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**A HOLISTIC APPROACH TO ASSESS THE FEASIBILITY OF TELEHEALTH FOR
PARKINSON'S DISEASE MANAGEMENT**

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A HOLISTIC APPROACH TO ASSESS THE FEASIBILITY OF TELEHEALTH FOR
PARKINSON'S DISEASE MANAGEMENT

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Acknowledgements

Abstract

This work of thesis has been entitled “*A holistic approach to assess the feasibility of telehealth for Parkinson’s disease management*” since it is aimed at exploring the feasibility of telehealth, understanding it as the use of technology and related services to deliver a disease management at distance, to provide a tool for the management of Parkinson’s disease (PD). The term *holistic* has been incorporated in the title since it tried to cover not only the feasibility of developing the appropriate technology for the continuous monitoring and assessment of the disease remotely and in unsupervised environment, i.e. at patients’ homes, but also because it covers the feasibility study from a wider perspective by incorporating the analysis of human factors and Health Technology Assessment (HTA). These two topics are aimed at incorporating the perspective and views of the patients and health experts and provide data for policy-makers, health care managers but also to the developers and researchers about the potential uptake of telehealth for Parkinson’s disease in the current clinical practice. This work was framed within the European project PERFORM, on this research project a Body Area Network (BAN) of wearable sensors was designed and developed for the automatic detection and quantification of the motor symptoms of PD which was then transmitted to a hospital platform also developed within the project. There, the motor assessment was analysed together with other sources of information also collected with the PERFORM system at patients’ homes such as food and drug intakes. Finally, all this information provided clinicians with suggestions about treatment modification when needed. On this context, the research work presented on this thesis is divided into three independent parts.

The first part covers the use of the raw data collected with the BAN for the automatic assessment of the bradykinesia and the gait disturbances. On this regards, two different methodologies that have been previously explored on supervised environments were explored to be translated in the context of a home telehealth platform. In the gait case, the inverted pendulum model was used to estimate different gait features such as velocity, step frequency and step length. Other metrics like arm swing and entropy were also extracted. The feasibility study tried to explore whether the proposed BAN was feasible for the implementation of such algorithms. For the bradykinesia case, a different non-linear approach was followed, specifically machine learning has been used, exploring diverse configurations in order to find about the best setup for bradykinesia assessment, then a meta-analysis methodology was proposed to improve the outcomes of the machine learning algorithms. The results presented for the bradykinesia assessment showed the best outcomes taking the signals coming from wrist sensor as input while the subject was performing some hand movement, on this case the accuracy of the classifier achieved up to 86.48% of correct classified instances. The accuracy in the bradykinesia severity detection while the subjects were walking was slightly lower (ranging from 70.83% to 75%). In all the cases, the combination of the rms+range features showed the better performance. Using the proposed meta-analysis method an average of 74.4% of agreement between the clinical examination and the system outcomes was achieved, ranging from 91.9% to a 48.8%. To study the gait performance, SampEn was evaluated as a metric to characterize the degradation of the gait performance confronting PD patients and healthy subjects, the values of SampEn were significantly different and provide useful information especially in the waist sensor ($p<0.01$) and the left arm ($p<0.01$), right arm ($p=0.05$). Regarding the estimation of the gait features for PD, the mean error of Step frequency, Stride Length and Speed, calculated on 30 trials and 10 subjects are respectively: $3.36\%\pm 2.57$, $7.31\%\pm 4.69$, and $7.77\%\pm 5.34$. The average data loss satisfied that in all cases more than 95% of the data is successfully transmitted. Nevertheless, analysing the average burst length and the standard deviation of these values we found burst of up to 143.04 ± 240.10 ms. A burst of these characteristics in the middle of the transmission would compromise seriously the performance and accuracy of the system. Nevertheless, adding the most frequent burst length as an extra

measure and observing the raw data we can easily identify that 64ms is the most common burst in all the cases, moreover the longest bursts are always at the beginning of the session i.e. during the start-up process. That means that waiting for all the sensors to be properly connected before start computing the gait features will remove the longest burst errors.

The second part of this thesis addresses the human factors related to the use of a telehealth platform for PD. Particularly, the work encompassed on this thesis describes a methodological approach to extract and analyse the PD patients feedback regarding the wearability of the PERFORM system. A combination of several methodologies already validated have been emplaced, specifically the REBA, Borg and CRS scales have been used in combination with a body map when needed. A total of 32 PD patients have been involved in this study showing an excellent acceptance of the PERFORM system in wearability terms. The overall result of the evaluation can be broken down in the subsequent marks: average perceived exertion score (0.71 on the Borg CR-10 scale), average posture score (0 based on the REBA scale), average localized pain/discomfort score (0.11 on the Borg CR-10 scale), average emotion score (1.4 on the CRS scale), average attachment score (2.5 on the CRS scale), average harm score (0.15 on the CRS scale), average perceived change score (0.67 on the CRS scale), average movement score (0.59 on the CRS scale) and average anxiety score (1.63 on the CRS scale). Each individual component of the wearability assessment can be labelled as low level of effect according to the guidelines provided by each of the methodologies.

Finally, the last part of the thesis is aimed at identifying tools available and viable to carry out an early HTA on telehealth systems for Parkinson's disease (PD) management and apply such methodologies to assess the PERFORM system as a case of study. The whole chapter is divided in two parts addressing two complementary works which try to provide two complementary points of view. The first part is aimed at identifying the elements that a telehealth system for PD management should satisfy to be effective and aligned with the users' needs as well as to understand if clinicians and technicians share a common opinion when evaluating these systems. Instead, the second part provides a methodology to estimate the potential economic impact, in terms of cost-effectiveness, of a real implementation of telehealth systems for PD management. After the exploration of the available tools for early HTA two methodologies were selected. The first one, called Analytic Hierarchy Process (AHP), allows the elicitation of the user needs and the definition of a framework for the evaluation of telehealth solutions for Parkinson's disease patients. 16 experts in the domain both with clinical and technical background were involved in the study. The second part of the chapter explores how the use of Markov models with a minimal number of states were used to perform "what-if" and finally, to simulate and estimate potential scenarios for the economic impact, in terms of cost-effectiveness, of a telehealth platform. Then, this approach was used to estimate the potential cost-effectiveness of the PERFORM project. Finally, a sensitivity analysis will be carried out. According to the results of the responders, the three most important user needs are *Increase the wearability acceptance* (0.102), *Increase the self-management support* (0.093) and *On/Off fluctuations detection* (0.085), based on the values from the Global Weights (GW). In a second level of importance were found *Increase patient & carers knowledge* (0.080), *Assist care givers* (0.070), *User-friendly interfaces* (0.068), *Motor symptoms assessment* (0.064) and *Increase patient Quality of Life* (0.063). The agreements between the responders of the technical and clinical groups showed a significant correlation between both, $\rho = 0.590$ ($p=0.012$). Regarding the use of Markov modelling, six general "what-if" scenarios were simulated providing a general overview of how inputs variations could impact the ICER values. These scenarios provide a quantitative reference framework for any health technology related to Parkinson's disease and could be useful to understand and to orientate the research, particularly in early stages of development, towards an efficient cost-effectiveness path. Then, the PERFORM system was used as case of study with the Markov analysis. It was confronted with the base case and the cumulative costs and QALYs were calculated for each one and the ICER was calculated at year 5. The ICER values estimated by the model are 6397.36 for the societal perspective and 8977.20 for the third party perspective. These values suggest that PERFORM will not be a cost-saving technology (positive ICER) but these values are below most of the ICER thresholds commonly accepted worldwide (10,000€/QALY). Finally, by placing the PERFORM innovation from the societal and third party perspective in the Δ QALY- Δ C plane it was possible to see the margin in incremental cost to the different ICER thresholds. Taking the 30,000€/QALY as reference, the PERFORM system has a margin of 20855.28€ incremental cost in the societal perspective and 18575.73€ incremental cost in the third party perspective. A sensitivity analysis was also performed to explore the robustness of the results and the

limitations of this approach were properly identified.

Keywords

Telehealth, wearables, Body Area Network (BAN), Parkinson's disease (PD), mHealth, motor assessment

Resumen

Este trabajo de tesis ha sido titulado “*A holistic approach to assess the feasibility of telehealth for Parkinson’s disease management*” ya que pretende abordar la viabilidad de utilizar una plataforma de telesalud, definiendo esta como el uso de la tecnología y los servicios asociados a ella para la gestión de una enfermedad de forma remota, con el fin de proveer una herramienta que permita la gestión de la Enfermedad de Parkinson (EP). El término holístico ha sido incorporado en el título ya que este trabajo pretende cubrir no solo la viabilidad del desarrollo de la tecnología apropiada para la continua monitorización y evaluación de la enfermedad de forma remota y en un entorno no supervisado, esto es, en la propia casa de los pacientes, sino que también pretende estudiar la viabilidad desde una perspectiva más amplia incorporando un análisis de factores humanos y *Health Technology Assessment (HTA)*. Estos dos temas pretenden incorporar el punto de vista de los pacientes y los expertos y proporcionar la información necesaria a los responsables de la elaboración de políticas y regulaciones, así como a los gestores, desarrolladores e investigadores sobre el potencial de dicha tecnología para ser realmente incorporada a la práctica clínica. Este trabajo está enmarcado dentro del proyecto europeo PERFORM. En dicho proyecto, una Body Area Network (BAN) de sensores vestibles fue diseñada y desarrollada para la detección automática y cuantificación de los síntomas motores de la EP, que después eran enviados a un módulo instalado en el hospital y también desarrollado dentro de dicho proyecto. Allí, la evaluación motora era combinada con otras fuentes de información también recogidas con el sistema PERFORM en la casa de los pacientes como, por ejemplo, información sobre las comidas y los medicamentos. Finalmente, la plataforma para los neurólogos proporcionaba sugerencias acerca de posibles cambios en el tratamiento utilizando un motor de reglas y en función de la información recogida. Basado en esto, el trabajo contenido en esta tesis se puede dividir en tres partes.

La primera parte cubre el uso de las señales recogidas con la BAN para la evaluación automática de la bradiquinesia y alteraciones en la marcha. Dos metodologías, previamente validadas en entornos supervisados, fueron empleadas y la viabilidad para trasladarlas a entornos no supervisados fue estudiada. En el caso del estudio de la marcha, se utilizó el modelo del péndulo invertido para estimar diferentes características de la marcha como, por ejemplo, la velocidad, frecuencia de paso y la longitud de paso. Otras métricas como la frecuencia de braceo y la entropía de la señal también fueron calculadas. El estudio de viabilidad se centró en analizar si la BAN propuesta podía calcular dichas características de forma correcta. En el caso de la bradiquinesia, el procesado fue diferente, empleando una aproximación no lineal basada en algoritmos de aprendizaje automático. Después, una meta análisis fue propuesta de cara a mejorar los resultados de los clasificadores. Los resultados muestran que para la evaluación de la bradiquinesia las señales provenientes de los sensores en las muñecas ofrecían los mejores resultados. Concretamente, los clasificadores lograron hasta un 86.4% de instancias correctamente clasificadas. Analizando las señales cuando los sujetos están caminando la precisión es un poco inferior, fluctuando desde un 70.83% hasta un 75%. En ambos casos la combinación de rms+rango fue la que mostró mejores resultados. El meta análisis propuesto logró un 74.4% de acierto tomando como referencia la examinación clínica llevada a cabo por un neurólogo, fluctuando este valor desde un 91.9% hasta un 48.8%. En el estudio de la marcha, la entropía muestreada (SampEn) fue evaluada como una métrica que permitiese caracterizar la degradación de las señales de movimiento. Para ello se compararon muestras recogidas en sujetos sanos y pacientes de la EP, los valores de SampEn mostraron ser significativamente diferentes, especialmente en el caso de las señales provenientes del sensor situado en el cinturón ($p<0.01$) y en los brazos ($p<0.01$) y ($p=0.05$). Sobre la extracción de los parámetros de la marcha, los errores medios para caracterizar la frecuencia de paso, la longitud del paso y la velocidad fueron $3.36\%\pm 2.57$, $7.31\%\pm 4.69$ y $7.77\%\pm 5.34$ respectivamente calculados en 30 muestras de 10 pacientes. Analizando la pérdida de paquetes se encontró que en todos los casos más del 95% de los paquetes fue correctamente

transmitido. Un análisis más detallado sobre los errores de transmisión de ráfaga mostró errores de este tipo con una media de 143.04 ± 240.10 ms. Este tipo de errores de ráfaga podría comprometer significativamente el buen funcionamiento del sistema. Sin embargo, analizando más en detalle este tipo de errores se observó que el error de ráfaga que con más frecuencia aparecía era de 64 ms en todos los casos y los que los errores de ráfaga más largos se encontraban al principio de la sesión, es decir durante la fase de conexión de los sensores. Esto quiere decir que esperar a que todos los sensores estén correctamente conectados antes de comenzar con el análisis de los datos elimina los errores de ráfaga más críticos del sistema.

La segunda parte de esta tesis se centra en el estudio de los factores humanos en relación con el uso de un sistema de telesalud con pacientes de la EP. Particularmente, el trabajo incluido en esta tesis presenta una metodología para la extracción y análisis del *feedback* proporcionado por los pacientes en relación con el grado de *vestibilidad* y aceptación del sistema PERFORM. Una combinación de diferentes metodologías validadas fue utilizada, en concreto las escalas REBA, Borg y CRS fueron empleadas en combinación con un mapa corporal. Un total de 32 pacientes fue involucrado en este estudio. El resultado global de la evaluación fue muy positivo y se puede descomponer en las siguientes valoraciones: esfuerzo percibido medio (0.71 en la escala Borg CR-10), puntuación de postura media (0 basado en la escala REBA), dolor localizado medio (0.11 en la escala Borg CR-10), puntuación media de emoción (1.4 en la escala CRS), puntuación media de atracción (2.5 en la escala CRS), puntuación media de daño (0.15 en la escala CRS), puntuación media de cambio percibido (0.67 en la escala CRS), puntuación media de movimiento (0.59 en la escala CRS) y puntuación media en ansiedad (1.63 en la escala CRS). Cada una de estas puntuaciones individuales fue categorizada como nivel bajo según las guías y trabajos previos.

Finalmente, la última parte de la tesis se centra en la identificación de herramientas para llevar cabo una HTA en la fase temprana de desarrollo de un sistema de telesalud para EP y aplicar dichas herramientas para llevar a cabo un estudio utilizando el sistema PERFORM como caso de estudio. Dos herramientas complementarias fueron seleccionadas y empleadas: la primera de ellas trata de identificar de forma metodológica los requisitos que un sistema de telesalud para la gestión de la EP debe presentar para ser efectivo y alineado con las necesidades o requisitos de los usuarios. Este estudio también tenía como objetivo analizar si expertos con un perfil clínico y técnico tienen una visión común sobre cuáles son los requisitos clave de este tipo de tecnología. La segunda parte está centrada en el análisis del potencial económico, en términos de coste-efectividad, de este tipo de sistemas. Después de un análisis de las herramientas disponibles, para el primer caso se seleccionó el *Analytic Hierarchy Process* (AHP) que permitió la extracción de las necesidades de usuario y la definición de un marco de evaluación en función de dichas necesidades. 16 expertos en el campo, tanto con perfil técnico como clínico, participaron en el estudio. Para la segunda parte se empleó un modelo basado en cadenas de Markov para explorar diferentes escenarios y finalmente simular y estimar el potencial impacto económico en cada uno de estos escenarios, en términos de coste-efectividad, para los sistemas de telesalud para EP. Por último, esta herramienta fue empleada para estimar el potencial impacto económico del proyecto PERFORM. Dichos análisis fueron completados con un análisis de sensibilidad. De acuerdo con los resultados de los participantes, los tres requisitos de usuario más importantes son *Incrementar la aceptación de los sensores vestibles* (0.102), *Incrementar el apoyo a la auto-gestión* (0.093) y *Detección de las fluctuaciones On/Off* (0.085), basándonos en los valores de los *Global Weights* (GW). En un segundo escalón de importancia encontramos *Incrementar la educación de pacientes y cuidadores* (0.080), *Apoyo a los cuidadores* (0.070), *Interfaces amigables* (0.068), *Evaluación de los síntomas motores* (0.064) e *Incremento en la calidad de vida* (0.063). Además, las repuestas de los grupos clínicos y técnicos mostraron un alto grado de similitud, $\rho = 0.590$ ($p=0.012$). En cuanto al uso de los modelos de Markov, 6 “what-if” escenarios fueron simulados, generando una visión general de cómo las fluctuaciones de los diferentes parámetros de entrada afectan a la salida, esto es, al ICER obtenido gracias a la implementación de una nueva tecnología. Esta información define un marco de referencia que puede ser empleado por cualquier tecnología relacionada con la EP para explorar de forma preliminar los efectos que la adopción de dicha tecnología puede tener en términos de coste-efectividad. A continuación, el sistema PERFORM fue utilizado como caso de estudio empleando el modelo de Markov. Los valores de ICER estimados en el año 5 por el modelo fueron 6397.36 desde la perspectiva social y 8977.20 desde la perspectiva de un tercero. Estos valores sugieren que la adopción del sistema PERFORM no ahorraría dinero (ICER positivo) pero estos valores están por debajo de los umbrales comúnmente aceptados para la adopción de una nueva tecnología (10,000€/QALY). Por último, colocando la innovación propuesta por el

sistema PERFORM en un plano $\Delta\text{QALY}-\Delta\text{C}$, es posible calcular el margen del coste incremental que hay con cada uno de los umbrales ICER. Tomando por ejemplo el umbral 30,000€/QALY como referencia, el sistema PERFORM muestra un margen de 20855.28€ de coste incremental desde la perspectiva social y 18575.73€ desde la perspectiva de un tercero. El análisis de sensibilidad fue utilizado para explorar la robustez de los modelos y sus limitaciones.

Palabras clave

Telesalud, *vestibles*, Enfermedad de Parkinson (EP), Red de sensors, mHealth, evaluación motora

List of acronyms

AAL Ambient Assisted Living

ADL Activities of Daily Life

A&E Accident and Emergency

AFTT Alternate Finger Tapping Test

AmI Ambient Intelligence

ANN Artificial Neural Network

aPD Advanced Parkinson's Disease

API Application Programming Interface

BAN Body Area Network

BoD Burden of Disease

BPD Burden of Parkinson's disease

BS&AN Body Sensor & Actuator Network

BRF Bavarian Research Foundation

CBA Cost Benefit Analysis

CCM Chronic Care Model

CDS Continuous Dopaminergic Stimulation

CEA Cost Effectiveness Analysis

CI Confidence Interval

CKC Convolution Kernel Compensation

CMA Cost Minimization Analysis

CoM Centre of Mass

COMT Catechol-O-methyltransferase

CoQ10 Coenzyme Q10

List of acronyms

CPU	Central Processing Unit
CT	Computerized Tomography
CUA	Cost Utility Analysis
DALY	Disability-Adjusted Life Years
DB	Database
DICOM	Digital Imaging and Communication in Medicine
DNN	Dynamic Neural Network
DS	Dynamical System
DTW	Dynamic Time Warping
EC	European Commission
ECS	External Cueing Stimulation
EDA	Electro dermal Activity
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalography
EHR	Electronic Health Record
EOG	Electrooculography
EPMA	European Association for Predictive, Preventive and Personalised Medicine
ERC	External Rhythmic Cueing
ERS	External Rhythmic Stimulation
ET	Essential Tremor
EU	European Union
FDA	Federal Drug Administration
FFT	Fast Fourier Transform
fMRI	functional Magnetic Resonance Image
FP7	Seventh Framework Programme for Research
FSR	Force Sensitivity Resistor
FTT	Finger Tapping Test
FoG	Freezing of Gait
GBD	Global Burden of Disease

GP	General Practitioner
GPI	Globus Pallidus interna
GCM	Guided Care Model
HCI	Human Computer Interaction
HL7	Health Level 7
IADL	Instrumental Activities of Daily Living
ICD	International Classification of Diseases
ICT	Information and Communications Technology
IDE	Integrated Development Environment
IMU	Inertial Measurement Unit
IP	Internet Protocol
IPU	Integrated Practice Unit
ISO	International Organization for Standardization
IT	Information Technology
KOL	Key Opinion Leaders
KNN or k-NN	K-Nearest Neighbour
NMF	Non-Motor Fluctuations
NOS	Not Otherwise Specified
MAO-B	Monoamine oxidase B
MRI	Magnetic Resonance Imaging
MT	Music Therapy
LDA	Linear Discriminant Analysis
LCD	Liquid-Crystal Display
LCIG	Levodopa-Carbidopa Intestinal Gel
L-DOPA	Levodopa
LSVT	Lee Silverman Voice Treatment
PAN	Personal Area Network
PCA	Principal Component Analysis
PD	Parkinson's disease

PET	Positron Emission Tomography
PFT	Paced Finger-Tapping
PM	Personalized Medicine
PMC	Personalized Medicine Coalition
PMD	Patient Monitoring Device
POC	Point-of-Care
PNR	Pulse-to-Noise Ratio
QoL	Quality of Life
RAS	Rhythmic Auditory Cueing
RAS	Rhythmic Auditory Stimulation
REM	rapid eye movement
RFID	Radio-Frequency Identification
PHC	Personal HealthCare
RLS	Restless Legs Syndrome
RoI	Return of Investment
RoM	Range of Motion
RMS	Root Mean Square
ROC	Receiver Operating Characteristic
RSC	Rhythmic Somatosensorial Cueing
RSS	Rhythmic Somatosensorial Stimulation
SD Card	Secure Digital Card
SES	Summary Effect Sizes
SNN	Social Networks
SPECT	Single-photon emission computed tomography
SQL	Structured Query Language
SSL	Secure Sockets Layer
STN	Subthalamic nucleus
SVM	Support Vector Machine
SVR	Support Vector Repression

List of acronyms

SW Software

TFR Total Fertility Rate

TUGT Timed Up and Go Test

UCD User-Centred Design

UI User Interface

UK United Kingdom

UML Unified Modelling Language

UML Unified Modelling Language System

UN United Nations

ULMP Upper Limbs Motor Performance

UPDRS Unified Parkinson's Disease Rating Scale

US United States

USA United States of America

VAS Visual Analogue Scale

VIN Ventral intermediate nucleus

VR Virtual Reality

WHO World Health Organization

WLAN Wireless Personal Area Network

YLD Years Lost due to Disability

YLL Years of Life Lost Contents

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“Life is short, and Art long; the crisis fleeting; experience perilous, and decision difficult. The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants, and externals cooperate.”

Hippocrates, Aphorisms
400 BC

Chapter 1 Introduction

During the last decades, the terms of eHealth and telehealth have been around and many research works and efforts have been dedicated to these fields. Generally speaking, eHealth and telehealth are understood as the use of any kind of Information and Communication Technology (ICT) applied in the health context, understanding health in its wider acceptance, thus involving also prevention and promotion of health. Telehealth and eHealth have shown to be feasible for the improvement of diagnosis, treatment, management and follow-up of quite different patients, covering from communicable to chronic diseases. Nevertheless, many of these initiatives evolve up to a research prototype and fail to go a step forward. Usually, when a new technology is under study, it is evaluated under two main criteria: technical feasibility (i.e. to understand if from the technical point of view it is possible to build a solution that matches the expectation) and clinical validation (i.e. to certify whether a given intervention using a new device, tool or methodology has a specific impact on a specific group of individuals). Yet, the health care field is a complex scenario where many stakeholders interact together, and also, as it will be discussed within this thesis, to prove the technical feasibility and the improvement of health outcomes through a clinical validation does not guarantee the acceptance of a new technology in the clinical practice. For this reason, the scope of this thesis is wider, trying to cover two more facets, the compliance acceptance of the system – as a mean to understand the acceptance of the system by its final users – and the Health Technology Assessment (HTA) of the system – basically, it is aimed to understand if this kind of system makes sense and fits in the current health care landscape. With this holistic approach, this thesis is aimed at understanding the feasibility of using telehealth as a tool for Parkinson’s disease management.

1.1 Framework

A significant part of this thesis is based on the results and on the experience acquired within the research project PERFORM (a complete description of the project and its outcomes and results is provided in the section 4.4.17 *PERFORM*), partially funded by the European Commission (EC) under the 7th Framework Programme (FP7) of research and innovation. PERFORM has been used as two different ways for the elaboration of this thesis, firstly, some of the research activities carried out within PERFORM and their results have conformed the chapters 6 and 7 regarding motor and wearability assessment. In these cases, the framework of the research project has provided an optimal environment for the design, development and validation of the algorithms and methodologies to involve in those research tasks by putting together relevant stakeholders (patients, clinicians and engineers). On the other hand, due to the experience and knowledge of the project, PERFORM has been used as a case of study for the Health Technology Assessment (HTA) methodology proposed on chapter 8.

Moreover, some content of this thesis has been already published in different conference proceedings and peer-review journal. They have been adapted and they cover different topics contained within this thesis: motivation and state of the art [1]–[4], motor symptoms assessment (gait assessment [5]–[8], bradykinesia detection and quantification [9]–[11], On-Off detection [12]), wearability assessment [13], PERFORM system description and evaluation [14]–[17] and HTA [18]–[20].

1.2 Outline

The rest of the document is organized as follows:

Chapter 2 Motivation, this chapter introduces the current status of the health care systems, their limitations –

particularly dealing with chronic and long-term diseases efficiently– and then reasons how new technologies may contribute to improve these inefficiencies, even when the use and adoption of new technologies have their own limitations.

Chapter 3 Parkinson's disease, is an introduction to PD offered with special emphasis on the description of the symptoms, the description of the disease progression and the current methods for diagnosis and treatment of the disease.

Chapter 4 State of the art, offers a detailed description of different research works and innovative solutions where new technologies have been used to deal with PD patients.

Chapter 6 Methods and material, introduces the framework on which this thesis work was carried out as well as a first introduction to the methods and material used on each research topic.

Chapter 5 Hypothesis and objectives, offers a brief introduction to the methods and materials employed in the coming chapters. Nevertheless, each of these chapters will offer a more exhaustive and detailed description of methods and materials employed to facilitate the reading of this document.

Chapter 7 Motor assessment, covers the assessment and monitoring of the motor symptoms, particularly the gait and bradykinesia assessment and the feasibility of doing that using a telehealth platform at patients' homes.

Chapter 8 Human Factors, on this chapter a methodology for the wearability assessment and user compliance will be introduced and it will be used to evaluate the PERFORM system. The chapter is aimed at obtaining information about the final users' perspective regarding the usability of a wearable system for a continuous monitoring.

Chapter 9 Health Technology Assessment, this chapter explores the process of HTA in the case of emerging and novel technologies, exploring potential tools and methodologies for the early HTA of telehealth systems and applies them to the PERFORM system which is used as study case.

The last chapter, *Chapter 10 Conclusion and discussion*, offers the conclusions of the thesis and the final discussion linking the research hypothesis and research objectives with the results achieved within this work.

Chapter 2 Motivation

Significant demographics changes have been happening worldwide during the last decades with many countries involved in an ageing transformation. This new scenario, which is partially a consequence of the success of the health care systems as well as an improvement of the hygienic and nutritional conditions, brings along new challenges for the society but also for the health care systems themselves that should be transformed or evolved to this new reality and to deal efficiently with it. A particularly relevant topic is the management of chronic and long-term conditions. At the same time, the Information and Communications Technologies (ICT) have been growing during the last decades, transforming radically and suddenly many sectors and fields. Actually, ICT already contributed to improve the health care by developing diagnostic, monitoring and treatment devices. In this sense, the ICT and new technologies are an excellent ally to help the health care systems to take the next step in their evolution. The use of technologies, in fact, facilitates the creation of new tools and the optimization of processes, improving the response times and the use of resources and increasing the efficacy, quality, efficiency and the spending in the process of health care. Besides, the use of appropriate and cost-effective ICT may improve the compliance with the self-management and to provide an effective communication between patients with chronic illness and healthcare professionals to enhance care. The goal is to provide health technologies that could help health care systems to achieve appropriate cost-effectiveness levels in the management of the chronic and long-term conditions. On this regards, to aim is not only to increase life expectancy but to increase patients' Quality of Life (QoL), to guarantee the cost-effectiveness. Thus, the final goal for healthcare providers should be to improve the value for patients (where value is defined as the health outcomes achieved that matter to patients) relative to the cost of achieving those outcomes. Therefore it requires either improving one or more outcomes without raising costs or lowering costs without compromising outcomes, or both.

2.1 Sociodemographic changes and their impact in the global health

2.1.1 Population ageing

Populations are growing older in countries throughout the world regardless of their socioeconomic situation, *Figure 1*. While the populations of more developed countries have been aging for over a century, this process began recently in less developed countries, and it is being compressed into a few decades. Actually, these developing countries are facing now the so-called “double burden of disease” effect (struggle with infectious diseases, malnutrition and complications from childbirth and facing the rapid growth of non-communicable diseases at the same time) [21]. The big turnaround came with the industrial revolution, mainly because many more children survived into adulthood, thanks to better sanitation, more control over epidemics, improved nutrition and higher living standards [22]. Population aging may be seen as a success story in the world history due to the achievements on public health, medicine, hygiene and sanitation. Unfortunately, this success brings some side effects and new challenges, especially issues concerning the sustainability of families and the ability of states and communities for managing aged populations [22]. On this regards, the report “World Population Ageing: 1950-2050”, prepared by the Population Division of the United Nations (UN) [23], affords a profound analysis of the global trends in population ageing coming up with the following outcomes:

- Population ageing is unprecedented, without parallel in human history—and the twenty-first century will witness even more rapid ageing than did the century just past.

- Population ageing is pervasive, a global phenomenon. But countries are at very different stages of the process, and the pace of change differs greatly. Countries that started the process later will have less time to adjust.
- Population ageing is enduring (a stable, permanent and long-term phenomenon).
- Population ageing has profound implications for many facets of human life.

Life expectancy

Figure 1 - Life expectancy i.e. the average number of years a new-born is expected to live with current mortality patterns remaining the same. (Source: Google Public Data¹)

The global population age 65 or older was estimated at 461 million in 2004, an increase of 10.3 million just since 2003. Projections suggest that the annual net gain will continue to exceed 10 million over the next decade. Industrialized nations have the highest percentages of older people in the world today. But less developed nations also have large numbers of older citizens—and the numbers of older people are increasing rapidly [22].

2.1.1.1 The demographic drivers of ageing

In 2005 Kinsella and Phillips elaborated an exhaustive work analysing the origin and causes of the aging process [22]. This work pointed out four key factors contributing to this effect:

a) Fertility

In many industrialized nations during the last century the average number of children per woman in almost all more developed countries has been reduced below the replacement level of 2.1 children. Sustained low fertility since the late 1970s has reduced the size of successive birth cohorts and increased the proportion of older people in these countries' populations. Fertility decline in the less developed world has been more recent and more rapid. Although the aggregate Total Fertility Rate (TFR), the average number of children per woman given current birth rates, remains in excess of 4.5 children per woman in Africa and many countries of the Middle East, overall levels in Asia and Latin America decreased by 50 cent (from 6 to 3 children per woman) between 1965 and 1995. The TFR in many less developed countries is now at or below replacement level. The UN projects that, by 2050, three of every four of today's less developed countries will have below-replacement fertility. Populations with high

¹ <https://www.google.com/publicdata/directory> (Last date accessed: January 2016)

fertility tend to have low proportions of older people and vice versa. The term “demographic transition” is used to describe a gradual process of change from high rates of fertility and mortality to low rates of fertility and mortality. Figure 2 shows the evolution of the population pyramids in less and more developed countries and Figure 3 shows the forecast for particular case of the Spanish pyramid.

Figure 2 - Population Age-Sex structure in less developed and more developed countries, 1950, 1990 and 2030. (Figure source: Kinsella & Phillips 2005 [22])

b) Increasing importance of mortality

In countries where infant mortality rates are relatively high but declining, most of the improvement in life expectancy at birth results from helping infants to survive the high-risk early years of life. Reductions in maternal mortality also contribute to increased life expectancy at birth. But also, most countries today are experiencing a rise in life expectancy at older ages and even there is a tendency in the reduction of mortality rates at ages 80 and older [24], [25].

Figure 3 - Evolution of the population pyramid in Spain (Figures source: [26]).

c) Changes in Life Expectancy

Usually, increases in life expectancy (that began in the mid- 1800s) are thought solely as a result of medical progress and breakthroughs. In fact, the major impact of improvements in medicine and sanitation did not occur until the late 19th century. Prior innovations in industrial and agricultural production and distribution, which improved nutrition for large numbers of people, were more powerful forces in mortality reductions.

d) Changing age structure

In most less developed countries the effects of fertility and mortality project an age-sex pyramid for 2030, which loses its strictly triangular shape as the size of younger five-year cohorts stabilizes and the older portion of the total population increases. The picture in more developed countries has been and will be quite different. In 1950, there was relatively little variation in the size of five-year groups between the ages of 5 and 24. By 1990, the baby-boom cohorts (from the beginning of the post-World War II) were ages 25 to 44, and younger cohorts were successively smaller. If projected fertility rates are reasonably accurate through 2030, the aggregate pyramid will start to invert, with more weight on the top than on the bottom, and the size of the oldest old population (especially women) will increase substantially.

2.1.1.2 Aging and health implications

Aging brings along profound sociological and demographic changes as well as an important transformation in the diseases affecting our societies. Over the past several decades there has been an epidemiological shift in disease burden from acute to chronic diseases that has rendered acute care models of health service delivery inadequate to address current population health needs [27]. As *Figure 4* shows, the burden of disease, especially non-communicable disease, increases with age. This shift has become a global concern and for that reason most of the countries and policy makers have dedicated numerous resources to understand better this new scenario [28]–[30]. In 2001 the World Health Organization (Department of Health Promotion, Non-Communicable Disease Prevention and Surveillance) together with Health Canada carried out an in-depth study, entitled “Health and Ageing. A Discussion Paper”, analysing the implications of the ageing process in the global health which was published as a contribution to the Second UN World Assembly on Ageing held in Madrid in 2002 [21].

Figure 4 - The burden of disease across various life stages and regions due to specific cause categories, depicted as age-standardized YLL per 100,000 (sub-Saharan Africa (SSA); India (IND); China (CHN); Latin America and Caribbean (LAC); Central Europe, Eastern Europe, and Central Asia (EECA); and high income (HI)). (Figure source: Sepúlveda and Murray 2014 [31])

People's independence is threatened when physical or mental disabilities make difficult to carry out the basic Activities of Daily Living (ADLs) such as bathing, eating, using the toilet and walking across the room, as well as

the Instrumental Activities of Daily Living (IADLs) such as shopping and meal preparation. Age-related decline affects functional capabilities leading to a progressive deterioration in executive functions, memory performance attention and physical capabilities, moreover, after the arrival of these first signs, elder people tend to reduce their daily routines with negative effects on their physical, psychological and cognitive status as well as reducing their independence, social relationships and mental health [32], [33]. Even worse, with aging, many people perceive their own home and their local area as less friendly, becoming an extra risk factor of isolation [32]. All this contributes to create a malicious loop of deterioration in multiple domains (physical, psychological, social and cognitive). Physical and cognitive therapies may be for maintaining independence, preventing and delaying disease and improving the quality of life for older people [21], [33]. *Figure 5* shows a schematic evolution of the functional capacity (such as ventilator capacity, muscular strength, and cardiovascular output) over life time. Functional capacity increases in childhood and peaks in early adulthood, eventually followed by a decline. The rate of decline, however, is largely determined by environmental and life style factors (smoking, alcohol consumption, levels of physical activity, and diet) [21].

Aging consequences are not limited to a reduction of the functional capacity. Since the prevalence of chronic conditions increases with age, the highest prevalence is among the senior population. Furthermore, the development and use of new drugs as well as novel medical procedures sometimes are able to treat acute or fatal diseases by transforming them in long-term or life-long conditions [34]. Chronic and long-term conditions require a particular and specific care able to deal more efficiently with this kind of disorders as well as to keep or even to improve the patients' health outcomes and this is hardly achievable by dealing with them using a health care system designed to treat acute diseases. Long-term care has been defined by the WHO as:

"The system of activities undertaken by informal care givers (family, friends and/or neighbours) and/or professionals (health and social services) to ensure that a person who is not fully capable of self-care can maintain the highest possible quality of life, according to his or her individual preferences, with the greatest possible degree of independence, autonomy, participation, personal fulfilment and human dignity."

