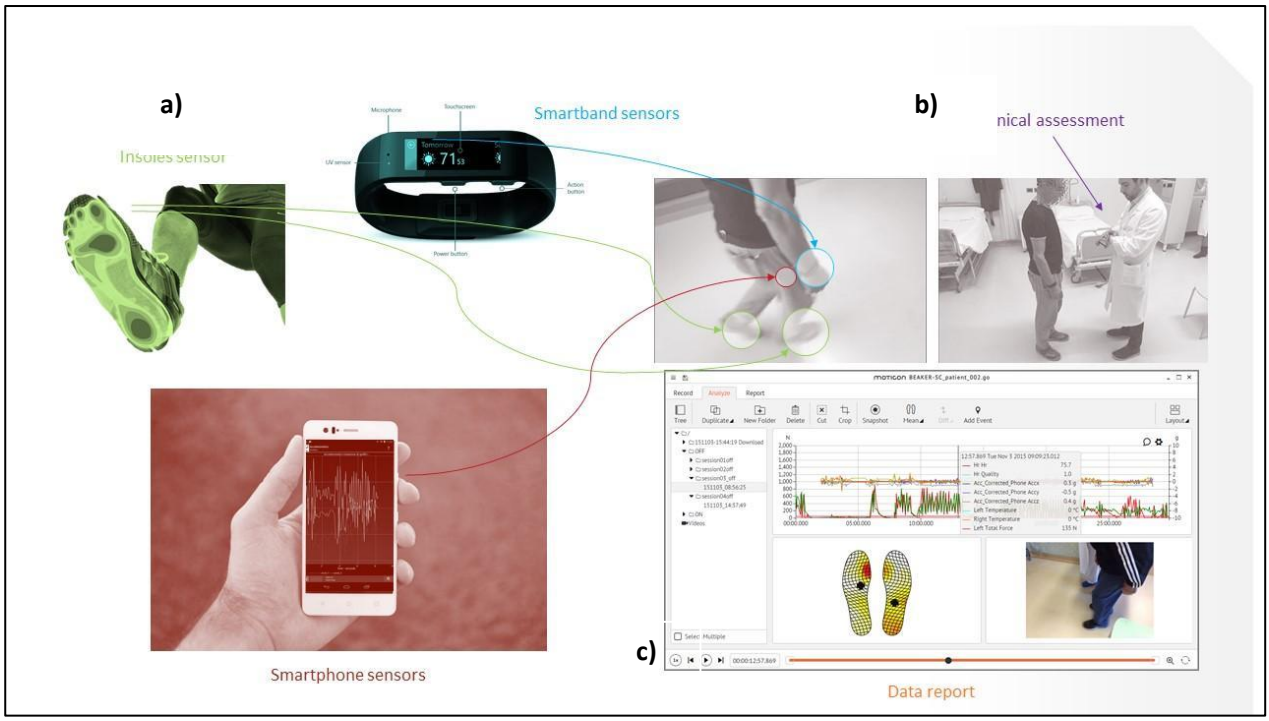


Figure 2 a) the wearable devices; b) clinical setting; c) Beaker Software

Figure 3 Data from all devices are merged in Beaker software and analysed together

Smartphone and PD_manager App

For the needs of the data gathering of Pilot Study, a monitoring and data collection mobile app was designed and developed. The App, based on Android operating system, is installed on a smartphone (Aquaris M5, BQ™, Spain) that will be located into patient's pocket during the motor recording protocol. The smartphone's brand

has been chosen by technical partners. The PD_manager App allows to gather raw data from the sensors of the Microsoft® Band to the paired smartphone, as well as raw data from the sensors of the smartphone itself. In this section the basic functionality (Fig. 4) of the mobile and its use in the context of data gathering is provided; a detailed analysis of the implementation will be presented in the Results section. Another BQ smartphone, with the PD_manager App installed, is used by the clinician to annotate the presence of motor symptoms during the recording sessions (Fig. 4 d)

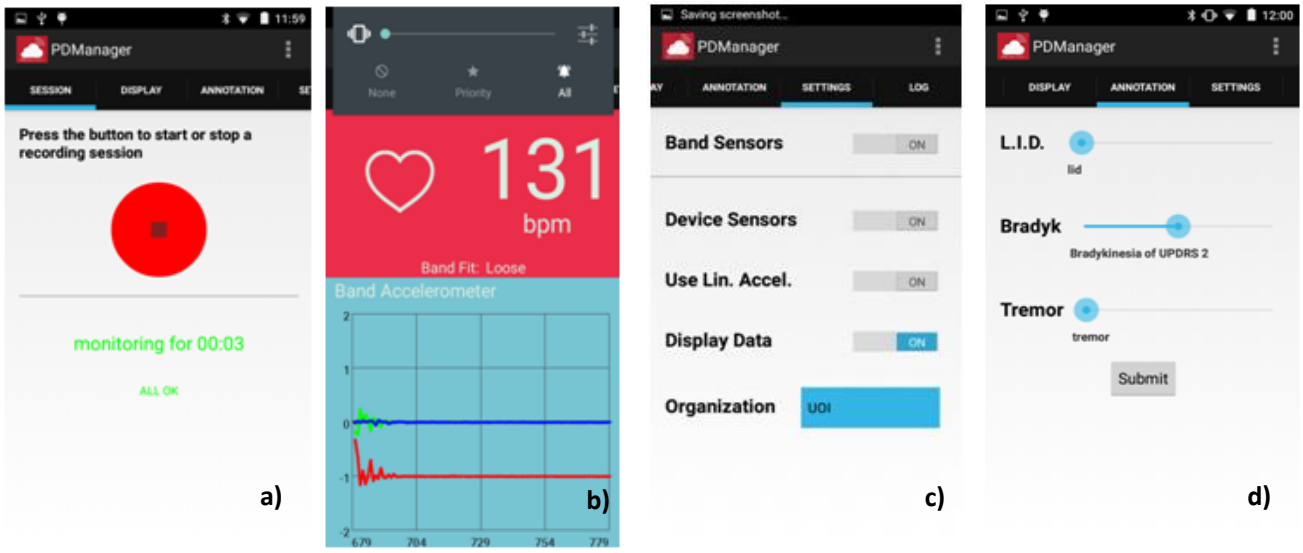


Figure 4 PD_manager App for Android Smartphone a) start/stop recordings; b) Signals monitoring; c) Sensors selection; d) clinicians annotations app

Wirstband and Microsoft® Health App

The Microsoft® Band 1 is a wearable device, a wristband, that can be used to track the user's activities, using several sensors (62) Measurements of the fluctuations in heart rate make Band's measurements of calories burned and exercise and sleep statistics more precise. In PD_manager we use the raw data coming from the wristband for correlations with other signals. A 3D accelerometer, along with the gyroscope the motion data are used to calculate statistics like number of steps taken, which can be combined with info from the profile and heart rate measurements. GPS that records routes and collects info about the distance. And the GSR (Galvanic Skin Response) that measure skin conductivity. The GPS data could be used to refine distance and speed calculations, but not in this project. For the purpose of this task we have collected raw data only from the 3-axis accelerometer, the gyroscope, steps and heart rate. Future versions can be extended to include more signals and raw data, e.g. from GPS or GSR. To correctly pair Microsoft® Band to PD_manager App, on the smartphone we have also installed Microsoft® Health app (63) that provides actionable insights based on the rich data gathered

from the band and any other fitness devices and apps the patient may use every day. Microsoft® Health makes tracking personal activity easier, more insightful, and more holistic. In this study, analysis of data performed by from Microsoft® Health will not be used, but in the future, this app can be integrated in the mHealth platform to monitor physical activities and also sleep quality.

Cognitive Test App

While the automatic detection and assessment of the motor symptoms is a topic that has been largely studied and is in the focus since mhealth is considered for PD, the evaluation of the cognitive status in PD patients and the integrated study of cognitive and motor progression is not so well addressed. With this purpose, in the context of PD-manager Project, a mobile application (Cognitive Test app) was designed and developed in collaboration with technical partners of Universidad Politecnica de Madrid, in order to track the neuropsychological trend of the patient, along with motor fluctuations. Before the Cognitive Test administration, the patient has to perform the Finger tapping task: the patient is asked to touch, with one finger at first and then with two, one or two buttons on the smartphone screen as fast as possible within 10 seconds. This simple motor task is aimed to set the Cognitive Test software, based on the reaction time of each patient, to calculate the time needed to perform each test. This mobile application has been used during the Pilot Study with two main objectives: 1) to explore the feasibility of a mobile application for this kind of assessment in PD patients, 2) to get actual feedback from the patient in terms of usability and user experience, in order to modify the app design and tests if needed. Several Cognitive tasks have been evaluated and, based on clinicians' indications, a Cognitive Test App has been developed. The following tests have been selected:

a) Paired Associates Learning: In the first part of the test boxes are displayed on the screen and opened in a randomized order. One or more of them will contain a pattern. In the second part of the test, the patterns are displayed in the middle of the screen, one at a time, and the participant must touch the box where the pattern was originally located. The difficulty level increases through the test. The number of patterns to locate will increase along with the difficulty level (from one in the first level to eight in the last level). If the participant reaches the 6th level, the number of boxes will increase from 6 to 8. If the participant locates correctly the pattern, a positive feedback will be showed (a green tick mark and a positive auditory signal), otherwise a negative feedback will be showed (a red x mark and a negative auditory signal). To skip to the next level, the

patient must locate correctly all patterns. In case of error, the level is repeated, and the pat-terns are represented to remind the participant of their locations. If participant locates wrongly all patterns in two consequent trials of the same level, the test will stop.

b) Pattern Recognition Memory: The participant is presented with a series visual patterns, one at a time, in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. After the presentation phase, there is a recognition, in which the participant is required to choose between a pattern he has already seen and a novel pattern. In each level, the test patterns can be presented in the reverse order to the original order of presentation (reverse mode) or in a totally random order (random mode). If the participant selects the correct pattern, a positive feedback will be showed (a green tick mark and a positive auditory signal), otherwise a negative feedback will be showed (a red x mark and a negative auditory signal). The difficulty level increases through the test, i.e., the number of patterns increases from two –first level - to six – last level -.

c) Spatial Working Memory: The test begins with eight white squares boxes being shown on the screen. The aim of this test is that, by touching the boxes and using a process of elimination, the participant should find one blue 'token' only in a few of the white boxes presented on the screen and use them to fill up an empty column on the right hand side of the screen. The number of blue 'tokens' is gradually increased, up to eight boxes.

d) Spatial Span: Eight white squares are shown, some of which briefly change color in a variable sequence. The participant must then touch the squares which changed color in the same order that they were displayed by the device. In each level, there are three trials with the same spatial configuration of white squares and the same length of variable sequence. The sequence of colored boxes will get as long as the level difficulty increases (from two colored boxes in the first level to eight colored boxes in the last level). To skip to the next level, the patient must make correctly at least two of three trials. However, with two or more incorrect trials the test stops.

e) Stop Signal Stop: This test consists of two parts. In the first part, the participant is introduced to the press pad, and told to press the left hand button when he sees a left-pointing arrow, and the right hand button when he sees a right-pointing arrow. In the second part, the participant is told to continuously press the but-tons on the press pad when he sees the arrow, as before, but, if the arrow presentation is combined with an auditory signal (a beep), he should withhold his response and not press the button.

The number of trials of each part is 50 and the length of each trial is three seconds.

f) Attention Switching Task: The test displays an arrow which can appear on either side of the screen (right or left) and can point in either direction (to the right or to the left). Each trial displays a cue at the top of the screen that indicates to the participant whether he has to press the right or left button, according to the "direction in which the arrow was pointing" (first part) or the "side on which the arrow appeared" (second part). Some trials display congruent stimuli (e.g. arrow on the right side of the screen pointing to the right) whereas other trials display incongruent stimuli which require a higher cognitive demand (e.g. arrow on the right side of the screen pointing to the left). The total number of trials of each part is 13.

g) Visual Analogue Scales: The participant must respond to 8 questions, as they appear on the screen by touching the on-screen slider and moving it to the appropriate position on the scale

Speech Recognition

Some people with PD experience changes in cognition and language, i.e. difficulty to think quickly, to manage multiple tasks, to find words or to understand complex sentences. These changes, even if subtle, can make it challenging for a person with Parkinson's to follow a conversation. In some cases, the patient cannot retrieve the word that he/she is thinking about; this condition is called anomia. At the same time, a typical feature of PD patients' language may consist in a 'flatter' voice (lack of prosody), associated with poor facial expressions. About 90 per cent of people with PD will experience changes in their voices or their ability to make speech sounds at some stage of their lives. Most commonly, the voice becomes quieter (hypophonia)(10). It can also develop a breathy or hoarse quality. These changes may result in less precise speech, which is more difficult to understand, especially when speaking to persons who have hearing loss. The speed of talking changes also due to PD. Some individuals with PD may speak more slowly, others accelerate their speech so much that they stumble over sounds and seem to be stuttering (tachyphemia). To perform the speech recordings the Smartphone have been used, with installed a Smart Voice Recorder app (64).

Recordings

Motor recording protocol and MDS-UPDRS Subitems evaluation

The motor recording protocol is a set of simple motor tasks that the patient performed during the recording sessions and which simulate daily activities such as sitting in a chair, opening a door, etc. Every task aims to trigger specific symptoms of the disease. The motor recording protocol is needed to standardize a reproducible

recording setting and to collect consistent data across the 3 clinical sites involved. As resumed in Table 2, for each enrolled patient the protocol has been repeated 8 times in 4 different days, in fact for each "recording day", two recording sessions have been planned: one in ON and one in OFF state.

		Clinical information	**MDS-UPDRS** sub items	Motor Rec. Protocol	Cognitive Test	Speech Test	Wearability Questionnaire	User Needs Interview
Recording Day 1	Session 1 (OFF)	✓	✓	✓				
	Session 2 (ON)		✓	✓				✓ (Part A)
Recording Day 2	Session 1 (OFF)		✓	✓	✓			
	Session 2 (ON)		✓	✓	✓			
Recording Day 3	Session 1 (OFF)		✓	✓		✓		
	Session 2 (ON)		✓	✓		✓		
Recording Day 4	Session 1 (OFF)		✓	✓				
	Session 2 (ON)		✓	✓			✓	✓ (Part B)

Table 2 Recordings schedule

In general, the patients have been asked when they usually are in OFF state and the first session of the day is performed at that time. If, thanks to medical treatment, the patient did not present a clear OFF state, in order to make sure to record a real "OFF state", the session have been planned in the morning, avoiding to administrate the first daily dose. The dose has been administered immediately after the recording session. To record an "ON state" it has been sufficient to plan the session from 30 minutes to 1 hour after any of the L-Dopa or Dopamine-agonists doses that the patient usually takes during the day.

Before each recording session, the clinician evaluates the patients scoring the MDS-UPDRS subitems showed in Table 3.

Symptom	**MDS-UPDRS Subitem number**	**Range**
Speech	3.1	0-4
Rigidity Severity on Right Arm	3.3b	0-4
Rigidity Severity on Left Arm	3.3c	0-4
Finger tapping Right Hand	3.4a	0-4
Finger tapping Left Hand	3.4b	0-4
Gait	3.10	0-4
Tremor Severity on Right Arm	3.17a	0-4
Tremor Severity on Left Arm	3.17b	0-4

Tremor Severity on Right Leg	3.17c	0-4
Tremor Severity on Left Leg	3.17d	0-4
Was dyskinesia present?	/	yes/no

Table 3 Selected Updrs Subitems with respective number and score range

When the patient is ready he/she has been asked to wear the insoles inside his/her shoes, the wristband on the wrist of the more affected side, and the smartphone inside trousers' pocket; the clinician keeps the other smartphone in order to annotate any motor symptoms that occurs during the recording session.

The core activity of the whole Motor Recording Protocol is the recording of motor tasks. During the recordings of motor tasks, 3 people are involved: the patient that must complete the tasks wearing the sensors (Smartphone, Wristband and Sensor insoles); the clinician that guide the patient and also annotates the symptoms; an operator that performs the video recordings. The annotation of symptoms, performed by the clinician, is made using a second smartphone as described. When all recordings are started, the patient is asked to complete a series of simple motor tasks:

1. Lie on the bed for 1 minute
2. Rise from the bed and sit on a chair located beside the bed for 1 minute
3. Perform Timed Up and Go Test (TUG) (65): "rise from a chair, walk three meters, turn around, walk back to the chair, and sit down".
4. Stand up from the chair and perform a series of activities:
    a. Stand (without move) for 1 minute (while standing, avoid communication with patient. Clinician stands in front of patient, not on patient's side, to avoid patient turning towards the clinician). The camera is placed in front of the patient, in order to capture postural abnormalities for the frontal plane.
    b. Walk for a distance of 5 meters, open the door (with the arm that wears wristband) and walk through the door, exit the room, go back in the room and close the door (repeat for 3 times, this should evoke freezing, if present).
    c. Two Minute Walking Test (66)
    d. Walk back to the room;
5. Make a stop and drink a few sips from a glass of water (repeat the sequence: take the glass, drink and leave the glass for 3 times);

6. Stand (without move) for 1 minute. While standing, clinician avoids communication with patient. Clinician stands in front of patient, not on patient's side, to avoid patient turning towards the clinician. This time the patient is recorded from one side (the side recorded is the one where the patient is wearing the wristband), in order to capture any postural abnormalities for the sagittal plane;
7. 360° turn test (67) clockwise + anticlockwise and record seconds and steps

Cognitive Test Protocol

The testing of the cognitive apps involved special care and provision in order to make the patient understand that did not testing him or her, the test regards the PD_manager application. Whenever the patient was blocked or felt insecure, we considered this as a mistake in the design of PD_manager apps. During the testing phase, which aimed to find out the errors in the apps and their design and therefore, it is very important that the patient does not feel ashamed. The patient should feel free to request changes if something is not intuitive, their requirements will make the application more feasible and therefore more functional for the patients themselves. For the validation phase a dashboard was implemented in order to facilitate the test. In the final design and implementation, the test will pop up in the smartphone of the patient as notification in fixed time points. For the initial validation during this task the test facilitator should simply open the test for the patient and ask him or her to take the test without additional instructions. Each test contains instructions in text, which are also reproduced with the text-to-speech feature (also make sure the volume level is adequate).

1. Open a test for the patient

2. Ask the patient to take the test without instructions or guidance and let him listen to the audio instructions on the phone.

3. If the patient gets stuck or he/she takes the test in a wrong way, help him/her with brief suggestions or ask to retake the test explaining better how it works. In this case, use the table/ questionnaires “User Needs Interview (Part A, B), Cognitive App Usability Questionnaire, and PD Manager system Wearability questionnaire (devices) - to take note of the issues raised.

4. Move to the next test.

5. At the end of the administration fill the usability questionnaire.

Speech Test protocol

A protocol for speech data collection was defined in order to collect data that will clearly represent the above mentioned symptoms and PD speech aspects. MDS-UPDRS 3.1 subitem (speech and language) scoring has been collected as clinical measure. Different tasks have been selected (Table 4) and each task is thought to evaluate the voice using different specific speech analysis software that aims to recognize whether symptoms are present or not: Speech Analysis deals with cognitive aspects of language whereas the Sound Analysis deals with motor aspects of speech.

Main Speech Symptoms	***Speech Tasks***	***Type of analysis***
Anomia, tachyphemia, lack of prosody	❑ Anamnestic Interview (MDS-UPDRS I, II scales)[3]; ❑ Mood questionnaire (see Appendix E); ❑ Complex scene description (see Appendix E);	Speech Analysis
Hypophonia, unclear phonation	❑ Sustained Vowels;	Sound Analysis

Table 4 Speech test tasks and relative type of analysis performed for Speech test Protocol

The audio recording was performed 2 times: one in ON and one in OFF state. In order to avoid the bias due to the repetition of the same questions during anamnesis, mood questionnaire or figure description, which would have resulted different, we split the sample of patients in two groups and assigned them randomly (see Table 5). Then two similar figures, used for speech assessment, were chosen. Group 1 performed anamnesis interview, figure description in ON state, whereas Group 2 performed mood questionnaire and figure description. In OFF state, groups inverted their tasks mutually. The task of sustained vowels was executed in both groups in ON and in OFF state as well as the MDS-UPDRS 3.1 scoring. Both groups underwent to the following procedures (shown in Table 5) during the voice recording. The procedure for sustained vowels recordings consists in 5 recordings of a sustained phonation. After activating the Smart Voice Recording App on the smartphone, the operator asks the patient to perform “AAAAAH” sounds that have to last for at least 3 -5 seconds. The repetition of these phonations is needed to obtain enough samples for the training of the algorithms.