Figure 5 - Functional Capacity over the Life Course (Figure source: WHO/NMH/HPS [21]).

The growing number of older adults increases demands on the health care systems as well as on medical and social services (e.g. pensions, health care and long-term care [30]) [28]. Chronic diseases, which affect older adults disproportionately, contribute to disability, diminish QoL, and increased health- and long-term-care costs. Health care and long-term care systems need to be adapted to the changing needs and aspirations of an aging society and the increasing number of chronic and long-term conditions, with a better alignment of incentives facing medical staff and patients on the rational consumption of scarce resources [30].

Thus, long-term care includes both informal and formal support systems. The formal care include a broad range of community and public health, primary care, palliative care and rehabilitation services as well as institutional

care in supportive housing, nursing homes, hospices, etc. and treatments to halt or reverse the course of disease and disability [21]. In 2002, the leading chronic diseases—cardiovascular disease, cancer, chronic respiratory disease, and diabetes—caused 29 million deaths worldwide. Despite growing evidence of epidemiological and economic impact, the global response to the problem remains inadequate [35]. In developed countries, chronic disease now accounts for more than 75% of health care expenditure and nearly an equivalent percentage of disease-related deaths [36]. It is estimated that the population affected by chronic conditions will increase steadily in that next two decades, so that by 2025, 164 million people (almost 50% of the population) will have a chronic condition [37] (*Figure 6*). According to a study of the Department of Health in the UK in 2005 it was estimated that [38]:

- Around 80% of General Practitioner (GP) consultations were related to any kind of long-term condition and a quarter of those consultations were due to a minor complaint.
- Care of long-term conditions accounts for 60% of bed days in hospitals.
- By 2030, incidence of long-term conditions in the over 65s was estimated to double.

Figure 6 - Prevalence of chronic disease in the US (Figure source: Wu, Shin-yi et al. 200 [37]).

Furthermore, most of the chronic patients do not suffer only one unique condition but they usually suffer multiple conditions at the same time. Approximately 125 million Americans (around 45% of the population) had one or more chronic conditions in 2000 and 61 million (21% of the population) had multiple chronic conditions [37]. Similar trends are reported in the analysis of the 2004-2005 National Health Survey conducted by the Australian Bureau of Statistics² showing that the proportions of having a condition increase with age, as do the proportions of people reporting more than one chronic condition as shown in *Table 1*. According to Wu et al. (200) projections it is expected 81 million of Americans suffering two or more conditions by 2020 [37].

This scenario, with an increasing sector of the population suffering not only one but multiple chronic conditions at the same time is especially problematic and burdensome. First of all, people with multiple chronic conditions necessarily requires to see multiple providers. People with five or more chronic conditions see almost 14 different physicians in a year (the average for a regular patient is six), average 37 physician visits annually and they fill almost 50 prescriptions in a year [37]. More important, minimal level of coordination between different providers and clinicians, and in many cases its absence, leads to potential adverse outcomes for patients, and a harder task for the physicians and an inefficient or wasteful health care spending. Apart from the statistics, a survey sponsored

² www.abs.gov.au (Last date accessed: December 2015)

by the Agency for Healthcare Research and Quality³ found that patients reported that they received conflicting medical advice and different diagnoses from different providers, whereas on the other hand, physicians reported that they found difficult to coordinate care for people with chronic conditions and that poor care coordination led to adverse outcomes such as hospitalizations and nursing home stays [39].

Number of chronic conditions	0-14 years	15-24 years	25-44 years	45-64 years	65+ years
None	87.7	80.8	74.0	47.0	18.4
One	12.3	17.0	21.0	32.0	32.0
Two	-	1.9	3.8	14.1	26.7
Three	-	0.3	1.1	5.1	15.3
Four	-	-	0.2	1.4	5.0
Five or more	-	-	-	0.5	2.6

Table 1 - Proportion (%) of chronic conditions reported, by age group, 2004-05 (Table source: the 2004-2005 Australian National Health Survey [40]).

Patients on such situation are most likely to experience an acute exacerbation (increasing the health care spending) that could has been prevented. Adjusting the delivery of health care to better meet the needs of people with chronic conditions could bring a better outcomes for patients as well as a reduction of costs for health care systems. Nevertheless, it will require a renewed focus on preventing disease when possible and implementing secondary and tertiary prevention strategies that slow disease progression and the onset of physical limitations that often accompany chronic conditions. Also, in the case of people with multiple chronic conditions, it will require better care coordination across the numerous treating providers and settings where care is delivered [39].

Figure 7 - Percentage point change in total health expenditure as a share of GDP in selected countries by decade (Figure from The Henry J. Kaiser Family Foundation website [41] with data from the OECD Health Data 2010⁴)

2.2 The transformation of the health care systems

This new scenario requires a transformation of the healthcare systems, a movement from episodic care to continuous care, from institutional care to community and home-based care, extending the disease treatment to disease prevention and continuous monitoring, and from a specialized approach to a multidisciplinary team approach [27]. This does not mean that current health care systems were mistakenly designed, they were designed to solve different problems in a completely different scenario. Examples include the creation of a public health

³ www.ahrq.gov (Last date accessed: December 2015)

⁴ www.oecd.org/health (Last date accessed: December 2015)

system in the early 20th century to combat communicable diseases, and the development of services and financing systems to effectively treat acute conditions such as heart attacks in the latter half of the 20th century [39]. Primary care was largely designed to provide ready access and care to patients with acute, varied problems, with an emphasis on triage and patient flow. It was characterized by short appointments, diagnosis and treatment of symptoms and signs, support on laboratory analytics and prescriptions, brief patient education and patient initiated follow-up [42]. Yet, it is interesting to mention that the rise of general or family practice at the end of the 20th century grew out of the idea that medicine needs more integration, not less [43]. Now, on the 21st century the system must transform itself again by reorienting to the major challenge of the period, e.g. the effective prevention and management of chronic conditions [39].

Policy makers and health care providers are paying more and more attention about how to deal with chronic and long-term conditions more efficiently, and more especially in subjects suffering multiple conditions at the same time [39]. This requires a substantial transformation of the health care systems which could reverse the negative trends in the global incidence of chronic diseases and long-term conditions [35]. On this new iteration the intervention of the healthcare system should start before the disease onset and must follow the patient once he leaves the hospital.

Figure 8 - Per capita health care spending vs. average life expectancy in OECD countries 2011 (Figure source Forbes magazine website [44] with data from the OECD Health Data 2011⁵)

Thus, the healthcare transformation is demanded by the rising costs in the delivery of health care. As an example, between 1980 and 2008, the US share of GDP devoted to health grew by 7 percentage points and this is a common trend in many countries, Figure 7. A report of McKinsey and GSMA claims that the share of GDP devoted to healthcare in several OECD countries is forecast to amount to over 15 per cent by 2030 putting significant pressure on fiscal balances, consumer spending, and employer liabilities [45]. This report pointed to four major factors as drivers for this increase [45]:

- Aging populations. It was already discussed on this chapter the repercussion of the ageing process in the healthcare systems. According to this report of McKinsey and GSMA, the impact of chronic disease accounts for the 80% of the cost growth.
- Medical procedure costs. As medical knowledge and technology become more sophisticated, complexity and cost of hospital procedures and equipment seem to increase unless significant they come along with innovations in the delivery models. A previous McKinsey study revealed that the growing complexity of

⁵ www.oecd.org/health/ (Last date accessed: December 2015)

medical procedures raised costs by 7 per cent between 2003 and 2006 alone [46] in the US hospitals.

- Resource constraints. Healthcare resources are not unlimited and not equally distributed. As an example the report mentions that physicians in developed markets seem to be increasingly choosing more lucrative career specializations over generalist primary care practice. And in developing markets, physicians are often in short supply, with experienced specialists unevenly distributed (tending to be found in major urban centres).
- Patient empowerment. Particularly in markets with broad Internet access, available in-depth information on medical conditions and their treatment has enhanced patients' knowledge, generating an increasingly consumerist attitude toward medicine and higher expectations regarding treatment.

Figure 9 – Wagner's model for improvement of chronic illness care (Figure source: Wagner 1997 [42]).

On the other hand, increasing healthcare spending is not necessarily linked with better health care outcomes. Actually, analysing in detail the particular case of the US, the increasing expending of the last decades was not translated into an increasing of life expectancy as shown in Figure 8 (life expectancy vs. health care spending is usually used as metric, although it has been questioned [47]). Also, many reports have revealed that large proportions of chronically ill patients are not receiving effective therapy, have poor disease control, and are unhappy with their care [48].

In order to deal with this scenario, many ideas, ranging from conceptual models and frameworks to ICT tools and guidelines, have been emerging and have proposed as potential solutions during the last decades although all of them have their particularities. Also, healthcare systems follow significant different approaches on each country and region (ranging from 100% public to almost 100% private health care systems). Likely for this reason there is no common solution for all of them. In this section, conceptual models, frameworks, mechanisms, tools and the assessment of real experiences are analysed trying to identify which are the strategies that have been carried out and the solutions that have been proposed to build more cost-effective systems adapted to today's requirements.

The MacColl Institute for Healthcare Innovation⁶ was one of the pioneers with the development of the Chronic Care Model (CCM). In 1998, the director and senior investigator Edward H. Wagner at that time published the editorial "*Chronic disease management: what will it take to improve care for chronic illness?*" in response to the disparity of approaches for the management and care of chronic illness [42]. According to Wagner, both patients and their families are struggling with chronic illness have particular needs that are unlikely to be met by an acute care organization and culture. Planned and regular interactions with their caregivers (e.g. systematic assessments,

⁶ <http://maccollcenter.org/> (Last date accessed: December 2015)

attention to treatment guidelines, and behaviourally sophisticated support for the patient's role as self-manager) and a special focus on function and prevention of exacerbations and complications are some of the particular needs of this kind of patients. Also, they must be linked through time by clinically relevant information systems and continuing follow-up initiated by the medical practice [42]. Using the work experience of the Group Health Cooperative⁷ and literature reviews, they developed a model for improving chronic illness care [42], [48]–[55]. This model, is actually a collection of good practices found in health care organizations where care improvements were found when:

- Well-developed processes and incentives for making changes in the care delivery system were set.
- The organization guarantees behaviourally sophisticated self-management support for the patient, increasing patients' confidence and skills transforming them in managers of their illness [51].
- Team function and practice systems (e.g., appointments and follow-up) were restructured to meet the needs of chronically ill patients.
- Evidence-based guidelines were developed and implemented as well as supported through education, reminders, and increased interaction between actors.
- Information systems were used to facilitate the development of disease registries, tracking systems, and reminders and to give feedback on performance.

Wagner identified six essential elements for good chronic care, which are represented in a schematic way in the *Figure 9*: community resources and policies, health care organization, self-management support, delivery system design, decision support, and clinical information systems. He states that improvements in those interrelated components can produce system reform in which informed, activated patients interact with prepared, proactive practice teams [56]. Also, segmentation based on a risk stratification may make good sense if it is accompanied by efforts to improve care for each stratum of health care utilizers [42].

Later, Kaiser Permanente⁸ took the CCM to create the Guided Care Model (GCM) over it based on their own experiences [57]. GCM does not requires a radical change, instead, it proposes an adaptation of the primary health care with some innovations to ensure optimal outcomes for patients with chronic conditions. The final idea was to build a more efficient system easy to deploy over the former one. One of the novel ideas of the GCM is the active involvement of the nurse team. Kaiser Permanente designed a case-based, three-week curriculum (including self-learning material and interactive workshops) combined with a five-month practice for nurses. The content of this training included the use of the Electronic Health Record (EHR), transitional care, motivational interviewing, evidence-based guidelines for managing chronic conditions, health insurance coverage, and working with family caregivers and community agencies. They conducted a pilot study for one year to assess the feasibility of providing GCM in a community primary care practice in the Baltimore-Washington, DC area reporting better results for patients [58] as well as lower cost for treatment compared with those patients receiving usual care [59]. Then the GCM was validated in a larger pilot, involving 14 primary care teams and 904 patients during 18 months. The results of this trial showed that GCM improves self-reported quality of chronic health care for multi-morbid older persons [60]. In 2005, the National Health Systems (NHS) of the UK elaborated the report "*Self-Care – A Real Choice Self-Care Support – A Practical Option*" [38] proposing self-care as a key component of the model for supporting people with long term conditions. Self-care is part of the daily activities and it includes the actions people take for themselves and their relatives to stay fit and maintain good physical and mental health; meet social and psychological needs; prevent illness or accidents; care for minor ailments and long-term conditions; and maintain health and wellbeing after an acute illness or discharge from hospital [38]. Any particular example of care lies on a spectrum ranging from 100% self-care (e.g. brushing teeth regularly) to 100% professional care (e.g. neurosurgery). This idea is synthetized in chronic-care management pyramid shown on the *Figure 10*. A well-known example of this approach is the Type 1 Diabetes Mellitus patients. These patients are used to self-

⁷ www.ghc.org (Last date accessed: December 2015)

⁸ <https://healthy.kaiserpermanente.org/> (Last date accessed: December 2015)

monitoring their glucose levels from their children hood. As reference, on this report the NHS estimated that people with diabetes in UK have on average about 3 hours of care professional and do self-care for the remaining 8757 hours in a year (using the advice given by professionals during the 3 hours or using skills learnt through structured self-care education programmers).

Figure 10 - Self and professional care distribution depending on the patient profile (Figure source: author elaboration based on NHS report [38])

According to that report, there is space for more self-care, around 40% of GP consultations are for minor ailments and 75% of Accident&Emergencies (A&E) attendances are for minor illness or injury. With extended support for self-care, many of these episodes could be better taken care of by people themselves bringing along significant benefits for patients such as better symptom management and reduction in pain, anxiety, depression and tiredness and consequently bringing improvement in quality of life and a greater independence.

But also, it would also impact the performance of the healthcare providers. The NHS estimations, applied to the UK context were:

- Visits to GPs can decrease (40% of GP time is spent dealing with patients with minor self-treatable illness and almost two-thirds of GP consultations result in a prescription being written which could have been treated by over-the-counter medicines provided by pharmacists)
- Outpatient visits can reduce by 17%.
- A&E visits can reduce by up to 50%.
- Hospital admissions can be halved.
- Hospital length of stay can be halved.
- Medicines intake is regulated or reduced.
- Days off work can reduce by 50%.

Obviously, to implement this new model it is requested to deploy and transform some procedures in order to support the self-care implementation and to provide patients with the appropriate tools. Self-care involves increasing the capacity, confidence and efficacy of the individual for self-care by providing a range of options [38]. Figure 11 shows some of these tools.

Self-care can be used for the promotion of good health as well as for the prevention of ill health (e.g. stopping smoking, cutting alcohol intake, doing physical activity and regular exercise, following a balanced diet, using a care plan or regularly monitoring health aimed to prevent illness and injury [38]), it can be also applied for minor ailments and, of course, it can also be extended to the care of chronic and long-term conditions. With the right support these patients can be empowered and learn to be active participants in their treatment, improving existing

symptoms management, avoiding flare-ups, slowing deterioration & preventing development of complications and other conditions. This can help them in achieving a better quality of life while living with and taking care of their conditions. The majority of this kind of patients falls in the lower base of the care triangle *Figure 10*; which represents the majority of the population affected by these conditions and consequently even a small percentage increase in self-care can have a huge impact on demand for professional services [38]. Basically, self-care requires the conversion of the patient's role from a passive to active in the healthcare process [61]. Angela Coulter and Jo Ellins carried out a systematic review to assess the effectiveness of strategies for informing, educating, and involving patients in the care process [61]. Their results evidenced that providing patients with the right tools and promoting the self-care can lead to a significant improvement in the healthcare process:

- a) Improving health literacy. Health literacy is fundamental to patient engagement and it is strongly related with the patient empowerment. Patients with low health literacy have poorer health status, higher rates of hospital admission, are less likely to adhere to prescribed treatments and self-care plans, experience more drug and treatment errors, and make less use of preventive services [62]. Furthermore, simple but well-designed written information (such as leaflets), combined oral and written information and websites can improve health knowledge and recall (especially if information is personalized [63]) as well as to reduce the use of health service resources [61]. Targeted mass media campaigns have been used to inform patients and the general public for example, to increase uptake of screening or to reduce inappropriate use of certain drugs, procedures, or services [64], [65].

Figure 11 - Self Care Support and Self-Care (Figure source: NHS report [38])

- b) Improving clinical decision making. In many cases different options are often available for treating a problem and the difference between the benefit to harm ratios of each may be uncertain or small. In those cases the patient's preferences should lead the treatment choice guided by the clinicians. This process improves patients' knowledge and understanding of their condition and of the treatment options and outcome probabilities [66] and increase their participation in decision making [61]. Barriers include lack of awareness, knowledge and skills, concerns about time and resource pressures, and fear that patient involvement could undermine clinician-patient relationships [67].
- c) Self-care and self-management in chronic diseases. Self-care includes staying fit and maintaining good physical and mental health, as well as the day to day management of long term conditions such as diabetes or Parkinson's disease. Approaches that provide information only are mostly unsuccessful, but educational and self-help programs that are actively supported by clinicians improve health outcomes

for patients [61]. Short self-management courses run by voluntary groups [68], health professionals [69] and interactive computer seem to improve knowledge, coping behaviour, adherence, self-efficacy, and cost effectiveness, but the effects may diminish over time [61].

- d) Patient held records can enhance patients' knowledge and sense of control as well as the use of self-monitoring and remote telemonitoring. Improving patient safety.

Going back to the schematic representation of the self-care model showed in Figure 11, the NHS in the UK proposed to extend this conceptual model beyond the disease management (long-term disease, chronic diseases, acute illness and minor ailments) to self-care for the maintenance of good health and lifestyle and prevention of ill health [38]. Such as the promotion of good health and prevention of ill health (stopping smoking, cutting alcohol intake, doing physical activity and regular exercise, following a balanced diet, using a care plan or regularly monitoring health are all examples of self-care and are important to promote good health and prevent illness and injury) or the self-care with social support (care homes, home visitors, social workers and community networks of lay people can also have a role in providing self-care advice and support where appropriate for social and emotional problems). The concept of extending the self-care to healthy population is also known as the continuum of care, or Health Management in contrast with the Disease Management approach used to deal with acute, chronic and long-term condition. This concept extends the health status in five different stages: healthy status, people at risk, people suffering a critical or acute episode, chronic and/or long-term patient and finally advanced patient (multichronic, comorbidities). For each stage and depending on the disease a different intervention is requested balancing the self-care and the professional care according to the self-care pyramid model. A number of studies have shown that most chronic conditions are preventable through behaviour change, and some studies have shown specific interventions can be successful leading this change [70]. However, even if these actions are successful and the number of people with chronic conditions is less than forecast, changes in the health care system are still necessary to help those who already have chronic conditions [39]. Managing long-term conditions requires "care" to be provided over a long period of time rather than a "cure" at a single point in time. Actually, frequent emergency admissions to hospital are a symptom of weakness in the care system for these people. This could be due to failure in different points of the care path: poor self-management by the patient; poor care management by health and social care professionals or a breakdown in a patient's social support circumstances. In any case the default location for care is concentrated in a hospital settings, nevertheless, most people agree that the best place to care for older people is at home. This prerequisite introduces another actor in the care path, the care giver. But caregivers (who are often old themselves) must be supported if they are to continue to provide care without becoming ill themselves. Visiting nurses, home care, peer support programmes, rehabilitation services, assistive devices, respite care and adult day care are all important services that enable informal caregivers to continue to provide care to older people [21]. One of the greatest challenges in health policy is to strike a balance among support for self-care (older people looking after themselves), informal support (family members and friends helping to care for older people) and formal care (health and social services) [21].

Most recently, in 2013, Michael E. Porter and Thomas H. Lee published the "*The Strategy That Will Fix Health Care*" [71], a detailed analysis of the current health care practice and a proposal for a strategic transformation of the health care systems. Again, their aim is to maximize the value for patients in an efficient way. That means achieving the best outcomes at the lowest cost. In the introduction of their work they state:

"We must move away from a supply-driven health care system organized around what physicians do and toward a patient-centred system organized around what patients need. We must shift the focus from the volume and profitability of services provided—physician visits, hospitalizations, procedures, and tests—to the patient outcomes achieved. And we must replace today's fragmented system, in which every local provider offers a full range of services, with a system in which services for particular medical conditions are concentrated in health-delivery organizations and in the right locations to deliver high-value care."

According to them, in health care the goal for providers should be improving value for patients (where value is defined as the health outcomes achieved that matter to patients) relative to the cost of achieving those outcomes. Therefore it requires either improving one or more outcomes without raising costs or lowering costs without

compromising outcomes, or both [71]. This work was developed with the US healthcare system in mind, nevertheless, some of the mechanism and ideas can be extended to other health ecosystems like the European one. Actually the work covers not only the clinical and healthcare organization but the reimbursement and business mechanisms. The strategic agenda of Porter and Lee for moving to a high-value health care delivery system has six interdependent and mutually reinforcing components. The six components are not theoretical or radical changes. Instead, all are already being implemented to varying degrees in organizations ranging from leading academic medical centres to community safety-net hospitals or even large-scale changes involving multiple components of the value agenda. This partial validation has been striking improvements in outcomes and efficiency, and growth in market share, no organization, however, has yet put in place the full value agenda across its entire practice[71].

Figure 12 - Proposal for a health care transformation by Michael E. Porter and Thomas H. Lee (Image source: Porter&Lee 2013 [71])

- a) Organize around the customer and the need, conforming the Integrated Practice Units (IPUs). At the core of the value transformation is changing the way clinicians are organized to deliver care. That requires a shift from today's siloes organization by specialty department and discrete service to organizing around the patient's medical condition, defined as an IPU. IPUs treat not only a disease but also the related conditions, complications, and circumstances that commonly occur along with it (clinical and non-clinical). They also assume responsibility for engaging patients and their families in care (education and counselling, encouraging adherence to treatment and prevention protocols, and supporting needed behavioural changes). IPU have proved to achieve faster treatment, better outcomes, lower costs, and, usually, improving market share in the condition.
- b) Measure outcomes and costs for every patient. Rigorous measurement of value (outcomes and costs) is perhaps the single most important step in improving health care. Outcomes should be measured by medical condition (such as diabetes), not by specialty (podiatry) or intervention (eye examination) covering the full cycle of care for the condition, and track the patient's health status after care is completed.
- c) Move to bundled payments for care cycles. Payment is tied to overall care for a patient with a particular medical condition, aligning payment with what the team can control.
- d) Integrate care delivery systems. A large and growing proportion of health care is provided by multisite health care delivery organizations. In 2011, 60% of all U.S. hospitals were part of such systems, up from 51% in 1999. Multisite health organizations accounted for 69% of total admissions in 2011. Those proportions are even higher today. Unfortunately, most multisite organizations are not true delivery systems, at least thus far, but loose confederations of largely stand-alone units that often duplicate services. There are huge opportunities for improving value as providers integrate systems to eliminate the fragmentation and duplication of care and to optimize the types of care delivered in each location.

- e) Expand geographic reach. Health care delivery remains heavily local, and even academic medical centres primarily serve their immediate geographic areas. Geographic expansion should focus on improving value, not just increasing volume. Geographic expansion takes two principle forms: a hub-and-spoke model (satellites deliver less complicated care, with complex cases referred to the hub) and the clinical affiliation model (an IPU partners with community providers or other local organizations, using their facilities rather than adding capacity).
- f) Build a horizontal supporting information technology platform as an enabler of the previous components. Historically, health care IT systems have been siloes by department, location, type of service, and type of data (for instance, images). Often IT systems complicate rather than support integrated, multidisciplinary care. But the appropriate IT system can help the parts of an IPU work with one another, enable measurement and new reimbursement approaches, and tie the parts of a well-structured delivery system together. A value-enhancing IT platform has six essential elements:
 - It is centred on patients. The system follows patients across services, sites, and time for the full cycle of care, including hospitalization, outpatient visits, testing, physical therapy, and other interventions. Data are aggregated around patients, not departments, units, or locations.
 - It uses common data definitions, enabling data to be understood, exchanged, and queried across the whole system.
 - It encompasses all types of patient data. Physician notes, images, chemotherapy orders, lab tests, and other data are stored in a single place so that everyone participating in a patient's care has a comprehensive view.
 - The medical record is accessible to all parties involved in care. Sharing information needs to become routine both for physicians and patients. Offering also a centralized way to schedule appointments, refill prescriptions, and communicate with clinicians.
 - The system includes templates and expert systems for each medical condition. Making easier and more efficient to enter and find data, execute procedures, use standard order sets, and measure outcomes and costs. Expert systems help clinicians identify needed steps (for example, follow-up for an abnormal test) and possible risks (drug interactions that may be overlooked if data are simply recorded in free text, for example).
 - The system architecture makes it easy to extract information. In value-enhancing systems, the data needed to measure outcomes, track patient-centred costs, and control for patient risk factors.

Porter and Lee remark in several points that health care is suffering the effects of an excessive fragmentation, for that reason they suggest the IPU and the integrate care delivery systems to address that problem. Of course, this is not something new, actually Porter and Lee stated that their agenda is based in already validated ideas. Ouwens et al. [56] carried out a review of systematic reviews regarding integrated care programmes for chronically ill patients. Despite the heterogeneity in the reviews regarding the interventions used, patient populations, provider populations, and processes and outcomes of care, positive trends in effects were reported and integrated care programme seemed to have a positive effect on the quality of patient care. In spite of the disparity, all of them share common aims: to reduce the fragmentation, to improve the continuity in the management and to coordinate the care of the patient. Actually, is in the implementation where most of the divergences appear although, again, common mechanics can be found. *Table 2* shows a summary of such mechanisms compiled by Ouwens et al.. Integrated care is most frequently equated with managed care in the US, shared care in the UK, trans mural care in the Netherlands, and other widely recognized formulations such as comprehensive care and disease management [43].

This lack of conceptual clarity stands as a major barrier to promoting integrated care in both theory and practice. Health care organization are usually hierarchical structures conformed by separate, but interconnected components – actually they are among the most complex and interdependent entities [72] - which should play

complementary roles in order to accomplish joint tasks. However, the division, decentralization, and specialization interfere with efficiency and quality goals [73], patients get lost, needed services fail to be delivered, or are delayed, quality and patient satisfaction decline, and the potential for cost-effectiveness diminishes [74]–[76]. Instead a better cooperation and collaboration, or integration, would enable the achievement of common goals and optimal results [77], [78]. Furthermore, fast-growing medical scientific knowledge is leading to more diagnostic procedures and treatment modalities which, on the other hand, requires again optimal collaboration and coordination between professionals in the delivery care [56], [79]. Healthcare improvement programmes at hospitals usually focus on isolated interventions rather than on the total care process of the patient [80]. Integrated care programmes have begun to receive greater support as approaches to reduce fragmentation and to achieve improved results for patients at acceptable cost [81], [82].

Component	Description
Self-management support and patient education	Self-management support involves collaboratively helping patients and their families acquire the skills and knowledge to manage their own illness, providing self-management tools and routinely assessing problems and accomplishments. Education is giving the patients information (materials and/or instructions) regarding their condition and possible management.
Clinical follow-up	Follow-up is monitoring the patient after or during treatment on a close regular base. This is often done by a nurse case manager who uses a phone, mailings, or visits. Clinical follow-up can be seen as part of self-management support.
Case management	Case management is explicit allocation of coordination tasks to an appointed individual (a case manager) or a small team who may or may not be responsible for the direct provision of care. The case manager or team takes responsibility for guiding the patient through the complex care process in the most efficient, effective, and acceptable way.
Multidisciplinary patient care team	A multidisciplinary patient care team is composed of a group of professionals who communicate with each other regularly about the care of a defined group of patients and participate in that care.
Multidisciplinary clinical pathway	Clinical pathways or integrated care pathways are structured multidisciplinary care plans which detail essential steps in the care of patients with a specific clinical problem and describe the patient's expected clinical course. Clinical pathways should be derived from evidence-based guidelines translated into practice.
Feedback, reminders, and education for professionals	The aim of feedback, reminders, and education is to provide health care providers with information regarding appropriate care for patients. This information can come from clinical pathways, medical records, computerized databases, patients, or audits by colleagues. Feedback is given after the consultation; education is given before consultation; reminders are given before or during consultation.
Additional requirements	(i) Supportive clinical information system; (ii) specialized clinics or centres; (iii) shared mission on integrated care; (iv) leaders with a clear vision on integrated care; (v) finances for implementation and maintenance; (vi) management commitment and support; (vii) patients capable and motivated for self-management; (viii) culture of quality improvement.

Table 2 - Description of components of integrated care programs according to Ouwens et al. (Table source: Ouwens et al. 2005 [56])

A continuum of strategies—from the macro to the micro—are available to foster integrated care [83]–[85]: funding (the division, structure and flow of funds for health and social care), administrative (regulatory and administrative functions can help eliminate program complexities and a better management of resources), organizational (networking, both vertically and horizontally and through formal or informal means, is a major method to work together and to optimize resources), service delivery (how staff are trained, perform their responsibilities and tasks, work together, and relate to patients and their families and their needs) and clinical (understanding of patient needs, common professional language and criteria, the use of agreed-upon practices and standards throughout the lifecycle of a particular disease or condition, patient-provider communication and feedback). Finally, an element that usually is forgotten is the involvement of the patient social network or patient

eco-health system. They experience difficulties in everyday living, requiring a mix of services to cover both cure and care in home, community and institutional settings and extending this care to their medical, physical, psychological, and social needs [43], [86].

In 2005 the World Health Organization elaborated the report “*Preparing a health care workforce for the 21st century*” where the organization promotes the “patient-centred” care in contrast with the classical “provider-centred” care [87]. Patient-centred means allowing patients' values, preferences, needs and expertise to direct care. It also transforms patients and their families into experts in their own care and their role is transformed from passive recipients of care to active decision-makers. Patient-centred care is broad in scope and requires a multitude of skills of the workforce. The components of patient-centred care include [87]:

- identifying, caring about and respecting patients' preferences, values, differences and expressed needs
- coordinating continuous and timely care
- relieving pain and suffering
- listening and communicating
- providing education and information
- sharing decision-making and management
- preventing disease, disabilities, and impairments
- promoting wellness and healthy lifestyles

Continuing with the approaches around the patient the so called Personalized Medicine (PM) is found. PM refers to the tailoring of the medical interventions to the individual characteristics of each patient. It does not strictly requires the creation of drugs or medical devices that are unique to a patient, but rather the ability to create clusters of subjects that respond similarly to a specific intervention. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not [88].

Figure 13 - PHC tailors preventive, predictive, diagnostic and therapeutic activities to the specific characteristics of each patient (Figure source: IBM Institute for Business Value [89]).

Recently, the IBM Institute for Business Value published in 2010 the “*IT-enabled personalized healthcare*” discussing about the PM and also, a broader term termed as Personalized Health Care (PHC). PHC expands the PM definition in four key areas. First, PHC is broader than PM in scope, PHC also emphasizes health promotion and ongoing monitoring and management of patients (not only diagnosis and preventive or therapeutic interventions) (Figure 13). Second, while PM is frequently and appropriately associated with genomics (the study of genes and their function), proteomics (the study of the full set of proteins encoded by a genome), epigenomics (the study of chemical compounds that modify, or mark, the genome in a way that tells it what to do, where to do it and when to do it) and other types of “-omics”, PHC is also aimed at extracting knowledge of “-omics”. Third, PHC requires closely linked research and care delivery by incorporating new findings into future decision making both for the

individual treatment as well as for a better understanding of the disease and treatment outcomes. And fourth, PHC must be participatory [89].

Medicine generally has been practiced with limited availability of both patient information and clinical knowledge as illustrated in *Figure 14*. Starting with practicing medicine based on the knowledge and experience of individual practitioners evolving to intuitive or consensus-based approaches when evidence is sparse, then to evidence-based approaches grounded in large populations (sometimes referred to as a “one-size-fits-all” approach) and finally arriving to PHC. Much of care delivery today is based on “trial and error” – the expertise and knowledge of the individual clinician, with limited access to relevant patient information and clinical knowledge that is not already “in the clinician’s head” [89].

Sources: IBM Global Business Services; IBM Institute for Business Value.

Figure 14 - The ability to personalize healthcare requires better access to a wider variety of relevant patient information and clinical knowledge [89].

According to the report from IBM there are five ways to provide PHC by leveraging information and knowledge available today and how each can be enhanced with “-omics” information and knowledge [89]:

- Incorporate patient preferences into decision making.
- Improve prediction and early detection. Identify high-risk patients earlier enabling more accurate and earlier preclinical detection of a disease.
- Support clinical decision making. By using tools to better integrate key data (e.g. HER data).
- Develop multiple channels for delivering care e.g. telemedicine and remote monitoring.
- Help activate and sustain lifestyle and behaviour changes.

To summarize, a common aim has been detected across all the conceptual models, programmes and frameworks analysed, namely to reduce fragmentation and improve the continuity and coordination of care by placing the patient in a central position in the process of health care delivery. Many of the current efforts are looking for a more coordinated, integrated and continuous management of the patient, shifting the concept from disease to health management, also referred as integrated care as this puts the patient, not the disease, in the centre [56]. In general it has been detected that specialization in the health care systems led to an excessive fragmentation, too focus on the acute episodes. Instead the burden of the current diseases requires a continuous following of the

patient with a multidisciplinary team. All the actions described in this section can be grouped in:

- a) Horizontal integration. This refers to a continuous integration in the treatment and management of the patient in the time with a continuous, integrated and seamless management for chronic and long-term conditions.
- b) Vertical integration. Building a multidisciplinary team around the disease where all the clinically relevant stakeholders must be involved, i.e. not only specialists but primary care physicians, nurses, pharmacist, etc.
- c) Integration around the patient. Placing the patient in the centre of the health management, transforming his role to an active stakeholder in the health process and by providing tools to him and his eco-health system.

Finally, it is important to highlight that although improved chronic illness care can save money by reducing exacerbations and institutionalization, emphasizing cost reduction rather than quality improvement may be dangerous if it reduces access to effective services [42]. This may be the case with several chronic illnesses. The best approach to cost savings is to improve health status: that is, to ensure access to services that are proven to improve outcomes. This may require an initially higher outlay of funds [42]. Nevertheless in order to align financial incentives within health care systems to promote coordination within the medical care system and among medical and supportive care systems. Ultimately, care coordination for people with multiple chronic conditions must become a standard of quality care, against which health plans and providers are measured [39].

2.2.1 The health care transformation for Parkinson's Disease

So far, some of the key aspects for the transformation of the healthcare systems have been explored and a special focus was given to chronic and long-term diseases and conditions. In this subsection the requirements for the Parkinson's disease transformation are sectioned in more detail. PD patient must become a partner in the care process, transforming his profile from a passive recipient of medical care to an active partner in the process. This is not just because patients deserve to be partners in their own healthcare but also because with this approach health care can be delivered more effectively and efficiently, for example by learning to identify the wearing-off events and also by taking active part in the monitoring and adherence to treatment. On the other hand, patient education has been established as a tool to improve adaptation to chronic diseases. PD patients Quality of Life (QoL) have been shown to be positively affected by information on the disease and on coping activities, improving the emotional, psychosocial and physical conditions. Education health programs for people with chronic disease usually combine health information with peer support, decision support, or help with behaviour change [90].