Group 1 (50% patients)	**Group 2 (50% patients)**
Motor State: ON • MDS-UPDRS 3.1 scoring • Anamnesis MDS-UPDRS I, II • Picture description 1 • Sustained vowels	Motor State: ON • MDS-UPDRS 3.1 scoring • Mood questionnaire • Picture description 2 • Sustained vowels
Motor State: OFF • MDS-UPDRS 3.1 scoring • Mood questionnaire • Picture description 2 • Sustained vowels	Motor State: OFF • MDS-UPDRS 3.1 scoring • Anamnesis MDS-UPDRS I, II • Picture description 1 • Sustained vowels

Table 5 Speech Test protocol and design

Decision Support System (DSS)

An important task of the PD_manager DSS is related to the change of medication. When the disease progresses and new symptoms emerge, it is essential to assess the patient's situation and identify the need for changing the medication plan. In this case, the DSS should issue a warning to the responsible physician and provide reasons for it. Decision models have been developed to suggest whether or not to change the patient's medication. The suggestion is made using data available in the PD_manager DSS for each individual patient, i.e. data about motor and non-motor symptoms, and epidemiological data. The approach used was *expert modelling*: by asking medical experts to formulate their rules for medication change, based on their medical expertise and experience, the technical partners have studied the possible combinations of DSS output. In this approach, decision-support models are developed in collaboration between the expert and the decision analyst, taking into account clinical guidelines and medical practice. The expert modelling approach was based on the method DEX (68). DEX is a qualitative multi-criteria modelling method. DEX models have a hierarchical structure, which represents a decomposition of some decision problem into smaller, less complex sub-problems. The hierarchy is formulated in terms of attributes and decision rules. All attributes are discrete (qualitative), and each attribute has an associated value scale that consists of words, such as {low, medium, high}. Optionally, scales are preferentially

ordered. Attributes in DEX form a hierarchical structure, i.e. a directed acyclic graph or, most often, a tree. Aggregation is defined in terms of decision rules, grouped in decision tables. Decision rules, while being formulated, are checked for completeness and consistency. All elements of a DEX model are acquired interactively from experts, i.e. no data mining is involved. The principal output studied is the so called *yes/no model*, that suggest if change or not change medication plan.

Wearability and user's needs interview

After the last recording session, the patient is asked to fulfil the survey about the wearability of all the tools employed during the recording sessions (insoles, wristband, smartphone). The aim of this questionnaire is to detect any critical issue, raised by the patient, about wearing this kind of equipment. During the first recording session in ON state, the part A of the User need Interview has been administered to the patient, while during the last recording session in ON state, the part B of the interview has been administered.

Educational Video Gallery

One of the secondary objectives of the Project was the creation of a video gallery for patients and caregivers' education, regarding disease issues and main symptoms. In a first phase, a series of symptoms or troublesome situations has been selected on the basis of the experience of the involved clinicians. The structure of each video was divided in a first part explaining the problem/symptom and in a second part with the possible tricks/solutions to cope with the specific problem/symptom. In a second phase a screenplay and a storyboard have been created for each educational video and they have been submitted to a subcontractor company, expert on video making. The video shooting has been co-directed by the clinicians involved.

Multicentric study

The Multicentric Study is a clinical trial for the overall evaluation of the PD_manager mHealth platform, during which patients will try the PD_manager system at their home. The data captured from these recordings will be processed in the cloud backend and clinicians will evaluate the effectiveness and usefulness of the information acquired. The clinician partners involved will enrol patients that will be equally divided and randomly assigned to intervention group or Control group. The intervention group tests PD_manager system, while Control group fills symptom diaries: the results from both groups have been compared and analysed. In current clinical practice the gold standard for symptoms monitoring is represented by patients'home diaries (1): this modality is obviously not completely objective and difficult to carry out for some patients. The key point of the Project is to find an innovative, objective and easy-to-use tool for PD symptoms monitoring, so the system implemented during the Pilot study will be compared to patients' diaries of symptoms, to verify if the experimental approach could represent a solution to satisfy patients' and clinicians' needs in terms of reliability, practicality and better care. The main scopes are to assess patients' perspective of the PD_manager mHealth platform with respect to comfort, acceptability, ease of use and to assess the clinician's perspective of the PD_manager mHealth platform with respect to usefulness of intervention/value of the information provided by PD_manager for decision making with respect to patient management; acceptability in clinical practice; confidence/reliability in the information.

Study design

The multicentric Study is a non-blinded parallel two group randomized controlled study (See Figure 5). The data obtained with this case-control study gave the possibility to have a clear comparison between the two groups. Blinding of participants, researchers and clinicians was not possible given the nature of the intervention. The randomisation has been necessary to exclude possible sample bias during the recruitment procedures, in particular concerning age, disease duration and stage and the ability in using electronic devices. The monitoring time has been set to 2 weeks. This period is closer to the possible exploitation path discussed in the Project, since the aim of the PD_manager is not to build a simple alerting system, but a tool that possibly allows to detect changes in symptoms (e.g. related to therapy changes or disease progression, when comparing two different monitoring sessions). In this perspective it has not been necessary to monitor the patients for longer to detect

changes induced by drugs and, on the other hand, even a monitoring of a few months is not a long enough session to detect disease progression. Also, from the analysis performed in Pilot Study, a duration of 2 weeks ensures the recording of a sufficient amount of data to be analysed.

In the first phase the researchers have selected a list of possible participants and contacted patients and caregivers during clinical routine ambulatory visits or by phone calls, to verify the availability to participate. Once the subject has been enrolled by signing the informed consent, the researchers have started with the baseline data collection. At the same time, the randomization has been performed: participants, previously recruited have been assigned to the experimental group or to the control group by random cases selection. Participants have been informed of their group allocation immediately, and a researcher have provided the PD_Manager devices (intervention group) or the symptom diary (control group). The subjects assigned to the experimental group have been trained for the correct devices usage and have tried the PD_manager system at home. The subjects assigned to the control group have been trained only for the proper filling of home diaries, that have to be completed for three consecutive days during each of the two weeks (Houser Diary) or for just one day each week (PD Well Being Map). At the end of the two weeks, patient and caregiver returned to the Centre and will be asked to fulfil a questionnaire on acceptability of the study (different for each group). The researchers have collected the devices or the diaries and downloaded the data from the devices. This data and the data from the CRFs (Case Report Forms) have been stored online in B3D protected Servers, to be evaluated by the clinicians.

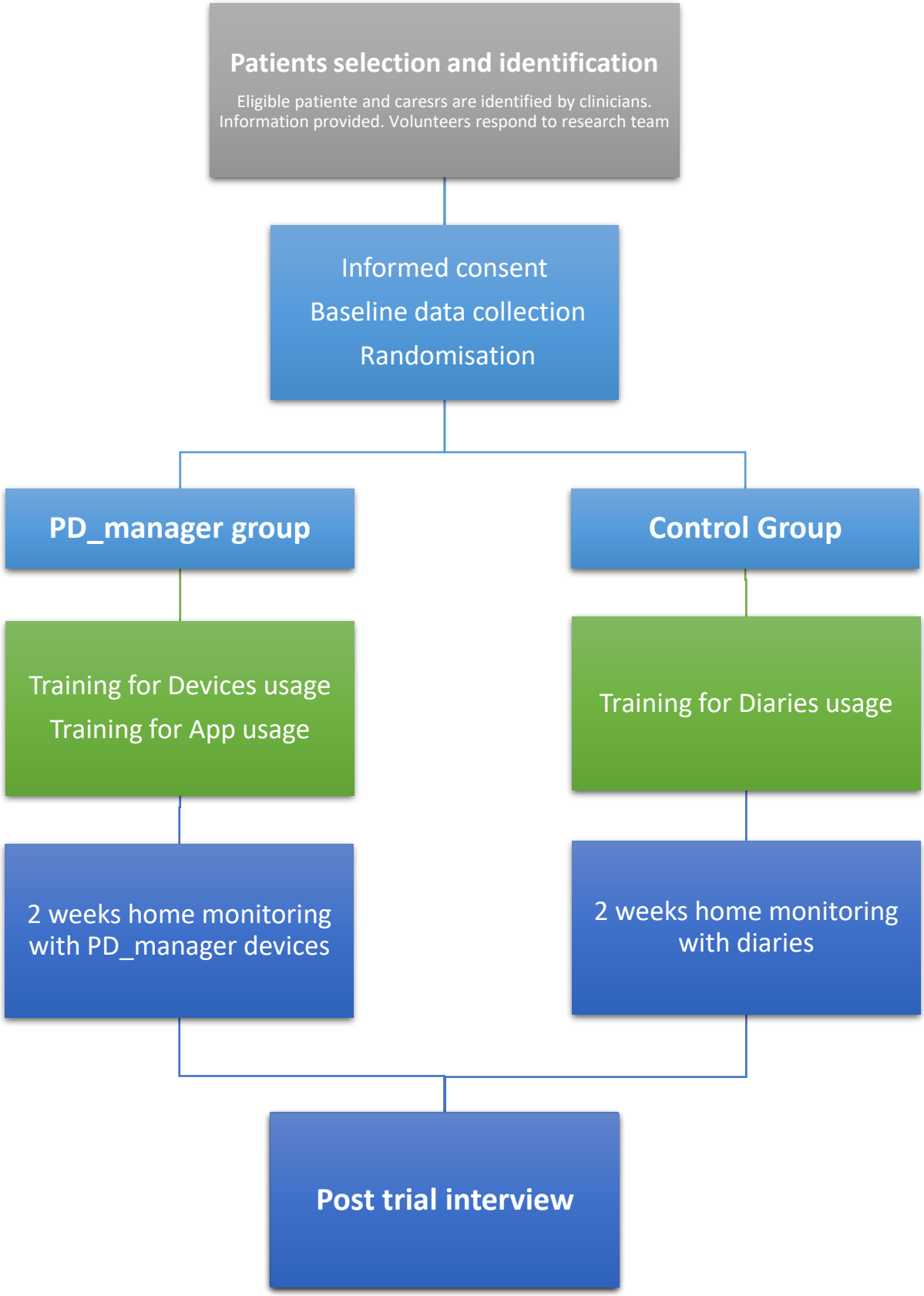


Figure 5 Multicentric Study design

Patients and clinical evaluations

People with Parkinson's and caregivers are recruited as dyads. The inclusion criteria for people with Parkinson's were a diagnosis of idiopathic Parkinson's disease according to the UK Brain Bank Criteria, an Hoehn & Yahr disease stage 3 in OFF state, the presence of motor fluctuations with an average of at least 2 hours of OFF state during the day and the presence of a live-in carer who is willing to take part in the study.

The exclusion criteria for people with Parkinson's were the presence of severe cognitive impairment (Parkinson's Disease Dementia) or co-morbidities with stroke or other brain disease and the absence of a caregiver living with the patient. Each project Partner has identified his own modality to get in touch with an adequate number of patients, based on the total number of subjects allocated per clinical site participating to the study.

For a complete and correct analysis of the recorded data, the sample's clinical characteristics have to be precisely determined. Patients' evaluation has considered the many aspects of each patient: disease severity (motor and non-motor symptoms), overall clinical status (with possible comorbidities) and pharmacological treatment (PD related medications and other drugs). Also, the cognitive status and the patient's and caregiver's propensity to use technological devices have been evaluated. To gather all this data and obtain a clear profile of each enrolled patient, several evaluation scales have been selected to be administered at the baseline evaluation:

- MDS-UPDRS: this is the universally recognized and widely used rating tool in clinical management of Parkinson's Disease. It is divided in four sections covering 1) Mentation, Behaviour, and Mood, 2) ADL, 3) Motor sections, 4) Motor complications. MDS-UPDRS includes Hohen & Yahr scale for PD stage assessment (2).
- NMSS (Non Motor Symptom Scale for Parkinson's Disease): this scale evaluates severity and frequency of several common non-motor symptoms (69).
- EQ-5D-5L, a commonly used generic measure of health-related quality of life that provides a utility index for use in economic evaluations (70);
- PDQ-8, the short form of a Parkinson's disease specific measure of health-related quality of life (71);
- MMSE (Mini Mental State Examination): the most used clinical scale to perform a rapid and reliable evaluation of patients' cognitive status (72).

- Questionnaire on technophobia: to evaluate dyad relation to technology, their opinions about possible use of technologic devices in daily life and their opinions about the PD_manager Project future implications on disease management (73).
- Caregiver Burden Scale: to assess live-in carers' perception of the disease (74)

Baseline data have been collected by the physician by interview with patient and the carer and through reference to the clinical records. Data gathered includes:

- for both members of the dyad: age, gender, education level, comorbidities, Global Attitude towards Technology Measure - Technophobia, Technology Acceptance Model Measure for E-health (75)
- for the patients: comorbidities, disease duration, disease stage (Hoehn and Yahr scale), side of onset, current symptoms (tremor, bradykinesia, rigidity, dyskinesia), more affected side, Parkinson's medications, MMSE score, MDS-UPDRS, EQ-5D-5L, PDQ-8 and the NMSS;
- for live-in carers: Caregiver Burden Scale.

	Scale	Patient	Caregiver
Pre intervention	MDS-UPDRS	✔	
	NMSS	✔	
	EQ-5D-5L	✔	
	PDQ-8	✔	
	MMSE	✔	
	Questionnaire on technophobia	✔	✔
	Zarit Caregiver burden scale		✔
Post	Acceptability Questionnaire (Devices/diaries)	✔	✔

Table 6 Evaluations for Patients and caregivers

Participants have been notified in the information sheet that they are randomly assigned to one of two alternative ways of gathering more detailed information on Parkinson's symptoms to help in the management of the condition (PD manager or symptom diary). Both patients and live-in carers have been asked at baseline, prior to randomisation, if they have a preference, and about their attitudes and expectations from each approach as this may affect the views they express after the trial. At the end of the 2 weeks, the dyads in both experimental and control group are asked to answer a Post Trial interview (Table 7) with an acceptability questionnaire regarding the devices (experimental group) or the home diaries (control group).

Question number and topic	Scale
Q1 Ease of use	5 point Likert scale (1 "Very"- 5 "Not At all")
Q2 Time spent using the diary/device	5 point Likert scale (1 "less than 30 min"; 5 "more than 2 hours")
Q3 Usefulness of Information	5 point Likert scale (1 "Very"- 5 "Not At all")
Q4 Usefulness for Symptoms self-management	5 point Likert scale (1 "Very"- 5 "Not At all")
Q5 Usefulness for Interactions with Doctor	5 point Likert scale (1 "Very"- 5 "Not At all")
Q6-A* Ease of use	1 "Very"; 2 "Little"; 3 "Not At all"
Q6-B* Comfort	1 "Very"; 2 "Little"; 3 "Not At all"
Q6-C* Usefulness for self-management	1 "Very"; 2 "Little"; 3 "Not At all"
Q6-D* Usefulness for Doctor	1 "Very"; 2 "Little"; 3 "Not At all"
Q7 Recommend - Device/Diary	1 "Yes"; 2 "Maybe"; 3 "No"
Q8 Future use	1 "Yes"; 2 "I don't know"; 3 "Definitively not"
Q9 Preference - Device/Diary	1 "Diary"; 2 "I don't know"; 3 "PD_manager"
Q10 PD Manager VS Diary on treatment	1 "Both useful"; 2 "Both not useful"; 3 "Diary more useful"; 4 "PD_manager more useful";

Table 7 Post trial Interview. *for each subcomponent used (devices or diaries)

Devices, Applications and Diaries

The set of devices used in the Multicentric study is the same tested in the Pilot study: the Moticon® sensor insoles, the Smartphone and the Microsoft® Band wristband. Patients and caregivers have been trained for the correct usage of the devices, in particular how to wear the devices and how to charge the Smartphone and the Wristband using the battery charger provided. The patient had to wear the insoles inside a pair of shoes (the same pair for the entire period of intervention) and use them for the max possible time during the day. The patient also had to wear the smartphone inside the trousers' pocket or in a small bag and the wristband on the

upper arm of the more affected side. The recording started automatically at 8 o'clock in the morning and stopped at 10 pm, so the patient had to put in charge the phone and the wristband every night.

The mobile application developed within the project and used in the Multicentric study are:

- PD_manager App: it's the main application running on the smartphone which works as a gateway that collects motor and behavioural data (Cognitive Tests, Visual Analogue Scale Questionnaire, Nutrition). The App sends notifications to remember the patient to perform some test or to ask the patient if he/she has taken the medications on time. The patient can also perform tests whenever he/she wants, independently for the timing set. The researchers expressly avoided to explain in detail to the patients the app and test functioning to test if the system is comprehensible and easy to use.
- Moticon® software: in this task we used an updated version of Moticon® software (Beaker), previously used in Pilot Study. Moticon® improved Smart-Recording modality to prevent memory overflow and created a Cloud interface to upload and share online the data gathered from patients. All this data is stored in a safe digital environment created by B3D partner.
- Smart Lock App: in order to avoid incorrect usages of the Smartphones by patients during the Multicentric Study, we selected a free Android app (Kids Zone5) that allows to lock the access to all device settings and locks all the applications other than the ones that the patient is supposed to use. This App has to be installed in every Smartphone and activated with a 4-digit PIN, chosen by researchers. Besides restricting access to only Project's approved apps and limiting patients screen time, Kids Zone's app lock will also: prevent access to the Internet and block ad clicks, block in-app purchases or app installs from the Google Play store, re-lock the device automatically if it's rebooted, block patients from making phone calls or texts unless allowed to do such, block access to Home, selected notifications, system menus, all device settings and personal data.
- Microsoft® Band App: this App is specifically developed by Microsoft® to connect Smartphone and Microsoft® Band. It provides actionable insights based on the rich data gathered from the band and any other fitness devices and apps the patient may use every day. Microsoft® Band App makes tracking personal activity easier, more insightful, and more holistic. However, in this phase of the Project, this App is only used to ensure a connection between the APIs for the collection of aggregated sleep and activity data and, it is not used to analyse data.

The diaries used for control group monitoring were:

- Hauser diary (76): this is a validated instrument that allows the patient to record, in a dedicated form, his or her motor state every 30 minutes. This diary has been chosen because it is the current gold standard to monitor patient's symptoms at home and it is frequently used also in pharmacological clinical trials to assess drug's efficacy.
- UCB (77) Parkinson's Well Being Map™: The Map is a free tool created to help patients to prepare for consultations with their healthcare team and help clinicians to better understand how living with Parkinson's disease affects the subject. The Map allows to record and monitor the wide spectrum of Parkinson's symptoms. It covers all aspects of Parkinson's, so the patient can highlight the symptoms that are of most concern and list the most important questions to ask.

The participant characteristics have been analysed in order to explore whether the two groups (PD manager and Symptoms Diary) were found to be homogeneous. Continuous scalar variables have been compared using T-Test, while discrete/nominal and ordinal variables have been compared using Chi Square statistics. The methods used for data analysis of the main outcome of the study – opinion about acceptance, ease of use and usefulness – were mainly based on a Multinomial Regression in order to explore the difference of the opinions by weighting the effect of different clinical baseline characteristics which might have influenced the answer of the participants. Spearman correlations were run in addition to analyse the degree of accordance between Patients and Carers. Multinomial logistic regression is used to model nominal outcome variables, in which the log odds of the outcomes are modelled as a linear combination of the predictor variables. As predictor variable factors were selected all the items of the Post Trial Interviews ranging from Q1-Q5 and Q7 to Q10. As covariates, age and gender and attitudes towards technology for both patients and caregivers. Specific measures for patients and caregivers have been introduced in separate analysis. For caregivers: Zarit Caregiver Burden total score (High vs. Low Burden); for patients: PDQ-8 total score and Non-motor symptoms scale; UPDRS III total score. All the sub items of Q6 were analysed separately and grouped by focus area (ease of use, comfort, usefulness), and by subcomponent (smartphone, insoles, smart band, motor diary, non-motor symptoms diary). In order to compare the different subcomponent a non-parametric rank comparison was run (Friedman's test). The significance level was set for all the analysis at $p<.05$. All the data have been analysed using IBM SPSS Statistics for Windows, Version 23.0. 2015.

The usage of the devices for all the patients that were recruited for the PD_manager Group have been evaluated in a patient per patient basis. For each patient of the PD_manager Group the respective graph depicting the usage of the wristband and the smartphone, as extracted from the gyroscope recordings of both devices, has been analyzed to find any possible correlations with his/her main characteristics (age, disease duration, education, technophobia) or with the clinical scales' scores (TAMM, PDQ8, EQ-5D-5L, NMSS, Zarit, UPDRS), for a detailed insight regarding the implications and intrinsic motivations for the usage of the PD_manager mHealth system.

Clinicians Study

In order to get a feedback regarding the usefulness and the usability of the System, a study based on clinician perspective of PD_manager has been performed. A "Clinician App" has been developed by technical partners, based on clinicians' suggestions. It has been conceived to output clear and understandable reports of the patient's symptoms during the 2 weeks of trial. All functionalities of the app are designed to be smart, intuitive and to facilitate the clinician's analysis of the data coming from the recordings. Moreover, the Clinican's App is integrated with the DSS System and is able to recognize specific patterns of symptoms that could be troublesome for each patient and report an alert to the clinician. From this point of view, the clinician's feedback is crucial to establish if the information coming from the System could influence clinical decisions. Feedback was sought by means of a structured interview schedule on perceived usefulness to professionals: the clinicians were asked to comment on how easy it was to interpret the data generated by the devices and the symptom diary, to use this data in changing the treatment and care management of participants. Clinicians were also asked to report what action they would take (if any) for each patient following analysis of the data from PD_manager and the symptom diary, including changes in medications, management plan and referrals to other MDT (Multi-Disciplinary Team) members. Also, the ease of use of the user's interface of the Clinician App has been evaluated. To make a comparison between PD_manager system and symptoms Diaries we submitted to clinicians' judgment the outputs coming from 3 selected patients monitored with PD_manager and 3 patients monitored with diaries

Methods

For the evaluation of the Clinician App we have selected a group of clinicians, mainly neurologists, with various expertise, some of them even non-experts in PD management. Some of them were completely external from the PD_manager Project (external clinicians), others were the consultant neurologists of the patients enrolled, with a deeper knowledge on PD management issues and each patient clinical history and characteristics (internal clinicians). This last group of "more involved" clinicians was asked to evaluate the app also in terms of usefulness in clinical practice, not only from the usability point of view.