Even when the patient is a prominent role in the care plan, this would be incomplete without engaging the caregivers (both formal or professional care givers and informal care givers). Many caregivers have a crucial role in assisting more severely affected patients. In the particular case of PD, the majority of care for the patients is provided by informal caregivers offering both physical and emotional support. Consequently, both the caregiver and the patient qualities of life are closely linked and emphasize the importance of including caregiver-burden among the problems associated with PD in order to improve patient and caregiver lives [91]. Caregivers and the patient social environment of the patient are strongly side-affected by PD and almost never considered in the design of the healthcare model. Caregivers may also benefit by improving their ability to cope with complex situations and to gain more competence in supporting the patient.

PD patients show motor disorders but also non-motor symptoms are a frequent feature of advanced PD and have been considered significant factors of disability at all stages of the illness. Nonetheless, these non-motor comorbidities of PD are usually under-reported, unrecognized and untreated by physician - but they are in fact a key determinant for QoL. A multidisciplinary and integrated care approach, promoting the collaboration of different specialist as well as collaboration between different level carers (primary, secondary, home and self-care), is necessary to obtain optimal therapeutic efficacy. The current clinical practice approach for PD is often "monodisciplinary", i.e. only one medical discipline (the neurologist) is involved in the care for patients. The

majority of the cases the focus is a symptomatic treatment aimed at minimizing motor symptoms and reducing disease severity through pharmacotherapy. However, there are weaknesses in current pharmacotherapy in PD (see section 3.8 *Treatment*) based on levodopa, especially in the long-term, for example the wearing-off effect or the disabling dyskinesias [92]. Given the complexity of PD, a multidisciplinary and integrated team able to deal effectively with both motor and non-motor symptoms approach would benefit the health outcomes for the patient. Nevertheless, this is not always possible in real practice due to the lack of intercommunication between the different health professionals involved. Multidisciplinary care teams for PD patients should include an integration in all direction, firstly a horizontal between different medical specialists (e.g. neurologist and psychologists) but also a vertical integration between these specialists and the primary care, the nurse teams and the pharmacists. In addition, nutritionists, social workers or sexologists could also be included in the team. Important elements of inter-professional team work are, among others, shared goal setting and shared contribution to treatment plans, effective communication and appropriate referrals to other team members [92].

In this case, the incorporation of novel ICT solutions for the management of PD by enhancing the collaboration within different care professionals, improving the multidisciplinary care approach and a coordinated treatment would be extremely useful. They could be also used to promote the engagement of patient and caregivers as active members of the care process. It is important to engage patients and their relatives as active members of care team, improving the interaction between them and the health professionals in the clinical practice as well as the coordination and the collaboration between different level carers i.e. primary, nursing and specialist. Furthermore personalized and effective services should be provided to the patients, allowing the future integration in a more comprehensive system for PD patients' management.

2.3 The role of the ICT in the health care

2.3.1 The digital age

Nowadays we are fully immerse in what can be defined as the "The Digital Age", Internet access is present almost everywhere and a large and growing percentage of the population use it in their daily life. In the 1990s, the Internet migrated from universities and research institutions to corporate headquarters and homes [93] transforming almost everything we know, revolutionized the communications and the spread of information. The Information and Communication Technologies (ICT) term refers to a broad field encompassing computers, communications equipment and the services associated with them. It started in 1875 with the invention of the telephone, then the first AM radio in 1910, the TV in the 1940s and the first electronic computer in 1943. Nowadays, it includes the telephone, cellular networks, satellite communication, broadcasting media and other forms of communication [93]. The ICT innovation leading the revolution that we are living is the so called Internet. It is not only an infrastructure, an interconnection between nodes and networks that allow the transmission of information without centralized governance. According to Lessig [94], it is a shared resource that enables the creation of new and/or innovative goods and services. It has transformed the way we consume goods and services (e-Commerce, music and video streaming), the way we communicate with each other (email, instant messaging, social networks, etc.), the way we enjoy our leisure time (online video and audio) or the way we read and get ourselves informed (online newspapers, eBooks). Internet has transformed many activities of daily life and also it has impacted many industries that should transform their business models to get adapted to this new reality.

Internet was designed following the end-to-end (e2e) principle. That means, the intelligence is at the ends, and the main task of the network is to transmit data efficiently and flexibly between these ends. Lessig identifies at least three important consequences of this approach on innovation. First, because applications run on computers at the edge of the network, innovators with new applications need only to connect their computers to the network to let their applications run. Second, because the design is not optimized for any particular existing application, the network is open to innovation not originally imagined. Third, because the design has a neutral platform the network cannot discriminate against a new innovator design [93], [94]. Vinton Cerf, recognized as one of the "Internet fathers" wrote this foreword for the book "Todo va a cambiar" (in English "Everything is going to

change”) [95] written in 2010 by the Spanish professor at the Insituto de Empresa Business School⁹ and well-known blogger¹⁰ Enrique Dans:

“[...] It is becoming apparent that we are evolving an online society. About 25% of the world’s population is on the Internet and perhaps an additional 5% are gaining access to the Internet exclusively by way of mobiles. The most highly penetrated countries appear to have on the order of 75-80% of the population online. In highly penetrated countries, the use of Internet technology for distribution of all forms of information and to support collaborative activity is increasing. Every information medium of the past is being re-created and re-invented in the Internet. Print formats, radio, television, telephony and computer interactions are all melting together in the cauldron of the Internet.

There are many consequences of this convergence. The economics of the Internet underscore the dramatic difference in cost between digital storage and distribution and paper, film, or DVD storage and distribution. The businesses built around physical media may need serious changes to their business models to adapt to the new economics. Online advertising is clearly changing the face of the advertising-based business models of newspapers, magazines, radio and television. Targeted advertising is far more precise, potentially, in the online world than its offline counterpart. New businesses will arise and older ones will adapt or, as Enrique says, disappear. [...] Finally, it is clear that the Internet, that has spawned a remarkable social revolution in personal networking, is also going to be home to an Internet of Things – billions of devices connected to each other by means of the net. Sensor networks will be a part of that environment as will the Smart Grid system. The demand for connectivity will spawn increased interest in wireless access to the Internet and increased demand for absolute capacity. The sheer number of instruments online will force the adoption of the new IPv6 packet formats that accommodate 340 trillion trillion trillion unique addresses.”

Figure 15 - Internet users per 100 inhabitants (Figure from Wikipedia[96] elaborated with statistics from the International Telecommunications Unit [97])

According to the statistics from the International Telecommunications Unit [98], by end 2014, the number of Internet users globally will have reached almost 3 billion (two-thirds of them from the developing world). This corresponds to an Internet-user penetration of 40 per cent globally, 78 per cent in developed countries and 32 per cent in developing countries, Figure 15. Europe’s Internet penetration will reach 75 per cent (or three out of four people) by end 2014, the highest worldwide.

⁹ www.ie.edu (Last date accessed: December 2015)

¹⁰ www.enriquedans.com (Last date accessed: December 2015)

Motivation

Figure 16 - Gartner's 2012 Emerging Technologies Hype Cycle (Figure source: Gartner Inc. [99])

Figure 17 - Gartner's 2013 Emerging Technologies Hype Cycle (Figure source: Gartner Inc. [100])

Figure 18 - Gartner's 2014 Emerging Technologies Hype Cycle (Figure source: Gartner Inc. [101])

Talking about the access point to the Internet, fixed-telephone penetration has been declining for the past five years. In contrast, mobile-cellular subscriptions will continue growing, and they will reach almost 7 billion by end 2014. The increase is mostly due to growth in the developing world where mobile-cellular subscriptions will account for 78 per cent of the world's total. Penetration rates in the Commonwealth of Independent States, Arab States, the Americas and Europe have reached levels above 100 per cent and are expected to grow at less than two per cent in 2014. Growth in fixed-broadband penetration slowing in developing countries, and by end 2014, it is estimated to reach almost 10% globally. Mobile-broadband subscriptions will reach 2.3 billion globally with a penetration of 32% by end 2014 (84% in developed countries and 21% in developing countries). Home internet access approaches saturation levels in developed countries. By end 2014, 44% of the world's households will have Internet access. Close to one-third (31%) of households in developing countries will be connected to the Internet, compared with 78% in developed countries. The analysis shows that household Internet access is approaching saturation levels in developed countries.

Internet provides an excellent ecosystem for the development of new ideas and projects as we never saw before in the history of the humanity. Together with the development of novel powerful ICT tools such sensors, smartphones, computers, actuators and so on, all of them interconnected through the Internet has allowed that these new ICT solutions have been pouring into different and diverse fields and nowadays they are present in practically any kind of technology application.

Figure 16, Figure 17 and Figure 18 show the Emerging Technologies Hype Cycle of 2012, 2013 and 2014. A hype cycle is a graphic representation of the maturity, adoption and social application of specific technologies. The term was coined by Gartner Inc.¹¹, an American information technology research and advisory firm. Since 1995, Gartner has used hype cycles to characterize the over-enthusiasm or "hype" and subsequent disappointment that typically happen with the introduction of new technologies. Hype cycles also show how and when technologies move beyond the hype, offer practical benefits and become widely accepted.

In 2012 Home Health Monitoring was highlighted as one of the emerging technologies in the "*Trough of Disillusionment*" phase and with an expected time of 5-10 years to reach the "*Plateau of Productivity*". In 2013 and 2014, Mobile Health Monitoring was move forward but it still placed at the "*Trough of Disillusionment*" phase with a projection of 5 to 10 years before it becomes available to the mass public. The first conclusion is that even health technologies have been around for a long time, still it is required some years to reach the consumer marketplace.

The phases of technology adoption described by Gartner Inc. are closely related with the profiles of the consumers adopting new technologies according to the model developed by Joe M. Bohlen, George M. Beal and Everett M. Rogers at the Iowa State University. Beal, Rogers and Bohlen. All together developed a technology diffusion model and later Everett Rogers generalized the use of it in his book "*Diffusion of Innovations*" [102], describing how new ideas and technologies spread in different cultures [103]. The technology adoption lifecycle model describes the adoption or acceptance of a new product or innovation, according to the demographic and psychological characteristics of defined adopter groups. The process of adoption over time is typically illustrated as a classical normal distribution or "bell curve". The model indicates that the first group of people to use a new product is called "*innovators*" followed by "*early adopters*", next the early and late majority come and eventually the product will arrive to the "*laggards*" [103].

2.3.2 ICT in the health care field

ICT-based health technologies can be developed to improve the prevention, diagnosis and treatment of disease and in alleviating disability and functional deficiency. It has important implications for cost, quality and access. The use of technologies, in fact, facilitates the creation of new tools and the optimization of processes, improving the response times and the use of resources and increasing the efficacy, quality, efficiency and the spending in the process of health care [104]. Besides, the use of appropriate and cost-effective ICT may improve the compliance with the self-management and to provide an effective communication between patients with chronic illness and

¹¹ www.gartner.com (Last date accessed: December 2015)

healthcare professionals to enhance care [105]. The evolution of ICT played a major role in the development of all ICT health domains, beginning with basic telecommunication (origins of telemedicine), followed by expanding the scope of telemedicine (telehealth), the networking of ICT (eHealth), and most recently, the “personalization” of ICT networks (mHealth and uHealth). These macro domains are not well defined, often overlap, and have created a confusion that hinders the conceptual development of telemedicine. One way to resolve the problem is to consider them as an extension of the basic telemedicine concept driven by changes in technology, enabled functionality, and innovative applications [106].

As it has been discussed previously, effective management of chronic illness requires a close partnership between the patient and all healthcare providers [107]. These patients are responsible for their own day-to-day care [105]. They must be active participants in the treatment, and, indeed, must adopt self-management as a lifelong task [107], [108]. Home telecare, supported by dedicated multidisciplinary care teams, can promote partnerships between the patient and other caregivers, facilitate patient self-management, improve compliance and medications management, and reduce the readmission rate for those with chronic disease [105].

Additionally to the direct monitoring of the patients, the amount of clinical information that can be generated from a telehealth monitoring system is substantial and comes in several modalities (physiological, questionnaires, pharmacotherapy data, nutritional information, quality of life, etc.). Analysis of these data and correlation with clinical history by the Decision Support System (DSS) can be used to highlight important sections of patient results, provide summary analyses and recommendations, assist in the efficient review and risk stratification of multiple patient results, alert care givers in case of deterioration of the health status of a patient. And even, advice about changes in work flow [27]. This information can be also translated into accurate predictors of health risk, and can be combined with electronic alarm systems as a platform to initiate an appropriate course of action. This work on prevention and early detection can dramatically affect the outcome, function and overall wellbeing of a patient with chronic disease. For example in the case of GPs, this will enhance their ability to manage chronic disease, by providing the necessary support to continue care outside the standard consultation and the ability to monitor treatment progress. Programs aimed at community groups at highest risk are more likely to improve long-term function, decrease hospital admissions and reduce mortality [105].

A term usually employed to talk about the use of ICT on the health care environment is electronic-health or eHealth (although as we will see later the borders of the terms are not strictly defined). eHealth covers the interaction between patients and health-service providers, institution-to-institution data transmission, or peer-to-peer communication between patients or health professionals; it also includes health information networks, electronic health records, tele-medicine services, and personal wearable and portable communicable systems for monitoring and supporting patients. Also, ICT is driven a transformation on the healthcare delivery with the deployment of homecare services with sentinel devices being fitted into homes. The eHealth paradigm opens up the possibility of giving patients more responsibilities for managing their health conditions [104]. Eysenbach elaborate a list with the ten e's in "eHealth", as well as three additional features (Easy-to-use, Entertaining and Exciting) which according to Eysenbach should be also fulfilled by eHealth systems [109]:

1. *Efficiency* - one of the promises of e-health is to increase efficiency in health care, thereby decreasing costs. For example by avoiding duplicative or unnecessary diagnostic or therapeutic interventions, through enhanced communication and patient involvement.
2. *Enhancing quality* of care - increasing efficiency involves not only reducing costs, but at the same time improving quality. E.g. by allowing comparisons between different providers, involving consumers as additional power for quality assurance, and directing patient streams to the best quality providers.
3. *Evidence based*, effectiveness and efficiency should not be assumed but proven by rigorous scientific evaluation.
4. *Empowerment* of consumers and patients - by making the knowledge bases of medicine and personal electronic records accessible to consumers over the Internet, eHealth opens new avenues for patient-centered medicine, and enables evidence-based patient choice.

5. *Encouragement* of a new relationship between the patient and health professional, towards a true partnership, where decisions are made in a shared manner.
6. *Education* of physicians through online sources (continuing medical education) and consumers (health education, tailored preventive information for consumers)
7. *Enabling* information exchange and communication in a standardized way between health care establishments.
8. *Extending* the scope of health care beyond its conventional boundaries. This is meant in both a geographical sense as well as in a conceptual sense.
9. *Ethics* - eHealth involves new forms of patient-physician interaction and poses new challenges and threats to ethical issues such as online professional practice, informed consent, privacy and equity issues.
10. *Equity* - to make health care more equitable is one of the promises of eHealth, but at the same time there is a considerable threat that eHealth may deepen the gap between the "haves" and "have-nots". People, who do not have the money, skills, and access to computers and networks, cannot use computers effectively. As a result, these patient populations (which would actually benefit the most from health information) are those who are the least likely to benefit from advances in information technology, unless political measures ensure equitable access for all.

To really understand the definition and scope of the different terms of the field, it is necessary to take a look at the past and to study the origin and evolution of them. Bashshur et al. elaborated a brief historical overview of the ICT in the health care field [106]. In historical order of introduction and development, the domains (or classes) include telemedicine (1905 and 1969), telehealth (1978), eHealth (1999), and mHealth (2003). Each of these concepts shares a common attribute with the others, namely the substitution of ICT for physical presence during the exchange of information between the participants. However, despite the shared attributes, the referents of these domains are distinct, and therefore, the terms are not interchangeable. Each of these domains, in turn, consists of several components or "orders". Despite the frequent "interchangeable" and overlapping use of these terms, they have distinct meanings and reflect different trends in society, in general, and healthcare, in particular [106]. Einthoven first used the prefix "tele" in a medical context in 1905. He referred to a successful telephonic transmission of electrocardiographic images as the "telecardiogram". Also, during the first decades of 20th century radio was used for putting in contact doctors with remote patients, e.g. on ships or people living in remote areas in Australia [110]. In 1950, inventor Cooley and radiologist Gershon-Cohen coined the term "telognosis" for the transmission of radiographs over wire or radio circuits [111]. Jutras followed in 1957, introducing the term "telefluoroscopy" [112]. The first documented use of the terms "telediagnosis" [113] and "telemedicine" [114] was made by Bird and his colleagues in 1967 and 1969, respectively. In the 60s and 70s closed-circuit and broadcast television was exploited for patient consultations and for transmission of medical images from several specialties like radiology, pathology, and dermatology [115]. Given the high cost of the equipment and the low quality of the transmission, these analogue technologies were not able to make telemedicine an efficient reality apart from specific scenarios like remote areas, military or exploration missions (e.g. the NASA) [106]. Bird defined telemedicine essentially as the delivery of medical care "without the usual patient-physician confrontation" [116]. Bennet and his associates coined the term "telehealth" in 1978 to extend the scope of telemedicine by incorporating a "broader set of activities, including patient and provider education" in addition to patient care [117]. In the 1980s computer-based approaches started to be explored, shifting from real-time applications to more asynchronous approaches where data are collected in digital form at an initiating site and are aggregated and stored for subsequent transmission to a receiving site [104]. In contrast to telemedicine, telehealth was intended to denote a more inclusive conceptualization of an ICT health domain. eHealth and mHealth are neologisms introduced to reflect technological innovations and their wider use in healthcare. Both terms have been mostly advanced by business and industry to emphasize the utility of emerging technologies in healthcare [106], [118]. They have been adopted in the literature, in some professional circles, and by highly reputable organizations, such as the World Health Organization [119]. For example, the term mHealth was introduced into the literature in 2003 [120] in response to the vast expansion of mobile communication technology and its

perceived usefulness in facilitating access to healthcare, especially in the developing world. As with telehealth and eHealth, some have suggested that mHealth incorporates the preceding domains of telemedicine, telehealth, and eHealth as long as their applications depend on mobile communications and network technologies. An important feature of mHealth is its person-centred nature and ubiquity enabled by mobile phone technology and connection to the Internet, as a Personal Area Network (PAN) [106].

Figure 19 - An early commercial ECG machine, built in 1911 by the Cambridge Scientific Instrument Company (Christoph Zywiets, A Brief History of Electrocardiography - Progress through Technology; S. L. Barron, The development of the electrocardiograph in Great Britain, British Medical Journal 1:720, 25 March 1950) to measure the human electrocardiogram according to the standards developed by Einthoven (Illustration source: Wikimedia¹²).

Some terms were advanced by academicians or professionals and some other by business or commercial interests. In different countries different terms may be used to describe the same services e.g. telemonitoring or telemetry. Their understanding or definition is usually influenced by people's experience or their personal or professional view [121]. The expansion of the initial concept of telemedicine to include a wide spectrum of applications and contexts has resulted in a parallel increase in concepts, labels, and definitions, some intersecting and others distinct. Unfortunately, this has also introduced a lack of clarity, if not confusion, as to the precise content and boundaries between the original concept of telemedicine and those that were introduced later, including telehealth, eHealth, and mHealth [106]. This problems regarding a lack of harmonization in the coding and naming of the different services has been identified as one important problem for the evolution of these kind of solutions to commercial available solutions in the market [105], [121].

Figure 20 - Scope of Telehealth by TeleSCoPE (Figure source: Rudel [121])

¹² http://commons.wikimedia.org/wiki/File:Willem_Einthoven_ECG.jpg (Last date accessed: December 2015)

Figure 21 - Scope of Telemedicine by COCIR (Figure source: Rudel [121])

For this reason the European Commission (EC)¹³ partially supported the TeleSCoPE project (Telehealth Services Code of Practice for Europe). The primary objective of TeleSCoPE was to develop a comprehensive Code of Practice for Telehealth Services (i.e. relating to that aspect of telemedicine delivered in the home and normally mediated through ICT) [122]. The result was a glossary of telehealth terms entitled “*European code of practice for telehealth services*” [123] which is public available through the TeleScope website¹⁴ and subset of the glossary is available in the Annex II. Different sources were used to obtain such definitions. The main sources of existing definitions were documents of professional bodies dealing with telemedicine and/or telehealth from European and wider international sources as well as relevant strategic and policy documents from the EC, articles in professional journals, outputs from relevant European projects, proceedings of some international conferences/workshops, Internet resources and, of course, the TeleSCoPE project partners experience [121]. Taking into account these sources, key interrelated terms were identified and defined, additionally, the partners agreed on an initial understanding of the scope and the relationships between these terms. The result is presented in *Figure 20*, two major sub-domains: assistive technologies aiming at supporting disabled and frail people, and eHealth covering needs of patients. The telecare domain falls almost completely into the eHealth domain – involving social alarms and telehealth. An element of social alarms is indicated as falling outside of eHealth in recognition of those applications that relate to e.g. personal security and property management. Telemedicine, being concerned more narrowly with the more clinical aspects of health and well-being (and including services within which clinicians exchange data and information) becomes a sub-domain of telehealth [121]. The domain model for telemedicine/telehealth offered by COCIR¹⁵ is, in some respects, different from that of the TeleSCoPE partners (*Figure 21*). For COCIR, the overarching telemedicine domain includes telehealth, ambient assisted living, telecare, telemonitoring and several teledisciplines [121]. Telehealth supports both health and well-being. In other words it is recognised that health cannot be seen purely in clinical terms. Actually, this approach matches with the discussion of the previous sections where it has been argued that the new approach of health care covers, not only patients but healthy citizens. As medical services are only a part of healthcare services, telemedicine should be a sub-domain of telehealth and not vice versa [121].

Bashshur et al. tried to bring clarity, structure and to facilitate conceptual development and research by introducing an explicit taxonomy of the domain of telemedicine (used as a general and inclusive term which refers to all systems, modalities, and applications for the personal health services delivery) [106]. The “*Taxonomy of Telemedicine*” proposed by Bashshur et al. based on the telemedicine experience the various configurations in the field can be initially grouped into three aspects or dimensions functionality, the specific applications, and the technological configurations. The second level of the taxonomy consists of the specific components and subcomponents of each of these dimensions [106].

1. **Functionality.** This dimension incorporates all aspects of the medical care process, including activities

¹³ ec.europa.eu (Last date accessed: January 2015)

¹⁴ www.telehealthcode.eu (Last date accessed: January 2015)

¹⁵ www.cocir.org (Last date accessed: January 2015)

involved in prevention, diagnosis, treatment, follow-up, and rehabilitation. These aspects are grouped into four component parts consultation, diagnosis, mentoring and monitoring. Consultation can occur between two or more physicians (often between primary-care and specialist physicians) as well as between provider and patient (consultation and diagnosis are not mutually exclusive as both can occur during the same encounter). Finally, mentoring includes remote guidance typically by specialists to others while performing new or complex procedures.

2. **Application.** This dimension includes processes of care across virtually all basic medical specialties, as well as subspecialisation based on disease entities, sites of care, and treatment modalities. Some of these categories are overlapping as medical specialization often incorporates multiple specialties. Programs also may differ by site of care, including the intensive care unit, outpatient psychiatry, the emergency department, and the home. Some programs have been organized around specific treatment modalities such as rehabilitation (e.g., speech/language pathology, physical therapy) and pharmacy.
3. **The Technology.** The components of the technological dimension can be grouped into three sets of variables: synchronicity, network design, and connectivity. Synchronicity, telemedicine may be either synchronous (i.e., in real time) or asynchronous (store-and-forward). Network design/configuration includes three modalities: Virtual Private Networks, the open Internet, and social networks varying in terms of security arrangements and the ability to protect confidential information.

Figure 22 - Dimensions of telemedicine and components (Image source Bashshur et al. [106])

Finally, it is interesting and necessary – due to the rising presence in our daily lives - to discuss the role of the Social Networks (SNN) in the health care ecosystem. SNN have more and more presence in our daily lives, from generalist networks to highly tailored platforms (e.g. social networks for photographers, for researchers, etc.). Somehow, social networks are the natural extension in the digital world of our traditional social relationships and we tend to trust the content of the network since it comes from people we know and trust. Facebook¹⁶ showed in a recent, controversial (from the ethical perspective) and massive (N = 689,003) experiment on their platform, that emotional states can be transferred to others via emotional contagion, leading people to experience the same emotions without their awareness [124]. Social networks are playing an increasingly prominent role in health care, both patient and professionals may benefit from using social networks to learn and share their experiences. Actually, social networks can be thought as the natural extension of the face-to-face patients groups where patients meet together physically to share their experiences and concerns, to clarify their doubts or just to share their experiences [125].

Health care

Participants

Impacted organizations

¹⁶ www.facebook.com (Last date accessed: January 2015)

application		
Maintaining health and wellness	<ul style="list-style-type: none"> • Consumers • Health coaches 	<ul style="list-style-type: none"> • Physicians • Health plans • Wellness facilities • Hospitals • Alternative providers/health coaches • Employers
Disease management	<ul style="list-style-type: none"> • Consumers • Physicians • Allied health professionals 	<ul style="list-style-type: none"> • Physicians • Retail clinics • Health plans • Device manufacturers • Drug companies • Alternative care providers • Disease management companies
Clinical trial recruitment	<ul style="list-style-type: none"> • Consumers • Clinical investigators 	<ul style="list-style-type: none"> • Academic medicine • Drug & biotech companies • Contract Research Organizations (CROs) • Device manufacturers
Personal Health Records (PHRs)	<ul style="list-style-type: none"> • Consumers • Health professionals 	<ul style="list-style-type: none"> • Drug & device manufacturers • CROs • Academic medicine • Health plans
Health professional training	<ul style="list-style-type: none"> • Physicians • Advanced practice nurses • Allied health professionals 	<ul style="list-style-type: none"> • Drug & device manufacturers • Licensing organizations • Hospitals • Schools
Public health announcements and campaigns	<ul style="list-style-type: none"> • Consumers • Regulators 	<ul style="list-style-type: none"> • Regulatory agencies • Public health agencies • Local/state/federal government
Treatment, physician or hospital selection	<ul style="list-style-type: none"> • Consumers 	<ul style="list-style-type: none"> • Drug & device manufacturers • Hospitals • Health plans • Retail clinics

Table 3 - Select social networking applications in healthcare from (Table source: Keckley et al. 2010 [125])

In fact, many health care organizations including Kaiser Permanente, Johns Hopkins, Cleveland Medical Center, and MD Anderson Cancer Center, provide access to online health communities aimed at offering empathic support to patients, specifically, by enhancing patient's compliance with treatment protocols and the pace of healing [126]. Patients in online communities interact with other members basically in three ways: 1) asking advice of a user with a particular experience, 2) offering advice to a user with a specific symptom or health problem, and 3) fostering relationships based on shared attributes [125]. Most online health communities are characterized by two main functions: informational support and social support. Nambisan et al. found that it is the information seeking effectiveness rather than the social support which affects patient's perceived empathy in online health communities [126]. Furthermore, it was found that the empowerment in online communities has similar effect to the physical meetings [127].

Apart from the institutional online communities, many social networks have been launched to cover this niche. The study "Social Networks in Health Care: Communication, collaboration and insights" carried out by the Deloitte Center for Health Solutions [125] provides a snapshot of social networking's evolution and explore its current and potential impacts on the health care industry. Public, Internet-based social networks can enable communication, collaboration and information collection and sharing in the health care space. About one-third of Americans who go online to research their health currently use social networks to find fellow patients and discuss their conditions [128], [129]. Social networks hold considerable potential value for health care organizations because they can be used to reach stakeholders, aggregate information and leverage collaboration. More and more people get information about a therapy or condition online [125], physicians are interested in using social networks for professional purposes [128]. Because both consumers and clinicians are using social networks, health care

organizations have an opportunity to leverage their influence across multiple audiences [125]. *Table 3* shows a good summary of the potential applications of the SNN for the healthcare field compiled by Keckley et al. 2010 [125].

For example, the website PatientsLikeMe¹⁷ gives users a way to track disease progress, access disease information and learn from the real-world experiences of other patients with the same medical condition and to share their findings with patients, health care professionals and industry organizations that are trying to treat the disease. Other consumer-directed sites include MedHelp¹⁸ which, in addition to being a social network, offers a number of tracking tools for pain, weight and other chronic conditions; CureTogether¹⁹, which helps people anonymously track and compare health data to better understand their bodies, make more informed treatment decisions and contribute data to research; DailyStrength²⁰, which allows patients and caregivers to give and receive support; Inspire, which hosts different communities, some of which are co-sponsored by non-profit foundations, to educate and offer support [125]. HealtheTreatment²¹ for sharing patient experiences and ratings for chronic disease. HealthTap²² is a website that enables patients to ask questions of physicians, who can earn status points by providing answers with which other physicians agree. Crohnology²³ lets patients with Crohn's, colitis, and other inflammatory bowel conditions track symptoms, trade information on different diets and remedies, and generally care for themselves [130]. As more patients use social networks to track their health conditions and care, industry organizations have an opportunity to interact with the members of these online communities and to leverage "real world" data sets to inform new treatments and care pathways ("From workforce to crowdsourcing" [131]) [125].

2.3.3 Benefits of ICT for health care

Several works have been analysed the impact of using ICT technologies in the health field [104], [132], [133] both regarding the potential improvements in the health outcomes as well as the potential benefits for the stakeholders involved:

- Payers. ICT can help payers to better account for expenditures, to manage the flow of funds and contain costs.
- Providers. Integrating the supply chain with hospitals by means of electronic scheduling and patient management could improve tests and procedures, it has the potential to reduce significantly administrative costs and improve the quality of service. Enable health care providers to offer better quality care through personalized health solutions assembled from a rich marketplace of interoperable health care devices and services. Enable medical and fitness device manufacturers to rapidly develop interoperable devices and services using industry developed connectivity standards.
- Practitioners. ICT can bring education, enriching knowledge and supporting its administration. Clinical Decision Support Systems (DSS) provide a key component for evidence-based care. DSS can help in prescribing drugs, calculating dosages, and scheduling, monitoring and documenting adverse reactions as well as help diagnosis based on actual measurements.
- Patients. ICT are leading more power to consumers and giving them the possibility for easier education and constant home monitoring. Moreover, patients can have access to more information about provider quality and costs. Empower individuals and patients to better manage their health

¹⁷ www.patientslikeme.com (Last date accessed: January 2015)

¹⁸ www.medhelp.org (Last date accessed: January 2015)

¹⁹ curetogether.com (Last date accessed: January 2015)

²⁰ www.dailystrength.org (Last date accessed: January 2015)

²¹ www.healthtreatment.com (Last date accessed: January 2015)

²² www.healthtap.com (Last date accessed: January 2015)

²³ crohnology.com (Last date accessed: January 2015)

by providing them with information regarding their fitness and health through personal medical devices and services. Allow loved ones and professional care givers to more accurately monitor and coach chronic disease patients and elderly individuals living independently.

Figure 23 - Stakeholders' barrier ranking (Figure source: [134])

2.3.4 Barriers and challenges

Dario Salvi made an extended compilation of some of the barriers that eHealth solutions should overcome to achieve a general acceptance, implementation and wide adoption. ICT for health is still promoted by technologists with little direct connection to health care professionals and the real world of clinical practice [104]. Also, recently Dehzad et al. studied the barriers in the adoption of health apps [134]. They investigated the main barriers in the adoption of mHealth, their underlying causes and their breakthrough possibilities. All the data are gathered from an international and multi-stakeholder point of view. First of all they tried to identify the main barriers by doing an international literature study. Then, they asked Dutch mHealth Key Opinion Leaders (KOLs) to rank the barriers to importance. These KOLs were from different stakeholder groups; policy-makers, users and developers Figure 23. Explanation for these barriers Explanations range from macro-level systemic barriers (such as lack of enabling healthcare policy) to micro level individual barriers (such as perceived complexity and resistance from physicians) [134].

1. Low user acceptance. Even when it has been proved that something could benefit the health status of a subject, it is not always easy to achieve a full compliance of the patients (actually, treatment adherence is one of the biggest concerning in the health sector). This issue is even worse when we talk about technological solutions. For this reason, methodologies that involve users in the design phase are already considered as key for successful products [135].
2. Regulatory issues. The main concerns are related to security and privacy of patients and the accountability of medical decisions when supported by electronic means [136]. Moreover, at the national level the situation changes among countries and it is seen as one of the most relevant issues to be resolved [135]. The health care sector is traditionally a conservative and late adopter, any innovation in the field requires a solid scientific validation and the compliance with several normative and recommendations.

3. Complexity. The main problem is related to the will of imposing a “one size fits all” solution for all national and European players, while national health-care and social-security systems varies from one country to another [135]. Scalability is also a big issue working with large populations. Comprehensive chronic disease assessment often involves a long consultative process by a clinician backed by a multidisciplinary team of other clinicians, allied healthcare staff and community healthcare workers. Such assessment and management is often difficult in general practice, because of time constraints imposed by practice costs and demands of other patients. Furthermore, GPs may sometimes only be made aware of a patient’s deteriorating condition after weeks or months [105].
4. Lack of well-established market. Even if there are already several products sold that can be accounted as eHealth, putting the numbers in perspective, the market size is still in its infancy, most of the current solutions are sold under an R&D, there are currently interesting pilots running, but most solutions are abandoned as the funding mechanism is stopped [137]. This relative immaturity is due to the lack of clear business models. Industry see a big potential in these systems, but not always develop them completely because of the high investments needed and the not evident return of investment (RoI). Most of large players are in a “wait and see” mode, they invest the minimum to be ready to enter the market when it raises [137]. On the public financing side, many social security reimbursement schemes in Europe do not encourage the adoption of technological innovations, although the situation can vary among countries [135]. This phenomenon triggers a vicious circle: no products are available on the market, thus no evidence exists about user acceptance and cost-effectiveness, no strong business models exist and industry is not pushed to create products [135]. The “Competing payment mechanism” is a much-heard barrier when KOLs are speaking about the transformation of a treatment focused healthcare system to a prevention based health system. However, users and developers rank the importance lower than policy-makers. This might be since users, such as doctors, benefit from the current payment mechanism; consequently they might not perceive it as an important barrier [134].
5. Lack of commonly accepted standards, integration and interoperability. Even if many initiatives that standardized the clinical or health related data (HL7, openMRS, DICOM, etc.) still no one of these solutions has been set as the standard, neither de facto standard. There are many reasons for this, there are many standardization organisms involved, a lack of bodies setting binding standards on interoperability, protocols and even clinical guidelines both at national and European level. On the side of health service providers, barriers are related to costs. Adopting standard solutions, or converting existing data to new standards, maybe more expensive. Cooperation between countries as well as case-study research on successful large-scale rollouts of mHealth strategies could give new information on how barriers have successfully been overcome and they might result in better uptake of mHealth [134].
6. Evidence of effectiveness as is common for most telemedicine applications, a strong evidence base for cost effectiveness and improved healthcare outcomes is still not available [105], [138] The reason for this is that most reports in the literature deal with short-term pilot projects and do not present either a business case or the potential for sustained viability. Reports on clinical outcomes and cost effectiveness of ICT for chronic disease are thus very limited, [138]–[140]. “*Lack of evidence*” and “*Technological obstacles*” are perceived as more important to users than to policy-makers and developers. A possible explanation for this is that the users face the liability question. This is specifically the case for doctors, who have to prescribe the mHealth solutions to patients, and for patients who have to weigh up the risks of using them).

Chapter 3 Parkinson's disease

Parkinson's disease (PD) is a degenerative neurological disease. Therefore, PD is a disease of the nervous system that increases in severity over time and leading to a declining Quality of Life (QoL) in the patients suffering it. PD is also chronic and progressive, so it is a long-term disease that does not go away and it gradually gets worse [141]. The average onset age is after 65 years old, therefore there are a significant number of "young" patients (in their 40) and at the same time the prevalence of the disease increase with age. The chronicity of the disease as well as the current trend of population ageing, lead to place PD as a more and more significant disease in several countries and with an increasing burden in the healthcare systems worldwide. Also, PD increased its visibility during the last decades since relevant and well known public figures suffered this disease, some of them are the Pope John Paul II, the boxing champion Muhammad Ali and the American actor Michael J. Fox who even founded one of the most relevant organizations aimed to find innovative solutions for PD, The Michael J. Fox Foundation for Parkinson's Research²⁴. Most people associate PD with tremor, nevertheless, not all the PD patients show tremors and not all the tremors are caused by PD. Each patient develops the disease in a different way, showing different symptoms and a different evolution. This chapter explores diverse aspects of PD, from the origin and causes to the description of the major symptoms and the progression of the disease. It is aimed to provide a clear understanding of the disease and it will be used as reference in later chapters.

3.1 Introduction

The disease was named after English physician James Parkinson made a detailed description of it in the essay entitled "An essay on the shaking palsy" on 1817, *Figure 24* shows the cover of his essay [142].

Figure 24 - Cover of "An essay on the shaking palsy" written by James Parkinson

Parkinson's disease belongs to a group of conditions called movement disorders. The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain [143]. There are also a number of conditions that can show similar signs and symptoms to true PD called Parkinsonian syndromes.

²⁴ www.michaeljfox.org (Last date accessed: January 2015)

Although uncommon, there are cases of "young-onset Parkinson's disease" in subject around their 40 and even more rarely the occurrence in people aged less than 20 years, but when it does it is referred to as "juvenile-onset Parkinson's disease" [142]. The International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) [144], is a coding of diseases and signs, symptoms, abnormal findings, complaints, social circumstances and external causes of injury or diseases, as classified by the World Health Organization (WHO). The *Table 4* provides a List of ICD-10 codes.

Chapter	Blocks	Title
I	A00-B99	Certain infectious and parasitic diseases
II	C00-D48	Neoplasms
III	D50-D89	Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism
IV	E00-E90	Endocrine, nutritional and metabolic diseases
V	F00-F99	Mental and behavioural disorders
VI	G00-G99	Diseases of the nervous system
VII	H00-H59	Diseases of the eye and adnexa
VIII	H60-H95	Diseases of the ear and mastoid process
IX	I00-I99	Diseases of the circulatory system
X	J00-J99	Diseases of the respiratory system
XI	K00-K93	Diseases of the digestive system
XII	L00-L99	Diseases of the skin and subcutaneous tissue
XIII	M00-M99	Diseases of the musculoskeletal system and connective tissue
XIV	N00-N99	Diseases of the genitourinary system
XV	O00-O99	Pregnancy, childbirth and the puerperium
XVI	P00-P96	Certain conditions originating in the perinatal period
XVII	Q00-Q99	Congenital malformations, deformations and chromosomal abnormalities
XVIII	R00-R99	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified
XIX	S00-T98	Injury, poisoning and certain other consequences of external causes
XX	V01-Y98	External causes of morbidity and mortality
XXI	Z00-Z99	Factors influencing health status and contact with health services
XXII	U00-U99	Codes for special purposes

Table 4 - List of ICD-10 codes (Table source: WHO [144])

Expanding the tree "Diseases of the nervous system" of Chapter VI, *Table 5*, we can find the WHO classification for the Parkinson's disease within the "Extrapyramidal and movement disorders". To many people, Parkinson's disease is synonymous of having or showing a tremor. However, PD is much more than suffering a tremor [142], [145], though it is indeed one sign of the disease that occurs in many patients. Equally, there are many causes for having a tremor apart from Parkinson's disease. PD is typically presented in a sporadic idiopathic fashion [146] and its cardinal signs are resting tremor, muscle rigidity, loss of spontaneous movements (i.e. bradykinesia and akinesia) and impaired posture, balance and gait disturbances [147]. The average onset of the disease is around 65 years old, but its prevalence increases with a age, consequently, PD is considered an age-related illness primarily affecting the elderly population and often resulting in a marked decline in the quality of life of both patients and caregivers [148].

Blocks	Title
G00-G09	Inflammatory diseases of the central nervous system
G10-G13	Systemic atrophies primarily affecting the central nervous system
G20-G26	Extrapyramidal and movement disorders: <ul style="list-style-type: none"> G20 Parkinson's disease <ul style="list-style-type: none"> Hemiparkinsonism Paralysis agitans Parkinsonism or Parkinson's disease Not Otherwise Specified (NOS) idiopathic primary G21 Secondary parkinsonism <ul style="list-style-type: none"> G21.0 Malignant neuroleptic syndrome G21.1 Other drug-induced secondary parkinsonism G21.2 Secondary parkinsonism due to other external agents G21.3 Postencephalitic parkinsonism G21.8 Other secondary parkinsonism G21.9 Secondary parkinsonism, unspecified
G30-G32	Other degenerative diseases of the nervous system
G35-G37	Demyelinating diseases of the central nervous system
G40-G47	Episodic and paroxysmal disorders
G50-G59	Nerve, nerve root and plexus disorders
G60-G64	Polyneuropathies and other disorders of the peripheral nervous system
G70-G73	Diseases of myoneural junction and muscle
G80-G83	Cerebral palsy and other paralytic syndromes
G90-G99	Other disorders of the nervous system

Table 5 - Chapter VI of ICD-10, Mental and behavioural disorder [144]

3.2 Origin and cause of the disease

3.2.1 Origin and pathophysiology

Nerve cells, or neurons, are the basic building blocks of the nervous system. They are responsible for sending and receiving nerve impulses or messages by exciting their neighbours [149].

Figure 25 - Neuron structure (Illustration from Mayfield Clinic [149])

Neurons have two different “interfaces”, dendrites which carry messages to the neuron body, and axons which carry messages away from the cell body. These messages are impulses travelling from the axon of one neuron to the dendrites of another, by crossing over a tiny gap between the two nerve cells called a synapse. Neurotransmitters are the chemical elements that allow the electrical impulses to overcome this gap [149]. Once the message is transmitted the neurotransmitter molecules are released back into the synapse, part of the remaining neurotransmitter is “recycled” and the other part is broken down by some other chemicals called MAO-

B (Monoamine oxidase B) and COMT (Catechol-O-metiltransferasa) so that the synapse area is clean and ready for the next transmission [149].

Figure 26 - Coronal cross-section of the brain showing the basal ganglia (Illustration from Mayfield Clinic [149]).

Parkinson's disease is a degenerative, progressive disorder that affects nerve cells in deep parts of the brain called the basal ganglia (or basal nuclei) and the *substantia nigra*, Figure 26. Body movement (motor plan selection as well as habitual behaviour) is controlled by a complex chain of decisions involving inter-connected groups of nerve cells in the basal ganglia [142], [149]. Nerve cells in the *substantia nigra* produce the neurotransmitter dopamine and are responsible for relaying messages that plan and control body movement. For some reason not yet totally understood, the dopamine-producing nerve cells of the *substantia nigra* begin to die off in some individuals. When a significant percentage of dopamine is lost (around 50% of neurons loss, see 3.6 *Progression*), PD symptoms such as tremor, slowness of movement, stiffness, and balance problems occur [149]. Dopamine is the neurotransmitter which is involved in many processes such as physical movement, memory, alertness, attention, emotions and perception of pain and pleasure. It is an inhibitory neurotransmitter, meaning that when it finds its way to its receptor sites in the neurons it reduces its tendency to transmit messages. Low levels of dopamine lead to torpor and slowed reactions. Parkinson's disease, in which dopamine levels in the substantia nigra circuit are greatly reduced, is characterized by stiffness and greatly reduced movement. Though there is not clearly understood and there are many ongoing research works trying to fully model the impact and effects of the lack of dopamine in the pathways related to motion control, the dopamine-acetylcholine balance hypothesis has been used for a long time (since the 1960) as a clinical model to understand the underlying mechanisms involved movement disorders of the basal ganglia. According to this model, a delicate balance between dopamine and acetylcholine (a neurotransmitter that allows messages to be passed from neuron to neuron across a synapse; released by cholinergic nerves) levels is maintained in the striatum, the main input structure of the basal ganglia. Loss of this balance leads to a hypodopaminergic situation. In Parkinson's disease subjects there is not enough dopamine to keep balance with the acetylcholine. When the neurons in the substantia *nigra* die and since the level of acetylcholine remains normal, an imbalance in the number of dopamine vs. acetylcholine neurotransmitters is created. This imbalance interferes with coordination and movement. The result of this imbalance is a lack of coordination in the movement that often appears as tremor (high acetylcholine) and stiff muscles and joints, bradykinesia and akinesia (low dopamine). The lack of dopamine affects directly the normal function of the direct and indirect pathways. The direct and indirect pathways thus have opposing actions; an increase in the activity of either one of these pathways might lead to an imbalance in motor control. Such imbalances, which are typical of basal ganglion diseases, may alter the motor output of the cortex [150].

3.2.2 Causes

The cause of Parkinson's disease is not yet well understood, although the area of the brain affected and some of the defective neuronal pathways have been established - as it was mentioned in the previous section - the specific cause for the death of the neurons in the substantia *nigra* is unknown. However, a number of factors have been linked to the development of the disease. Some of these at least are likely to play a relevant role either individually or in combination. The genetic approach has been largely explored, Alpha-Nuclein or PARK1, Parkin or PARK2, ubiquitin carboxy terminal hydrolase-L1 or UCHL1, DJ-1 or PARK7 and NR4A2 are some of the known genes involved in PD [142]. For example, autosomal recessive inheritance linked to the *PARKIN* gene has been reported

in a large number of early-onset [146]. Nevertheless, hereditary factors play a minimal role because only 10% of all PD cases are found to have genetic links involved, and these are most closely associated with early-onset PD [146]. Other suspected causes include environmental toxins (such as pesticides), medications, and viruses that all result in an increase in oxidative stress (which leads to generation of free radicals, which induces apoptotic cell death in dopamine neurons) [146].

3.3 Incidence and prevalence

The incidence and prevalence of Parkinson's disease increase with age. The incidence is about 1% over the age of 65 years. With increase in life expectancy, future demographic projections predict a larger population over the age of 60 years in the developing regions, with a corresponding increase in the number of Parkinson patients [151]. It is estimated that 6.3 million people have Parkinson's worldwide, affecting all ethnic groups and socioeconomic classes [151]. The age of onset is usually over 60, but it is estimated that one in ten are diagnosed before the age of 50, with slightly more men than women affected. It is not contagious and cannot be spread from one person to another [152]. Due to its chronic nature the prevalence of PD increases in the groups of older ages. The prevalence in the 60–69 age group is slightly higher than 400 in 100,000 and this figure increases threefold in the 70–79 age group to more than 900 people in every 100,000 suffering with the disease as shown in *Figure 27*. Remarkably, since Parkinson's disease most commonly affects the elderly, the number of sufferers will rise substantially in the years to come. In turn, the need for clinical and social services to care for and support patients with PD will increase at a rapid rate, with major implications for the resources that are allocated to healthcare.

Figure 27 - Spain's prevalence of Parkinson's disease (over 100.00) according to the European Parkinson's Disease Association estimations [152]

3.3.1 Gender issues

The prevalence of Parkinson's disease is slightly lower in females than in males but with very similar values, *Figure 28* details the impact by sex grouped by countries with high, middle or lower incomes based on "The Global Burden of Disease 2004" report elaborated by the WHO [153]. An important consideration is that in non-PD population female life expectancy is larger than male life expectancy. On this regards, PD could have an impact in the mortality rate. Also, it is important to highlight that this difference between the low income and high income countries are probably due to the difference in the population pyramid. High income countries are generally ageing and that leads to an increase on the prevalence of age related diseases such PD. Women develop PD less often, and when they do, the age of onset is two years later than in men [154]. The incidence is also related with the age and these effects have a diverse effect on men and women *Figure 29*. When women are first diagnosed, tremor is usually the dominant symptom. The initial symptom in men is usually slow or rigid movement (bradykinesia). The tremor-dominant form of PD is associated with a slower disease progression and higher quality of life. However, women often report less satisfaction with their quality of life, even with a similar level of symptoms [155].

Figure 28 - Deaths by sex grouped by income per capita, 2004 [153]

Regarding the treatment, drugs may affect men and women differently. Due to a lower body weight, women often are exposed to higher doses of medications (which are distributed in the standard dosages). This has been a problem with levodopa since higher exposure can lead to an increased rate of negative side effects like dyskinesias.

Figure 29 - Incidence of Parkinson's disease by age and gender [154]

3.4 Burden of Parkinson's disease

Worldwide populations are living longer, since 1930 the number of people living beyond 65 years of age has more than doubled, and it has been estimated that the number of people reaching the age of 90 will double in just 30 years; further details about this process will be provided and discussed in the next chapter (see 2.1.1 *Population ageing*). As it has been explained in the previous section, the prevalence of PD increases with age, therefore, the burden of this disease tends to growth as the population age. According to the WHO, neurodegenerative diseases are considered to be among the most burdensome [153]. Disease burden is the impact of a health problem on an area measured by financial cost, mortality, morbidity, or other indicators. It is often quantified in terms of Disability-Adjusted Life Years (DALYs), which quantify the number of years lost due to disease [156]. An important consideration about the Burden of Disease (BoD) is that the impact of premature mortality and disability due to a given medical condition may vary in different parts of the world. Hence, solid data about BoD within a region or territory is required to develop proper health care policies and strategies [148]. The burden of illness associated with PD is related not only to the disease itself, but also to the progressive disability that patients experience as their disease advances. Studies indicate that quality of life is affected not only by the motor symptoms of PD but also by non-motor complications such as dementia, depression, cognitive decline and other neuropsychiatric disorders are commonly reported comorbidities [91], [157]–[161], (in the section 3.6 *Progression* more details are provided about the progression of PD). This decline in quality of life affects both patients and their families, which

often act as informal caregivers [162]. DALY can be thought of as one year of healthy life lost, and the overall disease burden can be thought of as a measure of the gap between current health status and the ideal health status, where the individual lives to old age free from disease and disability [156]. DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for incident cases of the health condition (1):

$$DALY = YLL + YLD \quad (1)$$

The YLL basically correspond to the number of deaths multiplied by the standard life expectancy at the age at which death occurs. The basic formula for YLL (without yet including other social preferences discussed below), is the following for a given cause, age and sex (2):

$$YLL = N \times L \quad (2)$$

Where:

N = number of deaths

L = standard life expectancy at age of death in years

Because YLL measure the incident stream of lost years of life due to deaths, an incidence perspective is also taken for the calculation of YLD. To estimate YLD for a particular cause in a particular time period, the number of incident cases in that period is multiplied by the average duration of the disease and a weight factor that reflects the severity of the disease on a scale from 0 (perfect health) to 1 (dead) [148]. The basic formula for YLD is the following (again, without applying social preferences) (3):

$$YLD = I \times D_w \times L \quad (3)$$

Where:

I = number of incident cases

D_w = disability weight

L = average duration of the case until remission or death (years)

Figure 30 - Global burden of Parkinson's disease, measured in disability-adjusted life years per 100.000 inhabitants in 2004. Figure available on the Wikipedia [163] based on data from WHO [153].

Based on the World Health Report 2001 on mental health [164], PD DALY contributed 0.1% of the Global Burden of Disease (GBD) in the world, 0.6% in the European A subregion (European countries with very low children and adult mortality according to WHO classification), and 0.5% of the GBD in Spain [148]. In accordance with such data for the European A subregion, PD represented approximately 1/200 of the GBD. In Spain, based on the extended work done by Cubo et al. [148], (discounting rate 3%, K=1, see 9.1.4 Discounting and age-weighting modulation for

a detailed explanation of discounting), PD generated 67,582 DALY, comprising 6,351 (9.4%) YLL and 61,231 (90.6%) YLD. Most PD DALY (57.5%) occurred in the population 60 to 74 years of age. In order to calculate the YLD value PD was modelled as a progressive condition, with affected people passing through the three stages described in a previous study [165]. *Figure 30* shows the global burden in DALYs of PD with data from the WHO, generally speaking, countries with aged populations show a higher burden of PD.

In order to calculate the YLD value PD was modeled as a progressive condition, with affected people passing through the three stages described in a previous study [165]. On the basis of that it was assumed that two thirds of total PD duration was spent in the mild stage, with a disability weight of 0.48 (0.31– 0.64), and the rest in the intermediate and high end stages, with disability weight levels of 0.79 (0.72– 0.85) and 0.92 (0.89–0.95), respectively.

3.5 Signs and symptoms

PD is a neurodegenerative disease presentation both motor and non-motor [142], [145]. There are four cardinal signs of PD that can be grouped under the acronym TRAP: Tremor at rest, Rigidity, Akinesia (or bradykinesia) and Postural instability. In addition, flexed posture and freezing (motor blocks) have been included among classic features of parkinsonism, with PD as the most common form [166].

3.5.1 Motor symptoms

a) Tremor

Tremor is one of the main symptoms associated with PD and likely the most well-known by the general population. However, contrary to this popular belief, it is not universal in PD and approximately one-quarter of patients do not have tremor [142]. Characteristically, rest tremor disappears with action and during sleep [166]. However, sometimes the patient also has an “action tremor”, similar to that seen in patients with Essential Tremor (ET) [142]. Furthermore, recent works suggest that essential tremor is a risk factor for PD [167]. Tremors are unilateral, occur at a frequency range between 4 and 6 Hz, and almost always are prominent in the distal part of an extremity. In PD, rest tremor can also affect the legs or even the lips, chin and jaw but, unlike ET, rarely disturbs the neck, head or voice [166]. In addition to rest tremor, many patients with PD also have postural tremor that is more prominent and, therefore, could be more disabling than rest tremor and may be the first manifestation of the disease [168], [169]. Postural tremor (“re-emergent tremor”) in PD is differentiated from essential tremor since its appearance is often delayed after the patient assumes an outstretched horizontal position [168]. In approximately three-quarters of patients, tremor is the first symptom to be observed. However, since non-Parkinsonian tremor can occur, it is important to differentiate between Parkinsonian tremor and ET. Slowness, some loss of dexterity and a degree of awkwardness in carrying out some physical activities has often preceded the onset of a trembling hand. But patients frequently tolerate, or are not aware that these signs are symptoms indeed, and ask for advice only when the first tremors appear [142].

b) Akinesia, hypokinesia and bradykinesia.

Akinesia (a-, "without", -kinesia, "motion") refers to the loss or inability to initiate voluntary movements. A diminished dopaminergic cell activity in the direct pathway of movement leads to show difficulty selecting and/or activating motor programs in the central nervous system. Reduction in movement (hypokinesia) and slowed movement (bradykinesia) are strongly linked with akinesia and lead to a general “slowing down” as well as a progressive reduction in the amplitude of motor activity with developing fatigue [142]. These symptoms are difficult to identify for the patients and non specialist physicians. Specially in the early phases of the disease. Actually, they could be difficult to differentiate them from physical tiredness or by the physical decline due to the aging process. The term bradykinesia refers precisely to the slowness of movement (rather than being a slowness in initiation, i.e. akinesia), in the planning and execution of movements as well as performing sequential and simultaneous tasks [166], [170]. The initial manifestation is often slowness in performing activities of daily living and slow movement and reaction times [171], [172]. This may include difficulties with tasks requiring fine motor control (e.g., buttoning, using utensils) [166], loss of spontaneous movements and gesturing, drooling because of

impaired swallowing [173], monotonic and hypophonic dysarthria, loss of facial expression (hypomimia) and decreased blinking, and reduced arm swing while walking. Assessment of bradykinesia usually includes having patients perform rapid, repetitive, alternating movements of the hand (finger taps, hand grips, hand pronation–supination) and heel taps and observing not only slowness but also decrementing amplitude. In common with other Parkinsonian symptoms, bradykinesia is dependent on the emotional state of the patient [166]. Finally, hypokinesia refers to decreased bodily movement. It is characterized by a partial or complete loss of muscle movement. Patients experience muscle rigidity and an inability to produce movement. It also results in a reduction of facial expression. Other noticeable effects resulting from hyperkinesia include a reduction or loss of arm swing when walking, and difficulty experienced in attempting to carry out fine movements [142].

c) Rigidity

Rigidity is characterised by increased resistance present throughout the range of passive movement of a limb (flexion, extension or rotation about a joint). It may occur proximally (e.g., neck, shoulders, hips) and distally (e.g., wrists, ankles) [166]. Sometimes, it is described as the “cogwheel” phenomenon since the joints show a similar reponse when are pasively moved. The rigidity, or muscular stiffness, occurring in PD exacerbates the problems with movement resulting from akinesia, hypokinesia and bradykinesia. Moreover, it is a global effect since it could affects all the muscles in the body. When examining a patient, rigidity becomes apparent during a passive movement, for example when the relaxed limb of the patient is moved from someone else, e.g. the wrist is being bent or the head turned to the side by the examiner. The resistance to passive movement is constant throughout the range of movement, unlike spasticity where sudden relaxation can occur after movement has begun [142]. Rigidity may be associated with pain, and painful shoulder is one of the most frequent initial manifestations of PD although it is commonly misdiagnosed as arthritis, bursitis or rotator cuff injury [166], [174], [175].

d) Postural instability

Patients with PD develop a characteristic flexed posture resulting especially from flexion of the knees and hands [142]. It is generally a manifestation of the late stages of PD and usually occurs after the onset of other clinical features [166]. As the course of PD progresses, postural instability becomes a more troublesome feature. A steady posture is normally maintained by the nervous system making continuous reflex adjustments. Impairment of these mechanisms leads to a reduced ability to maintain balance, making the patient less steady when walking and particularly when turning [142]. Postural instability (along with freezing of gait) is the most common cause of falls and contributes significantly to the risk of hip fractures [176]. Several other factors also influence the occurrence of postural instability in patients with PD. These include other Parkinsonian symptoms, orthostatic hypotension, age related sensory changes and the ability to integrate visual, vestibular and proprioceptive sensory input (kinesthesia) [166]. The pull test, in which the patient is quickly pulled backward or forward by the shoulders, is used to assess the degree of retropulsion or propulsion, respectively. Taking more than two steps backwards or the absence of any postural response indicates an abnormal postural response [166]. In PD with postural instability, the patient will be unable to compensate and fall backwards. With normal control of balance, a person will take a step backwards to maintain an upright posture [142].

e) Gait disturbances

Gait symptoms are a common feature of Parkinson's disease, but usually occur around five years after initial diagnosis. Occurrence in the early stages of the disease is unusual, however in the elderly the development of gait problems tends to occur sooner compared to younger patients [142]. Parkinsonian gait is characterized by flexion of the trunk and reduced arm swing, most pronounced on the most affected body side. The stride length is shortened, the knees become flexed, and a shuffling gait develops [147]. The gait disturbances in PD may be divided into two types [177]:

1. Continuous, mainly characterised by a reduction of gait speed [178]
2. Episodic [179], [180]. The episodic gait disturbances occur occasionally and intermittently and appearing randomly.

The episodic gait disturbances include festination, gait initiation hesitation, and freezing of gait [181]–[184].

“Freezing” is the term used to describe the situation where a patient is either unable to initiate movement or suddenly stops the flow of movement. This is sometimes triggered by an external factor such as entering through a doorway or narrow space [142]. Freezing of gait is an incapacitating phenomenon that is experienced mainly by patients with advanced PD [181], [185]–[187]. The continuous changes refer to alterations in the walking pattern (temporal and spatial kinematic parameters). Both types of disturbances are due to dysfunction of the basal ganglia, although the mechanisms for such disturbances are independent and they are responsible for the increase in the incidence of falls in PD patients [181]. Falls are one of the most significant consequences of a disturbed gait in PD [181], [183], [188], [189]. As the disease progresses, gait impairment and falls become increasingly important and develop into one of the main complaints among PD patients and caregivers. The most relevant changes (temporal and spatial) affected by PD are apparent only when gait is evaluated quantitatively with gait analysis systems. Increased left-right gait asymmetry and diminished left-right bilateral coordination are changes affected by the disease [188], [189]. Another gait feature in PD patients seems to be the inability to generate a consistent and steady gait rhythm, resulting in an increase in higher stride-to-stride variability [190]–[192]. An increase of gait variability can be detected throughout the disease even in early the stages of the disease when patients have not started taking anti-Parkinsonian medications [191]. The magnitude of the variability is enhanced by disease severity. It has been shown the relationship between gait variability, fall history and other Parkinsonian features [192]–[195]. An effect of Levodopa administration has been described on gait variability and fall frequency in PD patients [196]. In the OFF state, stride time variability was significantly larger among fallers compared to non-fallers [194]. Stride time variability decreased significantly in response to levodopa in both groups (fallers and non-fallers) [196]. However, in the ON state, stride time variability remained significantly higher in the fallers than non-fallers. The locomotor control system that regulates gait variability and gait phases timing is impaired in PD patients with history of falls [194]. On the other hand, no significant correlation has been described between stride-to-stride variability with other motor features such as tremor, rigidity, or bradykinesia in the OFF state [194]. In addition, levodopa decreases stride-to-stride variability in non-fallers suggesting that dopaminergic networks regulate the control of gait variability and timing suggesting the possibility of damaged and exaggerated impairment of “internal clock” function in PD fallers [194]. In the ON state, when the motor performance is optimal, the PD fallers showed also a further increased control of stride-to-stride variability. Hausdorff et al. suggests the possibility of damaged and exaggerated impairment of “internal clock” function in PD fallers.

3.5.2 Non-motor symptoms

James Parkinson accurately described the motor problems of patients but also noted several non-motor features. Several studies have shown that the non-motor symptoms of Parkinson's disease, such as depression, psychosis, falls, and sleep disturbance, have greater significance when assessed by Quality of Life measures [197]. As it was already mentioned, dopamine is a neurotransmitter which is not only involved in execution of movements but also in other functions or processes such as cognitive execution, sleep and mood. It is important to highlight that, not all these symptoms have the same origin of PD or are consequence of it. Nevertheless, either they have the same origin or not, a significant number of PD patients show them. Indeed, non-motor symptoms dominate the clinical picture of advanced Parkinson's disease and contribute to severe disability and impaired quality of life. However, attention is focused on the recognition and quantitation of non-motor symptoms, which will form the basis of improved treatments. By contrast non-motor symptoms are often poorly recognised and inadequately treated. Some non-motor symptoms, including depression, constipation, pain, genitourinary problems, and sleep disorders, can be improved with available treatments. Other non-motor symptoms can be more refractory and need the introduction of novel non-dopaminergic drugs. Inevitably, the development of treatments that can slow or prevent the progression of Parkinson's disease and its multicentre neurodegeneration provides the best hope of curing non-motor symptoms [197].

a) Depression

There are psychological reasons why people who have been diagnosed with a neurodegenerative disease like PD can become depressed, but their brain pathways are also affected by the disease and these are closely associated

with mood [198]. The significance of depression as a feature of Parkinson's disease is often underestimated. Depending on the criteria used, depression can affect up to 10-45% of Parkinson's disease patients [199] with a strong impact on the patient QoL. Specific treatment for depression may not only improve mental wellbeing, but subsequently contribute to the improvement of other symptoms that may have worsened with the development of depression such as sleep problems, fatigue, bradykinesia and tremor [142].

b) Anxiety and apathy

Anxiety disorders are common in PD and can also be a preclinical risk factor. Anxiety can present as panic attacks, phobias, or generalised anxiety disorder, and can be related to drug-induced motor fluctuations in PD [200], [201].

c) Hallucinations

Up to 40% of patients have visual hallucinations, usually benign, whereas more sinister symptoms, such as delusions, paranoid ideation, and delirium, become more frequent as the disease progresses [202]. Occasionally, auditory hallucinations occur either alone or in combination with visual hallucinations. Delirium can occur in advanced dementia or can be induced by concurrent infection or dopaminergic drugs [197]. Unfortunately, some of the drugs used in the treatment of Parkinson's disease can themselves precipitate hallucinations as an adverse effect [142].

d) Cognitive

Dementia occurs in up to 40% of people with Parkinson's disease, a rate about six-times higher than that in healthy individuals [203]. Dementia is progressive and is clinically characterised by a dysexecutive syndrome with impairment of visuospatial abilities and memory on a background of loss of response to dopaminergic drugs including levodopa [204], [205]. Aspects of mental function such as reduced short-term memory, confusion, adverse effects on judgement and reasoning, and visual hallucinations are key features of dementia. Some of these deficits are strongly related to dopamine dysregulation and might be accentuated or, on the contrary, ameliorated by dopaminergic drug therapy (for example the attentional/executive domain) [142], [206]. Other deficits might reflect a cognitive decline and they are not susceptible to pharmacological therapy (such as associative learning or pattern and spatial recognition memory) [206]. Moreover PD patients have impairments in emotional recognition and empathy [207], [208].

e) Sleep disorders

Nearly all patients with Parkinson's disease report some kind of sleep disturbance. Rapid Behaviour Disorder (RBD) occurs in about a third of patients with Parkinson's disease [209], [210] and represents a parasomnia characterised by loss of the normal skeletal muscle atonia during REM sleep, thus enabling patients to physically enact their dreams, which can often be vivid or unpleasant [211]. Other symptoms have also a significant effect on the quality of sleep, e.g. nocturia (frequent urination at night) causes bed-wetting if the patient is too rigid to get out of bed or Restless Legs Syndrome (RLS) leads to frequent arousal [197]. Sleep disordered breathing due to obstructive sleep apnea and a narcoleptic pattern of rapid onset of sleep are also important hidden causes of sleep related morbidity in PD [212], [213]. Vocalisations (talking, shouting, vocal threats) and abnormal movements (arm or leg jerks, falling out of bed, violent assaults) are commonly reported by bed partners [197]. Excessive daytime sleepiness (EDS) and involuntary dozing affects up to 50% of patients with PD and could be a preclinical marker [212], [214].

f) Bladder problems

Nocturia, apart from affect the quality of sleep, is often the first indication that PD is affecting the bladder. The symptom is usually mild and occurs in later stages of Parkinson's disease. Detrusor hyperreflexia produces a sense of urgency and urinary frequency. Some patients notice that the problems are more common during the Off periods of Parkinson's disease [142], [215].

g) Constipation

The main gastrointestinal symptom associated with PD is constipation. This is the result of reduced stool transit in the colon, but severity may be made worse by inadequate intake of liquid and food caused by swallowing

difficulties. Constipation may cause abdominal distension, colicky pain and substantial discomfort [142], [215].

h) Sensory symptoms

Sensory symptoms such as olfactory dysfunction, pain, paraesthesia, akathisia, oral pain and genital pain are frequent but are often not recognised as Parkinsonian symptoms [166]. One study found that olfactory dysfunction (hyposmia), which eventually affects up to 90% of patients with Parkinson's disease, is a potential preclinical marker of motor symptoms and may be an early marker of PD [197].

i) Dysphagia

Dysphagia (difficulty in swallowing) is a common problem in up to one-half of patients, especially those in the more advanced stages of PD. The dysphagia can arise from a reduction in tongue movement passing food or saliva to the back of the throat, or difficulty in initiating the swallow [142].

j) Speech problems

It is estimated that 89% of people with PD have a speech or voice disorder including disorders of laryngeal, respiratory, and articulatory function. Despite the high incidence of speech and voice impairment, studies suggest that only 3-4% of people with PD receive speech treatment [216]. PD impacts speech performance in different ways. Dysphonia (an impairment in the ability to produce voice sounds using the vocal organs) and dysarthria (poor articulation of phonemes) are typical symptoms presented in PD. Decrease in muscle movement of the larynx could lead to reduced volume and articulation of speech [142]. Also, analyses revealed that fundamental frequency variability was diminished in PD patients. Moreover, this decline has shown to be sensitive to the early progression of the disease and to the initiation of pharmacologic intervention [217].

k) Handwriting

Micrographic, writing that is very small sometimes to the point of being unreadable, is often an early symptom of PD. The writing becomes smaller and smaller the longer the patient writes [142]. Rigidity and lack of fluency in the movements have also a direct impact on handwriting and other task requiring fine movements.

3.6 Progression

Parkinson's disease is a progressive neurodegenerative condition characterized and diagnosed by the presence of motor and non-motor symptoms [218]. Symptoms tend to appear gradually, normally in just one side of the body at first and eventually extended to both sides as disease progresses. PD follows a slowly chronic progressive course, and the motor cardinal symptoms of the disease appear only when the degenerative process has progressed for a long time [218], in some cases for more than 10 years [219]. Either the severity and presence of the symptoms and their progression over time are different from one patient to another. Some are more bothersome than others depending on what a person normally does during the day and some people with Parkinson's live with mild symptoms for many years, whereas others develop movement difficulties more quickly [220]. The long premotor phase is nevertheless not clinically silent since non-motor symptoms such as hyposmia [221], REM sleep behaviour disorder [222], and constipation [223] can antedate the occurrence of tremor and/or akinesia [197]. The association between preclinical Parkinson's disease and non-motor symptoms, such as olfactory disturbance and RBD, could lead to development of some presymptomatic testing (see 3.7 *Diagnosis, clinical examination*) [197]. In contrast, other non-motor symptoms, especially dementia, are known to occur later in the evolution of the disease and to reflect disease progression and severity [197].

Figure 31 - Schematic representation of the clinical progression of Parkinson's disease based on a figure from Lebouvier et al. [28] enriched with comments from the Parkinson's Disease Foundation [38] and the work of Cubo et al. about the progression of PD burden [148]

Figure 31 shows a schematic representation of the clinical progression of PD. The thin green line represents the continuous degeneration of the dopaminergic neurons of the *substantia nigra*. When dopaminergic neuronal loss reaches >50%, cardinal motor symptoms appear (thick dark blue line) and PD becomes fully symptomatic (white background). Motor symptoms worsen over time but respond to dopamine replenishment therapy. During the premotor phase (blue background) non-motor symptoms (dashed blue line) may already be present. Non-motor symptoms burden also increases with time but contrary to motor symptoms do not respond to treatment and constitute most of the disability in advanced PD [218]. Finally, as the disease evolves the burden of the PD increases, Cubo et al. modeled PD as a progressive condition, with affected people passing through three stages [148]. Based on this model, it is assumed that two thirds of total PD duration was spent in the mild stage, with a disability weight of 0.48, and the rest in the intermediate and high end stages, with disability weight levels of 0.79 and 0.92, respectively (dashed red line in the Figure 31).

Below are some descriptions of mild, moderate and advanced Parkinson's [220]:

a) Mild Parkinson's

- Motor symptoms occur on one side of the body.
- Motor symptoms do not affect the performance of daily activities.
- Some people may notice slight changes in posture, gait or facial expression.
- Drug therapy suppress symptoms effectively.
- Regular exercise could be beneficial, improving and maintaining mobility, flexibility, range of motion and balance.

b) Moderate Parkinson's

- Motor symptoms occur on both sides of the body.
- Body movements are slower.
- Patients could show balance and coordination problems.
- "Freezing of gait" (Fog) episodes may occur.
- "Wearing-off" between dosages of treatment could occur.
- Parkinson's medications may cause side effects, including dyskinesias (involuntary movements).
- Regular exercise and physical therapy could still contribute for a better mobility and balance.
- Occupational therapy may provide strategies for maintaining independence in the activities of daily life.

c) Advanced Parkinson's

- Great difficulty walking; in wheelchair or bed most of the day.
- Patients are not able to live alone and they could need assistance with daily activities.
- Cognitive problems may be prominent, including hallucinations and delusions.
- Balancing the benefits of medications with their side effects becomes more challenging.

While the severity and rate of progression may vary from person to person almost invariably all PD patients will develop motor and non-motor fluctuations along the day due to the wearing-off effect (see *3.8 Treatment*). At this stage patient's condition becomes very unpredictable and the number of medications intakes is also increased. Thus, the responsible clinician frequently has to adjust the medications dosage.

3.7 Diagnosis, clinical examination and management

Unlike the diagnosis of many other diseases, there is no universally accepted diagnostic tests or tool to conclude that a subject has Parkinson's disease. Instead, the clinical observations and the clinical history of the subject are inputs taken into consideration for the diagnosis of PD [142]. Because there is no definitive test for the diagnosis of PD, the disease must be diagnosed based on their medical history and an extensive neurological and physical examination. The diagnosis is likely when two out of the four cardinal symptoms of PD (tremor, rigidity, akinesia and postural instability) are present [146], implying that the diagnosis is made only many years after the real onset of the neurodegenerative process [224]. As it was already discussed in the previous section (*3.6 Progression*) could be up to 10 years after the onset of the disease. Thus, PD can be difficult to diagnose in its early stages, and may be mimicked by other diseases, such as essential tremor, multiple system atrophy and progressive supranuclear palsy [224]. Treatment strategies for PD are mostly aimed at relieving motor symptoms and not at modifying the disease process [225]. Moreover, some of the initial symptoms on PD such as rigidity and bradykinesia are erroneously imputed to the ageing process by the patients, therefore, they will not seek for professional advance.