The clinicians have been selected among those working within the Hospitals related to the clinical partners involved in the project. For external clinicians, focus groups of 3-4 clinicians have been organized. During this meeting, the aims and the main idea of PD_manager Project have been explained. Then each clinician was equipped with a tablet with the clinician app installed and the data coming from the recordings of three selected patients available for testing. The external clinicians were free to evaluate independently the app functionalities and to change or not the drug therapy referring on DSS suggestions. Scanned and anonymized copies of symptoms paper diaries collected by three selected patients from control group along with baseline clinical data were presented and evaluated by clinicians. The 6 cases (3 PD_manager + 3 diaries) have been chosen to be paradigmatic of fluctuating patients (high score on UPDRS IV). Finally, the questionnaire for Clinician App evaluation was administered. For Internal clinicians we performed the same test but with face to face interview and the questionnaire was finalised by Modified TAM2 scale.

For the evaluation we administered to all clinicians a technophobia scale, to estimate affinity towards technology in general. Then each clinician was asked to fill a questionnaire regarding their previous experience in neurology, patients management, anti-PD drugs administration, mHealth systems eventually used in the past. To complete the task, specific evaluation scales have been selected and administered to all clinicians involved:

- The Post-Study Usability Questionnaire (PSSUQ) is a 16-item survey that measures users' perceived satisfaction with a product or system. Obtaining an overall satisfaction score is done by averaging the four sub-scales of System Quality (the average of items 1-6), Information Quality (the average of items 7-12), and Interface Quality (the average of items 13-16). The PSSUQ is highly reliable (.94) and is entirely free.

- The System Usability Scale (SUS) is perhaps the most popular standardized usability questionnaire, accounting for approximately 43% of published usability studies. It is a 10-item questionnaire designed to measure users' perceived usability of a product or system. The SUS is highly reliable (.91) and is entirely free. The use of SUS is helpful to assess perceived usability, an added bonus to using the SUS is that recent psychometric analyses PD_manager project 16 shows that items 4 and 10 reliably measure the dimension of perceived "learnability". Therefore, by measuring these items separately, it's possible to gain an understanding of users' perceived usability and learnability of the product or system being studied.

The Technology Acceptance Measure (TAM) is an information systems theory that models how users come to accept and use a technology. The model suggests that when users are presented with a new technology, a number of factors influence their decision about how and when they will use it in terms of perceived usefulness and perceived ease-of-use. An update version of TAM, called TAM2 (3) extended the original TAM model to explain perceived usefulness and usage intentions in terms of social influence (subjective norms, voluntariness, image) and cognitive instrumental processes (job relevance, output quality, result demonstrability, perceived ease of use). The TAM2 model, was tested in both voluntary and mandatory settings. The results strongly supported TAM2. To prevent the presence of duplicate items (already tested in PSSUQ and SUS) and to avoid an excessively time-consuming questionnaire, we selected specific questions of the TAM2, focusing the attention on perceived usefulness of the System. The result is a TAM2 modified scale that will be administered only to those clinicians that were directly involved in the management of selected patients.

Data Analysis that have been used are Cohen's kappa for assessing the degree of agreement among physicians of the same group, and Multinomial Regression for the comparison analysis between groups and to explore evaluate the factors which may have influenced the outcome variables.

RESULTS

Pilot Study

A total of 20 patients with idiopathic Parkinson's disease diagnosis have been included in the study. Due to the different prevalence of the disease between man and women, the sample was composed by 14 men and 6 women. The mean age of this sample was above 65 and the mean disease duration was around 10 years, reflecting a sample of advanced PD patient. Cognition was almost preserved in all the patient and nobody reported severe impaired cognition (MoCA: 22.06 ± 5.63). Autonomy in executing daily life activity (ADL and IADL) was also not impaired for most of the subjects. Data that have been collected are shown in Table 8.

Clinical Data			
Variable	**N**	**Mean**	**SD**
Age	20	68.6	10.69
Education	20	8	5.04
Age of onset	20	57.65	12.10
Disease duration	20	10.45	5.35
LEDD	20	1008.875	624.40
DAED	12	220.25	131.33
ADL	16	5.56	0.63
IADL	16	4.25	1.61
MoCA	16	22.06	5.63

Table 8 Demographic and clinical data collected for Pilot Study

Patients included in this study presented a variety of motor symptoms: ~30% of the sample had motor fluctuations (frequent change from ON and OFF state) during the day and only 6/20 had dyskinesia. The whole sample showed bradykinesia and tremor pattern, and the majority had freezing of gait episodes. Falls occurred frequently only in 3 patients, 8 had rare episodes, while the others did not. Only 1 patient was treated with Levodopa intestinal infusion, and 3 had a STN-DBS.

Frequencies of clinical variables					
Gender	F	M			Total
	6	14			20
Fluctuations	No	Yes			Total
	13	7			20
Dyskinesia	No	Yes			Total
	14	6			20
Dystonia	No	Yes			Total
	19	1			20
FoG	NR	Both	None	OFF	Total
	2	4	3	11	20
Falls	NR	Frequent	None	Rare	Total
	5	3	4	8	20
Duodopa	No	Yes			Total
	19	1			20
DBS	No	Yes			Total
	17	3			20

Table 9 Main motor features and clinical characteristics

A total of 140 out of 160 (expected) session were recorded. Drop-out were due to excess of fatigue experienced by the patient, or because motor symptoms were highly severe, mainly during recordings in Off state. Here we report MDS-UPDRS data scoring during sessions grouped by Motor State (ON State vs. OFF state). We found consistent data within patients, congruently with the expectations of ON vs OFF changes (Table 10).

Variables	OFF State		ON State				
	M	*SD*	*M*	*SD*	*df*	F/X^2	*p*
UDPRS item 3.3b Rigidity severity R	1.20	0.88	0.65	0.61	1	17.5	.000
UDPRS item 3.3c Rigidity severity L	1.29	0.91	0.71	0.82	1	15.015	.000
UDPRS item 3.4a Finger tapping R hand	1.55	0.90	1.20	0.83	1	5.29	.023
UDPRS item 3.4b Finger tapping L hand	1.82	0.86	1.49	0.83	1	4.998	.027
UDPRS item 3.10 Gait	1.73	0.87	1.12	0.74	1	19.46	.000
UDPRS item 3.17a Tremor Severity R Arm	0.45	0.85	0.19	0.43	1	5.394	.022
UDPRS item 3.17b Tremor Severity L Arm	0.65	0.87	0.20	0.58	1	12.516	.001
UDPRS item 3.17c Tremor Severity R leg	0.30	0.70	0.07	0.26	1	6.521	.012
UDPRS item 3.17d Tremor Severity L leg	0.36	0.84	0.13	0.51	1	3.867	.05
2min Walk Test distance	91.37	48.09	113.73	49.48	1	6.35	.013
360Turn time R	14.26	16.05	6.03	2.91	1	15.735	.000
360 steps R	14.73	7.61	10.03	4.09	1	17.229	.000
2minWALK speed	0.76	0.40	0.95	0.41	1	6.35	.013
TUG sec	41.10	53.26	15.16	4.32	1	14.619	.000
360Turn time L	26.98	94.04	6.25	3.42	1	3.012	.085
360 steps L	13.62	6.75	10.23	4.50	1	10.012	.002
Dyskinesia (Y/N)	(64 No; 4 Yes)		(42 No; 28 Yes)		2	23.785	.000

Table 10 Clinical evaluations performed during Motor recording Protocol

Gait, Freezing of Gait, Tremor, Dyskinesia and Bradykinesia have been the main motor features studied. Gait and FOG have been evaluated using data coming from the insoles, while tremor and dyskinesia have been assessed analyzing data gathered with the wristband. Bradykinesia have been evaluated combining data coming from all the devices. All the raw data analysis and the signals processing have been performed by technical partners' engineers.

Gait and Freezing of Gait

To improve the step detection for Parkinsonian gait, the data of several patients was manually augmented by labelling steps events (heel strike and toe off events), thereby distinguishing walking phases from non-walking phases. Then, the algorithms and heuristics for detecting steps where adapted until a satisfactory success rate was achieved. The algorithms are based on both the pressure and the acceleration data measured by the sensor insoles. To further optimize results, the algorithm parameters underwent an automated parameter variation procedure which optimizes the parameters based on a cost function. This cost function penalizes false-positives and false-negatives of the step detection result. In summary, the modification of the step detection resulted in an algorithm which is capable of correctly identifying most of the steps in Parkinsonian gait data. Nevertheless, in few cases of severe gait impairment, a significant number of steps were not found by the software. Several

differences between Parkinsonian gait and normal gait were noticed, for example the shape of the total force curve during the step cycle had a different distribution, also the average gait line was shorter and the pressure distribution on the forefoot appeared to be different. Another example is the gait line length: since PD patients tend to walk on the fore foot without bringing significant load on the heel, it was assumed that the average gait line length is shorter as the disease severity increases (Fig. 7). The average gait line length for a UPDRS gait class of 3 is about 25% of the insole length, which is about half the gait line length for a score of 0.

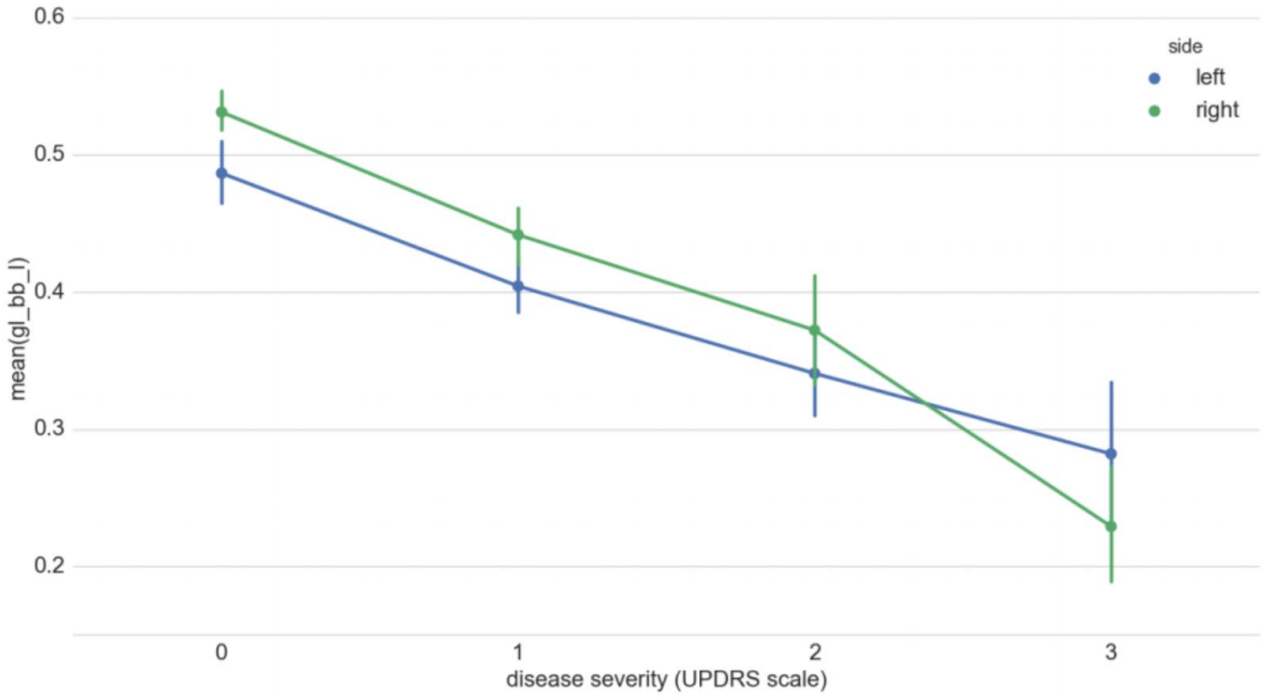


Figure 6 Gait line length grouped for each UPDRS Gait subitem score

Also, the total force curve depicted in Fig. 8 shows two peaks, which result from heel contact and foot off (patient with almost no visual gait impairments). In distinct Parkinsonian gait, significantly different total force

curves were observed, such as a missing second peak and missing local minimum between the peaks

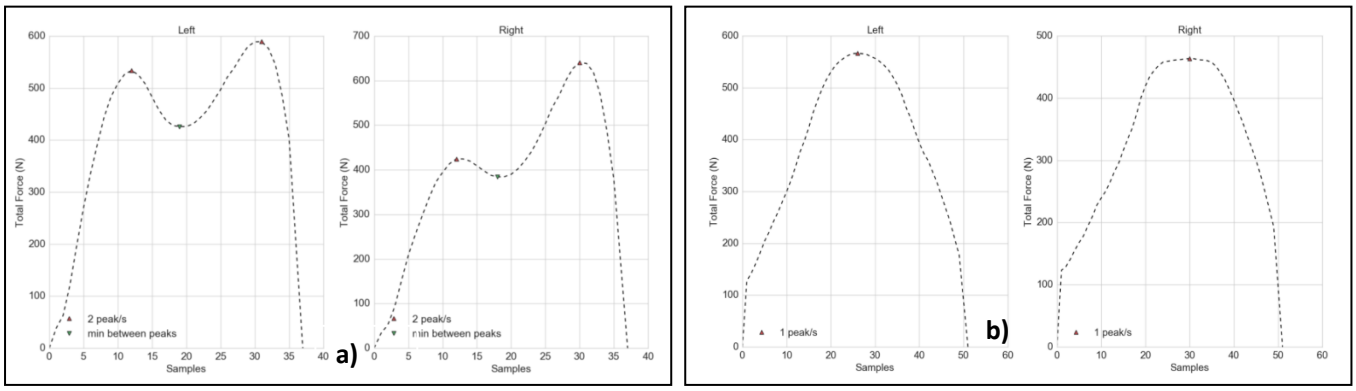


Figure 7 Total ground force for left and right foot in a) normal gait patient and b) patient with gait impairment

As an example for the features computed from the local peaks of the ground contact force curve, Fig. 9 shows the statistics of the average time between heel strike and the local force minimum between the two peaks (0 is assigned if second peak is missing) depending on the UPDRS gait class. In particular, the results for a UPDRS gait class of 3 clearly stand out against less severe scores.

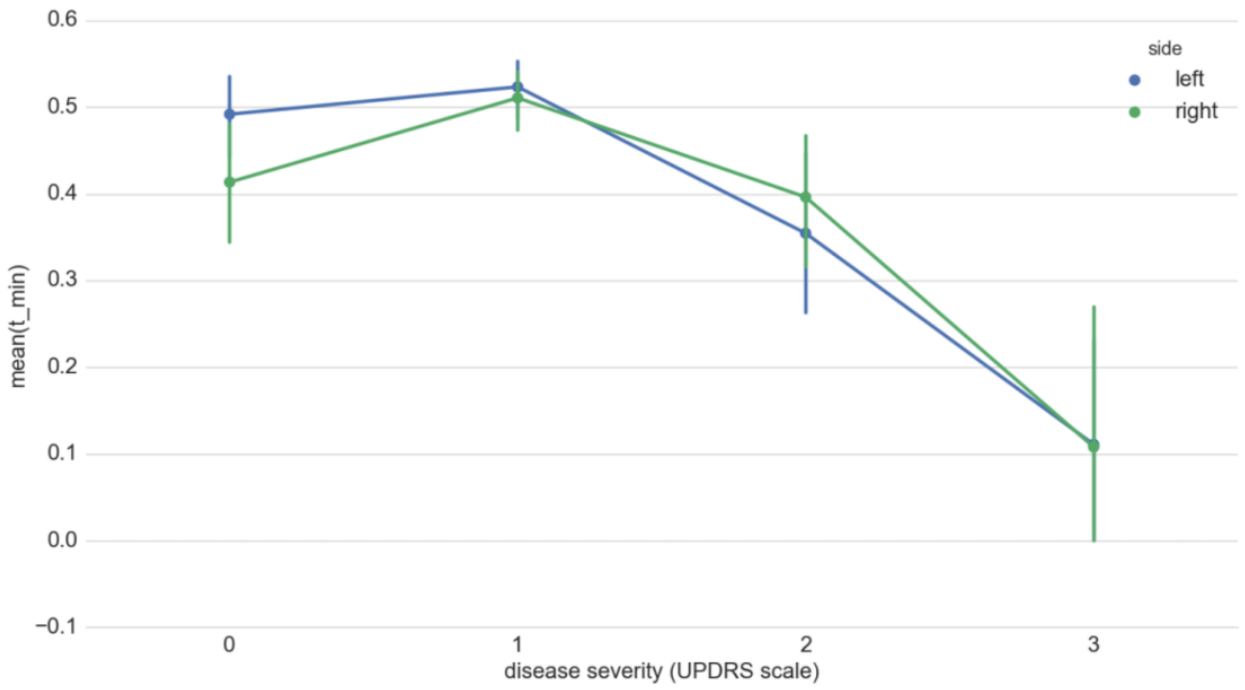


Figure 8 Average time between heel strike and local minimum force, grouped for UPDRS gait subitem score

An interesting observation is the fact that Fig. 7 and Fig. 9, both showing a feature which exists for both left and right foot, show similar results for left and right. This validates the computation of these features and suggests that the suspected statistical correlation with the UPDRS gait class in fact exists, even though the number of patient and the corresponding datasets is relatively low. A total number of 85 features were computed for all datasets. Some of them characterize the overall walking behaviour (e.g. cadence), others are parameters specific the left and right foot side (e.g. the gait line length). The 85 features include parameters which compare the left and right foot, e.g. the difference of the gait line length between left and right. All these features have been studied with correlation matrix and a machine learning analysis have been performed to find correlations between specific parameters and to find characteristics capable of UPDRS subitem 3.10 (gait) estimation. The methods do not allow for a direct detection of ON/OFF states essentially because the gait of a patient with low disease severity in OFF state can be “better” than the gait of a patient with high disease severity in ON state. However, looking at individual patients, the estimated UPDRS gait item can be a valuable characteristic for tracking the disease status, indicating whether the patient condition improves or deteriorates. Looking at the task of separating patients without gait impairments (class 0) from patients with gait impairments (class 1 and higher), the accuracy is 91%, the sensitivity is 97% and the specificity is 50%. The low value for the specificity is also caused by the fact that only few measurements with a UPDRS gait item of 0 exist in the data set. The most important feature turned out to be *p_mid_stance_asymmetry*, which describes the difference in the pressure distribution between the left and right foot during the mid-stance phase.

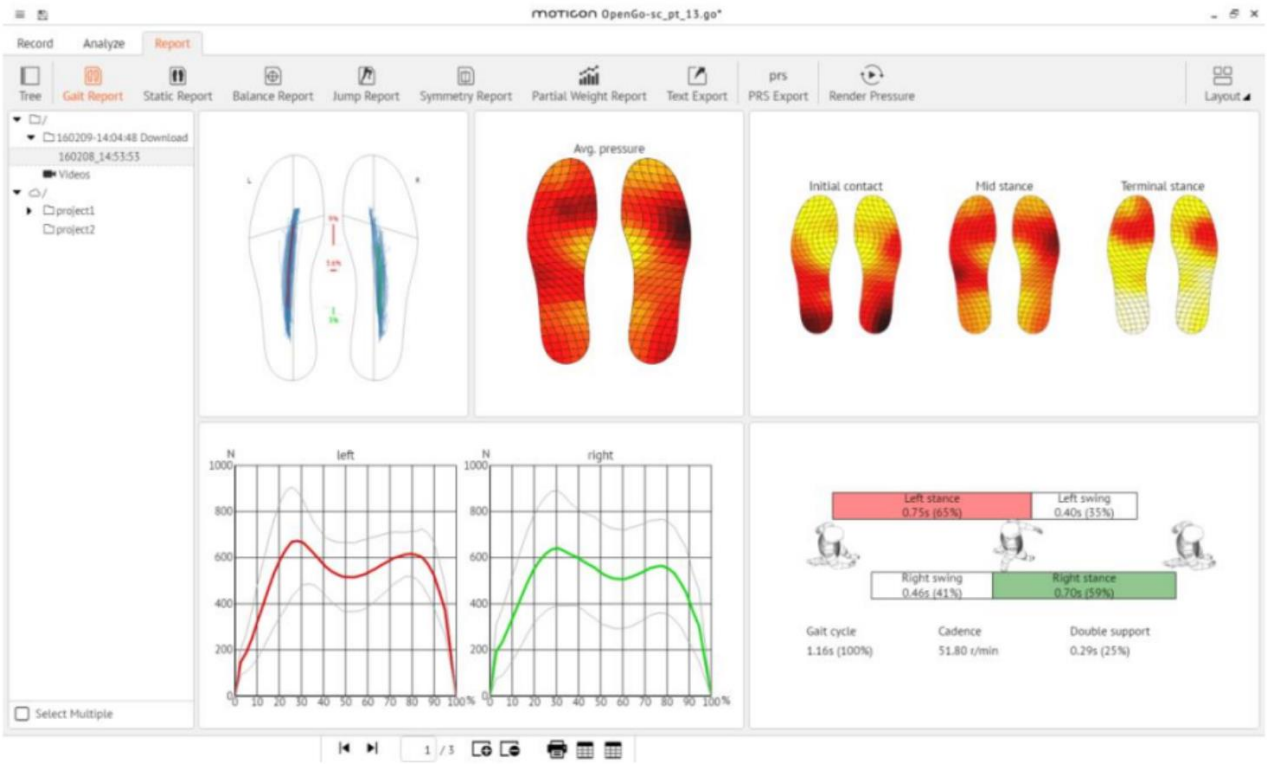


Figure 9 Screenshot of Moticon® Software showing analysis of pressure distribution during gait cycle

Regarding FOG detection, the overall procedure for working with the data gathered from the sensor insoles included the implementation of an automated extraction of FOG annotations from the data and computation of the overall FOG duration. An expert clinician reevaluated the video recordings and annotated every single FOG episode. For each FOG episode the clinician set start time, stop time and gave a score: FOG < 5 seconds = severity 1; FOG <10 seconds =severity 2; FOG >10 seconds (or FOG+imbalance/risk of fall) = severity 3. Then an inspection of the raw data in all possible parameters (pressure distribution, center of pressure, total force, and acceleration) have been performed with respect to patterns that are symptomatic for FOG periods. The following steps were computation of features reflecting these patterns and definition of a criterion function which is capable of indicating FOG. Finally, we found an optimal threshold on the criterion function, to separate FOG from non-FOG episodes and we calculated the accuracy of this approach with respect to the experts' annotations. In particular, all available FOG episodes have been analyzed so as to understand the motion signals during these episodes, and their difference to non-FOG signals. The automated assessment of FOG was tested against the annotated FOG events which are based on the observations of clinical experts. This verification was carried out in two steps: First, a direct comparison between the annotated FOG duration and the estimated

(detected) FOG duration for each measurement. Second, a threshold was applied on the detected FOG duration. All analyses have been performed using Moticon® Software for event tagging and signal processing, IBM SPSS Statistics v23.0 for descriptive and inferential statistics and MATLAB for the classification algorithm.