Parkinsonian disorders can be classified as four types: primary (idiopathic) parkinsonism, secondary (acquired, symptomatic) parkinsonism, hereditary degenerative parkinsonism and multiple system degeneration (parkinsonism plus syndromes) being the idiopathic the most common [146]. Several features in the presence and progression of the symptoms and response to treatment can be used to differentiate PD from other Parkinsonian disorders [166]. Technological advances in the field of molecular genetics and in in vivo imaging have allowed the development of some reliable biomarkers either for early diagnosis or to assess disease progression. For instance, transcranial ultrasound (2002) [226], high-field Magnetic Resonance Imaging (MRI) (2008) [227] and dosage of neuronal protein involved in the pathogenesis of the disease in the cerebrospinal fluid (2010) [228] are new tools that are likely to help in the diagnosis and management of PD patients in the near future. Also, the use of medical

images had been also explored to study the PD, functional Magnetic Resonance Imaging (fMRI) to assess the effects of levodopa [229] or the effects of the Deep Brain Stimulation (DBS) [230] and to study the automatic movements in patients with PD [231]. Positron Emission Tomography (PET) studies have been used to an early and differential diagnosis of PD [232] and to study the basal ganglia outflow [233], [^{123}I]-CIT Single-photon Emission Computed Tomography (SPECT) is used as a tool for the diagnosis of PD [146] and to measure the rate of progression [234], [235]. Likewise, there are some recent Information and Communication Technologies (ICT) projects such as *PVI* and *neuroQWERTY* that used voice analysis and keyboard typing for the early diagnosis of PD. Nevertheless no fully validated biomarker for PD is available yet [236] and there is still a need for new biomarkers that will complement the ones already available [218].

Nonetheless, the accuracy and sensitivity of this diagnostics method is similar to the clinical diagnosis [146]. Correctly PD diagnosis could be quite challenging. It can be difficult to distinguish idiopathic Parkinson's disease from certain other neurological conditions. It has been estimated that up to 24% of the diagnosis of PD are wrong, even when made by experts [237], [238] and approximately 5% of patients who do have pathology of Parkinson's disease (i.e. post-mortem-proven PD) have not been diagnosed with the condition. Misdiagnosis is often made in patients with essential tremor, vascular Parkinsonism or other parkinsonian syndromes.

3.7.1 The rating scales

In order to, somehow, objectivise and homogenise the clinical examination across different physicians, different rating scales are used for the evaluation of motor impairment and disability in patients with PD [166]. The first scales used in the clinical practice were focus on motor symptoms, but new scales include also information on non-motor symptoms. The fact that patients' symptoms can fluctuate widely needs to be taken into account when applying these scales in practice.

a) Hoehn and Yahr clinical rating scale

The Hoehn and Yahr scale defines extensive categories of motor function in PD and it is broadly used in the clinical practice. It is a simple scale and therefore quick and easy to apply. Progression in the stages of this scale has been found to correlate with motor decline, deterioration in QoL, and neuroimaging studies of dopaminergic loss. However, because of its simplicity and lack of detail (for example on issues of unilateral versus bilateral disease or by not including non-motor aspects) the scale is not comprehensive. Besides, it is not particularly sensitive in showing changes in a patient's functional ability [142]. A modified version is sometimes used [239]. This scale is mainly used to indicate the stage of a patient's disease based on the severity of the symptoms they are experiencing. *Table 6* provides a summary of the scale.

Scale	
1.0	Tremor or rigidity on one side of the body only (with or without bradykinesia).
1.5	Tremor or rigidity on one side of the body and axially (with or without bradykinesia).
2.0	Moderate tremor or rigidity on both sides of the body with bradykinesia but no impairment of balance.
2.5	Moderate tremor or rigidity on both sides of the body with bradykinesia, but recovery on retropulsion (pull) test.
3.0	Significant tremor or rigidity on both sides of the body with bradykinesia and some postural instability (patient still physically independent).
4.0	Severe disability, but still able to stand and walk without assistance.
5.0	Bedridden or wheelchair bound unless assisted (patient unable to function independently).

Table 6 - Hoehn and Yahr clinical rating scale

b) Unified Parkinson's Disease Rating Scale (UPDRS)

UPDRS is the more extensive scale assessing over 40 aspects of the disease. It includes motor performance assessment but also, the ability to perform activities of daily life. Some non-motor aspects, such as dysphagia and mental wellbeing, are also considered on this scale. The UPDRS is commonly used both in the clinical practice and

also within clinical trials to measure the effectiveness of a treatment [142]. Strengths of the UPDRS include its wide utilization, its nearly comprehensive coverage of motor symptoms and its reliability and validity. Weaknesses include several ambiguities in the written text, inadequate instructions for evaluators, some metric flaws, and the absence of screening questions on several important non-motor aspects of PD [240]. UPDRS Scale is the rating scale used in this project as “gold standard” and it enclosed as Annex I.

Section	
I	Mentation (4 items)
II	Activities of daily living (13 items)
III	Motor function (14 items)
IV	Complications of treatment (11 items)

Table 7 - Sections of the Unified Parkinson's Disease Rating Scale (UPDRS) [240]

c) Schwab and England Scale

This scale primarily focuses on the level of disability and independence of the patient. The measure is expressed in terms of a percentage from 100% (fully independent) to 10% (completely dependent). The Schwab and England scale is summarized in Table 8 [142].

Schwab and England scale rating scale	
100	Fully functioning; tasks performed with no difficulty; patient completely independent.
90	Some tasks take longer due to a degree of slowness and impairment; patient still completely independent.
80	Difficulty in performing some tasks; significant slowness; patient still completely independent.
70	Substantial slowness in performing tasks; some tasks quite difficult; patient no longer completely independent.
60	Very slow in performing tasks; some tasks now impossible; much effort required; patient now partly dependent another people.
50	Difficulty in performing many tasks; needs assistance with bathing etc.; patient now dependent on other people.
40	Unable to carry out many tasks without help; patient now very dependent on other people.
30	Can only carry out very few tasks without help; patient now highly dependent on other people.
20	Unable to carry out any tasks alone; severely disabled; patient now nearly completely dependent on other people.
10	Unable to carry out any tasks; completely disabled.

Table 8 - Schwab and England scale rating scale

d) Abnormal Involuntary Movement Scale (AIMS)

Section number	Section description
I	Facial and oral movements
II	Extremity movements
III	Trunk movements
IV	Global judgments
V	Dental status

Table 9 - Abnormal involuntary movement scale (AIMS)

The AIMS is a 12-item clinician-rated scale to assess severity of dyskinesias in patients taking neuroleptic medications. Additional items assess the overall severity, incapacitation, and the patient's level of awareness of the movements, and distress associated with them. The AIMS has been used extensively in clinical trials. Due to its simple design and short assessment time, the AIMS can easily be integrated into a routine clinical evaluation by the clinician or another trained evaluator[142].

e) Parkinson's Disease Sleep Scale (PDSS)

The PDSS scale has been developed to specifically measure the extent and impact that sleep problems cause. A visual analogue scale is used to assess 15 symptoms associated with disturbed sleep in Parkinson's disease. The

patient marks along the scale from 0 (severe symptoms and always experienced) to 10 (symptoms not experienced) for each of the 15 items included in the assessment. It is especially useful assessing the effectiveness of treatments aimed at treating specific symptoms that disturb sleep such as restless leg syndrome (RLS) [142].

3.8 Treatment

3.8.1 Pharmacotherapy

In the very early stages of Parkinson's disease, when functional disability is minimal [142], the use of pharmacological treatment is often unnecessary and not recommended due to the potential side-effects. However, as disease progresses and once symptoms are troublesome and begin to impact the patient quality of life a pharmacotherapy should be considered. The currently available pharmacotherapies for treatment of PD provide only symptomatic relief. These therapies attempt to replenish the dopamine content in the brain, nevertheless they do not prevent or control the progression of the disease, and accordingly the patient compliance and satisfaction are low. L-dihydroxyphenylalanine (L-DOPA), also known as levodopa, remains as the gold standard because it can readily cross the blood brain barrier and be converted to dopamine. Because L-DOPA is also converted into dopamine in the peripheral nervous system, causing undesirable adverse events such as nausea and vomiting, it is standard in clinical practice to co-administer L-DOPA with aromatic L-amino acid decarboxylase inhibitor such as carbidopa that does not cross the blood-brain barrier [146] and therefore increase L-DOPA delivery to the brain. The onset the L-DOPA effect is rapid [241] and it is the most effective treatment of PD cardinal symptoms [242]. Nonetheless, long-term levodopa treatment is associated with significant complications including involuntary movements, dyskinesias, and response fluctuations known as the "wearing-off" effect [243] (see 3.8.1.1 *Dyskinesias and wearing-off*). The relevance of patient age at disease onset for starting levodopa therapy is still debated and current guidelines have not yet properly assessed this issue [241]. Tarazi et al. (2014) carried out a review of the current pharmacotherapies available for PD management (Sinemet CR®, Sinemet®, Stalevo®, Parlodel®, Dopergin®, Permax®, Dostinex®, Mirapex®, Requip®) [146]. All pharmacotherapies have limited efficacy (do not provide adequate neuroprotection and are incapable of slowing the progression of PD), do not prevent the progression of the disease, and are associated with adverse motor and non-motor side effects. There are many ongoing research works aimed at developing novel pharmacotherapies with improved efficacy, safety, and long-term maintenance. These therapies include adenosine A_{2A} receptor antagonists, glutamate receptor antagonists, monoamine oxidase inhibitors, anti-apoptotic agents, and antioxidants such Coenzyme Q10 (CoQ10), N-acetyl-cysteine (NAC) and Edaravone (MCI-186, 3-methyl-1-phenyl-2-pyrazolin-5-one) [146]. It is also interesting to highlight that in parallel to the pharmacotherapies several non-pharmacotherapies have also emerged as adjunctive or alternative approaches for treatment – and even for delaying the onset of the disease and slowing its progression. These therapies, however, remain in different stages of preclinical and clinical development, and include the following: viral vector gene therapy, microRNAs, transglutaminases, RTP801, stem cells and glial derived neurotrophic factor [146].

3.8.1.1 Dyskinesias and wearing-off

In the early stages of PD the response to the L-DOPA treatment is often quite good, and the benefits of the pharmacotherapy persist even if the patient forget one intake along the day. However, with the disease progression, the effects of the treatment wear-off before the next dose (the "wearing-off" effect) and patients fluctuate between the so called "On" phases - in which the symptoms are properly controlled by the medication - and "Off" phases - proportions of waking time experiencing a loss of treatment effect [244]. Furthermore, "On" periods can be associated with involuntary movements or dyskinesias induced by L-dopa [245]–[248]. These are usually choreiform or dance-like movements but can consist of dystonia, myoclonus and other movement disorders. Typically, they may occur at peak plasma levels or during a "trough", when plasma levels are lowest just before the next dose [249]. Less commonly, patients experience large amplitude repetitive "kicking" dyskinetic movements of the legs [247]. These movements tend to appear before the L-dopa response commences, disappear during the "On" period, and re-emerge as the benefit disappears and as the patient turns "Off" [147]. Thus, patients

treated with L-DOPA can cycle between “On” periods in which the effect is complicated by dyskinesias, and “Off” periods in which the Parkinsonism is not controlled and patients can be akinetic and frozen. With disease progression, it becomes increasingly difficult to adjust the drug dosage to find the right trade off [147].

Factors involved in the development of motor complications are not completely elucidated and understood yet. Patients with motor fluctuations (“wearing-off” and “on-off” fluctuations) may show akinetic-rigid onset, longer disease and treatment duration (sometimes longer time latency since diagnosis), higher intake of levodopa dose per day (>300 mg/day), greater disability and also a genetic predisposition. Likewise patients showing dyskinesias tend to present higher severities and longer treatment duration, while association with levodopa daily dose is less consistent. Gender as well as genetic factors may also play a significant role [241]. Anyhow, the prevalence of motor fluctuations and dyskinesias increases with the duration and severity of the disease as well as with the duration of treatment (appearing typically after 3 to 6 years after initiation of treatment) [244], [250], [251]. Thus, after approximately five years of treatment, more than 50% of patients experience motor fluctuations and dyskinesias [252]. After ten years of L-DOPA therapy, motor complications have developed in around 70-80% of patients, and in almost 100% of those with disease onset below the age of 45-50 years [245], [246], [253]. Non-motor fluctuations (NMF) – involving cognitive, psychiatric, sensory/pain and autonomic domains – could also occur in response to levodopa, tend to increase with disease progression and contribute to the worsening of motor disability [241]. The management of motor fluctuations and dyskinesias is still a major challenge in the long-term treatment of PD as they affect ADL and QoL of the patient as well as it involves a considerable caregiver burden [241], [244]. Motor complications may improve when levodopa plasma concentrations are stabilised. Stabilisation is often attempted using levodopa controlled-release forms (e.g. levodopa/carbidopa, controlled release formulation or through an increase in dose administration frequency (i.e., divided dosage administration). However, all patients eventually need to increase their total daily dosage of levodopa by 24 to 85% to achieve desirable results [249], [254].

Figure 32 - Motor Complications in Patients Taking Levodopa for Advanced PD (Illustration from [255] based on previous research works [256]–[258])

Some levodopa formulations combines levodopa/carbidopa with the catechol-O-methyltransferase (COMT) inhibitor entacapone. Entacapone is a selective reversible inhibitor of COMT. COMT inhibitors prolong the availability of levodopa to the brain and are clinically beneficial as adjunctive treatment to levodopa therapy in PD patients with end-of-dose fluctuations. Intervention with entacapone optimises the benefits of levodopa and reduces off-time by 17% to 22%. Entacapone is approved by the Food and Drug Administration (FDA) for marketing in the US as an adjunct to levodopa/carbidopa to treat the symptoms associated with idiopathic PD in patients who experience end-of-dose wearing-off [146], [254]. On the other hand, the inclusion of entacapone may

result in levodopa-induced dyskinesias. Thus, when entacapone is added to a patient's regimen, levodopa dosage should be decreased by 10 to 12% to control these dyskinesias. Entacapone and levodopa have similar pharmacokinetic profiles and should be administered together, which also allows for ease of use. Patients benefit from immediate symptomatic relief with the first dose of entacapone [254].

3.8.2 Surgical interventions

The management of advanced PD (aPD) is challenging and there is a considerable unmet need for effective, symptomatic treatments that can reduce the amount of time patients spend in an "Off" state. Current treatments include oral strategies and, less commonly, infusion strategies (such as apomorphine or intraduodenal levodopa). Brain surgery such as deep brain stimulation (DBS), pallidotomy, thalamotomy and gamma knife surgery have emerged as alternative interventions for advanced PD patients who have completely utilized standard treatments and still suffer from persistent motor fluctuations [146], [244]. Attempts to alleviate the PD symptoms with surgery date back to the 1940s (20 years before the discovering of the levodopa) [142]. Nevertheless, the beneficial effects of these interventions, especially during the early decades of exploring these novel surgical procedures were very limited as well as with a high rate of mortality and substantial morbidity. This situation has changed significantly in the last years in parallel with the advance on surgery, innovations such as the stereotactic surgery and the use of more accurate biomedical images like Computerized Tomography (CT) or Magnetic Resonance Imaging (MRI) scans to build navigation maps aided to build better surgical procedures in the case of PD.

The employed techniques consisted primarily on lesioning areas of the brain (the motor cortex and the dentate nucleus of the cerebellum) and pathways in the spinal cord. In the 1950s, slightly more successful attempts were made by making lesions in the globus pallidus. In 1960s the discovery of the levodopa as an effective PD treatment diverted interest towards drug therapy. The interest for the surgical solutions come back when the dyskinesias and motor fluctuations were identified as a severe limitation of the treatment exclusively with levodopa [142].

3.8.2.1 Deep brain stimulation (DBS)

Deep brain stimulation (DBS) is a surgical technique that involves implantation of electrodes in specific regions of the brain (guided by imaging techniques such as CT or MRI). DBS uses a surgically implanted medical device, similar to a cardiac pacemaker, to deliver electrical stimulation to the parts of the brain that control movement. DBS is used to treat levodopa-responsive symptoms, tremor, "On-Off" fluctuations and dyskinesia, and the typical candidates for this surgery are PD patients with persistent motor symptoms despite optimal medical therapy. However, gait impairments, balance and speech have been reported to have less chance of improving and in some cases even worsening [146]. DBS at high frequency was first used in 1997 to replace thalamotomy in treating the PD tremor, and has subsequently been applied to the pallidum and the subthalamic nucleus (a strategic node in the functional control of motor activity in the basal ganglia) [259].

Target sites for DBS in the brain include the globus pallidus (GPi), the subthalamic nucleus (STN), and the ventral intermedius nucleus (VIM) - the last one is only effective for the treatment of tremors - of the thalamus which are clusters of nerve cells critical to the control of movement [260]. Targeting STN and GPi show similar results and benefits for the cardinal symptoms of PD, although in the long-term STN could be better [146]. The exact mechanism of how DBS improves symptoms of PD is not clearly understood, it is hypothesized that this kind of stimulation could contribute to normalizing the neurotransmission along the outputs of the basal ganglia. These stimuli lead also to release calcium and neurotransmitters including adenosine and glutamate. It also promotes neurogenesis and an increase in blood flow in stimulated areas [146]. It was found that, the benefits provided by the DBS intervention remained significantly improved after 3–4 years [261]. Also, the combination of stimulation and pharmacotherapy (which could be significantly reduced on this scenario) showed significant improvements in motor disability, activities of daily living, levodopa-induced motor complications and time with good mobility compared with patients who received medical therapy [146], [262]. Also, DBS significantly improved the survival of late-stage PD patients and it also reduced the percentage of patients death respiratory failure, the most frequent cause of death in PD [146]. On the other hand, the implantation of electrodes in the brain and the use of implantable

device bring along evident side effects and complications such as intracranial haemorrhage, infection and post-operative seizures. Cognitive impairment, memory deficits and psychological impairments are also reported as side effects of the DBS [146].

As practical example of DBS device, the Activa System of Medtronic [263] is analysed considering the information available in the website of the manufacturer. As general description of a DBS device we can talk about three implantable components:

- **Lead:** a thin insulated coiled wire with four 1.5 mm electrodes at the tip of the lead which deliver stimulation.
- **Extension:** a thin, insulated coiled wire that is threaded under the skin from the head, down the neck and into the upper chest.
- **Neurostimulator:** a small, sealed device which contains the battery and electronics. It is implanted beneath the skin in the chest. It produces the electrical pulses needed for stimulation.

External components of the system include a physician programmer (used to adjust in a non-invasive way the neurostimulator parameters) and the patient's hand-held magnet. The hand-held magnet is placed over the neurostimulator to turn the neurostimulator off or on. The DBS allows the adjustment of the amplitude (strength or intensity of stimulation), rate (number of pulses per second) and pulse width (length or duration of pulse).

Figure 33 - DBS configuration for bradykinesia/akinesia, rigidity and/or tremor (first and second from the left) and DBS configuration for the treatment of essential and Parkinsonian tremor (first from the right) [263]

3.8.2.2 Pallidotomy

Pallidotomy is a surgical procedure used to reduce motor fluctuations, tremor and dyskinesias by damaging the GPi, which is hypothesized to be overactive in PD patients. Pallidotomy in aPD reported significant improvements in Parkinsonism symptoms up to five years after surgery including tremor, rigidity and dyskinesias. However, in the long-term (ten years) bradykinesia and freezing of gait could even increase. Regardless of the decrease in motor complication reduction, the extent of the decrease is not as significant as in the DBS. Also, it could lead to reductions in cognitive and executive complications. Adverse effects are cognitive impairment, dysarthria and dysphagia [146].

3.8.2.3 Thalamotomy

Thermal radiofrequency thalamotomy is an invasive procedure for aPD patients who failed to respond to pharmacotherapy. It requires the passage of a probe into the brain toward the VIM nucleus of the thalamus guided by MRI. Significant improvement in PD symptoms including mobility, tremor, rigidity, emotional well-being, bodily discomfort, and activities of daily living has been reported after unilateral thalamotomy. The results of this intervention largely depend on the accuracy of locating and destroying a target as well as the size of the lesion. Side effects included paresthesia of lips, tongue, and fingers, head pain, and nausea at a one-year follow-up [146].

3.8.2.4 Gamma knife

Gamma knife is a non-invasive surgical intervention (takes around 15 to 40 minutes with local anaesthesia) utilized mainly in elderly PD patients with persistent tremor, comorbidities (such as cardiovascular diseases) that

ban other kind of surgical procedures where gamma radiation beams are pointed to the target destroying targeted tissue. This intervention creates a 3–4 mm centre of necrosis surrounded by a non-necrotic periphery. It has shown to improve tremor and activities of daily living (such as handwriting, and ability to drink) although no significant improvement was found in resting, postural, action, and head tremor. The main limitation of this intervention is that it has not the accuracy seen in invasive surgeries since no validation of the target site can be done. Nevertheless, progress in the imaging and brain atlas could improve the performance of this intervention. Potential adverse events include lesion accuracy and size and the delayed development of neurological complications secondary to radiation necrosis [146].

3.8.2.5 Duodenal administration of levodopa/carbidopa

Levodopa/Carbidopa Intestinal Gel (LCIG, produced by Abbott Laboratories and marketed as Duodopa®) is a method developed to minimize the fluctuation in levodopa plasma levels seen in oral administration by providing a continuous influx of steady levels of levodopa [146]. Patients are treated with LCIG if oral pharmacotherapy is not effective or if it is contraindicated (1% of the total PD population) [244]. LCIG uses a personal pump to administer the treatment into the duodenum, the main site of intestinal absorption, and therefore bypassing gastric emptying and preventing a suboptimal response to levodopa. Benefits of LCIG duodenal administration include a significant “Off” time and dyskinesia reduction. However, a significant variation was observed among aPD patients when answering questions about walking, being “off,” and being hyperkinetic. Especially during the morning since the infusion takes places only during the day. Also, due to this, patients could experience night time symptoms and it is suggested that they may benefit from 24-hour infusion. The adverse events of LCIG are those of the oral tablets but in this case including also the complications of using an implantable device (e.g. intestinal tube obstruction, infection, or accidental removal of the intestinal tube) [146].

Figure 34 - APO-go® pump (Image source: apo-go.com²⁵)

3.8.3 Other

3.8.3.1 Apomorphine pump

It is a pump for the subcutaneous infusion of the dopamine receptor agonist apomorphine, so as in the LCIG case it allows the Continuous Dopaminergic Stimulation (CDS). An example, the APO-go®, Figure 34, commercialized by Britannia Pharmaceuticals administers the treatment via a short and extremely fine needle into the subcutaneous fatty tissue of the abdominal area, to the right and left, under the level of the umbilicus and the thighs and upper arms. This approach in the delivery guarantee that almost 100% of the drug is absorbed into the blood stream. Again, continuous infusion is used when oral treatment is not enough to efficiently manage the symptoms of the patient. Generally it is used for 14-16 hours during the waking day, but can eventually be used at night if patient experience poor quality sleep or night time cramps. As adverse effects, continuous infusion can cause nausea and vomiting as well as low blood pressure, an anti-sickness medication during the first weeks to avoid nausea. Nodule formation occurs in some patients using APO-go®. For these reason it is important to rotate the injection site. In an APO-go® continuous infusion study, 75% of patients managed the Pump independently or

²⁵ <http://www.apo-go.com/what-is-apomorphine/continuous-infusion.html> (Last visit: 22 January 2016)

with some help from their family or carer – no nursing help was needed [264].

3.8.3.2 Patches

In the recent years new wearable-on-the-skin patch technology, based on stretchable electronics, nanomembranes, and nanoparticles, has been developed. This new technology has the potential to provide continuous movement monitoring as well as drug delivery in a device with the size and flexibility of a bandaid. Silicon nanomembranes have been fabricated to act as movement sensors and silica nanoparticles, activated by heat to release their payloads, can hold therapeutic drugs. The electronics include gold nanoparticles as a form of non-volatile memory, but the actual processing has to be done through an external device [265]. This kind of wearable systems able to monitor muscle activity and motor activity, store and transmit the data and deliver feedback therapy are the next frontier in personalized medicine and healthcare. However, they are still at a very early stage of development.

Figure 35 - Wearable electronic patch composed of data storage modules, diagnostic tools and therapeutic actuating elements [265].

3.8.4 Rehabilitation and exercise

Several studies pointed out that periodic exercise benefits physical functioning, health-related quality of life, strength, balance and gait in PD patients [266]–[268]. Tomlinson et al. (2012) carried out a systematic review and meta-analysis on 29 trials where different physiotherapy for PD were applied [269]. Significant short-term benefits were reported for nine of the 18 outcomes assessed: speed (0.04 m/s, 95% confidence interval 0.02 to 0.06, $p < 0.001$), Berg balance scale (3.71 points, 2.30 to 5.11, $p < 0.001$), and UPDRS scores (total score –6.15 points, –8.57 to –3.73, $p < 0.001$; activities of daily living subscore –1.36, –2.41 to –0.30, $p = 0.01$; motor subscore –5.01, –6.30 to –3.72, $p < 0.001$). Additionally, during the last decades several works have been using External Rhythmical Stimulation (ERS) techniques as recurrent tool to improve gait as well as other motor and non-motor symptoms such as bradykinesia in PD [270]–[284].

The impact of cueing is strongly linked with the phenomenon called “Kinesia paradoxa” which is often present in people with Parkinson's disease. Kinesia paradoxa refers to the sudden ability of some subjects to perform smooth, fluid movements temporarily and typically in the presence of external stimuli. For example, immobile patients who become excited may be able to make quick movements such as catching a ball (or may be able to suddenly run if someone screams “fire”). This phenomenon suggests that PD subjects have intact motor programmes but have difficulties accessing them without an external trigger, such as a loud noise, marching music or a visual cue requiring them to step over an obstacle [166]. Del Olmo & Cudeiro (2005) elaborated a rehabilitation program based on auditory cueing or Rhythmic Auditory Stimulation (RAS) showing that it facilitated locomotive function in patients with PD (N=15 idiopathic PD patients, N=15 control) and that it was a valid way to improve temporal stability in walking, or in other words, to improve or re-educate the timing of walking [270]. On this work gait velocity, cadence and stride length significantly improved ($p < 0.005$) when RAS cues were used. Nieuwboer et al. (2007) reported the results of the RESCUE study (see 4.4.21 RESCUE) a home physiotherapy programme using RAS on gait and gait-related activity on a PD population (N=153). The results revealed small but significant improvements after the intervention. In general terms, it was found an improvement of 4.2% on the posture and

gait scores ($p=0.005$). Severity of freezing was reduced by 5.5% in freezers only ($p=0.007$). Gait speed ($p=0.005$), step length ($p<0.001$) and timed balance tests ($p=0.003$) improved in the full cohort. Other than a greater confidence to carry out functional activities (Falls Efficacy Scale, $p=0.04$), no carry-over effects were observed in functional and quality of life domains. Effects of intervention had reduced considerably at 6-week follow-up [271]. Ford et al. (2010) also investigated the use of incremental RAS on PD patients ($N=12$) [274]. In this case the auditory cues rates were increased – starting from participant's comfortable walking pace – whether patients were able to maintain or increase stride length with increasing external auditory cues rate. The configuration of the rehabilitation sessions were sessions of 30min, 3 times per week during 8 weeks. And the results showed a significant ($p<0.01$) increase in walking velocity, stride length, and cadence after 8 weeks of training. And also, that a mean maximal rate of 157 BPM was achieved. Visual cueing was also explored as a technique to improve gait performance in PD. Schlick et al. (2015) run an experiment with PD patients ($N = 20$, follow-up $N=13$) to evaluate the effects of visual cues combined with treadmill training on gait performance comparing it with the training on the treadmill without visual cues [275]. After the training period, gait speed and stride length had increased in both groups ($p \leq 0.05$). But, patients that used visual cues scored better in the Timed Up and Go (TUG) Test ($p \leq 0.05$) and, at two months follow-up, they sustained better results in gait speed and stride length ($p \leq 0.05$) as well as in the TUGT ($p \leq 0.05$). Finally, haptic cueing or Rhythmic somatosensory cueing (RSC) has been also explored individually. Van Wegen et al. (2006) used a miniature vibrating cylinder attached to the wrist to explore whether PD patients ($N=17$) could adapt their walking pattern under conditions of changing walking speed and the presence of potentially distracting visual flow while walking on a treadmill. Walking guided by the haptic cueing resulted in lower stride frequencies, and thus larger step lengths ($p < 0.05$), regardless of walking speed. The presence of visual flow did not prejudice the use of RSC, no significant difference were found between both situations ($p > 0.05$). Thus, RSC could be an alternative or complement for auditory cueing, offering the additional benefit of robustness to changes in walking speed and visual distractors [276].

There are also available in the literature works confronting the effects of the different cueing stimulations. Spaulding et al. (2013) carried out a meta-analysis including 25 works until 2011 where the effect of visual and auditory cueing for PD gait exercise were explored [277]. Auditory cueing demonstrated significant improvement of cadence (Hedge $g=0.556$; 95% confidence interval [CI], 0.291–0.893), stride length (Hedge $g=0.497$; 95% CI, 0.289–0.696), and velocity (Hedge $g=0.544$; 95% CI, 0.294–0.795). In contrast, visual cueing significantly improved stride length only (Hedge $g=0.554$; 95% CI, 0.072–1.036). Previously, Nieuwboer et al. (2009) explored the short-term effects of different modalities of rhythmic cueing - auditory, visual and haptic - in turn speed strongly associated with instability, falls, and freezing in a population of freezers and non-freezers PD patients ($N=133$ idiopathic PD while in “On”) [284]. The results of this study –also part of the RESCUE trial – showed that all types of cueing increased the speed of the turn in all subjects. There was no difference between turn performance of freezers and nonfreezers in cued and noncued conditions. Auditory cues made turning significantly faster than visual cues ($p < 0.01$) but not compared with somatosensory cues, except in nonfreezers. There was a short-term carryover in the final noncued trial. It is suggested by the authors that one of the reasons of the improvement saw in the study is that cueing could enhance different attentional mechanisms during turning. Also, even no harmful effects were recorded during the study the safety of cueing for turning as a therapeutic strategy should be explored more in detail in further works. Also, some works explored the combined use of different cueing techniques at the same time. Suteerawattananon et al. (2004) run an experiment with idiopathic PD patients ($N=24$) where subjects were asked to perform a set of tasks in three different scenarios: without cues, with a visual cue (brightly colored parallel lines placed along the walkway at intervals equal to 40% of a subject's height), with an auditory cue (a metronome beat 25% faster than the subject's fastest gait speed) and with both cues simultaneously [272]. Gait velocity, cadence and stride length significantly improved ($p < 0.005$) when cues were used. Visual and auditory cues improved gait performance in patients with PD, but they did so in different ways. Auditory cueing significantly improved cadence, but visual cueing improved stride length. The simultaneous use of auditory and visual cues did not improve gait significantly more than each cue alone. Also, as part of the RESCUE study ($N=153$), Rochester et al. (2010) explored the acquisition, automaticity and retention of cued gait performance after training with ERS (auditory, visual and somatosensory) [273]. In order to achieve that, they defined motor learning as acquisition (single task), automaticity (dual task) and retention of single- and dual-task

performance (follow-up). Subjects received 3 weeks cued gait training and changes in cued gait performance were measured during single and dual tasks after training and 6 weeks follow-up. Also, gait was tested without cues to compare specificity of learning (transfer). The results of this work showed that walking speed and step length significantly increased with all cues after training during both single- and dual-task gait and these effects were retained. Training effects were not specific to cued gait and were observed in dual-task step length, and walking speed however was more limited in single-task non-cued gait. Additionally, Rochester et al. (2005) studied the effect of auditory and visual cueing on walking during a functional task in homes of PD patients (N=20 idiopathic PD, N=10 control group) [278]. The aim of this work was to study the influence of rhythmic cues on gait interference during a functional activity and the relationship of clinical symptoms to gait interference. Subjects were asked to perform a simple functional task that included a walking component and a dual-motor task with and without ERS (auditory and visual). The results of this test showed that the use of auditory cues during a dual task involving gait reduced the interference effect on the task; significant increases in step length were observed in PD subjects ($p = 0.018$), representing an increase of 19%. Therefore, using external cues may be useful in reducing interference and maintaining gait performance during more complicated functional activities. This could be specially relevant when other potential symptoms which also interfere in the performance of complex task coexist such as depression and fatigue.

Another recurrent tool used in PD is the employment of music. Music-based therapy or Music Therapy (MT) naturally combines cognitive movement strategies, cueing techniques, balance exercises and physical activity while it stimulates motor, affective and behavioural functions [279], [280]. It also offers an intuitive interface to transmit instructions to a patient for example to re-educate the brain in changes of velocity (where most of PD patients found a problematic situation). Actually, many centers and association of patients organize periodic sessions of music therapy. De Dreu et al. (2012) run a meta-analysis of the effects of MT on walking ability, balance and quality of life in PD patients [279]. The meta-analysis included individual rhythmic music training and partnered dance classes (studies N=6, patients N=168). Studies were generally small (total N= 168). Significant homogeneous summary effect sizes (SESSs) were found for the Berg Balance Scale, Timed Up and Go test and stride length (SESSs: 4.1, 2.2, 0.11; $p < 0.01$; I² 0, 0, 7%, respectively). A sensitivity analysis on type of therapy (dance- or gait-related interventions) revealed a significant improvement in walking velocity for gait-related, but not for dance-related. No significant effects were found for UPDRS-motor score, Freezing of Gait and Quality of Life. Pacchetti et al. led a prospective, randomized, controlled, single-blinded study during 3 months comparing MT and physical therapy in PD patients [280]. Their initial work hypothesis was that music improves rhythmic limb movements, gait, and freezing in patients with PD from a previous study [281] and the results demonstrated improvements in motor abilities and emotional status related to active MT. Along with the rhythmic aspect of the music; another factor involved in motor improvement is the affective arousal effect of music, which could influence both motivational and emotional processing. They also suggest a connection between emotions and the facilitation of movement. Motor improvement, especially in bradykinesia items ($p < 0.0001$). Over time, emotional status ($p < 0.0001$) and improvements in activities of daily living and in quality of life were also documented in the MT group ($p < 0.0001$). In accordance with the clinical literature, it may be argued that the MT-induced improvement in bradykinesia could be due to the effect of external rhythmic cues, which, acting as a timekeeper, may stabilize the internal rhythm [280]. MT show also benefits in improving facial expression in PD patients [283]. The use of external cueing techniques can be translated to the clinical practice in different ways. Most of the works suggest the development of rehabilitation or therapy sessions based on the use of external stimulation, and actually, several clinical institutions as well as associations of PD patients already implemented this kind of therapy. Unfortunately, the positive effects of the rehabilitations are not permanent and they fade away with time. Most of the studies showed the benefits of the cueing in the short-term and actually the decline in effectiveness of intervention effects underscores the need for permanent cueing devices and follow-up treatment [269], [271]. Cueing training may be a useful therapeutic adjunct to the overall management of gait disturbance in PD but also for the improvement in walking and complex task performance in the activities of daily life [271], [273]. Another typical application of the external cueing is in combination with a detector of FoG events [285], [286]. These systems provide real-time cueing after the onset of freezing episodes helping the patients with the initiation of the walking. Also, they can implement training exercises to learn how to deal with FoG episodes.

All these works as well as their benefits have been summarized on *Table 10 - State of the art of External Rhythmic Cueing for PD training*.

Type	Authors and year	Description	N	Results
RAS	Del Olmo & Cudeiro (2005) [270]	To explore the effects of RAS in PD patients (training session on a treadmill)	N=30	On this work gait velocity, cadence and stride length significantly improved ($p<0.005$) when RAS cues were used
	Nieuwboer et al. (2007) [271]	Run a home-based physiotherapy programme using RAS on a PD population	N=153	Posture and gait scores was improved by 4.2% ($p=0.005$). Severity of freezing was reduced by 5.5% in freezers only ($p=0.007$). Gait speed ($p=0.005$), step length ($p<0.001$) and timed balance tests ($p=0.003$) improved in the full cohort.
	Ford et al. (2010) [274]	Using incremental RAS on PD patients	N = 12	A significant increase ($p<0.01$) in walking velocity, stride length, and cadence after 8 weeks of training. And also, an average maximal rate of 157 BPM was achieved by the subjects involved in this study.
VC	Schlick et al. (2015) [275]	To evaluate the effects of VC combined with treadmill training taking the training on the treadmill without visual cues as control group	N = 20, N=13 (for follow-up)	After the training period, gait speed and stride length had increased in both groups ($p\leq 0.05$). Patients that used VC scored better in the Timed Up and Go (TUG) Test ($p\leq 0.05$) and, at two months follow-up, they sustained better results in gait speed and stride length ($p\leq 0.05$) as well as in the TUG test ($p\leq 0.05$).
RSC	Van Wegen et al. (2006) [276]	Using a vibrating cylinder attached to the wrist to explore whether PD patients could adapt their walking pattern under conditions of changing walking speed and visual distractions.	N = 17	RSC showed lower stride frequencies, and thus larger step lengths ($p < 0.05$), regardless of walking speed. The presence of visual flow did not prejudice the use of RSC, no significant difference were found between both situations ($p > 0.05$). RSC could be an alternative or complement for RAS, offering the additional robustness to changes in walking speed and visual distractors.
RAS vs. VC	Spaulding et al. (2013) [277]	Meta-analysis where the effects of VC and RAS for PD gait exercise were explored	N=25 works	RAS demonstrated significant improvement of cadence (Hedge $g=0.556$), stride length (Hedge $g=0.497$), and velocity (Hedge $g=0.544$). In contrast, VC significantly improved stride length only (Hedge $g=0.554$).
	Suteerawattananon et al. (2004)	To explore the combined use of ERS techniques at the same time. VC, RSC	N=24	Gait velocity, cadence and stride length significantly improved ($p < 0.005$) using cueing. RAS significantly improved cadence, but VC improved stride length. The simultaneous use of

	[272]	and with both cues simultaneously		auditory and visual cues did not improve gait significantly more than each cue alone.
RAS + VC + RSC	Nieuwboer et al. (2009) [284]	To explore the short-term effects of different modalities of rhythmic cueing - auditory, visual and haptic - in turn speed in a population of freezers and non-freezers PD patients	N=133	All types of cueing increased the speed of the turn in all subjects. There was no difference between turn performance of freezers and non-freezers in cued and non-cued conditions. RAS made turning significantly faster than VC ($p < 0.01$) but not compared with RSC, except in non-freezers. It was suggested by the authors that one of the reasons of the improvement saw in the study is that cueing could enhance different attentional mechanisms during turning.
	Rochester et al. (2010) [273]	To explore the acquisition, automaticity and retention of cued gait performance after training with ERS (auditory, visual and somatosensory)	N=153	The results of this work showed that walking speed and step length significantly increased and the effects were retained with all cues after training.
	Rochester et al. (2005) [278]	To study the effect of RAS and VC on walking during a functional task in homes of PD patients. Also, to study the influence of RAS on gait interference during a functional activity.	N=20 N=10 (control group)	Using of RAS during a dual task involving gait reduced the interference effect on the task; significant increases (19%) in step length were observed ($p = 0.018$). Therefore, this type of cueing might be beneficial in reducing interference and keep gait performance during more complicated functional activities.
MT	De Dreu et al. (2012) [279]	A meta-analysis about the effects of MT on walking ability, balance and QoL in PD patients.	N=168 From 6 studies	Significant homogeneous summary effect sizes (SEs) were found for the Berg Balance Scale, TUG test and stride length (SEs: 4.1, 2.2, 0.11; $p < 0.01$; 12 0.0, 7%, respectively). A sensitivity analysis on type of therapy (dance- or gait-related interventions) revealed a significant improvement in walking velocity for gait-related, but not for dance-related. No significant effects were found for UPDRS-motor score, FoG and QoL.
	Pacchetti et al. (2002) [280]	Prospective, controlled, randomized, single-blinded study during 3 months comparing MT and physical therapy in PD patients	N=32	Bradykinesia improvement ($p < 0.0001$), emotional status ($p < 0.0001$) and improvements in activities of daily living and in QoL were documented in the MT group ($p < 0.0001$). In accordance with the clinical literature.

Table 10 - State of the art of External Rhythmic Cueing for PD training

Chapter 4 State of the art

The aim of this section is to explore the current trends related to the use of Information and Communication Technologies (ICT) for the monitoring and management of Parkinson's disease (PD). New technologies could play a substantial role in the transformation of the healthcare, particularly in the case of PD, such solutions have the potential to, not only increase the quality of attendance and the health outcomes for the patients, also ICT could be a valuable tool for the continuous and automatic monitoring of PD patients, supporting the decision-making process providing clinicians with more and better information by providing them with Decision Support Systems (DSS) able to extract information and knowledge from the monitoring tools and improving the communication between the different stakeholders i.e. doctors, patients, care givers, pharmacists, etc. Finally, they can also provide beneficial information for the healthcare providers in order to improve the performance of the health care systems. This section explores different research works using the scientific search engines, as well as R&D projects and commercial solutions already available in the market. and improving the communication between the different stakeholders i.e. doctors, patients, care givers, pharmacists, etc.

The content of this chapter has been partially published in two chapters in book Cancela et al 2016 "Trends and New Advances on Wearable and Mobile Technologies for Parkinson's Disease Monitoring and Assessment of Motor Symptoms: How New Technologies Can Support Parkinson's Disease." on the Handbook of Research on Trends in the Diagnosis and Treatment of Chronic Conditions [287].

4.1 Monitoring and management of Parkinson's disease

In Europe, each neurologist or general practitioner (GP) normally cares for 50 to 800 patients with PD. The range in workload is a result of diversity both in national health systems and in the availability of clinical resources across Europe. Even in the best case of 50 patients per clinician, this represents a serious challenge to homecare monitoring for specialised conditions. PD patients normally visit their specialised clinician or GP every 4-6 months. As a result, any change in the patient's conditions may not be recognised for several months, unless the patients themselves make contact [3], [288]. Apart from the visits to the hospital, patients are frequently asked to self-report their health status, for example, by asking patients to recall the number of On and Off hours (motor fluctuations). Unfortunately, self-report is subject of several weaknesses: perceptual bias (e.g. patients often have difficulty distinguishing and assessing symptoms), recall bias (the patients do not remember exactly the duration, frequency and severity of the symptoms), it is highly subjective (specially in untrained people) and finally all the collected information it is difficult to analyse (it requires time and a huge effort). Another approach is the use of patient diaries on notebooks, which can improve reliability by recording symptoms as they occur, but does not capture many of the features useful in clinical decision making [3], [289]. Moreover, understanding the process is not an easy task and it even a more challenging task due to the time restrictions on the office visits. As it was well detailed on the previous chapter of this work, motor performance throughout the day depends on the intermittent dopaminergic drug intake modulated by timing and quantity of each individual dose of levodopa, stress, food intake and many other external factors. As result, treatment modifications are not always undertaken in time or are not properly personalized for the patient. This scenario reveals several flaws in the treatment and management of PD patients but also, it reveals the deficiencies in the management of PD from the healthcare systems, either from the clinical practice as well as from the healthcare providers which usually are overload to

deal efficiently with PD patients. This situation contrasts with other chronic conditions such as diabetes and cardiovascular diseases where available reliable low-cost monitoring tools are available for years (glucometers and portable Holters) allowing the clinicians to know much better the progression of the disease on their patients. In the particular case of PD management the objective is allowing the evaluation of the full range of PD symptoms through monitoring and testing routines while not hampering the patient's daily activities, identifying the correlation between the different dimensions affecting the severity of symptoms (medication, meals etc) and the evolution of the disease. And, at the same time, enable the clinicians to manage more efficiently the patient by providing timely indications on the effectiveness of the therapy and suggestions on therapy changes. Patients will greatly benefit from a quantitative objective assessment tool of their motor status in daily life in relation to the dosing schedule [3].

The concept of monitoring individuals in the home and community settings was introduced more than 50 years ago, precisely when Holter monitoring was proposed (in the late 1940s) and later adopted (in the 1960s) as a clinical tool. [290]. In an attempt to find more objective assessment in PD monitoring, several rating scales have been designed and used. Unfortunately, the use of these scales present some limitations like intra and inter observer inconsistencies and the accuracy depends on the experience of the physician. Besides, they can be time consuming and could be biased by subjectivity issues related to historical information. Moreover, the pattern and severity of PD symptoms may vary considerably during the day and finally, measurements of motor fluctuations made in the clinic may not accurately reflect the actual functional disability experienced by the patient at home [3]. Over the past decades various technologies, methodologies and systems have been developed and used to connect doctors and patients aiming at providing useful tools able to transmit information about the status of the patient to the doctor, generally known as teleconsultancy services [3]. The telehealth brings healthcare delivery to the home environment by connecting the patient with medical professionals. It is not intended to replace health professional care or visits, but rather to enhance the level of care [291]. The first initiatives on this area intended to show data related to patient's body measurements or to provide videoconference facilities to connect patients and doctors in real time. At that time, the challenge was the data transmission rate (i.e. to transmit as much as information as possible, in the most efficient way) and the ability of performing the remote diagnosis of the patient. Nowadays, a new generation of wearable sensors and systems able to transmit and store data continuously provides a novel "window of observation" in the home and community settings allowing to capture patients' activity level and exercise compliance, facilitate titration of medications in chronic patients, and provide means to assess the ability of patients to perform specific motor activities [292]. This evolution was possible thanks to the evolution of the monitoring devices which have significantly increased their computational capabilities reducing their size and cost at the same time. The development of miniature sensors made possible to unobtrusively attach them to different parts of the body or mimetize them as part of clothing items [293]. These new systems are expected to manage a bigger amount of data in order to extract the key information which could support clinicians in the decision-making process. To do that, signal processing and machine learning techniques have been explored to extract clinically relevant information from the raw sensor data [294], [295]. Furthermore, the current challenge is not only to transmit data, but analyze it and use it appropriately in the prevention, prediction and support of diseases and at the same time, to merge different data sources in order to integrate the knowledge from the diverse sources of information. In this sense, novel statistics methods and machine learning methodologies can contribute to properly analyze and extract knowledge from the data collected [3]. According to Bonato, researchers have focused on three main areas of work to develop tools of clinical interest [293]:

- The design and implementation of sensors that are minimally obtrusive and reliably record movement or physiological signals
- The development of systems that unobtrusively gather data from multiple wearable sensors and deliver this information to clinicians in the way that is most appropriate for each application
- The design and implementation of algorithms to extract clinically relevant information from data recorded using wearable technology.

Today, a wide range of sensors are available, either physiological sensors concerned with the measurement of parameters such as heart rate, blood pressure, blood oxygen saturation, respiration and muscle activation. Values

of these parameters are a definitive indicator of health status and have tremendous diagnostic value and biochemical sensors measuring the output of specific chemical reactions. These types of sensors can be used to monitor bio-chemistry as well as levels of chemical compounds in the atmosphere (e.g. for people working in hazardous environments). It is possible to identify several types of sensors, which are commonly used for ambulatory motion analysis studies: accelerometers, gyroscopes, goniometers and surface electrodes for electromyography (EMG) recordings. For sleep studies normally electroencephalography (EEG) and electrooculography (EOG) signal recording and processing are used. Wireless body area networks (WBANs) of intelligent sensors represent an emerging technology for system integration with great potentials for unobtrusive ambulatory health monitoring during extended periods of time [296]. However, system designers will have to resolve a number of issues regarding the sensors that conform these personal networks. Some examples of limitations are shown in the following lines [3]:

- **Size** - Sensors size is a very important factor. Moreover, lightweight and small sensors are convenient to patients, noninvasive and easily attachable to the body. Size is an important feature regarding the wearability of the whole system.
- **Mobility** - Therefore it is highly desirable to have sensors which are able to work properly and transmit the information properly while the patient is moving.
- **Cost** - Sensors redundancy may be required in order to provide effectiveness and context-awareness. However, this is only possible if they are affordable.
- **Power consumption** - Most sensors have to use battery as their only source of power. It is important for sensors to consume as little energy as possible so that the battery lasts as long as possible.
- **Processing capability** - System requires sensors capable of data processing tasks, some of them requiring intense signal processing activities such as digital filtering and noise removal.
- **Storage capacity** - A small amount of storage is highly desirable even if the sensors are transmitting the data continuously. In situations where channel communication is unavailable or interrupted, critical (or pre-processed) data should be saved prior to transmission.
- **Communication capacity** - In most of the cases the sensors are designed only to collect data while or to collect and perform some kind of signal pre-processing, but in they are aimed to transmit to a central node where a smarter processing is carried out (usually merging data from different sensors and data sources). For this reason sensor need to include communication capabilities in order to be able to transmit this information. Frequently it is important to find a trade-off between communication capabilities (bandwidth, radius of action) and battery consumption.
- **System Security**. Authentication, authorization, confidentiality, integrity, availability, and non-repudiation are all factors involved in general security system. In addition, extra security concerns must be addressed due to the nature of the information content. With medical remote monitoring, sensitive information (measurements of patient's vital signs) are processed and transported between secure environment (hospital) and the patient's home. Putting these systems in use lead to the consideration of additional security issues where patient's privacy must be protected.

Over the past decade, we have witnessed a great deal of progress in the field of wearable sensors and systems. Advances in this field have finally provided the tools to implement and deploy technology with the capabilities required by researchers in the field of patients' home monitoring [290]. Current research efforts are now focused on the development of more complex systems for home monitoring of individuals with a variety of preclinical and clinical conditions [297]. The transformation of healthcare brings also changes and duties for the patients. Therefore, they should play an active role in self-management of chronic conditions. Actually, new policies will focus in the transformation of the patient role not only during the disease but also with a more general scope, the promotion of the active ageing. Active ageing is the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age. It applies to both individuals and population groups [298].

Another area which is raising the general interest in the last years is the concept of the serious games and gamification for active ageing [2]. Active ageing allows people to realize their potential for physical, social, and mental well-being throughout the life course and to participate in society, while providing them with adequate protection, security and care when they need. The word “active” refers to continuing participation in social, economic, cultural, spiritual and civic affairs, not just the ability to be physically active or to participate in the labor force. Mike Zyda defined serious games as mental contest, played with a computer in accordance with specific rules, that uses entertainment to further government or corporate training, education, health, public policy, and strategic communication objectives [299]. Serious games can be applied to a broad spectrum of application areas, e.g. military, government, educational, corporate and healthcare [300]. In the healthcare case the most extended term to cover all of them is games for health. We can define serious games as the merge of game technology, other ICT technologies and research areas applied to a broad spectrum of application domains ranging from training, simulation and education to sports and health or any other societal relevant topic or business area. Apart from the application area, serious games can be also sorted depending on the final purpose of the game. There are games for training, advertising, simulation, or education that are designed to run on personal computers or video game consoles. Games for health applications related to health and healthcare are becoming more and more common every day. Currently there exist a large number of them. Some examples showing the variety of types and areas for applications related to physical or mental health include [300]:

- Physical fitness (also known as “exergaming”).
- Education in health/self-directed care. Games can be helpful for patients to adjust their habits and lifestyles to deal with their diseases and to motivate patients.
- Distraction therapy; some games are used as distraction therapeutic tools, for instance, to help chronically ill children to deal with pain, distract them during uncomfortable treatments, or to lessen anticipatory anxiety before medical procedures like surgery.
- Recovery and rehabilitation. Games for health can be used to fasten recovery for certain operations and conditions. They have also been used for increasing motor skills.
- Training and simulation, games can be used for, e.g., surgical training.
- Diagnosis and treatment of mental illness/mental conditions.
- Cognitive functioning; video games as well as traditional games can be used for memory training, development of analytical and strategic skills, etc.

It has been showed that games contribute to increase motivation in rehabilitation sessions, which is the major problem in therapy sessions, caused by the repetitive nature of exercises [301]. Regarding the long-term motivation, apart from methods and concepts for personalization and adaptation, multiplayer games can provide additional stimulation compared to single player games [302]. It is important not only to provide an innovative, playful and challenging sports application which arouses the players’ interest, but to provide a sustained motivation to keep them playing. Whereas single player games might lose their attraction after being played several times, the competitive aspects in multiplayer games can provide an ongoing and recurrent motivation for the users. Due to the increasing importance of serious games and the increasing number of research works using commercially available gaming platforms such as the Wii from Nintendo and the Kinect from Windows a specific search of this kind of works has been also carried out.

4.2 Search methods

The search was carried out using Google Scholar and introducing “Parkinson”, “Parkinson's” and “Parkinson's disease” combined with search terms: “monitoring”, “wearable”, “mHealth”, “remote monitoring”, “disease monitor”, “sensors for monitoring”, “disease automatic assessment”, “ICT”, “telehealth”, “monitoring”, “remote motor assessment”, “eHealth”, “tremor automatic assessment”, “bradykinesia automatic assessment”, “rigidity automatic assessment”, “dyskinesia automatic assessment”, “freezing of gait automatic assessment”, “gait

assessment”, “tremor automatic monitoring”, “bradykinesia automatic monitoring”, “rigidity automatic monitoring”, “dyskinesia automatic monitoring”, “freezing of gait automatic monitoring”, “gait monitoring”, “serious games”, “games for health” and “gamification”. The results were then filtered taking only those dealing with any kind of ICT technology. Then, to organize all the works found they were grouped by author and research institution, in many cases the published works are the result of a collaborative R&D project or combine different monitoring and/or treatment solutions, in these cases, all the related publications were grouped and presented in the section 4.3 *Research projects*. In other cases, the research activity led to a commercial product or to a patent; in this case the related works were grouped and presented in the section 4.6 *Patents and commercial solutions*. During, the analysis of the results several works were found related to video games platforms such as serious games, the works linked to this topic are presented in the section 4.5 *Serious games*. Finally, the works found are presented in the section 4.3 *Research works* grouped by the type of sensor employed for the monitoring.

4.3 Research works

This section presents the works that have not been included as a part of a R&D project or a commercial project. They have been grouped according to the input sensor employed for the monitoring of the PD.

4.3.1 Inertial sensors

An Inertial Measurement Unit (IMU) works by detecting the current rate of acceleration using one or more accelerometers, and detects changes in rotational attributes along the reference axis through one or more gyroscopes. It is important to understand that even the gyroscopic information is linked with the orientation of the device in the space (pitch, roll and yaw using) this information is not directly provided by the gyroscopes themselves, instead this kind of sensors provide the angular velocity respect to the different rotation axis. For this reason, some IMUs also include a magnetometer, mostly to assist calibrate against orientation drift. Since PD major symptoms are related to motor performance, inertial sensors have been used as monitor tool during the last years.

The use of IMU has been explored as feasible solution to monitor and assess the different motor symptoms of PD, with special emphasis on the cardinal motor symptoms. Salarian, Russmann et al. (2004-2007) at the École Polytechnique Fédérale de Lausanne, Switzerland, developed and validated a comprehensive system for PD motion monitoring based on a portable data-logger with body-fixed inertial sensors [303]–[307]. This equipment was used to the ambulatory monitoring of physical activities in Parkinson’s disease patients, the long term assessment of gait, tremor, dyskinesias, On-Off fluctuations and bradykinesia. Hanson et al. (2007) introduced a technique to provide an assessment of Essential Tremor (ET) severity by applying the Teager energy function to data collected with a inertial sensor integrated within a smartwatch [308]. Griffiths et al. (2012) worked in the continuous and automatic assessment of bradykinesia and dyskinesias using inertial sensors. The output of the algorithm calculates dyskinesia and bradykinesia scores every two minutes [309]. Lo et al. (2012) have been working also in the automatic detection of dyskinesias, using three pairs of wireless inertial sensors, aimed at identify the onset of dyskinesia as the prescription drug wears off [310]. Zwartjes et al (2010) built an ambulatory monitoring system that simultaneously analyzes the motor activity of the patient (e.g., sitting, walking, etc.) and the severity of tremor, bradykinesia, and hypokinesia using a set of four inertial sensors [311]. Kostikis et al. (2011) work describes a smartphone-based method for detecting and quantifying the hand tremor associated with movement disorders using signals from the accelerometer and gyroscope embedded in the patient’s phone [312].

IMU sensors are also recurrently used for the study of gait kinematics and the assessment of the human walking pattern in PD. Barth et al. (2011) built a sensor system to measure gait patterns in PD and to distinguish mild and severe impairment of gait. Subjects performed standardized gait tests while wearing sport shoes equipped with inertial sensors. Signals were recorded wirelessly and features were extracted in a computer. This method was able to classify patients and controls as well as to distinguish mild from severe gait impairment [313]. King et al. (2013) carried out a study to determine which outcome measures were more sensitive to a exercise intervention. They used 6 IMUs sensors to assess the gait performance of the subjects involved. Four of five variables at the function level changed after exercise: turn duration, stride velocity, peak arm speed, and horizontal trunk range

of motion [314]. Visser et al. (2007) measured trunk sway during a simple turning task aimed to serve as an instrument to objectively quantify turning while walking in PD [315]. Turn duration was longer in PD patients compared to controls. Peak yaw and peak roll angular velocities were lower in PD patients compared to controls during all turning tasks. Also, Gavriel and Faisal (2013) worked in a low-cost wireless system for human motor movement kinematics in unconstrained daily-life environments [316]. Ferrari et al. (2013) presented an algorithm to estimate gait features, from on-body mounted inertial sensors [317]. Difference of estimated step length and gold standard measure is below 5% when considering median values. Baston et al. (2014) introduced an instrumented method to characterize postural movement strategies to maintain balance during stance (ankle and hip strategy), by means of inertial sensors positioned on the legs and on the trunk. Coordination between the upper and lower segments of the body during postural sway was measured using a covariance index over time [318]. They also measured the amount of postural sway, as adjunctive information to characterize balance, by the Root Mean Square (RMS) of the horizontal trunk acceleration signal showing that control subjects were able to change their postural strategy, whilst PD subjects persisted in use of an ankle strategy in all conditions. PD subjects had RMS values similar to control subjects even without changing postural strategy appropriately.

Very linked to the gait assessment, many works focus their aim in the identification of the Freezing of Gait (FoG) episodes, especially due to their impact on the daily life of the patients. Steven T. Moore and colleagues at the Mount Sinai Hospital in New York, US have developed and validated a system for long-term monitoring of gait in PD. The characteristics of every stride were taken over 10-hour epochs were acquired using a lightweight ankle-mounted sensor array that transmitted data wirelessly to a small pocket PC at a rate of 100 Hz. A global threshold detected 78% of FoG events and 20% of stand events were incorrectly labeled as FOG. Individual calibration of the freeze threshold improved accuracy and sensitivity of the device to 89% for detection of FOG with 10% false positives. This system was also used to quantify the dynamic response of locomotion to the first oral levodopa administration of the day in patients with fluctuating PD [319]–[322].

Eventually, inertial sensors are combined with another kind of sensors or data inputs to enhance the characterization of PD abnormalities. Kimura et al. (2007) combined 3 inertial sensors and 8 dry-type EMG surface differential electrodes to study the perturbation occurrence during walking [323]. Tien et al. (2010) also employed a set of wireless inertial sensors for the characterization of gait abnormalities in PD [324]. Sanders et al. (2013) investigated how EEG readings can be used together with continuous smartphone gyroscope and accelerometer movement measurements to allow improved management of PD treatments [325].

Also, IMUs can be part of more complex systems, for example, the detection of FoG events can be combined with the use of auditory cues helping the patient to “unfreeze” when a FoG event is detected. Mazilu et al. (2014) presented a real-time auditory system for cueing after the onset of freezing episodes. It detects freezing episodes from ankle-mounted motion sensors, which stream data via Bluetooth to an Android phone [286], [326]. Furthermore, it also implemented training exercises for patients. Their final system was able to detect FoG events with an average sensitivity and specificity of more than 95%, and mean detection latency of 0.34s in user-dependent settings [327]. Jovanov et al. (2005, 2009) built a wearable, unobtrusive system for real-time gait monitoring, which consists of an inertial wearable sensor and wireless headset for the delivery of acoustic cues. The system recognizes FOG episodes with minimum latency and delivers acoustic cues to unfreeze the gait [328], [329]. Another example of application is the IMU integration on games, integrating a network of on-body inertial measurement units with a platform that allows patients to perform rehabilitation exercises through a variety of videogames and interaction methods [330].

Some works involving inertial sensors are related to the automatic identification of daily activities by PD patients, Zhang et al. (2011) proposed a solution using three sensors, each composed of a tri-axial accelerometer and a tri-axial gyroscope, attached to the chest and both thighs. Integrated with a smartphone to store, transmit, analyze and update data [331]. This system performs a continuous activity recognition algorithm (using a decision tree), it can identify activities of daily life in three general categories: postures (standing, sitting, lying), locomotion (walking) and transitions (sit-to-stand and stand-to-sit). The results showed an accurate angle measurement compared to the motion capture system and a reliable detection of all activities with sensitivity at least 96.2% compared to video recordings. Martín et al. (2013) characterized basic activities and their transitions using a single

sensor (an IMU equipped with a triaxial accelerometer, gyroscope, and magnetometer) located at the waist. Using this postural detection algorithm was able to detect and identify 6 different postural transitions, sit to stand, stand to sit, bending up/down and lying to sit and sit to lying transitions with a sensitivity of 86.5% [332].

Al-Jawad et al. (2012) and Adame et al. (2012) presented a feasibility study of an instrumented Timed Up and Go (TUG) test using a wearable inertial sensor unit attached on the lower back of the person. The developed algorithm is based on the Dynamic Time Warping (DTW) for multi-dimensional time series and has been applied with the augmented feature for detection and duration assessment of turn state transitions, while a 1-dimensional DTW is used to detect the sit-to-stand and stand-to-sit phases. The feature set is a 3-dimensional vector which consists of the angular velocity, derived angle and features from Linear Discriminant Analysis (LDA) [333], [334]. Al-Jawad et al. (2013) presented also a quaternion-based extended Kalman filter to characterize the postural steadiness during stance [335]. It uses low-cost inertial sensors attached on the lower back of the person at a known height in order to instrumenting the static balancing test. In this case, the Kalman filter was used as a data fusion algorithm to estimate the orientation of the body based on acceleration and angular rate signals. In order to get the coordinate of the body's centre of mass (CoM), the height of the sensor is projected on the horizontal plane by using the estimated orientation. Many parameters such as the mean velocity of sway, lateral/anterior-posterior range and others are then obtained from the sway path, which help the clinicians to assess the postural instability.

Figure 36 - Sensor used for physical activity monitoring The École Polytechnique Fédérale de Lausanne, Switzerland (Figure source: Salarian et al. 2007 [307]).

4.3.2 Accelerometers

Even whether the inertial sensors have been proved to be an outstanding tool for the detection and quantification of the motor symptoms in PD, some research works are focus on using exclusively the accelerometers for PD monitoring, in spite of the initial limitation, using only accelerometers brings the direct benefit of simplifying the hardware platform of the sensors and cost reduction. An accelerometer is a device that measures proper acceleration ("g-force"). Proper acceleration is not the same as coordinate acceleration or linear acceleration (rate of change of velocity). For example, an accelerometer at rest on the surface of the Earth will measure an acceleration $g = 9.81 \text{ m/s}^2$ straight upwards. In the same way that with the inertial sensors, different combinations of Body Area Networks (BAN) have been tested in combination with diverse kinds of algorithms in order to achieve the PD assessment of motor symptoms.

Van Emmerik and Wagenaar (1996) performed one of the first studies using an accelerometer to assess the dynamics of movement and tremor during gait in PD. Parkinson's disease patients showed overall less adaptations in relative phase than the control group, especially those involving the upper extremities [336]. In The Netherlands, Keijsers et al. carried out several research works using four pairs of triaxial accelerometers mounted on the wrist, upper arm, trunk, and leg on the most affected side in combination with neural networks to detect and quantify the dyskinesia and LID as well as to study the motor fluctuations in PD patients [337]–[340].

Le Moyne et al. (2009-2013) carried out a test with the iPhone's accelerometer for quantifying PD tremor. Moreover, they proposed a device with a wireless and potentially wearable 3D MEMS accelerometer mounted on the dorsum of the hand for quantifying PD hand tremor using accelerometer nodes and gloves [341], [342] [343]. Lord et al. (2008) validated an ambulatory monitoring device that uses accelerometer signals to assess the quality and quantity of walking. They measured gait speed, step length and step frequency during a test of functional gait that included single, dual and multiple task components [344]. Gil et al. (2010), Júnior et al. (2011) and Barroso et al. (2011) from the State University of Rio de Janeiro examined the effect of PD on the complexity of the tremor

time series of PD patients using the Approximate Entropy method (ApEn) from accelerometers signals (in the time and frequency domains). ApEn differenced physiological tremor from tremor in PD patients with high accuracy [345]–[347].

Dijkstra et al. (2008 - 2010) worked on the detection of the walking periods and postures using a single body-fixed accelerometer in patients with mild to moderate Parkinson's disease. They worked also in the development of algorithms for the detection of the step length, step frequency and other gait features based only on the fluctuations of an accelerometer in the patient trunk. The algorithm is known as the inverted pendulum model and some variations have also been proposed [348], [349]. Hoff et al. (2001-2004) addressed the accuracy of an ambulatory accelerometer in detecting motor complications (On-Off fluctuations). In the group of PD patients, comparing the “on” with the “off” state yielded statistically significant differences for tremor only. Objective dyskinesia measures correlated with time spent with dyskinesias ($r = 0.89$). Although validated for the measurement of hypokinesia, bradykinesia, and tremor, continuous ambulatory multichannel accelerometers cannot detect On-Off in individual PD patients [350], [351]. Louter et al. (2014) explored the use of a triaxial accelerometer as a tool to identify the risk of developing PD [352]. They used an accelerometer to quantify nocturnal movements during two nights per study participant. Outcome measurements included mean acceleration, and qualitative axial movement parameters, such as duration and speed. Compared with controls, patients with PD had an overall decreased mean acceleration, as well as smaller and shorter nocturnal axial movements. These changes did not occur in the potential “high risk PD” individuals.

4.3.3 Shoe sensors

As it was previously mentioned, PD disturbances have a huge impact on gait performance, for that reason the monitoring and assessment of the walking pattern subjects has been profoundly study. Thalen et al. (2007) integrated accelerometers into a shoe to study the gait performance in PD. This system called SensorShoe gives real-time feedback and therapy assistance to the patient, and provides the caregivers an effective remote monitoring and control tool [353]. Bae et al. (2011) developed a mobile gait monitoring system, based on a smart shoes, proposed for the diagnosis of abnormal gait and rehabilitation [354], it monitors PD patients' gait by observing the Ground Reaction Force (GRF) and the center of GRF, and analyzes the gait abnormality. It also provides visual feedback so patients can practice the rehabilitation treatment by trying to follow the normal GRF patterns without restriction of time and place. Mariani et al. (2013) also developed a wearable sensors on-shoe and processing algorithm, which provides outcome measures characterizing PD motor symptoms (the accuracy $\pm$ precision of 2.8 ± 2.4 cm/s and 1.3 ± 3.0 cm for stride velocity and stride length estimation compared to optical motion capture) [355]. In addition, they use a set of spatio-temporal parameters, including turning, swing width, path length, and their intercycle variability. Morris and Paradiso (2002) built a wireless wearable system that was developed to provide quantitative gait analysis outside the confines of the traditional motion laboratory [356]. It includes three orthogonal accelerometers, three orthogonal gyroscopes, four force sensors, two bidirectional bend sensors, two dynamic pressure sensors, as well as electric field height sensors. The GaitShoe was used to study healthy and Parkinsonian gait [357]. For pitch extreme, the healthy persons' gait range is much larger than that of the Parkinsonian range, with a mean 14.5 beyond for maximum pitch, and a mean 7.5 beyond for minimum pitch. Correspondingly, the normal stride length is a mean 0.26 m longer than the Parkinsonian stride length. Though the stride time of the normal subjects is shorter by 0.15 s, the percentage of the stride spent in stance is nearly equivalent, with the normal subjects spending only 2.2% less time in stance. Jamthe et al. (2013) proposed a embedded force sensor in the patient's shoe for monitoring of falls and FoG events [358].

Heldman et al. (2012) developed and evaluated the algorithms for quantifying gait and lower extremity bradykinesia in PD patients using kinematic data recorded on a heel-worn motion sensor unit [359]. Multiple linear regression models were developed showing average correlation coefficient of 0.86 respect to clinicians' assessments. Grandez et al. (2009) proposed a novel system for the monitorization of gait of patients affected by PD [360]. Force Sensitive Resistors (FSR) are used, embedding them in an insole, which allows the capture and analysis of the gait over long periods of time and while the patient interacts with a natural (non-controlled) environments.

Figure 37 - Insole patterns in the different walking phases (Figure source: Bae et al. (2011) [354])

4.3.4 Electromyography (EMG)

EMG is a monitoring tool that fits perfectly in the requirements for the automatic and accurate monitoring and assessment of motor disorder. The EMG is a diagnostic procedure to assess the health of muscles and the nerve cells that control them (motor neurons). Motor neurons transmit electrical signals that cause muscles to contract. An EMG translates these signals into digital signals. An EMG uses devices called electrodes to transmit or detect electrical signals. During a needle EMG, a needle electrode inserted directly into a muscle records the electrical activity in that muscle.

Kimura et al. (2007) combined EMG signals with motion sensors, specifically, 8 dry-type EMG surface differential electrodes and 3 inertial sensors, for the detection perturbations during walking. On that research, a back-propagation based Artificial Neural Network (ANN) model was validated resulting that the occurrence could be detected from four channels within 87.5ms, which could be considered as short enough for walking assist systems to response to the perturbation [361]. EMG and acceleration analysis showed also that could quantify the effects of medication in PD [362]. Spieker et al. (1998) developed a method of ambulatory long-term EMG monitoring for quantification of tremor using a Fast Fourier Transformation (FFT) concluding that EMG is useful for differentiation between Essential Tremor (ET) and PD with a high sensitivity and a high reliability and for tremor quantification [363]. Also, Breit et al. (2008) developed a long-term EMG-based automated analysis procedure that separates parkinsonian tremor from essential tremor using logistic regression, a linear formula based on the three parameters predicted the correct diagnosis in 93% of patients [364]. Cole et al. (2010) tested the feasibility of using a Dynamic Neural Network (DNN) solution for detecting time-varying occurrences of tremor and dyskinesia at 1 second using surface electromyographic (sEMG) sensors and tri-axial accelerometers worn by PD patients. During DNN testing, tremor was detected with a sensitivity of 93% and a specificity of 95%, while dyskinesia was detected with a sensitivity of 91% and a specificity of 93% [365].

A common application of the EMG is for sleeps studies, to compare the EMG signals from the chin during REM sleep between PD patients with or without REM sleep behavior disorder (RBD). For example, by measuring the automatic quantitative approach (Atonia Index) which indicates the occurrence of RBD [366] or to the percentage of REM time with excessive tonic or phasic muscle activity was calculated and compared across PD and RBD characteristics [367]. Although the information collected with this kind of devices provides high accuracy and reliability as well as an excellent temporal resolution, the main limitation of this method is related to the necessity of using an needle electrode on the subjects.

4.3.5 Video

Since the motor symptoms in PD have an external performance, several video-based solutions have been also proposed as feasible monitoring tools for Parkinson's disease patients. Nevertheless, one of the main limitations of this method for the home monitoring is related to the continuous video recording of people at home and its implications in the patients' privacy.