For the purpose of FOG detection, a clinician annotated all FOG events by looking at the video. Replaying the data along with the video and setting the start/stop markers was carried out using the Moticon® software. A detailed analysis of false-positive events (time periods which were detected as FOG while not being annotated as FOG event) showed that, in several of these cases the data misses FOG event annotations. Apart from some data periods with missing video, this is due to the fact that one of the FOG-provoking tasks was to leave the patient's room through a door, close and re-open the door, and then walk back into the room. Of course, FOG is not visible in the video while the door is closed. The algorithm was developed to match the total time span of FOG, and not to exactly match annotated start/stop events. The annotated FOG durations per measurement were between 0 and 417 seconds, with an average of 33 seconds. Out of all measurements, 38% contained annotated FOG events. In OFF state, the average duration of annotated FOG events was 61 seconds, compared to 7 seconds for ON state measurements. The FOG duration of measurements with long annotated FOG durations was generally underestimated, while in general the correlation with the true FOG duration was considered good enough for data mining purposes. Measurements with a detected FOG duration of more than rT = 0.7% of the measurement duration (optimal threshold obtained from parameter variation) were considered to be FOG measurements containing FOG, while those having less than rT = 0.7% of detected FOG were considered to be non-FOG measurements. This threshold filters out short-term motions which are falsely detected as FOG. As a result, 90% of the measurements have been correctly detected as either having FOG or no FOG. The false-positive rate was 6%, the false-negative rate 4%.

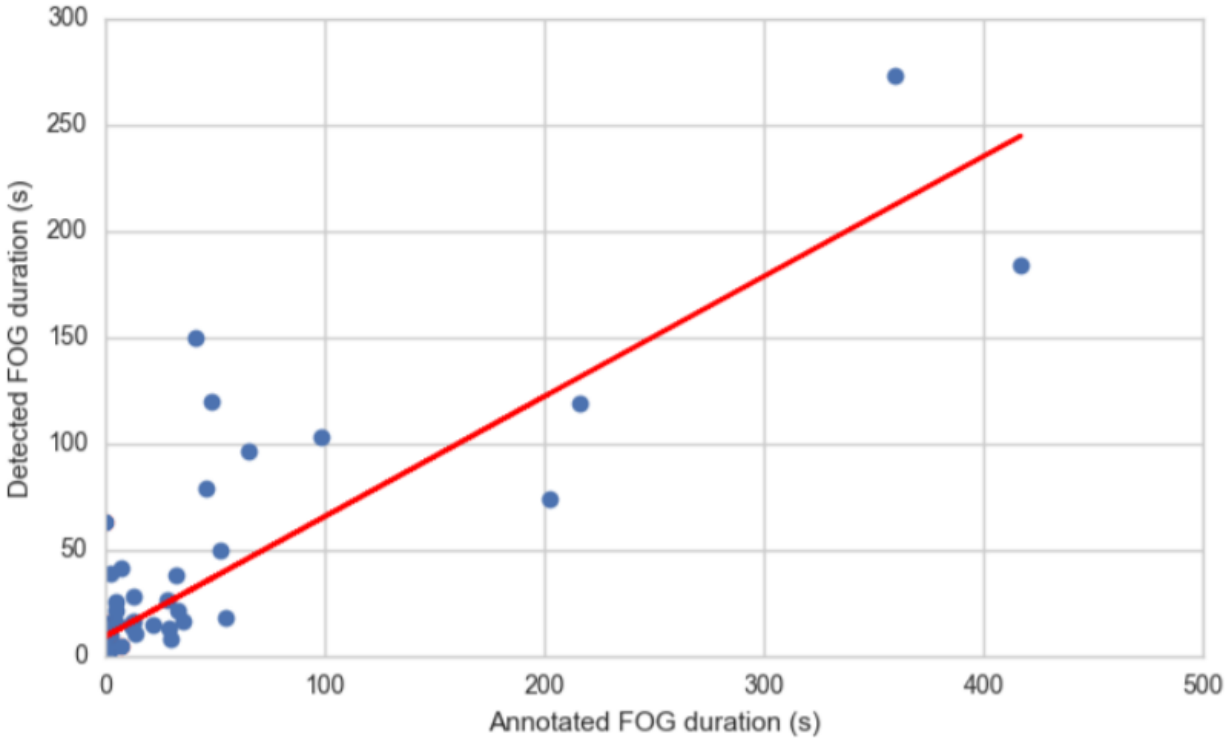


Figure 10 Correlation between automatically detected FOG duration and duration annotated by clinician

Tremor

For Tremor assessment the Microsoft Band have been employed, equipped with both accelerometer and gyroscope. The accelerometer was used mainly for hand posture/rest detection, whereas the gyroscope was used for tremor detection and assessment. The proposed method consists of

1. Signal Pre-processing: Three signals are produced from filtering (FIR) of the original gyroscope (G) and accelerometer (A) signals: 1. A1: Low-pass (< Tf) gyroscope signal mainly used for tremor detection. 3. G2: High-pass (> Tf) gyroscope signal mainly used for tremor detection and amplitude estimation.
2. Tremor Detection: Both detection and amplitude estimation are based on a 3-second window. Typically tremor has a dominant frequency on the 3.5-8 Hz frequency band, whereas voluntary movement frequency range is below 2.5-3 Hz. A number of features are extracted including the energy of the G1, G2 signals and their ratios compared to the whole signal energy. The results of the machine learning algorithm for tremor detection showed an accuracy of 94%.
3. Tremor Amplitude Estimation: In order to calculate the tremor amplitude, the G2 signal is used, which includes the tremor related frequencies. The UPDRS Tremor severity is divided in four scales based on

maximum observed tremor amplitude: i) 0-1.5, ii) 1.5-3, iii) 3-10 and iv) >10 cm. The UPDRS scale is approximated by a fuzzy linear function. For each recording the tremor UPDRS amplitude is estimated by the 90th percentile of the 3-second window tremor amplitude estimations and the tremor UPDRS constancy is estimated by the percentage of 3-second windows detected with tremor. The Pearson correlation between the estimated UPDRS tremor amplitude and expert is R=0.95 (Fig. 11a). Similar results are obtained for tremor constancy (R=0.97) as depicted in Fig. 11b. From the patients with tremor, two have also posture tremor with similar severity.

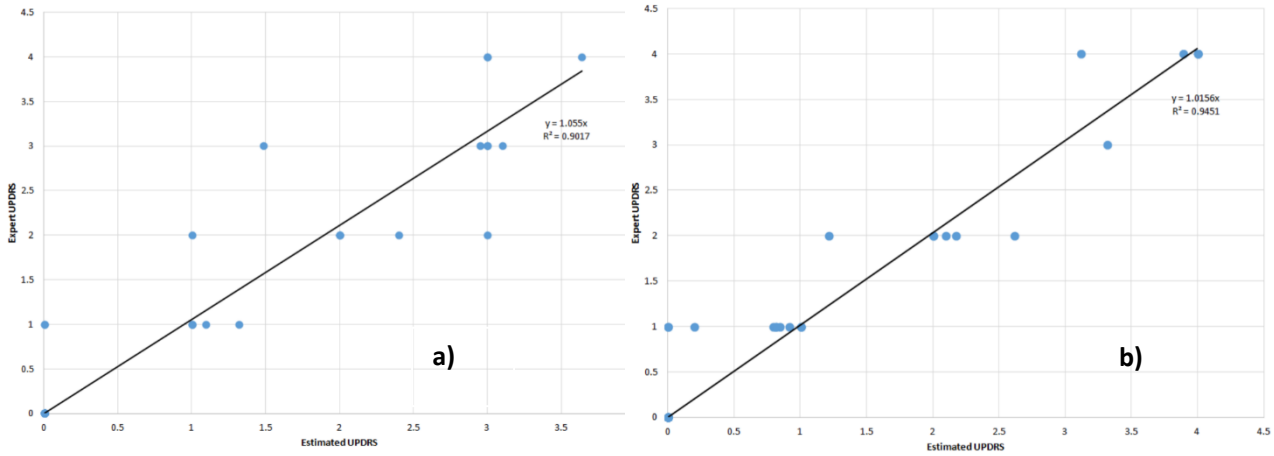


Figure 11 Comparison of a) Rest UPDRS Tremor amplitude (T.A.) estimation and b) UPDRS Tremor constancy (T.C.) estimation with experts annotation

4. ON-OFF differences: Using the developed tremor detection algorithm, tremor amplitude and constancy are evaluated for ON and OFF periods. For a subset of 5 patients (Fig. 12) with significant tremor, constancy is found statistically higher (P=0.0074) in OFF periods. Tremor amplitude is also higher but it does not reach statistical significance (P=0.12). More experiments are needed to have a statistically significant conclusion regarding changes of tremor amplitude and constancy in ON and OFF periods.

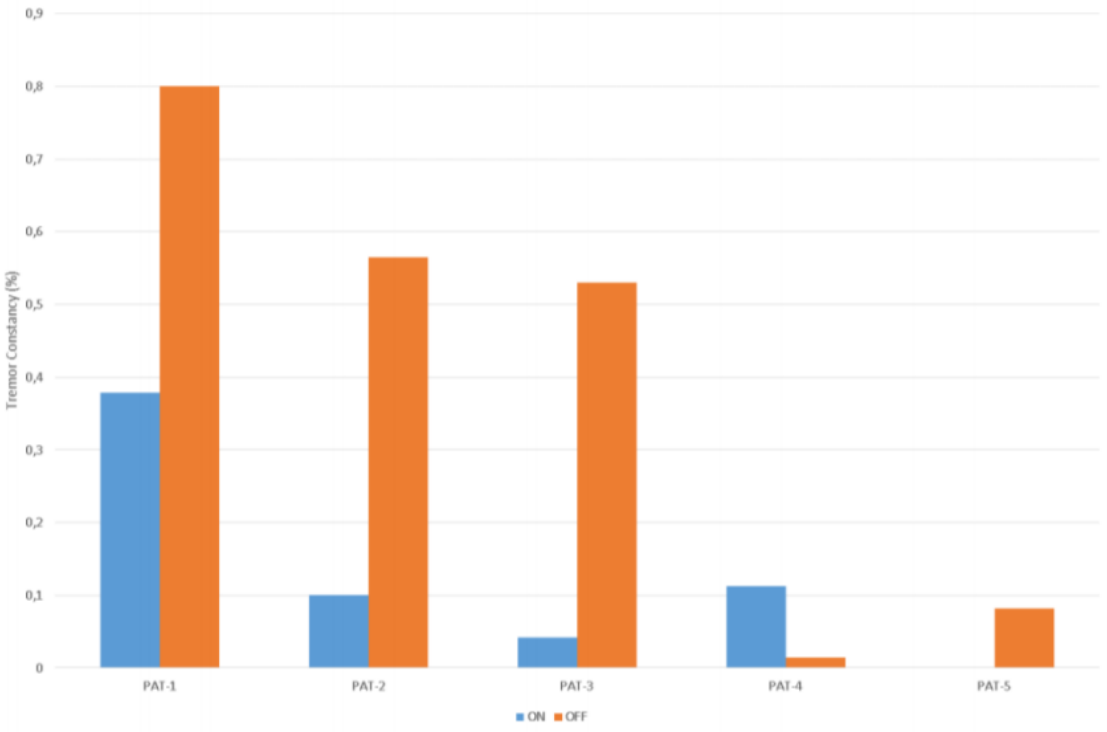


Figure 12 Tremor constancy in On and Off state for 5 patients

Dyskinesia

Dyskinesia consists of frequent wide involuntary movements of limbs, trunk or head, so the first goal was to measure the long term constancy and energy of patients' movements. At that point the algorithm must discriminate intense dyskinesia movements from voluntary movements. Normal intense voluntary movements with a long duration tend to be more regular than dyskinesia driven ones, so the algorithm used this feature to detect and analyze separately long "intense" movements with different patterns of constancy. Another important aspect is the discrimination between dyskinesia and tremor. Usually these two symptoms do not appear simultaneously because they are manifest in On or in Off state respectively, in fact dyskinesias appear as a side effect of excessive L-dopa blood concentration, while tremor appears when the medication effect is low (off state). However, since we could not exclude a priori the compresence of these two symptoms, the tremor detection algorithm have been used to discriminate windows with tremor. Also better results can be achieved in terms of dyskinesia detection if walking is excluded from analysis (using wrist accelerometer). Walking periods have been considered in order to exclude those time regions from input signals analysis for dyskinesia detection. The PD Manager Dyskinesia evaluation method is presented in Fig. 13. The methods for each signal window

consists of: i) tremor detection, ii) signal pre-processing, iii) detection of long continuous movements (LCM), iv) feature extraction from both LCM and whole signal window v) dyskinesia detection and severity estimation.

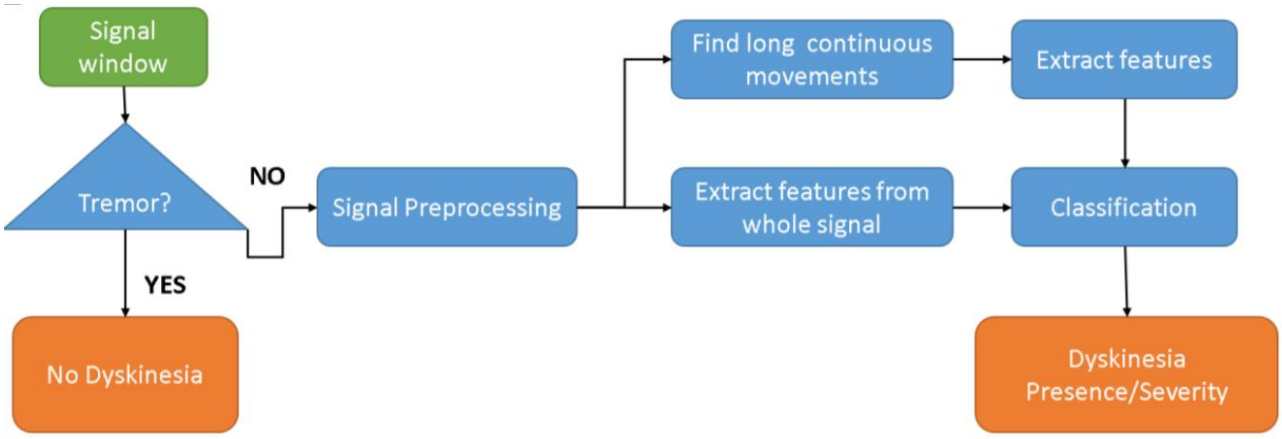


Figure 13 Dyskinesia evaluation method

Around 40 hours of home recordings from several patients have been employed for the evaluation of the method, including ~8 hours of dyskinesia. Dyskinesia detection accuracy in PD patients varies from 88% when a 5 minutes window estimation is used to a 98% for a 30 minutes window. The dyskinesia classification between slight/mild and moderate/severe had an accuracy of 0.92 for 5 minutes window estimation, using only one feature.

Bradykinesia

All the signals where tagged according to the activity that was performed by the patient: walking, drinking, sitting, lying and standing. This process was repeated for each session and state (ON, OFF). Based on this information the whole sessions were split depending on the activity. The performance of each sensors from each device was tested independently. The signal used were resultant vector of the accelerometer and resultant vector of the gyroscope from the smartphone; resultant vector of the accelerometer and resultant vector of the gyroscope from the wristband; resultant vector of the accelerometer, central pressure values and total force values both from the left and right feet from the sensor insoles. Since the bradykinesia is a symptom linked with the movement, the data regarding walking and hand movement were processed to extract a set of features. For the extraction of these features the signals should be split again using a sliding window where the features are extracted. Since the state-of-art works used windows length from 3 to 10 seconds, three different windows lengths were used in this case to explore the performance of the classifiers according to this value, particularly,

5, 15 and 30 seconds were tested using a 50% overlap between each window. Apart from the automatic assessment of the bradykinesia based on the signals coming from the different devices available in the PD_manager platform, an Android application has been developed to implement the Finger Tapping Test and the Alternative Finger Tapping Test which are two tests highly used in the current clinical practice. The participant must tap on the area as fast as he/she can during 10 seconds. The participant can start whenever he/she wants. When this test ends, the alternate finger tapping test will be automatically loaded. For each test, several parameters have been registered: Timestamp, i.e. start time of test; Test duration (ms), i.e total length of test in milliseconds; Total taps, i.e. total number of taps during the test; Error taps, i.e. number of no alternately taps during the test; Average time between taps (ms), i.e. mean of times between two consecutive taps in milliseconds; Standard deviation of time between taps (ms), i.e. standard deviation of times between two consecutive taps in milliseconds; Median time between taps (ms), i.e. median of times between two consecutive taps in milliseconds.

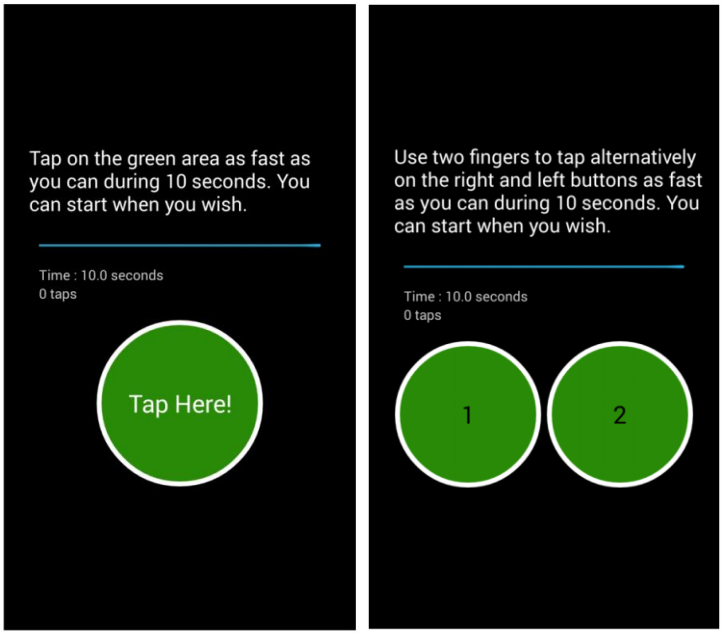


Figure 14 Screenshots from finger tapping App

The individual performance of each sensors available in the mHealth platform has been studied. Moreover, the effect of different windows lengths has been explored continuing the state-of-the-art works. In general, better performance has been achieved using larger windows lengths and using the insoles sensors. The best accuracy

result was achieved with the Center of Pressure (CoP) sensor from the insoles with a 30 seconds length window (81.66% accuracy). Since bradykinesia is a symptom linked with motion, two different scenarios have been studied: 1) signals from the smartband sensors during hand movements and 2) signals from all the sensors during walking movements. This second scenario provided the better results for the bradykinesia assessment. Moreover, two approaches have been explored, the first one, solving each UPDRS value as class of the classification problem and a second approach grouping the UPDRS values in the following three classes: None (UPDRS = 0), Mild (UPDRS = 1 & UPDRS = 2) and Severe (UPDRS = 3 & UPDRS = 4). The second approach provided better results achieving up to 81.46% of accuracy in the detection of the aggregated UPDRS category.

Cognitive App test results

All patients underwent the cognitive monitoring delivered via smartphone, although not all of them completed the whole protocol for several reasons. First, small technical issues arisen during the study have been adjusted along the way The Usability questionnaires, indeed, have highlighted critical issues related to the clarity of the instructions, the duration of the whole assessment, type of test and task that require to be redesigned. On the basis of this feedback the app has been modified with general improvements. The Text To Speech (TTS) function has been redesigned to increase the compatibility with more Android Devices, also the default pitch and speed were modified, using a slower speed and lower pitch according to the feedback from some of the users. The application has been modified to be more stable, each single test has been analyzed more accurately and also the feedback from the pilot study helped to detect some breaking points that were corrected and fixed. The visual and auditory feedback of the tests has also been included in some of the tests that did not show it. The stack of screens has been simplified and some use cases based on sequential actions leading to unexpected behavior were corrected as well. A specific layout for tablets was also implemented in order to improve the user experience and ensure the compatibility on this kind of devices.

Speech analysis results

speech data from four patients (N=4) was collected in ON and OFF conditions. The Synthema company engineers (now part of Live corp.) have tested four different machine learning algorithms to classify on or off condition based on sustained vowels test. The results showed that “Random Forest” algorithm has an accuracy of 99% in

discriminating between on and off condition and also 99% in detecting the correspondent UPDRS subitem 3.1 score.

For the Automated Speech Recognition (ASR) task, Synthema has provided speech to text technologies, using an innovative Speaker Independent ASR engine for audio transcription, which has been adapted to the project needs. In fact, within PD_manager the speech to text system must be able to operate according to a model of language which is not "usual", but enriched through the knowledge of the language production process typical of Parkinson's disease. A speech corpus (2 hours and 13 minutes of audio recorded from 21 patients) containing speech deficits typical of Parkinson's disease has been annotated to train an acoustic model. ASR was used for transcription and Text Mining algorithms to analyse the transcription in order to extract:

- Formal characteristics of the speech structure (speaking rate parameters) through a reading test
- Sentiment information (mood oscillations) through a spontaneous speech test
- Semantic information (to evaluate semantic knowledge of concepts, addressing conceptual attributes and conceptual relations) through a logical test in speech modality

Decision Support System (DSS)

Several expert models have been created. Models are composed of three subtrees of criteria, representing indications for medication change based on Motor and Non-Motor symptoms, and Epidemiologic data. The latter is used to determine if the patient's lifestyle is active or passive, which may largely affect the prescribed medication therapy. The majority of other attributes are binary, taking two values: normal and problematic. The latter represents the state of the corresponding symptom that is troublesome for the patient and may require a change of medication. The resulting models have been tested on PPMI database (78) and on the answers of 27 external clinician based on 15 real cases. The best accuracy on PPMI data in providing 'right' suggestions for given inputs, in accordance with medical guidelines, was 52.5% for "Model I", while comparing the models to experts' answers, the best accuracy found was 89.72% for "Model C".

Wearability and users' needs interview

The patients recruited have been asked to answer questions regarding comfort issues related to usage of the devices in Pilot study. All the devices resulted to be safe, comfortable and well tolerated, at least for the short duration of the measurements performed during Pilot Study.

Educational video gallery

With the help of a professional video recording and editing Studio, it has been possible to produce educational videos aimed to inform the users about the disease, explaining and visualizing the major symptoms and explaining good practices required for everyday management of the disease. The targets were patients and their caregivers, in order to suggest solutions and tricks to simplify the everyday life of a Person affected by PD. The result is the creation of 11 educational videos, in each one of them a crucial aspect of PD is treated: they represent an accurate selection of the most frequent, disabling and possibly dangerous symptoms/situations that a person suffering from PD need to recognize and surely will be found to cope with. (instability an falls, FOG and cueing strategies, tremor, orthostatic hypotension, personal hygiene care, writing, impulse control disorder, swallowing problems, hypophonia, depression, REM behaviour disorders). The educational modules also have the important function to guide the patient via a remote support. In fact, videos can be viewed remotely, the videos are playable on many devices and this methodology can easily meet the different needs of patients.

Figure 15 Screenshot from one of the educational videos produced

Multicentric Study

A total number of 136 patients and 136 caregivers have been enrolled and tested, 73 dyads tested the PD_manager System, while 59 were assigned to the control group with home diaries. Only 4 dropouts have been observed. The Interviews collecting the opinions about the 14 days' intervention period have been analysed and compared in order to assess the acceptance, ease of use, usefulness of information of the PD_manager system and the Symptoms Diary. More than 3,500 hours of recording have been collected and analysed case by case to evaluate the compliance to the PD_manager system and to assess the methods for symptoms evaluation developed within the whole project.

The mean age of participant was 67.91, and the 65.9% of the participants was above 65 years old. Gender ratio resulted in 63.9% of men and 36.1% of women, such ratio was also found to not be different between the two experimental group. Education level was normally distributed with a mean 10.28 (±4.98), years and a standard deviation of 4.97. The level of Technophobia was prominently composed by not technophobic subjects (45.5%), whether the highly technophobic subjects were just the 11.4%; the Technophobia level resulted also homogeneous between groups. Concerning the clinical aspects, the sample resulted composed for the 80.8% by patients with an H&Y stage ≥ 3 in ON state. The mean UPDRS total score was 58.97 (±3.73), UPDRS III M=29.56 (±16.23), UPDRS IV M=6.10 (±3.72). The sample resulted also with a disease duration mean of 9.43 (±4.68), with the 79.3% of subjects above 5 years from symptoms onset. Caregivers sample resulted homogeneous as well. No significant differences were found in any of the variables examined. The overall mean age of caregivers sample was 60.99 (±16.43) for the, gender ratio (43 males; 79 females) was somehow inverted if compared to the group, indicating a consistent percentage of husbands and wives as shown in "Relationship with patient" (87.2% husband/wife; 8.3% friend; 4.5% other). The level of education was 11.30 (±5.42). Considering a cut-off of 17/48 for severe/high burden, the Zarit Caregiver Burden scale score resulted slightly lower the mild burden threshold with a mean value of 8.90 (±6.41) (7.94 ± 5.55 in PD_manager group and 9.81 ± 7.22 in Diaries group). The attitudes toward technology were in large part (72.2%) above or equal to score 3 and 4 (low technophobic, not technophobic).

A group comparison has also been performed in order to find possible significant differences between the two groups (Table 11). The two groups were found homogeneous, for all variables. In PD_manager group, only 18.1

% has an H&Y stage <= 2 measured in ON condition, in Diaries group this percentage is even lower (8.9%) with a great majority of patients with an H&Y stage of 3 (71.4% of patients in Diaries group): this reflects a good selection of patients, representing a sample of moderate-advanced PD, even if collected ON state. In PD_manager group and Diaries group, the percentage of subjects older than 65 where respectively 58.1% and 63.8%, with a mean age of 69.24 years in PD_manager group and 66.67 years in Diaries group and a mean disease duration of 9.24 ± 4.30 years in PD_manager group and 9.73 ± 5.11 years in Diaries group. This is again a good representation of typical moderate-advanced PD patients. Despite the age, only 7.7% and 13.8% of patients respectively in PD_manager group and Diaries group, describe themselves as highly technophobic, with a great majority of subjects that is mild or not technophobic. The most common symptoms at the disease onset were tremor and rigidity for both groups. UPDRS Part III (measured in ON status) mean score was 28.42 ± 15.06 in PD_manager group and 30.56 ± 17.43 in Diaries group, which are values compatible with H&Y stage 2 while UPDRS IV score were respectively 5.86 ± 3.95 and 6.25 ± 3.40, that underline how our sample presents an higher score on motor complications UPDRS subitems, comparable with scores typical for H&Y stage 3 . This condition seems to be mainly related to overall time spent in OFF and motor fluctuations rather than time spent with dyskinesia. In fact 53.4% of patients in PD_manager group and 58.9% in Diaries group has no dyskinesia, while 80.8% and 82.2% respectively in PD_manager and Diaries group has a score of 1 or 2 in UPDRS subitem 4.3, that means up to 50% of waking time spent in OFF status. Moreover, 74% of patients in PD_manager group and 86% in Diaries group has an UPDRS subitem 4.4 > 0, this means that fluctuation of symptoms has a negative impact on daily life activities in the majority of patients. PDQ8 results show a mean value of 40.79 ± 20.75 in PD_manager group, adequate for patients with H&Y stage of 3 and 47.75 ± 22.71 in Diaries group, which is a higher value, more adequate for patients with H&Y stage of 4.

	PD_manager Group			Diaries Group			
	Mean	**SD**	**Frequencies**	**Mean**	**SD**	**Frequencies**	**p value**
N			75			57	.141
Age	67.94	8.82		67.88	8.88		.966
Gender (M; F)			(47;28)			(37;20)	.790
Education	10.71	4.69		11.94	4.18		.155
Disease Duration	9.22	4.35		9.73	5.11		.494
Hoehn &Yahr stage	2.7	0.6		3.0	0.5		.141
Height	169.16	8.95		169.74	9.05		.737
Weight	75.13	12.57		76.19	16.31		.700
MMSE	28.46	1.81		28.21	1.69		.473
LEDD	738.06	518.46		785.88	649.41		.231
DAEDD	221.44	145.51		185.15	84.55		.204
UPDRS_I_Total	10.00	5.20		10.84	5.43		.421
UPDRS_II_Total	9.88	6.76		11.44	8.05		.283
UPDRS_III_Total	26.36	14.28		29.58	18.61		.316
UPDRS_IV_Total	5.38	3.76		6.36	2.97		.155
UPDRS_Total	51.87	24.39		58.22	30.31		.237
PDQ8 Total	38.33	19.91		44.61	22.12		.126
TAMM_Total	22.09	10.35		24.02	12.34		.384
Technophobia (HT; MT; LT; NT)			(8;15;19;33)			(9;8;14;26)	.886

Table 11 Group comparison – Patients (MMSE: Mini Mental State Examination; LEDD: Levodopa Equivalent Daily Dose; DAEDD: Dopamin Agonist Equivalent Daily Dose; HT: highly technophobic; MT: mid technophobic; LT: low technophobic; NT: non technophobic)

	PD_manager Group			Diaries Group			
	Mean	**SD**	**Frequencies**	**Mean**	**SD**	**Frequencies**	**p-value***
Tested			75			57	.141
Gender (M; F)			(27;42)			(16;37)	.533
Age	59.91	18.67		62.43	12.91		.420
Relation with Patient (Family; Friend)			(67;5)			(48;6)	.656
Education	11.64	5.16		10.83	5.78		.438
Preferred Group (PD_manager, Both, Diaries)			(41;14;4)			(23;12;11)	.066
Zarit Caregiver Burden Scale	7.96	5.54		10.0	7.22		.135
Technophobia (HT; MT; LT; NT)			(4;9;21;34)			(7;13;12;19)	.115
TAMM Total	23.93	12.36		24.78	12.36		.715

Table 12 Group comparison – Caregivers (HT: highly technophobic; MT: mid technophobic; LT: low technophobic; NT: non technophobic)

Post trial interview

In the next section the results coming from the comparison of PD_manager Group and Diary Group (Control Group) opinions, after the 2 weeks intervention period, are reported. For each Question of the Post Trial Interview, the results for multinomial regression analysis are displayed in charts and tables including the statistics of the tests performed. As previously described in Data Analysis section, the Multinomial Regression Model took into account as predictor variable factors were selected all the items of the Post Trial Interviews ranging from Q1-Q5 and Q7 to Q10, in relation to the factor Group (PD_manager, Symptoms Diary). As covariates, age and gender and attitudes towards technology for both patients and caregivers. For caregivers: Zarit Caregiver Burden total score (High vs. Low Burden); for patients: PDQ-8 total score and Non-motor symptoms scale; UPDRS III total score. From a first run of the analysis, we observed no influence of any covariate in explaining the regression model. The randomization process resulted in a homogeneous composition of all the variables chosen as covariate, producing a non-significant effect of the model fit. So, the analysis was run excluding the above-mentioned covariates.

The regression model for PTI Question 1 – "How easy / difficult has it been for you to use the PD_Manager system?" – turned out to not fitting the parameters used as covariates. Although, the answers "Very easy" (B=20.156; W=871.00; df=1; p<.001) and "Quite easy" (B=20.110; W=775.50; df=1; p<.001) resulted significantly associated to PD_manager group. After the re-run of the analysis, the effect for "Very easy" (B=20.156; W=871.00; df=1; p<.001) and "Quite easy" (B=20.110; W=775.50; df=1; p<.001) were confirmed to be significantly associated with PD_manager group.

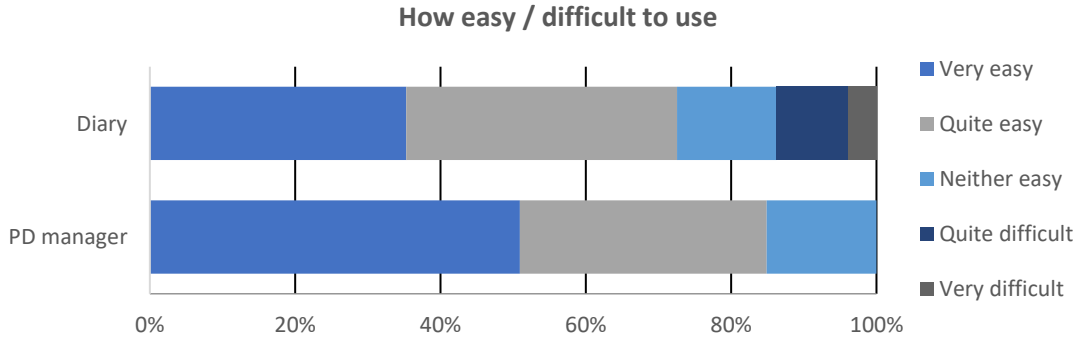


Figure 16 PTI Question 1 - Easy to use

The regression model for PTI Question 2 – "About how long each day did you spend using the PD_Manager devices?." – turned out to not fitting the parameters used as covariates. However, after the re-run of the analysis, excluding the non influencing covariates, the answers "Less than 30 min" resulted significantly different for the PD_manager group and inversely related to the Control Group (B= -2.25 W=4.01; df=1; p=.045), meaning that the ratio of the answer changes and revert itself for answer that goes from "30 min to 1 hour" to "More than 2 hours.

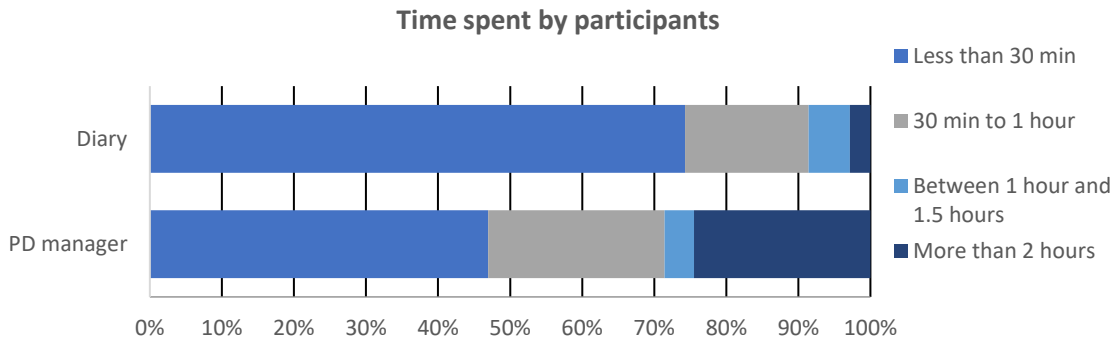


Figure 17 PTI Question 2 -Time spent using monitoring system

The regression model for PTI Question 3 – "How helpful do you think the information from the PD_Manager devices/Diary has been in helping your doctor to plan your treatment?" – didn't show any significant differences between the two groups (X^2= 8.630; df=9; p=.472). Moreover, no differences were found between the different factors, showing the same rating for both PD_manager group and Symptoms Diary Group.

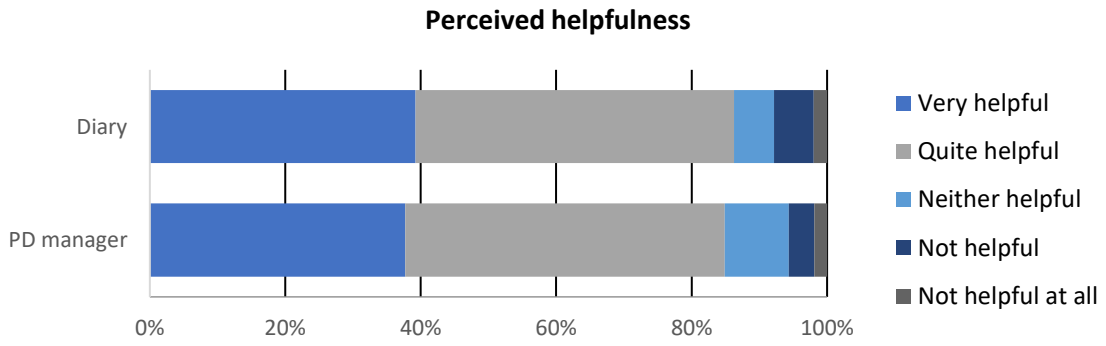


Figure 18 PTI Question 3 -Perceived hepfulness

The regression model for PTI Question 4 – "How helpful do you think the PD_Manager devices/Diary have been in helping you to manage your symptoms?" – didn't show any significant differences between the two groups

(X^2= 7.010; df=9; p=.636). No differences were found between the different factors, showing the same rating for both PD_manager group and Symptoms Diary Group.

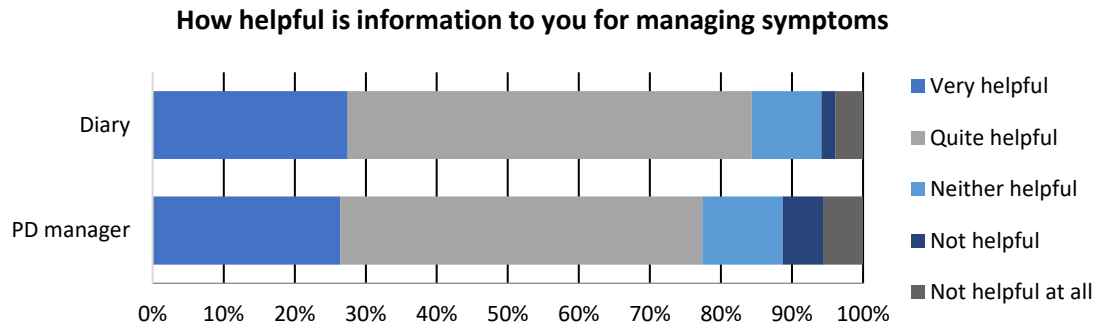


Figure 19 PTI Question 4- Perceived helpfulness in self-managing patient's symptoms

The regression model for PTI Question 5 – "How did the PD_Manager system affect the discussions with your doctor about your symptoms and treatments?" – turned out to not fitting the parameters used as covariates, so no differences were observed. The model didn't show any significant difference either after removing covariates (X2=3.331; df=3; p=.343).

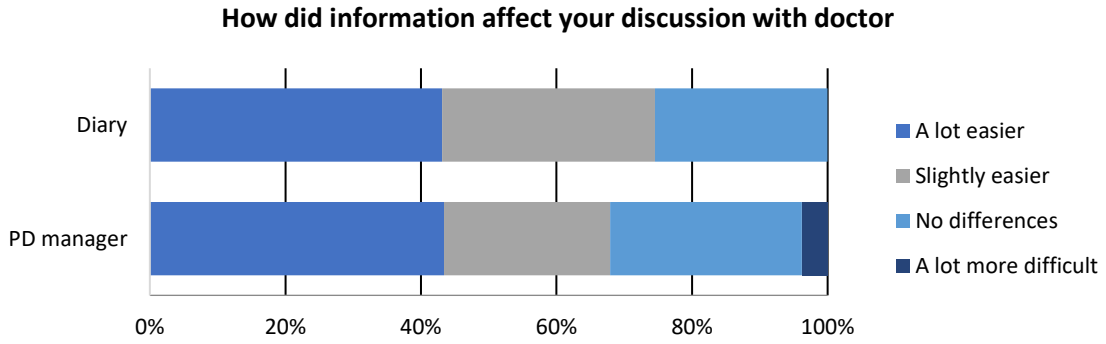


Figure 20 PTI Question 5 - Perceived helpfulness in managing patient's symptoms by doctor

In PTI Question 7 – "Would you recommend the PD_Manager system/Diary to other people with Parkinson's?", again, no effect for covariates were found. The model including just the main factors resulted instead significantly fitting the data, showing a difference for the answer "Yes" (B=20.079; W=728.29; df=1; p<.001) to be more likely associated to PD_manager group.