Cho et al. (2008) proposed a vision-based diagnostic system to aid in the recognition of the gait patterns of PD. The proposed system utilizes an algorithm combining principal component analysis (PCA) with linear discriminant analysis (LDA). The feasibility of the proposed system for the recognition of PD gait was tested by using gait videos of PD and normal subjects. Experimental results showed that LDA had a recognition rate for Parkinsonian gait of 95.49% [368]. Sofuwa et al. (2004) worked also in the quantitative gait analysis in PD using an 8 M-camera Vicon capturing system. The PD spatiotemporal results showed a significant reduction in step length and walking velocity compared with controls. In the kinematics, the major feature of the PD group was a markedly reduced ankle plantarflexion excursion (at 50%–60% of the gait cycle). Kinetics showed reduced ankle push-off power and hip pull-off power. Unlike the control subjects, the patients with PD did not show any correlation between ankle generation (push-off) power and stride length ($r=.19$) or with gait speed ($r=.29$). Correction for walking velocity did not result in significant changes in the kinetics between the groups [369]. Sharma et al. (2014) built a combination of smartphone and smartwatch in monitoring multidimensional symptoms – such as facial tremors, dysfunctional speech, limb dyskinesia, and gait abnormalities. In addition, SPARK allows physicians to conduct effective tele-interventions on PD patients when they are in non-clinical settings (e.g., at home or work) [370]. Synnott et al. (2010) built a system for the assessment of Parkinsonian tremor based on a computer vision technique with the aim of providing a more objective, frequent, yet unobtrusive means of assessment. Statistical analysis of tremor amplitude values recorded during control and tremor movements indicate a clear difference between the two groups, and the visualization engine highlights these differences in a clear and intuitive manner. [371].

4.3.6 Voice

Voice and speech is also affected in PD. Analyzing and monitoring the changes on PD patients respect to control subjects. Rusz et al. (2011) carried out a study to determine whether voice and speech disorder are present from early stages of PD before starting dopaminergic pharmacotherapy and to identify PD-related acoustic signatures for the major part of traditional clinically used measurement methods with respect to their automatic assessment [372]. Within this work, it was found that measurement of the fundamental frequency variations applied to two selected tasks was the best method for separating healthy from PD subjects. It was demonstrated that 78% of early untreated PD subjects indicate some form of vocal impairment. The speech defects thus uncovered differ individually in various characteristics including phonation, articulation, and prosody. In the specific field of the voice and speech the most significant results have been achieved within the PVI project, which is described in more detail in the section 4.4.18 *PD_manager*. Also, it has been showed that voice and speech can be largely benefited from telerehabilitation, see 4.3.7 *Telematic and remote visit*.

4.3.7 Telematic and remote visit

Following a different approach, ICT and new technologies have been used to connect patients and clinicians in order to allow physicians to carry out the examination through a telematic visit. Also, telerehabilitation has been employed. The telematic visit has the potential to deliver services in the home or local community via videoconferencing and through interactive computer-based therapy activities. This form of service delivery has the capacity to optimize functional outcomes by facilitating generalization of treatment effects within the person's everyday environment, and enable monitoring of communication and swallowing behaviors on a long-term basis.

Several works have been carried out to study the feasibility of using telematic services for remote assessment of Parkinson's disease patients [373], to test interactive video conference for the examination of PD patients [374], to explore the feasibility and effect of telephone-based cognitive-behavioral therapy for depression in PD [375], to explore a telemedicine-based care model for drug optimization [376] and to evaluate the usefulness and usability of a follow-up telehealth medication counseling (both videophone and telephone) with a sample of community-based PD patients taking three or more medications. All these studies shown the feasibility of this kind of service delivery, some of them also conclude that it can benefit the therapy optimization. Overall, the use of video for counseling sessions over the telephone sessions both for the patients and clinical staff. Cunningham et al. (2009-2012) designed a home-based assessment tool based on computer vision, which collects information on

people's hand and finger movements, to assess the bradykinesia, akinesia and rigidity, as well as to monitor and assess peripheral motor symptoms [377], [378] [379]. Tindall et al. (2008-2009) from the Department of Veterans Affairs Medical Center, Lexington, Kentucky, USA have been working in the feasibility of delivery the Lee Silverman Voice Treatment (LSVT)[®] treatment through videophones placed in the homes of individuals with idiopathic PD offers an alternative and could improve accessibility of treatment [380], [381]. Biglan et al. (2009-2013) from Department of Neurology, University of Rochester Medical Center, Rochester, New York, USA conducted a randomized, controlled pilot trial to evaluate the feasibility, effectiveness, and economic benefits of using web-based videoconferencing to provide specialty care to patients with PD in their homes [382]–[385]. The primary outcome variable was feasibility, as measured by the percentage of telemedicine visits completed as scheduled. Secondary outcome measures included clinical benefit, as measured by the 39-item Parkinson Disease Questionnaire, and economic value, as measured by time and travel. Compared with usual care, those randomized to telemedicine had significant improvements in quality of life, motor performance and patient satisfaction. The visits resulted in improvements in motor and cognitive symptoms and suggest that telemedicine may be useful for delivering care to this population. Likewise, researchers at the University of Queensland in Brisbane in Australia have investigated the validity and feasibility of online delivery of the LSVT[®] for the treatment of the speech and voice disorder of a patient with idiopathic Parkinson's disease, as well as to investigate the validity and reliability of a telerehabilitation application for assessing the speech and voice disorder associated with Parkinson's disease such as dysphagia (a swallowing disorder), hypokinetic dysarthria, swallowing disorders. According to their results telerehabilitation was feasible and effective in delivering the LSVT[®] to people with PD. Analyses revealed comparability between online and face-to-face environments for vocal sound pressure level, phonation time, pitch range, sentence intelligibility and communication efficiency in reading. Intra- and inter-rater reliability scores for all tasks were comparable between the online and face-to-face environments. Online assessment of disordered speech and voice in Parkinson's disease appears to be valid and reliable [386]–[392].

4.3.8 Other

Apart of all the abovementioned systems, other alternatives have been proposed to assess efficiently PD patients by using a wide range of technologies and methods designed ad-hoc or based on commercial solutions already available in the market but not specifically designed for PD assessment. Kupryjanow et al. (2010) proposed a virtual-touchpad for the automatization of some UPDRS tests for the diagnosis of PD patients, Finger Taps Test (FTT) and the Rapid Alternating Movement of Hands test (RAMHT) [393]. Tucha et al. (2006) presented a study comparing kinematic aspects of handwriting movements both on their usual dopaminergic treatment and following withdrawal of dopaminergic medication. A digitizing tablet was used for the assessment of handwriting movements. Compared with healthy subjects, the kinematics of handwriting movements in PD patients were markedly disturbed following withdrawal of dopaminergic medication [394]. Also, the results suggest that dopamine medication results in partial restoration of automatic movement execution. Aly et al. (2007) assessed the suitability and clinical value of a low cost system as an aid to diagnosis of PD, in particular the presence of tremor by asking the patients to perform a shape-tracing task using a graphic tablet [395]. A statistical spectral analysis of the moment-to-moment fluctuations in the position signal of the output from the digitizing tablet was performed. This allowed the comparison of power spectrums obtained from the control and patient responses respectively. A peak in log power between the 5 Hz & 6 Hz could be identified in the patient's spectrum and is indicative of Parkinson's related tremor and no similar peak could be seen in the control's spectrum. Smits et al. (2014) tried to assess whether standardized handwriting can provide quantitative measures to distinguish patients diagnosed with PD from age- and gender-matched healthy control participants [396]. In this study, a pen tip trajectories were recorded during circle, spiral and line drawing and repeated character “elelelel” and sentence writing, performed by Parkinson patients and healthy control participants. The results of this work showed that PD patients were slower than healthy control participants. Median time per repetition, median velocity and median acceleration of the sentence task and median velocity of the “elel” task differed significantly between Parkinson patients and healthy control participants (all $p < 0.0014$). PD patients also wrote smaller than healthy control participants and the width of the “e” in the “elel” task was significantly smaller in Parkinson patients compared to healthy control participants ($p < 0.0014$).

Westin et al. (2010, 2011) and Memedi et al. (2011) developed a test battery for assessing patient state in advanced PD, consisting of self-assessments and motor tests (tapping and spiral drawing tasks). This system was constructed and implemented on a hand computer with touch screen in a telemedicine setting. Using statistical and machine learning methods, time series of raw data are summarized into scores for conceptual symptom dimensions and an “overall test score” providing a comprehensive profile of patient's health during a test period of about one week [397]. The test battery could detect treatment effect in the two pilot patients, both in self-assessments, tapping tests' results and Archimedes spirals scores. Correlation analysis showed that tapping results provided different information as compared to diary responses. Internal consistency of the test battery was good and learning effects in the tapping tests were small [398], [399]. Cereda et al. (2010) used the SenseWear Armband (a wearable bracelet to monitor the physical activity continuously and provide estimates of daily energy expenditures, physical activity, number of steps, and metabolic rate) to assess the effects of dietary regimens on motor function in PD and they found data that support the role of upper-extremity involuntary movements in increasing total daily energy expenditure during an LP diet [400]. Likewise, the Lifecorder, an activity monitoring device, was used attached to a group of patients for several weeks for the continuous recording of motor activity in ten scaled magnitudes at two-minute intervals for 6 weeks [401]. The unique properties of Lifecorder make this device a useful adjunct to the UPDRS for the objective evaluation of Parkinsonian motor activity to quantitatively evaluate motor activity, its fluctuations, and drug effects in patients with PD. Someren et al. (1993-2006) worked for a long time with actigraphy. Sleep actigraphs are generally watch-shaped and worn on the wrist of the non-dominant arm [402]–[405]. They are useful for determining sleep patterns and circadian rhythms and may be worn for several weeks at a time. The actigraphic assessment of movement, motor symptoms, circadian rest-activity rhythms, and nocturnal agitation including studies on symptom fluctuations and medication responses in Parkinson patients.

4.4 Research projects

4.4.1 BeatHealth

BeatHealth is a STREP collaborative project co-funded by the European Union under the Seventh Framework Programme (FP7) under the ICT 2013 Call 10 in the Challenge 5.1 (Personalised health, active ageing, and independent living). BeatHealth is aimed at exploiting the pervasive link between rhythm and movement for boosting motor performance, enhancing health and wellness using a personalised approach.

4.4.1.1 Partners involved

- University of Montpellier²⁶ - France
- Ghent University²⁷ - Belgium
- National University of Ireland, Maynooth²⁸ - Ireland
- Fundación TECNALIA²⁹ - Spain
- Centre Hospitalier Régional Universitaire Montpellier³⁰ - France

4.4.1.2 Project description

The final goal of this project is to create an intelligent technological architecture to deliver embodied, flexible, and

²⁶ www.umontpellier.fr (Last date accessed: February 2016)

²⁷ www.ugent.be (Last date accessed: February 2016)

²⁸ www.maynoothuniversity.ie/ (Last date accessed: February 2016)

²⁹ www.tecnalia.com (Last date accessed: February 2016)

³⁰ www.chu-montpellier.fr (Last date accessed: February 2016)

efficient rhythmical stimulation adapted to the individual's skills with the goal of enhancing or recovering features of movement performance (i.e., kinematics and physiological performance). It involves research aimed at improving information parameters, for maximizing the beneficial effects of rhythmic stimulation on movement kinematics and physiology as well as technological development to achieve a new IT service in the form of a network-based application for collecting on the fly kinematic data and sharing them with online with others (e.g., medical doctors, family, coach, etc). BeatHealth is intended to be evaluated also in patients with Parkinson's disease and in healthy citizens of various ages with moderate physical activity. The applicable contribution of these novel findings is that music tempo could serve as an unprompted means to impact running cadence. As increases in step rate may prove beneficial in the prevention and treatment of common running-related injuries, this finding could be especially relevant for treatment purposes, such as exercise prescription and gait retraining. Van Dyck et al. 2015 showed that music tempo could impact exercise performance of repetitive endurance activities, it might also serve as a means to shape running cadence [406]. Bardy et al. 2015 reported the results of two studies, in which participants were instructed to cycle or exhale at a natural frequency or in synchrony with an external rhythmic sound, are discussed. The metronome was either absent or present and close to or far from the natural frequency of the cycling and breathing systems. The results evidenced a stabilization of cycling, breathing, and locomotor-respiratory coupling (LRC) when sound was present compared to when it was absent. A decrease in oxygen consumption was also observed, accompanying the increase in sound-induced LRC stabilization [407]. Finally, they have also started to explore the potential of using this kind of approach in Parkinson's Disease populations [282].

4.4.2 Cupid

CuPiD (Closed-loop system for personalized and at-home rehabilitation of people with Parkinson's Disease) is a 3-year European project to provide personalized rehabilitation exercises for people with Parkinson's disease at home. CuPiD is powered by an eight member consortium led by the University of Bologna and it is an FP7 ICT Collaborative Project.

4.4.2.1 Partners involved

- Coordinator: Università di Bologna³¹ - Italy
- Tel-Aviv Sourasky Medical Center³² – Israel
- Wearable Computing Laboratory at Eidgenössische Technische Hochschule (ETH) Zürich³³ - Switzerland
- KU Leuven³⁴ - Belgium
- Oxford Computer Consultants³⁵ - UK
- ST Microelectronics³⁶ - Italy
- EXEL³⁷ - Italy
- Fundació Illes Balears Innovació Tecnològia³⁸ – Spain

³¹ www.unibo.it/it (Last date accessed: December 2015)

³² www.tasmc.org.il (Last date accessed: December 2015)

³³ www.wearable.ethz.ch (Last date accessed: December 2015)

³⁴ www.kuleuven.be (Last date accessed: December 2015)

³⁵ www.oxfordcc.co.uk (Last date accessed: December 2015)

³⁶ www.st.com (Last date accessed: December 2015)

³⁷ www.exelmicroel.com (Last date accessed: December 2015)

³⁸ www.ibit.org (Last date accessed: December 2015)

4.4.2.2 Project description

CuPiD is a research project aimed to develop and test a combination of services for at-home rehabilitation and training of major motor impairments caused by Parkinson's disease. It is based on wearable sensors, audio biofeedback, virtual reality and external cueing to provide intensive motivating training as well as to engage patients with intensive exercise for a considerable length of time. The system enables real-time extraction of gait spatio-temporal features and their comparison with a patient's reference walking parameters captured in the lab under clinical operator supervision. Then, feedback is returned to the user in form of vocal messages, encouraging the user to keep her/his walking behavior or to correct it. Casamassima et al. (2013, 2014) describe the overall concept, the proposed usage scenario and the parameters estimated for the gait analysis. They also presented, in detail, the hardware and software architecture of the system together with a evaluation of the system reliability by testing it on a few subjects [408], [409]. CuPiD monitors and records remotely a patient's activity in training and clinicians are able to supervise their progression, change the training to fit an individual's needs and assess problems that occur using a computer interface.

Ferrari et al. (2013) presented an algorithm to estimate gait features, from on-body mounted inertial sensors, preliminary results show a difference of estimated step length and gold standard measure below 5% when considering median values [317]. Baston et al. (2014) introduced a novel instrumented method to characterize postural movement strategies to maintain balance during stance (ankle and hip strategy), by means of inertial sensors positioned on the legs and on the trunk. They showed that control subjects were able to change their postural strategy, whilst PD subjects persisted in use of an ankle strategy in all conditions and PD and control subjects had similar RMS values [318].

Mazilu et al. (2014) presented the real-time auditory system for cueing after the onset of Freezing of Gait (FoG) episodes detected from ankle-mounted motion sensors, which stream data via Bluetooth to an Android phone. Furthermore, it implemented training exercises to learn how to handle freezing situations. They tested the final system with 5 patients where they reported a reduction in the FoG duration as a result of the auditory stimulation. The system can be used as a daily-life assistant, but also three types of training and rehabilitation exercises that can be personalized are provided [286], [326]. In order to achieve this system, Mazilu et al. (2012) built a solution with recorded lab data from PD patients that experience FoG in daily life characterizing the system performance on user-dependent and user-independent experiments, exploring different machine learning algorithms, sensor placement and preprocessing window size. The final system was able to detect FoG events with an average sensitivity and specificity of more than 95%, and mean detection latency of 0.34s in user-dependent settings [327]. Later, Mazilu et al. (2013) compared feature learning approaches based on time-domain and statistical features based on Principal Components Analysis (PCA). The latter systematically outperforms the former and also the standard in the field - Freezing Index by up to 8.1% in terms of F1-measure for FoG detection. They also went a step further by analyzing FoG prediction, i.e., identification of patterns (pre-FoG) occurring before FoG episodes, based only on motion data. Modelling this as a three-class problem (FoG vs. pre-FoG vs. normal locomotion), they showed that FoG prediction performance is highly patient-dependent, reaching an F1-measure of 56% in the pre-FoG class for patients who exhibit enough gait degradation before FoG [410].

Tous et al. (2014) presented the architecture and technical implementation of a exergaming integrated with a network of on-body inertial measurement units which allows new motion-based interactions in serious games at home, and it also assesses the patient's movements in daily life [330]. Then, Dockx et al. (2013) evaluated the effectiveness of virtual reality exercise interventions for rehabilitation in patients with PD [411]. Additionally, Palmerini et al. (2013) studied the feasibility of deploy an instrumented Timed Up and Go Test (TUG) for PD subjects. A single accelerometer, worn at the lower back, was used to record the acceleration signals during the test and acceleration-derived measures were extracted from the recorded signals. A subset of three features (two from Turning, one from the Sit-to-Walk component), combined with an easily-interpretable classifier (Linear Discriminant Analysis), was found to have the best accuracy in discriminating between healthy and early-mild PD subjects [412]. Also, Palmerini et al. (2013) assessed the feasibility of using accelerometers to classify early PD subjects (two evaluations over a 1-year follow-up) with respect to age-matched control subjects. Two functional tests were instrumented by a single accelerometer (quiet standing, Timed Up and Go test); satisfactory accuracies

were obtained by using an ad hoc wrapper feature selection technique [413].

Figure 38 - Cupid pre-study system (Figure source: Mazilu et al. 2014 [326])

4.4.3 DAPHNE

DAPHNE (Detection of Activity Performance for Health with New Equipment) is an European R&D funded project, allowing for quantitative measurement of neurological and psycho-physical health state. It proposes a portable computerized instrument that measures fundamental parameters of Parkinsonian reactive capabilities.

4.4.3.1 Partners involved

- Coordinator: ST Microelectronics³⁹ - Italy
- Jump Studio Limited - UK
- Politecnico di Milano⁴⁰ - Italy
- Università degli Studi di Milano⁴¹ - Italy
- Philips Medical Systems SpA⁴² - Italy

4.4.3.2 Project description

The system, called DAPHNE allows the diagnosis of neuro psycho-physical conditions, whether the subject is healthy or is affected by nervous system pathologies as Parkinson's disease, etc. The research is started from a study of evaluation of human biofeedback response in virtual reality and in direct view [414]. DAPHNE is a portable device that performs an analysis of multiple parameters, such as: reaction time, speed, tremor, force, and ability of coordination and synchronization of the motion of a finger [415]. It is able to measure the reaction of a person evaluating the time response in the motion of one finger of the hand, the velocity of phalanxes, the force exerted from the finger against a button. It allows to quantitatively analyse the performances of the human hand both of mechanical phenomenon and electromyographic of neuromotor diseases, which provoke a decrease in upper and lower limbs action [415].

The patient can perform several tasks like button pressing and vocal feedback in response to acoustic and visual stimuli. The system collects all reactive parameter changes, caused by different reasons such as stress or fatigue,

³⁹ www.st.com (Last date accessed: December 2015)

⁴⁰ www.polimi.it (Last date accessed: December 2015)

⁴¹ www.unimi.it (Last date accessed: December 2015)

⁴² www.healthcare.philips.com/it_it (Last date accessed: December 2015)

and transmits them. Rovetta et al. (2001) published some works describing the portable system, detailing the measures of multiple parameters such as reaction time, speed, strength and tremor which are processed by means fuzzy logic; additionally, the device includes a voice detection system [416], [417]. Also, Rovetta et al. (2001) published the protocols for clinical tests on PD patients and the comparison with healthy people using DAPHNE g [418].

Figure 39 - DAPHNE prototype (Figure source: Canina et al. [414])

4.4.4 DAPHNET

DAPHNET (Dynamic Analysis of Physiological Networks) is a European project established under the roof of the Information Society Technologies Sixth Framework Programme (FP6).

4.4.4.1 Partners involved

- Atos Origin SA⁴³ - Spain
- Bar Ilan University⁴⁴ - Israel
- Beacon Tech Ltd⁴⁵ - Israel
- Charité - Universitätsmedizin Berlin⁴⁶ – Germany
- Eidgenössische Technische Hochschule Zürich⁴⁷ - Switzerland
- Fondazione Istituto per l'Interscambio Scientifico⁴⁸ - Italy
- Justus-Liebig-Universität Gießen⁴⁹ - Germany
- Oulun yliopisto (University of Oulu)⁵⁰ – Finland
- The Foundation for Medical Research, Infrastructure Development and Health Services – Israel

4.4.4.2 Project description

DAPHNET suggested to apply novel analysis methods to study physiological functions such as cardio vascular capacities, brain activity (EEG), motor control, gait, posture, sleep and sympathetic and parasympathetic effects. Algorithms to assess the long-term effects and inter-relations between signals representing these functions were

⁴³ <http://es.atos.net> (Last date accessed: December 2015)

⁴⁴ www1.biu.ac.il (Last date accessed: December 2015)

⁴⁵ <http://beacontech.eu> (Last date accessed: December 2015)

⁴⁶ www.charite.de/en/charite (Last date accessed: December 2015)

⁴⁷ www.ethz.ch/de.html (Last date accessed: December 2015)

⁴⁸ www.isi.it (Last date accessed: December 2015)

⁴⁹ www.uni-giessen.de/cms (Last date accessed: December 2015)

⁵⁰ www.oulu.fi (Last date accessed: December 2015)

at the core of this project. The simultaneous collection of several long-term signals enabled the construction of physiological networks using dynamical synchronization and cross-correlations patterns. The DAPHNET project conducted several clinical trials where they tried to validate the research hypothesis outlined within the project. One particular case was the study of the phenomenon of freezing of gait (FoG) on PD patients.

Bächlin et al. (2009, 2010) developed a real-time wearable FoG detection system that automatically provides a cueing sound when FoG is detected, the assistant provides a rhythmic auditory signal that stimulates the patient to resume walking [419]–[421]. On-body acceleration sensors were used to measure the patients' movements and automatically detects FoG by analyzing the frequency components. The device detected the FoG events online with a sensitivity of 73.1% and a specificity of 81.6% on a 0.5 sec frame-based evaluation [422]. They also showed that the theoretical maximum performance of this algorithm with patient specific optimal parameter sets is 88.6% sensitivity and 92.8% specificity. By separating the patients into saccadic and smooth walker with separate feature sets a detection accuracy of 85.9% sensitivity and 90.9% specificity was measured [423]. The majority of patients indicated that the context-aware automatic cueing was beneficial to them [419]. The vertical axis of the sensor at the knee showed to be the best sensor position and orientation for FoG detection. However the detection performance is relatively insensitive to the location and orientation [423].

Moreover, Bächlin et al. (2009) and Benocci et al. (2010) acquired data on trunk, limb and foot during gait. With this information they were able to detect five walking tasks on loaded conditions: two-straps backpack carried on shoulders, backpack carried with a single strap on right and left shoulder, bag carried with the right and left hand. The activities were classified for a single user by use of KNN, naïve Bayes and SVM classifiers. KNN achieved the best recognition accuracy of 96.7% for day dependent classifier training. The sensors placement, which resulted to be different along consecutive days, affects performance evaluation: a +3° rotation on the coronal plane decreases the accuracy to 76.0% [424]. And also, they analyzed the effect of walking speed, different shoes, extra load, and the natural variation over days on the gait. Showing that these factors may affect the gait of an individual at a level comparable to the variations between individuals and it limits the applicability of gait-based authentication approaches [425]. Finally, Schumm et al. (2008) studied the continuous measurement of electrodermal activity (EDA) for stress research presenting the effect of continuous, stationary movements on the EDA [426].

4.4.5 DiPAR

DiPAR (Diagnosing Parkinson's Disease by neuromuscular function evaluation) was aimed to deliver a novel diagnostic system for the early diagnosis of the onset of Parkinson's disease. The research is enabled by a grant awarded to the consortium by the European Union under the 7th Framework Programme.

4.4.5.1 Partners involved

- Coordinator: Hispafuentes SL⁵¹ - Spain
- Inotec mbH⁵² - Germany
- Olaf Schroder - Germany
- Fraunhofer-Institut⁵³ - Germany
- Academisch Ziekenhuis Groningen⁵⁴ - The Netherlands
- Manus Neurodynamica Ltd - UK

⁵¹ www.hispafuentes.com.es (Last date accessed: December 2015)

⁵² www.inotec-feg.de (Last date accessed: December 2015)

⁵³ www.fraunhofer.de (Last date accessed: December 2015)

⁵⁴ www.umcg.nl (Last date accessed: December 2015)

- University of Glasgow⁵⁵ - UK
- Valtion Teknillinen Tutkimuskeskus⁵⁶ - Finland
- Avantrasara Limited - UK

4.4.5.2 Project description

The consortium worked together to deliver an enhanced version of technology developed by Manus Neurodynamica Ltd. as a proof of concept. DiPAR implemented a decision support system including a hand held device supporting also secure patient data transfer between remote clinics and healthcare centres. The final validation was conducted at the University Medical Centre Groningen (Netherlands) to demonstrate the efficacy of the system. DiPAR's final goal was to provide an early diagnosis of Parkinson's disease. Manus Neurodynamica, a high-tech startup based in the North East of England which developed a novel system to detect and characterize the earliest changes in the neuromuscular system associated with the onset of PD. In the framework of DiPAR, Smits et al. (2014) tried to assess whether standardized handwriting can provide quantitative measures to distinguish patients diagnosed with Parkinson's disease from age- and gender-matched healthy control participants. In this study, a pen tip trajectories were recorded during circle, spiral and line drawing and repeated character "elelelel" and sentence writing, performed by Parkinson patients and healthy control participants. Parkinson patients were tested after overnight withdrawal of anti-Parkinsonian medication. The results of this work showed that PD patients were slower than healthy control participants. Median time per repetition, median velocity and median acceleration of the sentence task and median velocity of the "elel" task differed significantly between Parkinson patients and healthy control participants (all $p < 0.0014$). PD patients also wrote smaller than healthy control participants and the width of the "e" in the "elel" task was significantly smaller in Parkinson patients compared to healthy control participants ($p < 0.0014$) [396].

4.4.6 EDUPARK

EDUPARK (Patient education in parkinson's disease). The overall objective of this project was to improve the quality of life of people suffering from a chronic degenerative disease, i.e. Parkinson's Disease through patient education and psychosocial support.

4.4.6.1 Partners involved

- Coordinator: University of Wuerzburg⁵⁷ - Germany
- Finnish Parkinson's disease association⁵⁸ - Finland
- Fundación de Neurocirugía Funcional - Spain
- Leiden University⁵⁹ - The Netherlands
- Tartu Parkinson's Disease Society⁶⁰ - Estonia
- Università di Bologna⁶¹ - Italy

⁵⁵ www.gla.ac.uk (Last date accessed: December 2015)

⁵⁶ www.vtt.fi (Last date accessed: December 2015)

⁵⁷ www.uni-wuerzburg.de (Last date accessed: December 2015)

⁵⁸ www.parkinson.fi (Last date accessed: December 2015)

⁵⁹ www.leidenuniv.nl (Last date accessed: December 2015)

⁶⁰ www.parkinson.ee (Last date accessed: December 2015)

⁶¹ www.unibo.it (Last date accessed: December 2015)

- University of Portsmouth⁶² - UK

4.4.6.2 Project description

The importance of patient education and psychosocial support (in addition to medical treatment) cannot be overemphasised given the complexities of PD. Recommendations for patient education and psychosocial support took into account the existing situation of PD patients in the 7 European countries participating in this project. Three treatment modules were implemented which focus on the patient's problems as well as those of the caregivers. These modules formed part of a standardised patient education and training programme, which were developed by national experts of the participating countries and were implemented by interdisciplinary rehabilitation teams. A manual called "*Patient Education for People with Parkinson's Disease and their Carers: A Manual*" (M. Smith Pasqualini & G. Simons, 2006, Wiley) was published in several languages at the end of the project, *Figure 40* [427]. Macht et al. (2007) published an evaluation of this programme in seven European countries (Spain, Finland, Italy, The Netherlands, United Kingdom, Estonia, Germany) with 151 patients diagnosed with idiopathic PD. The results showed that the patient education has potential complementing medical treatment in PD, the programme was feasible to run, and patients were able to understand its elements. Patients reported mood elevations following individual sessions and reduced disease-related psychosocial problems after completing the programme. There were no substantial differences in results between cultures. [428].

Figure 40 - Cover of the "Patient Education for People with Parkinson's Disease and their Carers: A Manual" [427]

Later on, Tiihonen et al. (2012) evaluated EDUPARK program in a controlled study, regarding its influence on the participants' Quality of Life (QoL), depression and psychosocial well-being. Results showed improved social support for treatment group compared to a worsening for control group. General QoL remained stable for treatment group while it worsened for control group patients. No differences were found in psychosocial stress or depression. Results of the mood-measurements revealed elevated levels of mood after each session and progressively rising mood throughout the program. Most participants reported finding the program useful [429].

⁶² www.port.ac.uk (Last date accessed: December 2015)

4.4.7 E-MOTIONS

E-MOTIONS (Decision support in treatment of Parkinson's disease).

4.4.7.1 Partners involved

- Dalarna University⁶³ - Sweden
- Uppsala University⁶⁴ - Sweden
- Mälardalen University⁶⁵ - Sweden

4.4.7.2 Project description

The research project E-MOTIONS includes the development of a test battery system and an analysis of its cost-benefit. Westin et al. (2010, 2011) and Memedi et al. (2011) developed a test battery for assessing patient state in advanced PD, consisting of self-assessments and motor tests (tapping and spiral drawing tasks) using a hand computer with touch screen, a service node for data storage and processing and a web application for data presentation. Using statistical and machine learning methods, time series of raw data are summarized into scores for conceptual symptom dimensions and an “overall test score” providing a comprehensive profile of patient's health during a test period of about one week [397]. Both un-cued and cued tapping tests and spiral drawing tests were designed for capturing upper limb stiffness, slowness and involuntary movements. In tapping tests, speed and accuracy were calculated and in spiral tests, standard deviation of frequency filtered radial drawing velocity was calculated. An overall test score, combining repeated assessments of the different test items during a test period, was defined based on Principal Component Analysis (PCA) and linear regression. An evaluation with two pilot patients before and after receiving new types of treatments was performed. Compliance and usability was assessed in a clinical trial (65 patients with advanced PD, the IBM Computer System Usability Questionnaire was administered to assess nurses' satisfaction with the web application) and correlations between different test items and internal consistency were investigated. The test battery could detect treatment effect in the two pilot patients, both in self-assessments, tapping tests' results and spiral scores. It had good patient compliance and acceptable usability according to nine nurses. Internal consistency of the test battery was good and learning effects in the tapping tests were small [398]. On each test occasion, three Archimedes spirals were traced and analyzed using wavelet transforms and PCA to generate a spiral score. Another selection of spiral drawings was used to estimate the Spearman rank correlations between the raters ($r = 0.87$), and between the mean rating and the spiral score ($r = 0.89$) [399]. Memedi et al. (2013) examined repeated measures of fine motor function in relation to self-assessed motor conditions in PD (tapping and spiral drawings). The motor tests scores were found to be the best during self-rated On. Self-rated dyskinesias caused more impaired spiral drawing performance (mean = 9.8% worse, $P < 0.001$) but at the same time tapping speed was faster (mean = 5.0% increase, $P < 0.001$), compared to scores in self-rated Off. The spiral impairment showed to be related to dyskinesias presence whereas the tapping speed captures the Off symptoms [430]. They also carried out a validation this battery in home environment. 35 patients in stable and fluctuating conditions (15 age- and gender-matched pairs) used the test battery for 1 week, and they were then assessed with UPDRS and PDQ-39. This procedure was repeated 1 week later, without treatment changes. Median compliance (93%) and test-retest reliability (0.88) were good. The correlations between overall score and total UPDRS (-0.64) and PDQ-39 (-0.72) were adequate. Median overall score was 18% better in the stable compared to the fluctuating group ($p = 0.0014$) [431].

Additionally, Khan et al. (2013) presented a computer-vision based marker-free method for gait-impairment detection in PD patients. Cosine similarity between an imaginary perfect gait pattern and the subject gait patterns

⁶³ www.du.se (Last date accessed: December 2015)

⁶⁴ www.uu.se (Last date accessed: December 2015)

⁶⁵ www.mdh.se (Last date accessed: December 2015)

produced 100% recognition rate of PG for 4 normal-controls and 3 PWP [432].

4.4.8 FitForAge

Within the research consortium of the Bavarian Research Foundation⁶⁶ (BFS) FitForAge⁶⁷ project is aimed at researching new technological means in order to be able to offer assistance to senior citizens. For this purpose, new technological solutions are developed for both the working environment and the private living situation.

4.4.8.1 Partners involved

A team of scientists and engineers affiliated to 13 departments of the Bavarian universities Erlangen-Nürnberg, München, Regensburg and Würzburg works together with 25 industrial partners (ABF Apotheke Breitscheidstrasse Fürth, bayme vbm - Die bayerischen Metall- und Elektro-Arbeitgeber, BIJO-DATA Informationssysteme GmbH, BIOSIGNA GmbH, BMW AG, BMW Group Forschung und Technik, BMW M GmbH, BSH Bosch und Siemens Hausgeräte, Chimaera GmbH, EURO-LOG AG, Geis Industrie-Service GmbH, Geromed GmbH, GEV Grundstücksgesellschaft Herzogenaurach mbH & Co. KG, Handicare GmbH, Metabowerke GmbH, MTM-Institut, NAVIGON AG, nuinno, Pearson Assessment GmbH, Praxisnetz Nürnberg-Süd e.V., Reis GmbH & Co. KG Maschinenfabrik, Softgate GmbH, Sympalog Voice Solutions GmbH, szenaris GmbH, Trikon Engineering GmbH, Zelenka GmbH).

4.4.8.2 Project description

FitForAge is articulated into five work areas: Fit4Work (working environment), Fit4Mobility (mobility and orientation), Fit4Life (at home), and the cross-sectional projects Fit4Use And Fit4Product (to assure acceptance of new developments by the user). Under the Fit4Life area there are several developments to enable people to live more independently in their own homes and it is also divided into different sub-projects. One of them was aimed at developing intelligent in-house infrastructure and services for the measurement and evaluation of vital signs in daily operations. Different intelligent integrated technologies and services for independent living and to assist the elder people. Through the use of unobtrusive and integrated sensors and other system components such as RFID technology, sensor networks and localization systems.

Niazmand et al. (2010 - 2012) carried out an extensive work using wearable sensors for the detection and quantification of some PD symptoms and signs. A washable measuring system (by a waterproof encapsulation) for the everyday detection of activity was presented and evaluated. It is composed of an ordinary pullover with eight acceleration sensors sewn in at the arms and the torso and integrated detection electronics with a radio module and an interchangeable microSD card. Based on the acquired acceleration data, an activity index is calculated and saved on the microSD card [433]. Then, they extended this platform to study the feasibility of using it to estimate the severity of tremor in patients with PD. Algorithms were implemented to estimate the severity of rest and postural tremor of hands from accelerometer data features [434].