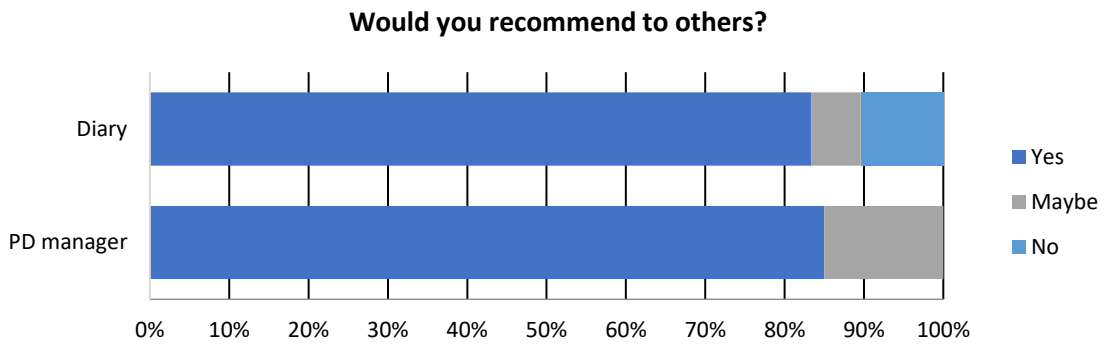


Figure 21 PTI Question 7 - Patient's recommendation

In PTI Question 8 – "Would you use the PD_Manager system again in the future if your doctor suggested it?", no influence for covariates were found. The test was re-run including just the main factors which resulted instead in a model significantly fitting the data, which showed a difference for the answer "Yes" (B=20.186; W=490.73; df=1; p<.001) to be more likely associated to PD_manager group.

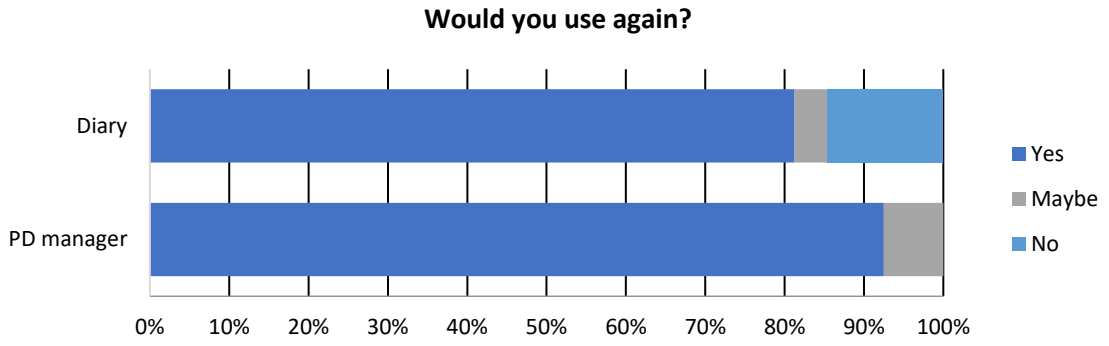


Figure 22 PTI Question 8 - patient's desire to use again the monitoring system

The regression model for PTI Question 9 – "Would you have preferred to have completed a daily diary/PD_manager over the last 2 weeks than having the PD_Manager system" – turned out to not fitting the parameters used as covariates. However, after the re-run of the analysis, excluding the non-influencing covariates, the answers "Diary" and "Maybe, I don't know" resulted significantly different for the PD_manager group and inversely related to the Control Group (B= -3.93 W=13.36; df=1; p<.001) and (B= -2.78 W=15.58; df=1; p<.001).

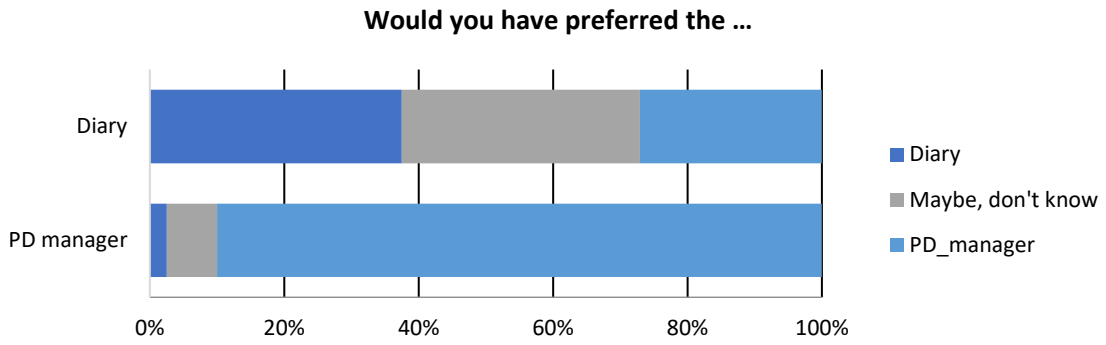


Figure 23 PTI Question 9 - Preference on monitoring system, regardless the system tried

The regression model for PTI Question 10 – "How do you think the symptom diary would compare to the PD_Manager system in helping your doctor to understand your problems and plan your treatment?" – turned out to be fitting the data, by removing the non-influencing covariates. The answers "PD_manager more helpful" resulted significantly different for the PD_manager group (B= 2.22; W=4.38; df=1; p=.04) and (B= -2.78 W=15.58; df=1; p<.001).

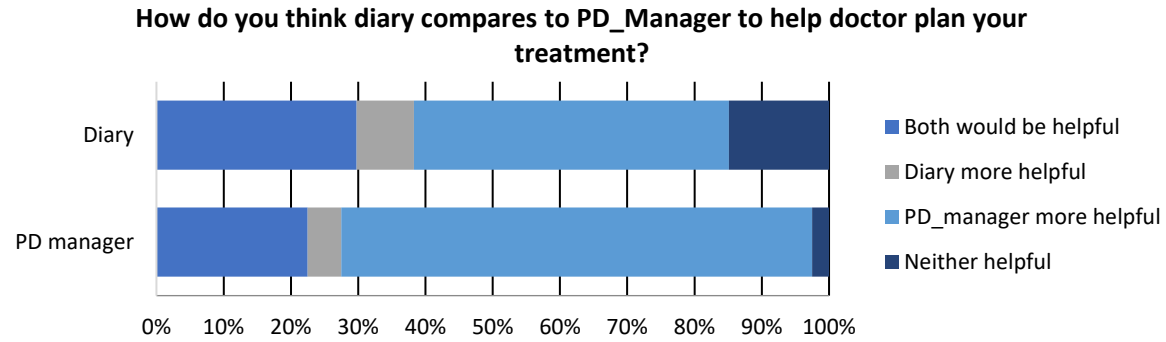


Figure 24 PTI Question 10 - Comparison between Monitoring systems in perceived helpfulness for doctors

The ratings observed from patients have been related also to the ratings provided by the Caregivers, showing that a significant degree of agreement was present for all the answer going from PTIQ1 to PTIQ5, and PTIQ8 and PTIQ10 for both groups. A different pattern, of non-significant agreement was found for the answers to PTIQ7 and PTIQ9 for the PD_manager group and for PTIQ9 for the Control Group (symptoms diary). The correlation matrix and respective value of Spearman R and significance are displayed in tables 13 and 14.

Group	Item	PTIQ1-CG	PTIQ2-CG	PTIQ3-CG	PTIQ4-CG	PTIQ5-CG
PD_manager	PTIQ1	.782**	.012	.166	-.039	.047
	PTIQ2	-.132	.900**	-.103	.089	-.119
	PTIQ3	.066	.111	.661**	.447**	.552**
	PTIQ4	-.054	.137	.524**	.774**	.262
	PTIQ5	.154	-.152	.603**	.287*	.813**
Diary	PTIQ1	.898**	.574**	.167	.436**	.045
	PTIQ2	.674**	.917**	-.121	.387*	-.048
	PTIQ3	.074	-.049	.669**	.000	.176
	PTIQ4	.438**	.457**	-.006	.760**	-.105
	PTIQ5	-.057	-.085	.302	-.092	.647**

Table 13 . Correlation between patients and caregivers answer to PTI. * Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

Group	Item	PTIQ7-CG	PTIQ8-CG	PTIQ9-CG	PTIQ10-CG
PD_manager	PTIQ7	.253	-.067	-.031	.096
	PTIQ8	.053	.563**	.125	.111
	PTIQ9	.044	-.298	.248	.061
	PTIQ10	.193	.009	-.114	.277
Diary	PTIQ7	.860**	.540**	-.030	.106
	PTIQ8	.477**	.858**	.131	.223
	PTIQ9	-.244	.015	.188	-.064
	PTIQ10	.236	.243	.084	.676**

Table 14 . Correlation between patients and caregivers answer to PTI. * Correlation is significant at the 0.05 level (2-tailed). ** Correlation is significant at the 0.01 level (2-tailed).

Correlation with Technology Acceptance Measure

The relationship between the expectations before starting the trial – measured with the Technology Acceptance Measure – and the answer and opinion about the PD_manager/Diary were also explored. The correlation of TAM score with PTI answer showed just two significant associations between the level of positive expectations and the answer to PTIQ3 and PTIQ4 both insisting on the usefulness information area. No associations were found for the Diary Group (Table 13).

PD_manager Group		**Symptoms Diary Group**	
PTI	**TAM**	**PTI**	**TAM**
PTIQ1	.029	PTIQ1	.019
PTIQ2	.219	PTIQ2	-.169
PTIQ3	.321*	PTIQ3	.061
PTIQ4	.376**	PTIQ4	.032
PTIQ5	.182	PTIQ5	.079
PTIQ6-1A	-.094	PTIQ6-1A	.
PTIQ6-1B	-.093	PTIQ6-1B	.
PTIQ6-1C	.063	PTIQ6-1C	.
PTIQ6-1D	.009	PTIQ6-1D	.
PTIQ6-2A	.010	PTIQ6-2A	.
PTIQ6-2B	.233	PTIQ6-2B	.
PTIQ6-2C	.147	PTIQ6-2C	.
PTIQ6-2D	.019	PTIQ6-2D	.
PTIQ6-3A	.037	PTIQ6-3A	.
PTIQ6-3B	-.081	PTIQ6-3B	.
PTIQ6-3C	.117	PTIQ6-3C	.
PTIQ6-3D	-.015	PTIQ6-3D	.
PTIQ6-4A	.042	PTIQ6-4A	.
PTIQ6-4B	.089	PTIQ6-4B	.
PTIQ6-4C	-.061	PTIQ6-4C	.
PTIQ6-4D	-.129	PTIQ6-4D	.
PTIQ6-CNT-1A	.	PTIQ6-CNT-1A	-.097
PTIQ6-CNT-1B	.	PTIQ6-CNT-1B	.076
PTIQ6-CNT-1C	.	PTIQ6-CNT-1C	.099
PTIQ6-CNT-1D	.	PTIQ6-CNT-1D	.007
PTIQ6-CNT-2A	.	PTIQ6-CNT-2A	-.033
PTIQ6-CNT-2B	.	PTIQ6-CNT-2B	-.067
PTIQ6-CNT-2C	.	PTIQ6-CNT-2C	-.004
PTIQ6-CNT-2D	.	PTIQ6-CNT-2D	-.074
PTIQ7	.122	PTIQ7	-.002
PTIQ8	.170	PTIQ8	.141
PTIQ9	.049	PTIQ9	-.160
PTIQ10	.058	PTIQ10	-.242

Table 15 Correlation is significant at the 0.05 level (2-tailed); ** Correlation is significant at the 0.01 level (2-tailed); "." Cannot be computed because at least one of the variables is constant.

PD_manager Subcomponent Evaluation

This sub-section analyses the opinion expressed from participant about the single subcomponents (Insoles, Smartband, Smartphone) within the PD_manager Group. The sub components have been assessed in terms of Ease of Use, Comfort and Usefulness of information. The ordinal values collected per each area in means of (1, "Very"), (2, "Quite") (3, "Not"), have been analyzed using the Friedman test for non-parametric related-sample comparison.

- Ease of use: the ease of use analysis of subcomponent revealed a significant difference between the three different devices PTIQ6-1A(Insoles), PTIQ6-2A and PTIQ6-3A (Smartphone) (X^2=7.524; df=2; p=.023). The lower mean rank – closer to value 1 ("Very) - was associated with the Smartband (M= 1.87), whether Smartphone (M=2.19) and Insoles (M=1.94).
- Comfort: Comfort analysis didn't show any significant difference between devices (X^2 =2.191; df=2; p=.334), with mean ranks which display around 2 (Quite).
- Usefulness for self-management: usefulness for self-management didn't show any significant difference between the devices (X^2=2.00; df=2; p=.368), with mean ranks which display around 2 (Quite).
- Usefulness for doctor: usefulness for self-management between subcomponent didn't show any significant difference (X^2=2.60; df=2; p=.273), with mean ranks which display around 2 (Quite).

Symptoms Diary Subcomponent Evaluation

This sub-section analyses the opinion expressed from participant about the single subcomponents (Motor Symptoms Diary, Non-Motor Symptoms Diary) within the Symptoms Diary Group. The sub components have been assessed in terms of Ease of Use, Comfort and Usefulness of information for self-management and for doctor. The ordinal values collected per each area in means of (1,"Very"), (2, "Quite") (3, "Not"), have been analyzed using the Friedman test for non-parametric.

No significant differences in terms of Ease of Use, Comfort and Usefulness of information for self-management and for doctor have been found between the two different diaries used by the control group.

Compliance, Data Usage And Statistics

A descriptive and quantitative analysis of compliance and usage have been performed for each patient in PD_manager group. Here reported just two examples of two different patients, one with good compliance, one with poor compliance.

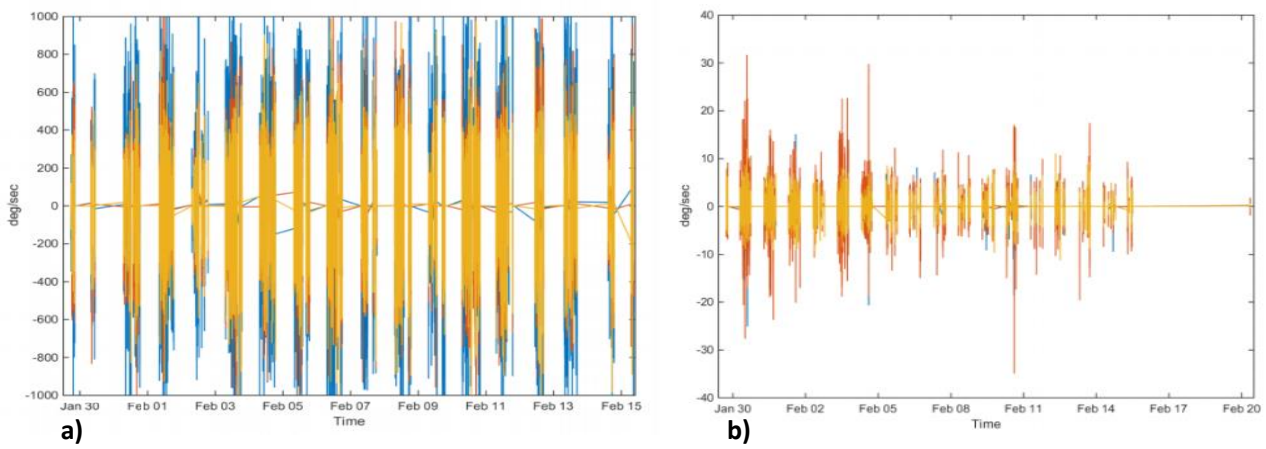


Figure 25 Patient SC033 Usage from a) wristband and b) accelerometer recordings

Patient SC033 used the band as well as the smartphone and the insoles for the whole 2 weeks period. This Patient is a 75 years old female, who was diagnosed 20 years ago. She has primary education. Her self-rated health status was mediocre (EQ is 14). This health status is reflected in the clinical scales: NMSS score is 45, which indicates severe problems, mostly related to seep/fatigue, mood/cognition and gastrointestinal problems. The patient described himself as Highly Technophobic. The caregiver was the patient's 51 years old son who has Bachelor education. He feels he has high burden due to PD (Zarit was 24) and described himself as Not Technophobic. The caregiver didn't have a positive attitude towards the PD_manager. These attitudes and the fact that the patient described herself as highly technophobic didn't affect the usage rates which were high. Conclusion: disease duration itself seem to not affect the compliance in an old female patient with severe clinical status, and the attitudes towards technology may not be primary issues to take into account.

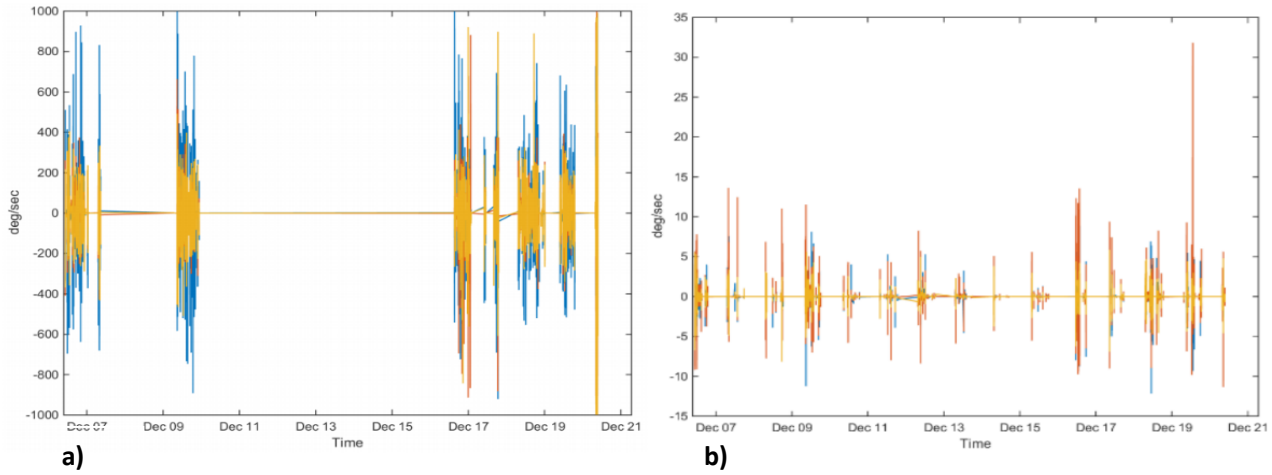


Figure 26 Patient SL045 usage from a) wristband and b) accelerometers recordings

Patient SL045 used the band for 2 days during the first week he got them and for 4 more days the second week. He was carrying the smartphone and wearing the insoles for the whole 2 weeks' period. Patient SL045 is a 63 years old patient, which was diagnosed 6 years ago. He has secondary education. His perceived quality of life was below average (PDQ8: 46.9%) and his self-rated health status was good (EQ is 10). This health status is reflected in the clinical scales: NMSS score is 45, which indicates moderate problems, mostly related to salivation and olfactory system problems, and the UPDRS total is 28 which is low for a H&Y stage 3 patient. The patient described himself as Not Technophobic. The caregiver was the patient's 58 years old partner who has primary education. He feels she has very little burden due to PD (Zarit was 5) and described himself as Not Technophobic. Both the patient and the caregiver thought it would be easy to use PD_manager, they were very enthusiastic about its perceived usefulness and they behaviourally intended to support its use, but they were not being intrinsically motivated to use it. These attitudes and the fact that both described themselves as Not technophobic are in controversy with the relatively low usage rates. Conclusion: a younger patient (63 yo) with mild problems who seems to think that the system is useful and easy to use has ca very supporting younger caregiver (58 yo) is also very keen to support that use may end up using the band for fewer days the PD_manager system than one would suppose. In this case a mildly depressed mood and pain (as reported by the patient in EQ and PDQ8) could be the reasons for low usage. Of course, also Bluetooth connection issues between Wristband and Smartphone could have affected the amount of recording hours from Wristband.

More than 3.500 hours of data were recorded in total. The total hours recorded per patient are presented in Fig. 27. The histogram of recording usage is presented in Fig. 26. Only two patients didn't use the system at all, while

10 were very compliant and used it for more than 100 hours over the 14 days. Overall for all the patients we had more than 30 hours of recorded data we were able to extract clinically meaningful information and consistent with the baseline UPDRS evaluation.

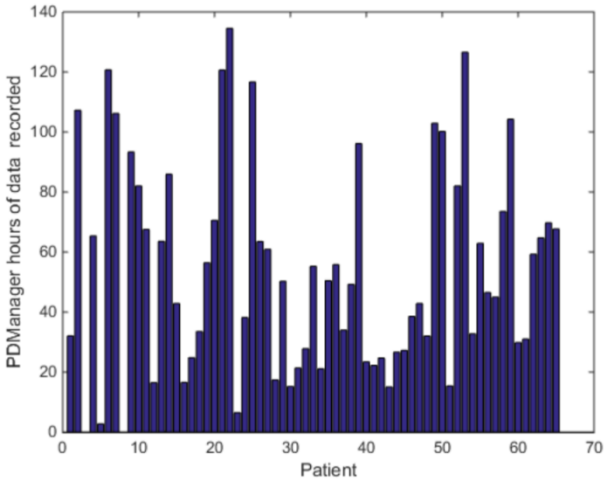


Figure 28 Total hours recorded per patient

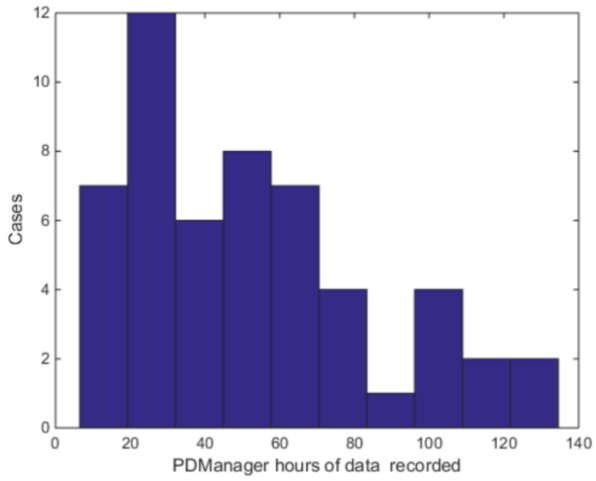


Figure 27 Number of patients grouped for hours of recordings

The total hours of recording were dichotomized in two equally sampled groups (low usage and high usage) in order to compare the distribution of each variable against the usage of PD_manager. For numeric variables the Spearman correlation against the original (not dichotomized) usage variable was used. For numeric variables we also used a t-test in case the variable was normally distributed comparing its value for low and high usage groups. If the variable was not normally distributed, then the Wilcoxon signed-rank test was used. For ordinal variables the Spearman correlation was used. For mobile phone usage we extracted two measures. The first one was the actual data recorded in the 2 weeks of trial, the second measure was the percentage of one-minute recordings with motion to the total number of minutes recorded. Minutes with motion are considered those having at least one sample with gyroscope energy larger than 2. Based on the results showed in Table 11, the UPDRS sub-total scores are the only variables that have some statistical significance for PD_manager usage. In fact, usage result to be higher for patients with higher UPDRS, (UPDRS II 7.28 vs 12.92). This trend was also observed also in the per patient analysis from which a clear profile of compliant patients could not be extracted.

Variable	Low Usage Group		High Usage group		T-test/Wilcoxon	Spear
	Mean	Std	Mean	Std	P-value	
Disease duration	7,65	3,20	8,88	4,50	0,26	0,36
Caregiver Education	10,85	6,36	12,71	4,83	0,26	0,20
Caregiver Technophobia	2,35	1,38	2,67	1,61		0,27
Patient age	69,63	11,88	70,31	9,62	0,50	0,69
Patient Gender (M=1.F=2)	1,44	0,51	1,35	0,49		0,47
Patient Education	11,00	3,62	11,08	4,78	0,87	0,74
Patient Technophobia	2,30	1,35	2,58	1,47		0,38
EQ_5D_5L_1	1,92	0,80	2,19	1,06		0,39
EQ_5D_5L_2	1,65	0,85	1,65	1,13		0,73
EQ_5D_5L_3	1,58	0,70	1,65	1,02		0,91
EQ_5D_5L_4	2,50	0,86	2,12	1,18		0,24
EQ_5D_5L_5	2,15	0,92	1,88	1,11		0,39
EQ_5D_5L_Total	9,81	2,81	9,50	4,47	0,77	0,34
NMSS_Total	39,60	20,43	49,23	49,92	0,74	0,75
PDQ8_1	1,71	1,08	1,60	1,15		0,80
PDQ8_2	1,46	0,88	1,96	1,40		0,23
PDQ8_3	1,96	1,27	1,92	1,50		0,82
PDQ8_4	1,25	1,07	1,36	1,08		0,67
PDQ8_5	1,38	0,97	1,40	1,19		0,88
PDQ8_6	1,17	0,70	1,40	1,04		0,49
PDQ8_7	2,75	1,33	2,16	1,43		0,15
PDQ8_8	1,58	0,97	1,96	1,31		0,24
PDQ8 Total	41,41	17,34	43,00	21,60	0,78	0,71
Zarit_2	0,91	1,00	1,27	1,28		0,40
Zarit_11	1,26	1,21	1,05	0,95		0,57
Zarit_total	8,57	6,67	9,41	5,24	0,64	0,30
udprsHY	2,71	0,62	2,90	0,48	0,62	0,83
UPDRS_I_Total	10,36	3,44	11,12	6,39	0,75	0,69
UPDRS_II_Total	**7,28**	**4,62**	**12,92**	**8,33**	**0,01**	**0,04**
UPDRS_III_Total	23,27	10,15	31,52	18,25	0,05	0,24
UPDRS_IV_Total	5,36	3,29	5,52	4,41	0,88	0,76
UPDRS_Total	46,72	16,13	61,08	31,81	0,05	0,39

Table 16 comparison of main Clinical scores between low and high usage groups

Based on this observation a further analysis was performed on the population with low UPDRS score, in particular UPDRS Part II score equal to 15 or less.

Variable	Low Usage Group		High Usage group		T-test/Wilcoxon	Spear
	Mean	Std.	Mean	Std.	P-value	
Disease duration	7,55	3,42	7,28	2,24	0,78	0,78
Caregiver Education	11,86	5,97	13,28	4,39	0,48	0,22
Caregiver Technophobia	2,50	1,37	2,72	1,41		0,53
Patient age	67,50	7,42	67,17	9,25	0,90	0,77
Patient Gender (M=1.F=2)	1,41	0,50	1,39	0,50		0,90
Patient Education	11,09	3,69	12,50	3,97	0,29	0,61
Patient Technophobia	2,36	1,33	2,56	1,62	1,00	0,47
EQ_5D_5L_1	1,86	0,71	1,67	0,77		0,36
EQ_5D_5L_2	1,55	0,74	1,33	0,59		0,36
EQ_5D_5L_3	1,55	0,74	1,39	0,70		0,62
EQ_5D_5L_4	**2,55**	**0,91**	**2,00**	**0,91**		**0,06**
EQ_5D_5L_5	2,18	0,96	1,72	0,89		0,16
EQ_5D_5L_Total	**9,68**	**2,63**	**8,11**	**2,87**	**0,07**	**0,03**
NMSS_Total	39,68	20,11	36,33	29,44	0,24	0,22
PDQ8_1	1,64	1,09	1,50	0,99		0,90
PDQ8_2	1,45	0,91	1,39	0,85		1,00
PDQ8_3	1,95	1,33	1,67	1,28		0,41
PDQ8_4	1,18	1,10	1,33	1,08		0,52
PDQ8_5	1,36	1,00	1,17	0,92		0,56
PDQ8_6	1,14	0,71	0,94	0,73		0,46
PDQ8_7	**2,82**	**1,37**	**1,94**	**1,11**		**0,02**
PDQ8_8	1,50	0,96	1,67	1,24		0,63
PDQ8 Total	40,77	17,85	36,28	16,78	0,42	0,29
Zarit_2	0,95	1,02	0,72	0,96		0,46
Zarit_11	1,24	1,26	1,11	0,96		0,84
Zarit_total	8,71	6,91	7,56	4,42	0,54	0,69
udprsHY	2,75	0,55	2,78	0,39	0,75	0,28
UPDRS_I_Total	10,36	3,62	9,56	4,68	0,54	0,17
UPDRS_II_Total	6,55	3,47	7,61	3,27	0,24	0,59
UPDRS_III_Total	22,14	9,24	21,67	8,55	0,87	0,56
UPDRS_IV_Total	5,55	3,42	4,22	3,14	0,21	0,46
UPDRS_Total	44,59	14,75	43,06	14,03	0,74	0,46

Table 17 Comparison between low usage and high usage in patients with low UPDRS part II score

3 variables are statistically important and seem to affect the usage of the system:

- PDQ8 Item 7: Had painful muscle cramps or spasms? (Likert: 1-never to 5-always)
- The total EQ-5D score which provides the patient's overall self-rated health status
- EQ-5D Item 4: PAIN / DISCOMFORT (Likert: 1-"I have no pain or discomfort" to 5-"I have extreme pain or discomfort").

Clinicians Study

Another important task of the project was the creation of Clinician App. This Android based application has been conceived to output clear and understandable reports of the patient's symptoms during the 2 weeks of trial. All functionalities of the app are designed to be smart, intuitive and to facilitate the clinician's analysis of the data coming from the recordings. Moreover, the Clinician App is integrated with the DSS System and is able to recognize specific patterns of symptoms that could be troublesome for each patient and report an alert to the clinician. The App provides the necessary data visualization functionalities required by clinicians, including: assessment (summary reports and charts); clinical information (patient's History); Motor Symptoms (summary reports and charts); tests (scores of clinical scales and questionnaires); a calendar(for retrieving data for the patients); Medication (past and current plans). The main functionality is the presentation of symptom charts allowing the clinician to explore the patient symptoms and assess his motor status. There are five main types of symptoms charts: 1) Symptom Trend Chart: the symptom trend chart provides an overview of a symptom for a period of time aggregated per day. This chart allows clinicians to monitor the trend of the symptom and whether there are any significant changes related to patient status, change of habits or medication. 2) Symptom Daily Pattern Chart: the symptom daily pattern chart present symptoms aggregated per time of day. Moreover, medications are overlaid and the tool gives the user the ability to compare daily patterns between different periods of time. The specific chart is probably the most useful tool for the clinician for treatment planning since using those charts can easily check the occurrence of symptoms related to medication times and decide whether some change is required. 3) Symptom Day Chart: clinicians can use the calendar to navigate to specific days and view the symptoms as well as medication intakes for the specific day. 4) Symptom Summary: the symptom summary presents the most important information of symptoms. 5) Patient Chart: the patient chart displays the patient's clinical information including allergies, demographic data, other clinical problems, etc.

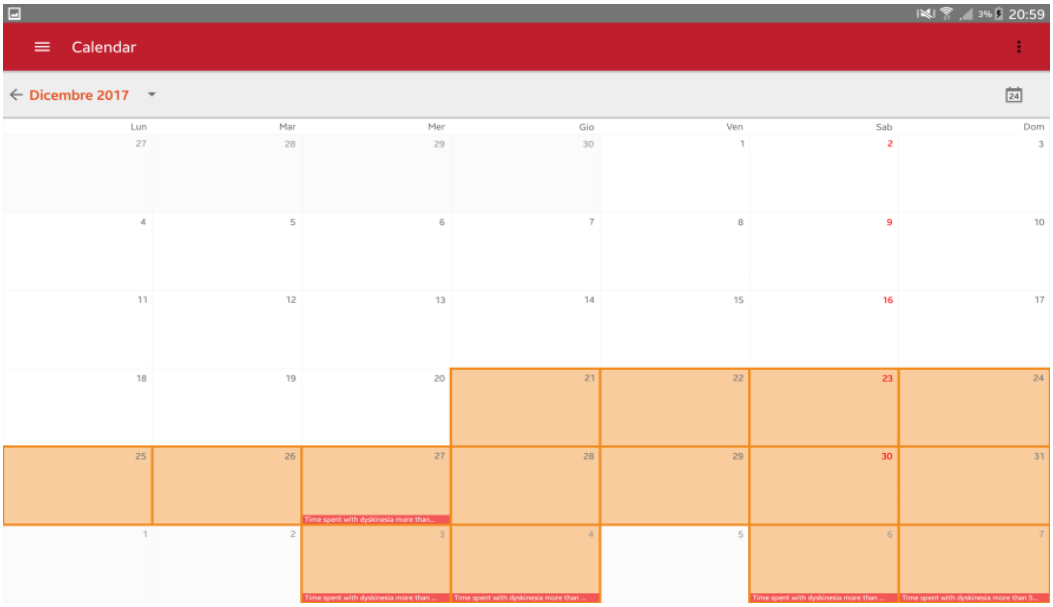


Figure 29 Screenshot from Clinician App: calendar of recordings. In orange, days with data available. Red bars: alerts for time spent with dyskinesia > 50% of the day

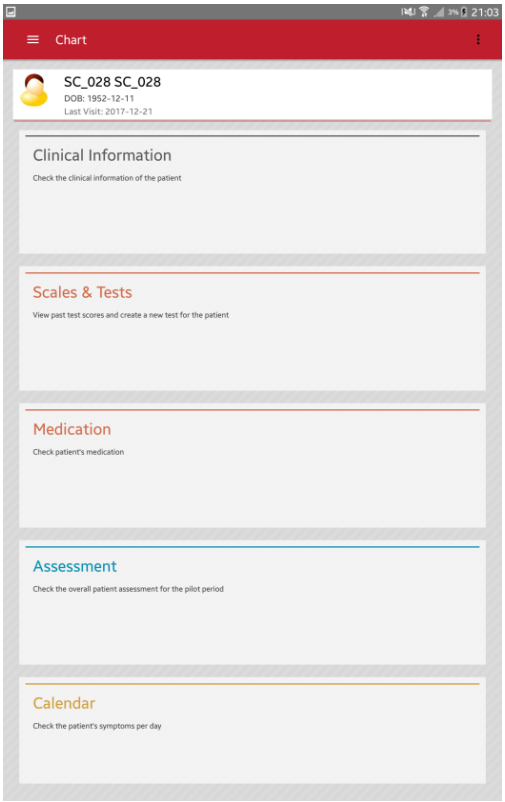


Figure 31 Clinician App's Main Manu

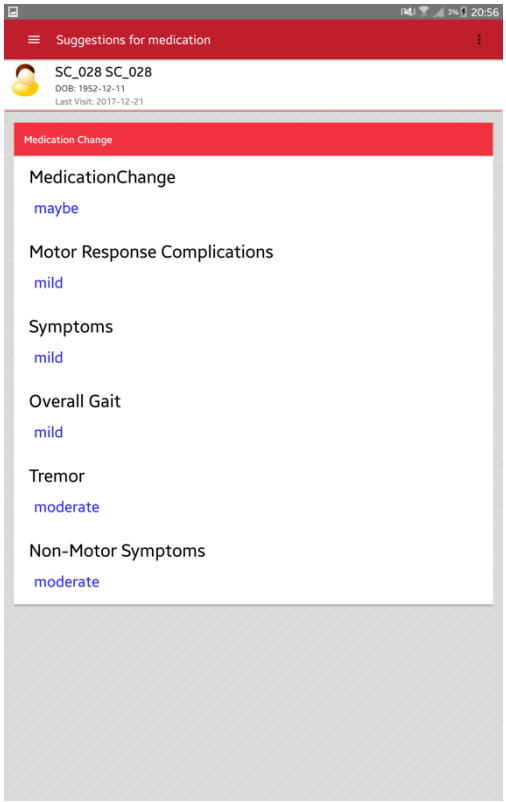


Figure 30 DSS suggestion and evaluation of main symptoms

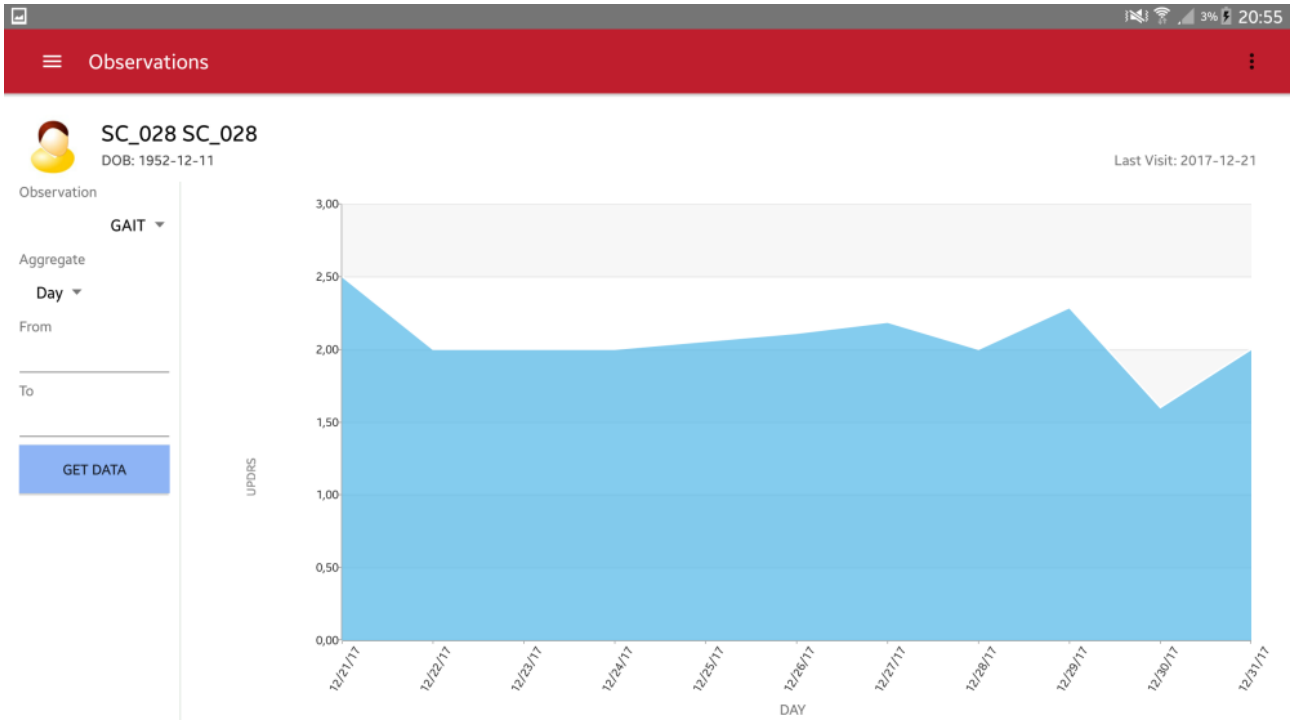


Figure 33 Example of Symptom Trend Chart for bradykinesia. The Bradykinesia estimated UPDRS subitem score is depicted for each day of the recordings. Patient SC_28 seems to have medium bradykinesia, quite stable during the 2 weeks

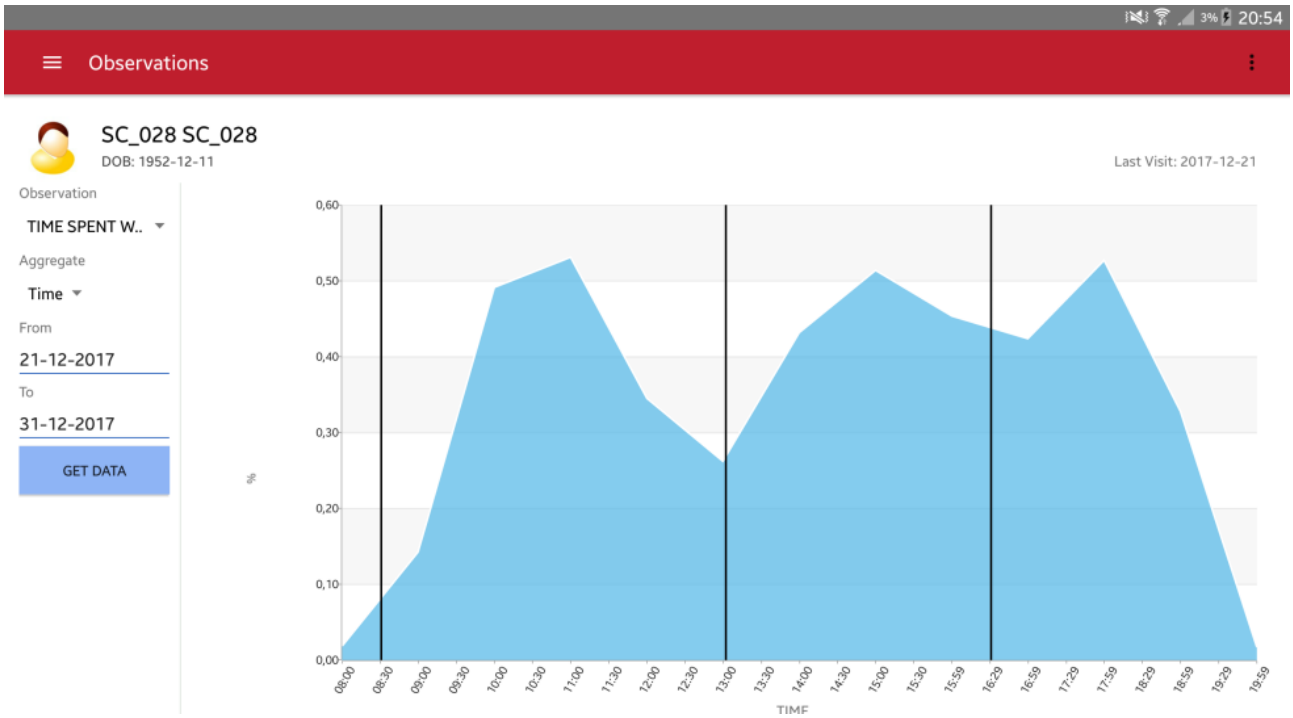


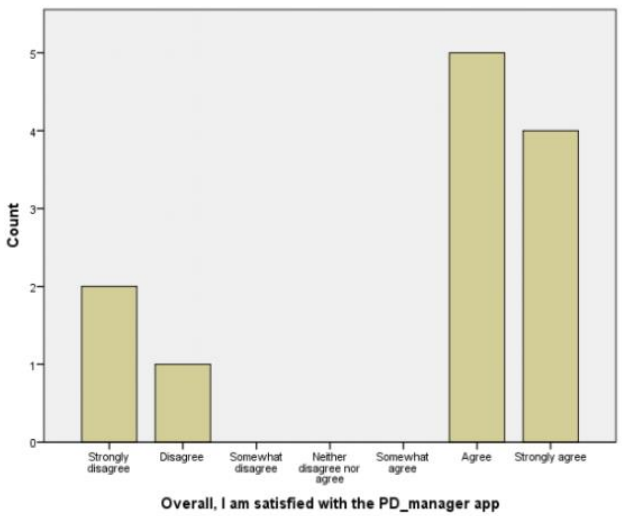
Figure 32 Symptoms Daily Pattern Chart for Tremor: the graph shows the 2 weeks mean time spent with tremor, for each hour of the day. The black bars represent the Levodopa doses. Patient SC_28 has tremor, but it is responsive to Levodopa administration

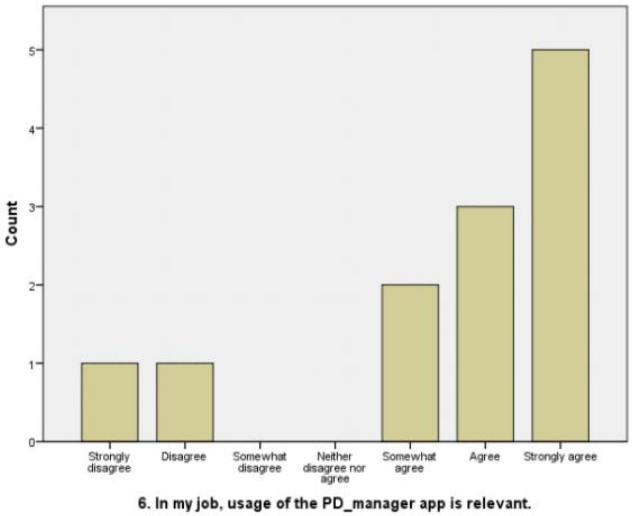
From this point of view, the clinician's feedback is crucial to establish if the information coming from the System could influence clinical decisions. Feedback was sought by means of a structured interview schedule on perceived usefulness to professionals: the clinicians were asked to comment on how easy it was to interpret the data generated by the devices and the symptom diary, to use this data in changing the treatment and care

management of participants. A total of 12 Clinicians were recruited and provided feedback data. Table 18 shows the characteristics of the clinicians who responded. Most had been practicing as neurologist for at least 5 years and dealt with significant numbers of people with Parkinson's on a monthly basis. Most also were familiar with smart phone use. The average score for PD_manager on the System Usability Scale was to the 72.5 which is above the widely accepted threshold of 68. The range was 12.5 to 100. For the other various components of SUS questions, more than 75% of the Clinicians have consistently highly rated the PD Manager system, but as depicted in the graphs below, 2 or 3 clinicians were consistently not satisfied or did not find the system helpful.

Characteristic	N			
How long have you been dealing with neurological patients?	N	< 5 years (%)	5 – 15 years (%)	> 15 years (%)
	12	3 (25%)	4 (33.3%)	5 (41.7%)
How frequently manage anti Parkinson's medications?	N	Almost every day (%)	About once a week (%)	About once a month (%)
	11	9 (81.8%)	1 (9.1%)	1 (9.1%)
Number of people with Parkinson's seen a month	N	<=20 (%)	30 - 50 (%)	60 - >=100 (%)
	12	3 (25%)	7 (58.3%)	2 (16.7%)
How frequently use smart phone	N	Every day (%)	Sometimes (%)	Rarely/ never (%)
	12	10 (83.3%)	1 (8.4%)	1 (8.3%)

Table 18 Clinicians' characteristics





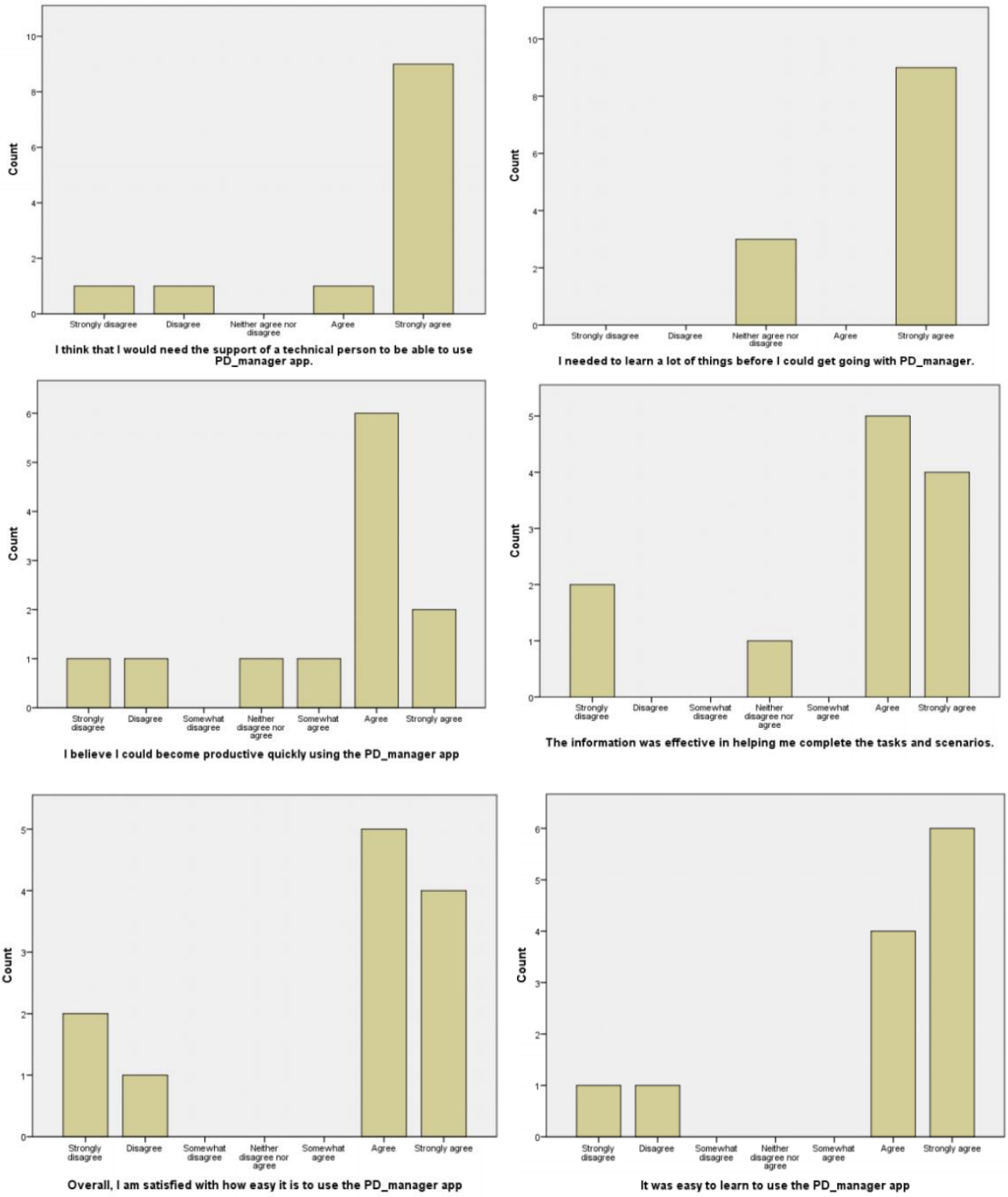


Figure 34 graphs showing clinicians' perspective on Clinician App

DISCUSSION

In this PhD project, a novel mHealth platform for Parkinson's disease management has been designed, implemented and tested on patients and caregivers. The first phase of the project was focused on devices selection and on the development of algorithms that could be able to recognize and detect the main motor symptoms of the disease, based on the raw data gathered from the selected devices. To do that, a Pilot Study have been designed and the devices have been tested on 20 patients in controlled environment (hospital or ambulatory room). Several recordings have been performed for each patient (both in On and Off condition) and all the tests have been video recorded. The patients' performances have been evaluated and scored using validated clinical scales during the recording sessions and also by analysing video recordings. In parallel, technical partners have studied the raw motor data coming from the devices and have found the right algorithms to detect and quantify tremor, dyskinesia, bradykinesia, gait impairment and FOG episodes. By comparing the results coming from the symptoms quantification and detection to the clinical scores given by doctors, we found a high accuracy in symptom recognition. For example, the gait algorithm is able to discriminate patients without gait impairment from patient with gait impairment with an accuracy of 91% and also regarding FOG detection, 90% of the measurements have been correctly detected as either having FOG or no FOG. The false-positive rate was 6%, the false-negative rate 4%. Analyzing tremor algorithm, we found a high correlation between estimated Tremor UPDRS amplitude and constancy, compared to those scored by clinicians. Dyskinesia detection accuracy varies from 88% with a 5 minutes time window a 98% for a 30 minutes window. The dyskinesia classification between slight/mild and moderate/severe had an accuracy of 92%. During the Pilot study, also the cognitive App has been developed and tested, with the achieved goal of gathering useful feedback by patients regarding possible improvements of test/games functionality and app usability. Also, for the Voice Recognition App a sufficient amount of audio recordings has been gathered, in order to feed algorithm that is now able to analyze patient's voice and evaluate the degree of vocal impairment in terms of UPDRS subitem 3.1 estimation, with a good sensitivity for Off and On conditions. This is the first step for a more ambitious goal, that aims to perform a "Sentiment analysis" by recognizing selected words and parameters during patients' free speech. In this way it will be possible, for example to estimate the degree of depression or anxiety.

Given these promising results, a Multicentric Study has been planned to test PD_manager system at patient's home and assess its acceptability and usability, compared to current gold standards for motor symptom home-based monitoring. We have recruited a total of 136 couples of patients and carers, that, given the clinical characteristic reported, represents a good sample of moderate-advanced PD. It was crucial to test PD_manager on patients with moderate-advanced disease because is exactly in this stage that a monitoring system could give the maximum benefit in terms of standard care improvement. As depicted in the graph PTIQ1 (Fig. 16), patients in PD_manager group tend to consider the system quite easy to use, while some patients in diary group consider the diaries quite difficult or very difficult to use. This suggests that the system has been accepted and quite well tolerated during the intervention period of two weeks in their everyday life. The ease of use is also reflected by the low rate of drop-out occurred in the study and by the high compliance in wearing the devices proposed. PTIQ2 (Fig. 17) shows how in both groups the majority of patients interact with the monitoring for less than 30 minutes every day. This is much evident when considering only diaries group, in fact there is a relevant quote of patients in PD_manager group that spend more than 30 minutes or even more than 2 hours per day using the monitoring system. This suggest that patients were positively involved in using the system, reflecting a higher compliance if compared to diaries which were, quite often, hard to fill on time and with a good accuracy. PTIQ3 (Fig. 18) and PTIQ4 (Fig.19) indicated how for both groups a monitoring system could be quite helpful for self-management of the disease. The analysis did not show any difference between PD_manager system and Symptoms Diary about giving useful information to patients for their self-management. Both systems were evaluated as useful, however we must consider that patients were asked to fill a diary, and most of them do not use such technique in the everyday life. The majority of diaries filled contained different gaps and the bias related to the self-assessment should be always taken into account. On the other side PD_manager might not have shown a difference because patients were not allowed to see their own data during the Study. However, there was a good consideration regarding the usefulness of monitoring techniques. This shows how important could be a monitoring system for PD patients, no matter if based on diaries or on automated mHealth system, in order to give information on their clinical status. In PTIQ5 (Fig. 20) is depicted the distribution of patients based on the perceived level of usefulness for interaction with doctors. There are not clear differences between the two groups, but for both the majority find that the systems could be very or at least slightly useful in facilitating their interaction with doctors. The PTIQ7 (Fig.21) analysis observed how almost all patients would suggest a

monitoring system (diaries or PD_manager) to another patient. However, the significant association between the high recommended value of the system used and the PD_manager group, might indicate how patients trust and promote new innovative and automatic systems for monitoring the clinical status of Parkinson's disease. PTIQ8 (Fig. 22) results showed how people who have tried the PD_manager system, trust the innovative technique for monitoring their symptoms. They're more likely to use a similar system if it would be present on the market and if the doctor would advise them about using it. PTIQ9 (Fig.23) graph shows the distribution of the desired system to try before the randomization. There is a homogeneous distribution between patients from diary group, while the majority of patients in PD_manager group desired to try PD_manager system. PTIQ10 graph (fig. 24) shows the results of a judgement on which of the two systems would be more helpful, no matter which one the patient has tested. Interestingly also the majority of patients that tried diaries said that PD_manager would be better, while only a few patients from PD_manager group said that diaries would be better. The degree of agreement was found to be high for all the opinion emerging about the ease of use and the usefulness of information related to the two systems proposed. Although Caregivers tend to have a less degree of agreement about the willingness of using PD_manager in the future. On the other hand, interestingly for the Symptoms Diary Group, Caregivers show a low degree of accordance with patients about re-using the same system, showing as much more oriented in trying also an innovative mHealth system. Concerning the attitudes toward technology and the positive expectation toward PD_manager system resulted in a major influence in giving more positive ratings regarding the usefulness of information, whether no other relationships where found to be influencing the rest of opinions. Finally, the analysis of subcomponent showed how the ease of use was less accentuated for the smartphone and the sensor insoles, while the wristband resulted to be more appreciated. These results are in line with the usage and compliance data and indicate how different kind of technology should be differently address in order to obtain a good user experience. The wristband resulted to be a wearable device for meeting the requirement of quality movement data gathering and good acceptance and wearability. The smartphone werability – used in the study both as gateway and application - might be improved in terms of clarity and intuitive interaction and access to the different functionalities of the app (e.g. user interface designed for reducing the impact of motor deficits). The sensor insoles might not be easy to use in the everyday life context for prolonged period of time, however the high technical performance in detecting walking abnormalities and freezing of gait, showed during the validation study, makes the sensor insoles a more

appropriate and useful device for a short-time assessment. Motor symptoms diary and non-motor symptoms diary didn't show difference in ratings in any of the area explored. Patients have positively evaluated such kind of technique for self-monitoring, however despite the consistency of the answer, both diaries showed gaps and missing data, which do not overlap with the opinion given at the end of the trial. We might say that completing a daily diary it's easy to use, it's useful in providing information to the doctor, whilst perpetrating such task for longer period of time could affect the quality and reliability of data collected. From the usage analysis, we found a higher adherence in patients with higher UPDRS scores, in particular in those with high UPDRS II score, that evaluates daily living impairment. This is reasonable, since they are eager to provide more data to their clinicians and receive better management of their symptoms. This is even more clear when considering only patients that have motor problems with an impact on daily life activities. One of the most interesting finding is that 2 out of 3 items are consistent and are directly linked to the feeling of pain and/or discomfort which was observed in patients with low usage of the devices (even among patients with lower total UPDRS). Pain is a common, but perhaps unexpected, non-motor symptom of PD. At least 55% of PD patients can experience some form of discomfort during the course of their disease. Usually, pain is more frequent in women and in subjects with medical conditions that predispose to painful symptoms. However, some types of pain are related to Parkinson's motor or non-motor symptoms, for example sleep/fatigue disturbances or mood/cognition disorders. Pain, like most PD symptoms, can fluctuate, in fact an amount of PD patients reports a positive pain response to assumption of dopaminergic medications. This kind of patients are usually more affected by dystonic pain, characterized by cramps and muscular pain, that is generally worse during Off periods. It is possible that in patients with low motor disability, pain represents an obstacle for the compliance of wearable devices usage. The other finding is that worse perceived patient's self-rated health status the day of study inclusion which of course is influenced by pain, can be related to lower usage of PD_manager and similar systems. The motor data gathered during the Multicentric study underwent to further evaluation by the engineers, to test the efficacy of the algorithms developed during the Pilot study. The result is that PD_manager can be used to accurately discriminate patients with mild to severe Tremor (UPDRS subitem 3.18 >1) and Dyskinesia (UPDRS subitem 4.1 >1) versus patients with no or slight tremor and dyskinesia (Area under the curve is 97% and 92% respectively). The number of patients with UPDRS subitem 4.1 >1 (mild to severe dyskinesia) was limited. Finger tapping test results are also significant and correlated with UPDRS subitem 3.4. The correlations between the PD_manager

system and the patient-reported scores for freezing and gait are medium (about 0.4) but comparable to the doctor-rated scores and the patient-reported scores correlations (approximately 0.5). To sum up PD_manager modules can be used in for PD symptom home-monitoring for making informed decisions and providing better and personalized treatment. However, the efficacy of PD_manager in terms of modification of drug treatment or changes in other therapeutic choices cannot be assessed the moment, since the platform has not yet the C.E. approval for medical device. Any intervention that can influence patient's safety can't be applied if based on information obtained by devices or software that had not yet received this approval, so this will be one of the next steps of the PD_manager development.

PD_manager system has several possible exploitations. The main application could be in clinical routine, allowing clinicians to obtain objective data about motor and non-motor features, and therefore giving an help in taking therapeutic decisions, also with possible reduction of time spent per single patient in ambulatory room. A possible scenario could be represented by a 2 steps visit, where in the first the clinician modify the drugs plan and then gives PD_manager to patient. The patient uses the System at home for a limited period of time (e.g. 2 weeks) and in the meantime his/her data are sent in cloud and stored on a safe server, where the clinician can access. In this way the clinician can assess in real time the efficacy of the pharmacologic modifications and eventually change the therapeutic suggestions during the second visit, when de patient came back to return the devices. During PD_manager Project, a DSS system has also been developed. The DSS can put a "red flag" on symptoms that appear to be particularly severe or troublesome for patient and that must be more accurately evaluated by clinician. The DSS has been developed based on the therapeutic decisions of expert clinicians. The classification accuracy, measured on the PPMI data, was generally quite low There are many possible reasons for that, from a high variability and inconsistency of decisions captured in the PPMI, to the fundamental difference between normative knowledge, which is captured in DEX models, and descriptive, real-life performance, which is reflected in the PPMI. For the PD_manager DSS, which is aimed at identifying situations that require medical response rather than giving instructions of how to react, the normative aspect seems more relevant. When measured in comparison with physicians on selected use cases, the performance of the models turned out to be much better. Obviously, PD_manager, like any other medical monitoring system, can't be used as a surrogate of medical examination or patient's interview. From

patient's perspective, PD_manager can be used as a useful tool for self-monitoring and self-care, for example watching at the educational video gallery or annotating the most disabling symptoms. The system can be implemented also with a pill administration reminder, that helps patient and caregiver on maximizing the adherence to pharmacological therapy suggested. Unfortunately, at this level of development, the pill reminder is considered an intervention that can influence patient's safety, so for the reasons explained above, this functionality has not yet been tested. However also some critical issues emerged from the multicentric study. For example, all involved actors need some time to be trained before using the system for the first time. This time has been estimated in at least one hour, in particular when considering patients with limited familiarity to smartphone technology, in fact we observed that some patients were not able to use the smartphone while they had no problem wearing the band and the insoles. The system should be plug and play and independent from charging for as long as possible, at the moment the duration of home recordings is limited mainly by the data storage in insoles' built-in memory. Technical support should be provided at least at the beginning of any large-scale deployment. In a possible scenario of a clinical use of PD_manager, delivery and return of the devices should be organized also through a courier agency, especially for patients living in remote areas. Also, the fact that many patients tend to not wear closed shoes during summer season must be taken into account for a correct insoles' usage. A possible pitfall of the System could be represented by cognitive impairment that commonly affects patients in advanced stages of the disease and that could reduce its efficiency in a context of real-life usage. The selected exclusion criteria cannot allow to have objective data about this aspect since we have purposely decided to not include cognitive impaired patients in this study. However, we can hypothesize that also in demented subjects, an automated way to detect motor symptoms could be anyhow more effective than self-reported symptoms, since for these patients is even more difficult to correctly report their symptoms and they surely cannot properly fill the home diaries. Obviously, in this particular subset of patients, the presence of a caregiver will be essential to wear devices and for their management at home. Another issue that could affect the reliability of the System is the grade of education. We have observed no differences in terms of years of educations when dividing the PD_manager group in high and low usage groups, pointing out that the usage is not influenced by education. However, this aspect needs to be taken into account when an analysis of efficiency/efficacy of the System will be performed. We also have to consider that this kind of monitoring system is designed to be used by patients of future, that probably now are in their 50s or 40s. This population will be

much more familiar with technological devices than over 65 years of age patients that have currently tested the System.

A cost analysis has also been performed by health economics partners in University of Surrey (UK). Costs are obviously higher for PD_manager group because of technical devices and software used for system set up. In particular the main costs are represented by insoles and Moticon software, however they fall if spread on more patients, since software costs are fixed and devices can be re-used by many patients. Costs of diaries usage are almost negligible. It is expected, however, that with future refinements in the technology and scaling up of use, costs per patient will decline. In addition, health professionals will become more familiar with the use of the technology and the time that they spend on managing and interpreting the data will decline. Modifications to the technology following feedback from early testing will result in improvements in features such as comfort and ease of use, which coupled with marketing initiatives will result in increased uptake and the opportunity to capitalize on economies of scale in production. An effective costs/advantages analysis can be performed only in the context of a study that evaluates the efficacy of the systems in terms of optimization of therapies and reduction of consultation time on the basis of data generated by PD_manager system

In clinicians' study, a good attitude towards Clinician App was observed: the app was found easy to use and relevant in terms of information provided for medical management of PD. Only two clinicians were skeptic about the usefulness of PD_manager in clinical routine, but we have to consider that someone of them obtained low scores at the TAMM scale and 1 of them reported to never use a smartphone in daily life. However, the App was tested only on 12 clinicians and larger sample should be obtained to perform a better data analysis.

In conclusion, this PhD study generated new insights into the use of wearable sensors in daily living by PD patients, and given the potential of the data gathered, it will make further contributions with significant impact on the integration of self-collected information into clinical practice for PD patients. This project represents the first step towards building a reliable system that integrates real-life information into clinical decisions. The next step for PD_manager will be an evaluation of effectiveness of medical intervention based on data coming from the mHealth platform, compared to effectiveness of traditional management based only on data reported by patients and clinical examination.

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