Also, Zhao et al. (2012) and Niazmand et al. (2011) presented an online approach for FoG identification using a washable jogging-trousers with integrated accelerometers together with an online test software to study the accelerations of shanks and belt in the time and frequency domains. 6 patients were recorded while walking on two standardized courses. FoG events were equally identified and recorded both by the online approach and by a physician [435], [436]. Finally, Niazmand et al. (2011) worked also in a wireless smart glove for the evaluation of severity of motor dysfunction in PD. This glove has two touch sensors, two 3D-accelerometers and a force sensor to assess the cardinal motor symptoms of PD (bradykinesia, tremor and rigidity of hand and arm) [437].

⁶⁶ www.forschungsstiftung.de (Last date accessed: December 2015)

⁶⁷ www.fit4age.org (Last date accessed: December 2015)

4.4.9 HELP

HELP (Home-based Empowered Living for Parkinson's Disease) project is a research project funded by the Ambient Assisted Living (AAL) Joint Programme as part of the European Union's Seventh Framework Programme.

4.4.9.1 Partners involved

- Coordinator: Telefónica I+D⁶⁸ - Spain
- Universitat Politècnica de Catalunya⁶⁹ - Spain
- ABAT⁷⁰ - Spain
- NEVET⁷¹ - Israel
- Peh-Med - Israel
- Telecom Italia⁷² - Italy
- University of Palermo⁷³ - Italy
- HSG-IMIT⁷⁴ - Germany
- MSG⁷⁵ - Germany

4.4.9.2 Project description

The HELP Project consortium designed a monitoring system specifically targeted for the needs of PD patients. It proposed a solution to improve quality of life of PD patients based on a Body Sensor and Actuator Network (BS&AN) made up of portable, wearable and home devices to monitor health parameters (e.g. blood pressure) and body activity (e.g. to detect gait, absence of movement). The HELP system also supplies specific amounts of drug according to their physical activity requirements at any moment. Because it is a continuous drug delivery system, drug peaks and "valleys" in the blood stream are avoided and so improving classical PD symptoms. The HELP system is made up of a wearable subcutaneous pump, an intraoral cartridge inserted in patients' mouth, a wearable movement sensor, blood pressure device and a control system that is constantly sending data, checking the patient and calculating the right quantity of drug to be supplied. HELP is based on an intraoral device for drug administration. This device is a removable implant or attached to a partially removable prosthesis loaded with a configurable cartridge. The concept allows the patient to adjust his/her daily medication according to his/her needs within boundaries that are pre-set by a medical supervisor or doctor. With an accessory device (base station) the cartridge will be identified before and after usage and the administered amount of drug can be measured [438], [439].

⁶⁸ www.tid.es (Last date accessed: December 2015)

⁶⁹ www.upc.edu (Last date accessed: December 2015)

⁷⁰ www.fhcsaa.cat (Last date accessed: December 2015)

⁷¹ www.maccabi4u.co.il (Last date accessed: December 2015)

⁷² www.telecomitalia.com (Last date accessed: December 2015)

⁷³ portale.unipa.it (Last date accessed: December 2015)

⁷⁴ www.hsg-imit.de (Last date accessed: December 2015)

⁷⁵ mobile-solution-group.de (Last date accessed: December 2015)

4.4.10 Mercury

4.4.10.1 Partners involved

- Harvard Medical School – Department of Physical Medicine and Rehabilitation⁷⁶
- Spaulding Rehabilitation Hospital⁷⁷

4.4.10.2 Project description

Mercury is designed to support long-term, longitudinal data collection on patients in hospital and home settings. Patients wear up to 8 wireless nodes equipped with sensors for monitoring movement and physiological conditions. Individual nodes compute high-level features from the raw signals, and a base station performs data collection and tunes sensor node parameters based on energy availability, radio link quality, and application specific policies. Mercury is designed to continuously collect data for 12 to 18 hours a day. Mercury provides a high-level programming interface that allows a clinical researcher to rapidly build up different policies for driving data collection and tuning sensor lifetime [440]. Data mining and artificial intelligence systems were developed by Bonato et al. (2004) [441], Sherrill et al. (2005) [442], Patel et al. (2006 -2009) [443]–[447] and Lorincz et al. (2007) [448] to predict the severity of symptoms and motor complications in late stage Parkinson's disease using wearable devices. Within these works they determined the optimal window length to extract features from the sensor data, the optimal parameters for the SVM's and how well individual tasks performed by patients captured the severity of various symptoms and motor complications. A significant decrease in the prediction error (for tremor, bradykinesia, and dyskinesia) was seen when increasing the window length from 1 second to 4 second, whereas prediction error values appear to plateau with a window of 5 second or longer. Average prediction errors for a window of 5 second were below the 5% target set when simulations were performed for all the symptoms and motor complications. Selecting longer windows would require collecting more data for each motor task, in order to avoid high correlation among observations utilized to derive each feature set. They tested also the performance of the algorithms by using different SVM's kernels. Even, no major differences were observed across them. Interestingly, differences were noted when the misclassification cost parameter "C". In general, a decrease in prediction error values was observed for all kernels when misclassification cost parameter "C" was increased from 0.1 to 1000. No significant decrease in prediction error values was observed for the results derived using the polynomial kernel for "C"-values greater than 10, whereas a significant decrease in prediction error values for the exponential and the radial basis kernels was observed when the "C"-value was further increased to 100. According to the authors, it was suggested that symptoms and motor complications in PD lead to distinct features of movement that can be captured irrespective of the specific motor task a patient is engaged into. Later, they indicated that it is possible to reliably estimate clinical scores on the basis of three feature types that are compatible with implementation on the SHIMMER platform: the rms value, the data range value, and two frequency-based features (i.e., the dominant frequency and the ratio of energy of the dominant frequency component to the total energy). They achieved average estimation error values of 3.4% for tremor, 2.2% for bradykinesia, and 3.2% for dyskinesia. In 2011, they perform a longitudinal validation of severity of motor symptoms showing that they were able to track UPDRS scores for two tasks (Alternate Hand Movement Task and Leg Agility Task) by using a regression Random Forest to within 0.5 points on a scale of 0-4 [449].

Finally, Patel et al. (2010) and Bor-rong Chen et al. (2010, 2011) built and validated the integration of these wearable technologies with a web-based application. The system, named MercuryLive, is a web-enhanced extension to a body sensor network platform for continuous home-based body motion sensing, interactive supervised data collection sessions, and long-term activity data analysis. Testing results showed an average data latency of less than 400 ms and video latency of about 200 ms with video frame rate of about 13 frames/s when 800 kb/s of bandwidth were available and we used a 40% video compression, and data feature upload requiring

⁷⁶ pmr.hms.harvard.edu (Last date accessed: December 2015)

⁷⁷ <http://srh-mal.net> (Last date accessed: December 2015)

1 min of extra time following a 10 min interactive session which proved to be feasible for the requested task [450]–[452].

4.4.11 MoMoPa

MoMoPa (Motor monitoring of Parkinson’s disease patients with therapeutic aim) is a R&D project partially funded by the Spanish Instituto Carlos III - Ministry of Economy and Competitiveness.

4.4.11.1 Partners involved

- Hospital Quirón Teknon⁷⁸
- Consorci Sanitari del Maresme⁷⁹
- Hospital Universitari Bellvitge⁸⁰
- Associació Catalana per al Parkinson⁸¹
- Fundació Privada Sant Antoni Abat⁸²

4.4.11.2 Project description

MoMoPa was aimed at developing a technological solution for the motor monitoring in idiopathic PD, with the final objective of getting accurate information to adjust the therapeutic treatment in an appropriate way. Samà et al. (2010 - 2012) worked in the the automatic estimation of spatio temporal gait properties from signals provided by inertial body sensors. Based on accelerations provided by a sensor, known as the “9×2”, three approaches were presented extracting kinematic information from the user motion and posture. First, feature extraction and SVM classification was employed for daily living activity monitoring. Second, Support Vector Regression (SVR) was applied on heuristically extracted features for the automatic computation of spatiotemporal properties during gait. Finally, the human gait was modelled as a dynamical system with hidden internal states. Sensor information is interpreted as an observation of a particular trajectory of the dynamic system from which a reconstruction space can be obtained which can be then transformed using standard PCA. Finally, the transformed space was used to estimate step length and velocities [453], [454]. Step length and velocity regression has been performed using a single feature extracted from two latent variables which were obtained through a reconstruction space. Results show good prediction performance for both measures but step velocity prediction is more precise than those obtained for the length. The gait analysis proposed has the advantage to be able to work without extracting gravity and therefore, a real-time implementation of the analysis on a low-cost processor then could be obtained, since low power-computing is required [453].

Also, they studied classifying motor states and dyskinesia from 20 PD patients by using a belt-worn single tri-axial accelerometer. The algorithms obtained were validated in a further study with 15 PD patients and enhanced in the *REMPARK* project (go to section 4.4.20) [455][456].

4.4.12 mPower

mPower proposes a monitor for Parkinson’s Disease using a mobile app with the final aim of understand why some people with PD have different symptoms than other, why a the progression of the symptoms and side effects can vary over time, and how to better manage these differences in symptoms day to day.

⁷⁸ www.teknon.es (Last date accessed: December 2015)

⁷⁹ www.csdm.es (Last date accessed: December 2015)

⁸⁰ www.bellvitgehospital.cat (Last date accessed: December 2015)

⁸¹ www.acaparkinson.org (Last date accessed: December 2015)

⁸² www.fundacioabat.cat (Last date accessed: December 2015)

4.4.12.1 Partners involved

- Sage Bionetworks⁸³ – USA
- University of Rochester⁸⁴ – USA
- Radboud University Medical Center⁸⁵ - The Netherlands
- Aston University⁸⁶ - United Kingdom
- University of California San Francisco⁸⁷ -USA

4.4.12.2 Project description

mPower is an iPhone app-based study designed to monitor and understand the causes of variations in symptoms of Parkinson disease . The Parkinson mPower app collects data from questionnaires, sensor data from your phone, and optional wearable device data to help you track your condition 24x7, allowing you to review trends and share this information with researchers. The mPower application uses a mix of surveys and tasks that activate phone sensors to collect and track health and symptoms of PD progression - like dexterity, balance or gait. The data collected are queationanires (UPDRS and PDQ-8), memory (through a short visuospatial game related to the Corsi block tapping test), tapping, voice (saying “aaah” for 10 seconds) and walking (participants walk back and forth for 20-30 seconds with their smartphone in their pocket). The mPower Parkinson's Study has released the first six months of data from this study donated by more than 9,500 mPower participants. These participants consented to share their data with Qualified Researchers worldwide to help speed scientific progress toward treatments for people with Parkinson’s disease.

4.4.13 NeuroTREMOR

NeuroTREMOR (A novel concept for support to diagnosis and remote management of tremor) is an European research project, partially funded by the EC under the FP7 programme. The main objective of the project was to validate technically, functionally and clinically, a novel system for understanding, giving support to diagnosis, and remotely managing tremors.

4.4.13.1 Partners involved

- Coordinator: Agencia Estatal Consejo Superior de Investigaciones Científicas (CSIC)⁸⁸ – Spain
- Georg-August-Universität Göttingen Stiftung Öffentlichen Rechts Universitätsmedizin⁸⁹ - Germany
- Fraunhofer-Gesellschaft Institute⁹⁰ – Germany
- Servicio Madrileño de Salud (SERMAS)⁹¹ – Spain
- Össur hf⁹² - Iceland

⁸³ <http://sagebase.org> (Last date accessed: March 2015)

⁸⁴ www.rochester.edu (Last date accessed: March 2015)

⁸⁵ www.ru.nl (Last date accessed: March 2015)

⁸⁶ www.aston.ac.uk (Last date accessed: March 2015)

⁸⁷ www.ucsf.edu (Last date accessed: March 2015)

⁸⁸ www.csic.es (Last date accessed: December 2015)

⁸⁹ www.med.uni-goettingen.de (Last date accessed: December 2015)

⁹⁰ www.fraunhofer.de (Last date accessed: December 2015)

⁹¹ www.madrid.org (Last date accessed: December 2015)

⁹² www.ossur.com (Last date accessed: December 2015)

- Univerza v Mariboru⁹³ - Slovenia
- The Trustees of Columbia University in the City of New York⁹⁴ - US

4.4.13.2 Project description

The system is composed of two platforms, a hospital-based platform which implements a novel machine tool to support diagnosis of tremors as well as a neuroprosthetic platform for remote management of upper limb tremors. It exploits neural and kinematic recordings both to drive a closed loop system to attenuate tremors based on neurostimulation of the afferent pathways, and to evaluate the status and evolution of the disorder. This system is based on the decomposition of surface electromyogram (sEMG) into contributions of individual motor units allowing the decoding of neural drive to muscles [457]. Holobar et al. (2012 - 2014) introduced a signal-based metric for assessment of accuracy of motor unit identification from high-density sEMG. This metric, called pulse-to-noise-ratio (PNR), correlated significantly with both sensitivity and false alarm rate in identification of motor units discharges. Practically all the motor units with $\text{PNR} > 30$ dB exhibited sensitivity $>90\%$ and false alarm rates $<2\%$. The study also showed that high-density sEMG can be reliably decomposed at contraction forces as high as 70% of the maximum [458], [459]. They also presented a work for the fully automatic identification of motor unit spike trains from high-density sEMG in pathological tremor [460].

Farina et al. (2014) presented the decomposition (using the CKC technique) of high-density sEMG signals detected from three targeted muscle reinnervation patients into the individual motor unit spike trains. The results showed that the spike trains of 3 to 27 motor units could be identified for each task, with a sensitivity of the decomposition $>90\%$, as revealed by PNR opening a path for a new generation of noninvasive human-machine interfaces [461]. Glaser et al. (2013) proposed a method based on a previously published CKC technique and shares the same decomposition paradigm, in contrast to previously published version of CKC, which operates in batch mode and requires ~ 10 seconds of EMG signal, the real-time implementation begins with batch processing of ~ 3 seconds of the EMG signal in the initialization stage and continues on with iterative updating of the estimators of MU discharges as blocks of new EMG samples become available. The real-time CKC identified slightly fewer MUs than its batch version (experimental EMG, 4 MUs versus 5 MUs identified by batch CKC, on average), but required only 0.6 s of processing time on regular personal computer for each second of multichannel surface EMG [462]. Gallego et al. (2013) implemented a neuroprosthesis that regulated the level of muscle co-contraction by injecting current at a pair of antagonists through transcutaneous neurostimulation adapting it to the instantaneous parameters of tremor (estimated from the raw signals of a gyroscope). For the validation, they enrolled six patients suffering from parkinsonian or essential tremor of different severity. The results showed that the neuroprosthesis attained significant the tremor ($p < 0.001$), and reduced its amplitude up to a $52.33 \pm 25.48\%$. Furthermore, it alleviated both essential and parkinsonian tremor [463].

In other work, Bržan et al. (2013) ran a study comparing the discharge characteristics of individual motor units, identified noninvasively from flexor carpi radialis and extensor carpi ulnaris muscles of nine essential and four Parkinsonian patients during three repetitions of rest, postural and kinetic conditions showing potential differences in motor unit discharge properties between essential and Parkinsonian tremor [464].

4.4.14 neuroQWERTY

neuroQWERTY is aimed at developing an algorithm to detect the subtle psychomotor impairment typical of neurodegenerative diseases by analysing the interaction of the subjects with smart devices, with the final aim of perform a motor tracking and potentially an early detection of neurodegenerative disease onset.

⁹³ <http://www.um.si> (Last date accessed: December 2015)

⁹⁴ <http://secretary.columbia.edu/trustees-columbia-university> (Last date accessed: December 2015)

4.4.14.1 Partners involved

- M+Visión⁹⁵
- Hospitales de Madrid⁹⁶

4.4.14.2 Project description

Team neuroQWERTY is developing a technology capable of detecting early signs of neurodegenerative disorders, i.e. Parkinson's disease, via the finger interaction through keyboards with electronic devices. It is studying the level to which changes in brain function are associated with a change in the way someone interacts with a mobile device. The final goal is to allow a mass screening of individuals at risk for these diseases enabling the development of neuroprotective therapies.

4.4.15 PARREHA

PARREHA (PARkinsonians REHAbilitation) was a R&D project concerned with the assessment of motor performance and the design of therapeutic Virtual Reality (VR) exercises supervised by video-conferencing partially funded by the EC. In May 2003 the PARREHA consortium formed ParkAid, a start-up company whose sole aim is to exploit ParkWalker and build a supporting service around it (ParkService). More details about this company and services are provided in the section 4.6.2.7 *ParkAid*.

4.4.15.1 Partners involved

- Coordinator: Oxford Computer Consultants Ltd⁹⁷ - UK
- Advanced Business Technologies Limited – UK
- Europark - Spain
- Joint Research Centre (JRC) - European Commission is Ispra⁹⁸ - Italy
- Institute of Communications and Computer Systems (ICCS)⁹⁹ – Greece
- Tardito Costruzioni E Impianti s.r.l.. – Italy
- Zenon SA Robotics and Informatics – Greece

4.4.15.2 Project description

The project incorporated virtual reality, visual stimulation, auditory biofeedback and interactive video conferencing technologies with conventional kinematics analysis. Their aim was to improve care provision and provide rehabilitation services to Parkinsonians. Scientists had previously shown that visual stimulation of PD patients with "virtual" obstacles and auditory stimulation with rhythmical sounds could significantly improve the efficacy of traditional rehabilitation schemes, a phenomenon known as "kinesia paradoxa".

Then, PARREHA project was aimed at the design and development of a system for the assessment of motor performance of PD patients and the design of training programmes for patients suffering from PD by incorporating visual stimulation, auditory biofeedback and interactive video conference technologies to conventional kinematics analysis and rehabilitation exercise protocols. Through the use of personalised virtual reality glasses, virtual

⁹⁵ mvisionconsortium.mit.edu (Last date accessed: March 2016)

⁹⁶ www.hmhospitales.com (Last date accessed: March 2016)

⁹⁷ www.oxfordcc.co.uk (Last date accessed: December 2015)

⁹⁸ <https://ec.europa.eu/jrc/en/about/jrc-site/ispra> (Last date accessed: December 2015)

⁹⁹ www.iccs.gr (Last date accessed: December 2015)

exercise and training systems, and personalised remote consultation, the PARREHA project developed tools that can significantly improve on the results of traditional rehabilitation methods. Prototypes of the PARREHA system were shown remarkable results in helping lethargic patients become significantly more active. Greenlaw et al. (2002) described the PARREHA in this work published in 2002 [465]. The first prototype displayed visual cues (vertical blue and horizontal pink stripes) into a headset via a laptop PC. The headset was the semi-transparent Sony Glasstron so the subject can view the real and virtual worlds together (augmented reality). One subject with PD, unable to walk, could walk and carry the PC using this prototype. The second prototype allowed PARREHA to explore a truly wearable solution in which visual cues are presented to the user over one eye via a small monitor mounted on a headset *Figure 41* [465].

Figure 41 - Prototype visual cues from a laptop PC being tested (Image source: Greenlaw et al. 2002 [465])

4.4.16 PAULINA

PAULINA (Home-assessment of Parkinson's disease symptoms) is a research project partially funded by the Swedish government through the Knowledge Foundation (Kontakta KK-stiftelsen¹⁰⁰).

4.4.16.1 Partners involved

- Dalarna University¹⁰¹ - Sweden
- Uppsala University¹⁰² - Sweden
- Animech AB¹⁰³ - Sweden
- Nordforce Technology AB¹⁰⁴ - Sweden

4.4.16.2 Project description

This project is a multidisciplinary applied research effort targeting home monitoring of PD symptoms. It is an extension of a previous project (see 4.4.7 *E-MOTIONS*) resulting in a touch phone test battery system for assessment consisting on questions and tests for the patient [466]. PAULINA consists of a patient diary section for collecting patient-based self-assessments, a motor test section for collecting fine motor movements through upper limb motor tests, and a scheduler for restricting operation to a multitude of predetermined limited time intervals. The system processes and compiles time series data into different summary scores representing symptom severity [467]. Memedi et al. (2013) carried out an open longitudinal 36-month study at 10 clinics in Sweden and Norway where they found that it was possible to monitor PD progression over time using this test battery in the home environment [468].

¹⁰⁰ www.kks.se (Last date accessed: December 2015)

¹⁰¹ www.du.se (Last date accessed: December 2015)

¹⁰² www.uu.se (Last date accessed: December 2015)

¹⁰³ www.animech.com (Last date accessed: December 2015)

¹⁰⁴ www.nordforce.se (Last date accessed: December 2015)

Khan et al. (2013, 2014) presented a method for assessing PD based on speech. A set of 13 features, including the cepstral separation difference and Mel-frequency cepstral coefficients were computed to represent deficits in each individual speech component and used in training a SVM using n-fold cross validation. The dataset used for method development and evaluation consisted of 240 running speech samples recorded from 60 PD patients and 20 healthy controls rated using the UPDRS of Speech. The classification accuracy of SVM was 85% in 3 levels of UPDRS scale and 92% in 2 levels with the average area under the ROC curves of around 91% [469]. Furthermore, the Guttman (μ_2) monotonic correlations between the features and the speech symptom severity ratings were strong (up to 0.78). This correlation increased with the increasing textual difficulty in different speech tests. The high intra-class correlation coefficient (>0.9) and analysis of variance indicates that features can be used reliably to distinguish between severity levels of speech impairment [470]. Khan et al. (2013) defined and evaluated a computer-vision method for scoring Paced Finger-Tapping (PFT) in PD using quantitative motion analysis of index-fingers and to compare the obtained scores to the UPDRS - Finger-Tapping *Figure 42*. A total of 15 features were classified using K-Nearest Neighbor (KNN) classifier to characterize the symptoms levels in UPDRS-FT. The target ratings provided by the raters were averaged. A 10-fold cross validation in KNN classified 221 videos between 3 symptom levels with 75% accuracy. An area under the ROC curves of 82.6% supports feasibility of the obtained features to replicate clinical assessments [471].

Figure 42 - Computer-Vision method for scoring Paced Finger-Tapping (Figure source: Khan et al. 2013 [471])

Memendi et al. (2013) designed, developed and set up a web-based system for enabling graphical visualization of upper limb motor performance of PD patients to clinicians through a set of upper limb motor tests (finger to tapping and spiral drawings) [472]. Different animation and visualization techniques were used to facilitate the interpretation of the results by the neurologists. For the scoring of alternating tapping performance a logistic regression classifier was trained using a 10-fold stratified cross-validation. Results showed that the computed scores correlated well to visually assessed scores and were significantly different across UPDRS scores of upper limb motor performance. In addition, they had good internal consistency, had good ability to discriminate between healthy elderly and patients in different disease stages, had good sensitivity to treatment interventions and could reflect the natural disease progression over time [473].

Figure 43 - Performance of upper limb motor tests using the handheld computer; a) spiral tracing, and b) alternate tapping of two buttons [472]

Memendi et al. extend also the work in order to automatically use spirography for clinical evaluation of individualized drug-related complications such as over- and under-medications. Using time series analysis techniques like discrete wavelet transform, approximate entropy and dynamic time warping they extracted 13

quantitative measures for representing meaningful motor impairment information. Then, PCA was used to reduce the dimensions of the quantitative measures and a logistic regression model was used as a classifier. A stratified 10-fold cross-validation was applied to assess the generalization ability of the logistic regression classifier to future independent data sets. Their findings suggested that spirometry-based objective measures are valid measures of spatial- and time-dependent deficits and can be used to distinguish drug-related motor dysfunctions between Off and dyskinesia in PD [474], [475].

4.4.17 PERFORM

PERFORM (A sophisticated multi-parametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson's disease and other neurodegenerative diseases) was a research project partially funded by the EC under the PF7.

4.4.17.1 Partners involved

- Anko Anonymos Etaireia AE Kai Viomichanias - Greece
- Centro de Estudios e Investigaciones Técnicas de Guipuzcoa¹⁰⁵ – Spain
- Logicom Public Ltd¹⁰⁶ – Cyprus
- Kingston Computer Consultancy Limited¹⁰⁷ – United Kingdom
- Medtronic Iberica SA¹⁰⁸ – Spain
- Michalis Papasavas AE¹⁰⁹ – Greece
- Oxford Computer Consultants Limited¹¹⁰ – United Kingdom
- University of Ioannina¹¹¹ - Greece
- Patmos Srl –Italy
- Politechnika Gdanska¹¹² – Poland
- Talanton SA Business Consulting and Marketing Services¹¹³ – Greece
- The University of Westminster¹¹⁴ – United Kingdom
- Universida de Navarra^{115 116} – Spain
- Universidad Politecnica de Madrid^{117 118} –Spain

¹⁰⁵ ceit.es (Last date accessed: December 2015)

¹⁰⁶ www.logicom.net (Last date accessed: December 2015)

¹⁰⁷ www.kccltd.com (Last date accessed: December 2015)

¹⁰⁸ www.medtronic.com (Last date accessed: December 2015)

¹⁰⁹ www.papasavas.gr (Last date accessed: December 2015)

¹¹⁰ www.oxfordcc.co.uk (Last date accessed: December 2015)

¹¹¹ www.uoi.gr (Last date accessed: December 2015)

¹¹² www.pg.gda.pl (Last date accessed: December 2015)

¹¹³ www.talanton.gr (Last date accessed: December 2015)

¹¹⁴ www.westminster.ac.uk (Last date accessed: December 2015)

¹¹⁵ www.unav.edu (Last date accessed: December 2015)

¹¹⁶ www.cima.es (Last date accessed: December 2015)

¹¹⁷ www.lst.tfo.upm.es (Last date accessed: December 2015)

¹¹⁸ www.upm.es (Last date accessed: December 2015)

- Azienda Unita' Sanitaria Di Modena¹¹⁹ - Italy

4.4.17.2 Project description

PERFORM system was aimed at increasing the performance of the medication through a better and more objective monitoring of the patients' symptoms, reducing costs by utilizing communications technology, which eliminates the need for transportation, reduces the waiting and/or consultation time can be reduced via telemedicine consultations, transferring health knowledge transfer from the practitioner to the patient, ability to self-care, and medication adherence [14], [15], [288], [434]. PERFORM platform was composed by a set of wearable sensors for the continuous recording of the motion signals and a set of software algorithms for the signal processing. The hardware was formed by a set of four tri-axial accelerometers positioned at each patient limb used to record signals from legs and arms; a belt sensor, composed by an accelerometer and a gyroscope, used to record body movement accelerations and angular rate; and a data logger used to receive and store all recorded signals in a SD card. All sensors transmit data using Zigbee protocol to the logger device, with 62.5 Hz sampling rate before a synchronization phase. The software sub-system is called Local Base Unit and is responsible for the identification and quantification of the patient symptoms and the recording of other useful information for the evaluation of the patient status. For each symptom, a dedicated algorithm processes the relevant signals, detects the symptom episode and quantifies it into a severity scale from 0 to 4, according to the UPDRS scale for PD's patients. About the technical performance of the system it shows an accuracy of up to 93.73% of accuracy for the classification of LID severity [476], an 86% for the classification of bradykinesia severity [477] and 87% for tremor severity [478]. Also, a specific module was developed for the assessment of gait [5]. The system is able to propose treatment changes, based on the clinical assessment [479]. Then, a Central Hospital Unit module is dedicated to processing all patient data and assisting the treating clinician in making appropriate treatment decisions which contains an Alert Manager. This module produces the alerts corresponding to the patient condition based on the outcomes generated by the Clinical DSS.

Tsipouras et al. (2010-2012) proposed an automated levodopa-induced dyskinesia (LID) assessment based on the analysis of signals recorded. The results were compared with the clinical annotation of the signals, provided by two expert neurologists. Different topologies of sensors and different classification techniques were examined were explored. The ability of the methodology to be generalized was also evaluated using leave-one-patient-out cross validation. The obtained results indicate high classification ability (93.73% classification accuracy) [476], [480], [481]. Gait performance has been largely studied and it is part of this thesis work [5], [6], [17], [482], also, Pansera et al. studied the variation of Sample Entropy in the acceleration signals as indicator of the gait performance. Four PD patients are compared to four healthy using a set of five wireless sensors located in the limbs and in the trunk. A metric to assess the level of symmetry during locomotion, an important clinical feature, is proposed. Results show considerable differences between the patients and the subjects, both for sample entropy (in 3 of the 5 sensors) and in the gait asymmetry index (left vs. right limbs). Future work is proposed including age-matched subjects and a larger sample [8]. Rigas et al. (2009-2012) built a system able to perform a real-time quantification of resting tremor in the PD. Five healthy subjects were asked to simulate several severities of tremor in hands and feet in three static activities. The classification of RT severity based on those features, provided accuracy 76%. Then, they extended the system to automatically detect both resting and action/postural tremor. The estimation of tremor type (resting/action postural) and severity is based on features extracted from the acquired signals and hidden Markov models. For the validation data collected from 23 subjects (18 PD patients and 5 control) was used. The obtained results quantifies tremor severity with 8 % accuracy and discriminates resting from postural tremor [478], [483], [484]. Cancela et al. (2010) and Pastorino et al. (2011) described a methodology to automatically detect the severity of bradykinesia in motor disease patients using wireless, wearable accelerometers. This methodology was tested with cross validation through a sample of 20 Parkinson's disease patients [9], [477]. The assessment of methodology was carried out through some daily living activities which were detected using an activity recognition algorithm. The UPDRS severity classification of the algorithm

¹¹⁹ www.ausl.mo.it (Last date accessed: December 2015)

coincides between 70 and 86% from that of a trained neurologist depending on the classifier used. These severities were calculated for 5 second segments of the signal with 50% of overlap. A bradykinesia profiler was also presented on that work. Bustamante et al. (2010) and Grandez et al. (2010) proposed a testing device for PD and Amyotrophic Lateral Sclerosis (ALS) patients. The device is designed to carry out two of the most used tests for these patients: the finger-tapping test and the hand-grip strength test. It consists on a glove, equipped with Force sensitive Resistors (FSR) [360], [485]–[488]. Additionally, intelligent algorithms were built on top to work as DSS. Partial decision trees and association rules were used for the prediction of the symptoms. Using this tool, the expert can prescribe specific medications that will not cause, or postpone the appearance of specific symptoms to the patient [484] and the medication change proposer module proposes treatment plans to alleviate the symptoms. The methodology is based on the analysis of the outputs of the symptoms detection modules, taking into account the uncertainty (confidence) propagated by their respective classification algorithms. The evaluation of such methodology was performed using artificial follow-up data produced by a specially built simulation environment. The obtained results demonstrate that its outputs compare well with the experts' decisions, indicating high performance [489].

4.4.18 PD_manager

PD_manager aims to build and evaluate an innovative, mhealth, patient centric ecosystem for Parkinson's disease (PD) management.

4.4.18.1 Partners involved

- Institut Josezf Stefan¹²⁰ – Slovenia
- Fondaziones Ospedale San Camillo¹²¹ – Italy
- University of Ioannina¹²² – Greece
- Biotronics 3D Limited¹²³ - United Kingdom
- Universidad Politécnica de Madrid¹²⁴ – Spain
- Synthema¹²⁵ -Italy
- University of Surrey¹²⁶ - United Kingdom
- Univerzitetni Rehabilitacijski Institute Republike Slovenije¹²⁷ -Slovenia
- Moticon¹²⁸ – Germany
- Fondazione Santa Lucia¹²⁹ - Italy

4.4.18.2 Project description

PD_manager project is aimed at building a novel mHealth platform for PD patients able to integrate motor and non-motor assessment including cognitive, speech, sleep monitoring and treatment adherence monitoring. It is

¹²⁰ www.ijs.si/ijsw (Last date accessed: January 2016)

¹²¹ www.ospedalesancamillo.net (Last date accessed: January 2016)

¹²² www.uoi.gr (Last date accessed: January 2016)

¹²³ www.biotronics3d.com (Last date accessed: January 2016)

¹²⁴ www.upm.es (Last date accessed: January 2016)

¹²⁵ www.synthema.it (Last date accessed: January 2016)

¹²⁶ www.surrey.ac.uk (Last date accessed: January 2016)

¹²⁷ www.ir-rs.si (Last date accessed: January 2016)

¹²⁸ www.moticon.de (Last date accessed: January 2016)

¹²⁹ www.hsantalucia.it (Last date accessed: January 2016)

also aimed at delivering different services for the patients, caregivers and professionals based on this holistic monitoring. Primary motor symptoms such as tremor, bradykinesia and postural imbalance and non-motor symptoms, such as sleep, speech and cognitive disorders, will be evaluated with data captured by light, unobtrusive, co-operative, mobile devices: sensor insoles, a wristband and the patient's or caregiver's (the role of which is of paramount importance) smartphone. The PD_manager system is aimed at covering both motor and non-motor symptoms in PD. It covers aspects such as patients' and caregivers training and focuses on adherence to the medical recommendations. Once the data is processed and symptoms are assessed a knowledge management platform will be developed as well as the studies analysing the clinicians diagnostic and prescribing behaviour and the mobile apps for empowering patients adhere to nutrition and physiotherapy plans are novel and along with the effort to build a Decision Support System (DSS) that suggests modifications in the medication plan take the PD management a step beyond the existing systems. Compliance with medical recommendations will also be studied; the patient will be motivated to adhere to his medication and diet, will be empowered to exercise and make physiotherapies and will be educated about occupational and speech therapy in order to self-manage his condition. The PD_manager Knowledge Management platform will be built with a cloud-based, open architecture approach based on FI-WARE that will support the use of any commercial set of sensors within the Internet of Things concept. Around 200 patients will be involved in the validations study of this project where clinical effectiveness, acceptability and usability of the developed platform and mobile apps will be studied together with a detailed study for the potential health outcomes, quality of life, care efficiency gains and economic benefits will also be conducted. The first phase of development within the PD_manager project has involved the data collection from 20 advanced PD patients showing motor complications which carried out in three different hospitals across Europe: Fondazione Ospedale San Camillo (in Venice), Fondazione Santa Lucia (in Rome) and University of Ioannina. Data was collected prospectively using the first a prototype of the PD_manager. A specific protocol was designed to collect motor data (patients were asked to carry out activities of daily life such as walking, sitting or lying on a bed in the hospital facilities), as well as non-motor symptoms (cognitive tests were implemented in Android environment to collect data), speech signals were also collected using the smartphone microphone. First works reported user needs analysis [20] and a preeliminary assessment of motor [490] and non-motor symptoms [491].

4.4.19 PVI

4.4.19.1 Partners involved

- Max Little, Ph.D. Project Director. A Wellcome Trust/MIT fellow currently at the Media Lab, MIT.
- Thanasis Tsanas, M.Sc. Algorithms. Currently finishing up his PhD at the University of Oxford
- Ladan Baghai-Ravary (Former members), Ph.D. Programming. Ladan is a research fellow and expert in speech recognition and analysis based at the Oxford University Phonetics Lab.

4.4.19.2 Project description

This project was aimed to collect 10.000 sustained phonations ("aaah" vocal sounds) through telephone-quality digital audio lines, under realistic, non-lab conditions, to test the hypothesis that it is possible to detect PD through these recordings. This works continues a previous research using lab-quality digital audio recordings of sustained phonations [492]–[498]. Furthermore, they were able to accurately predict the severity of PD symptoms using the UPDRS [493]. To detect Parkinson's from the voice, they extract a large number of dysphonia features (specifically 132 in previous studies [492], [499]) from digital audio signals of sustained phonations ("aaah" sounds). These features cover a wide range of classical and novel clinical dysphonia analysis algorithms (see [493] for a comprehensive list). Then several feature selection algorithms (Lasso, mRMR, RELIEF, LLBFS [492]) were applied, and passed the selected features to standard supervised classifier algorithms (random forests and SVMs). To address overfitting, cross-validation was used, both "leave audio samples out" and "leave subjects out" schemes [492], [493], [499]. Another approach followed was the use of multinomial logistic regression classifier with Haar

wavelets transformation as projection filter that outperform logistic regression is used [494].

They found that using only ten dysphonia features were able to discriminate healthy controls from PD subjects reaching almost 99% overall classification accuracy [492]. Also, using non-parametric regression and classification algorithms they achieved an accurate replication of the UPDRS assessment with clinically useful accuracy (about 2 UPDRS points difference from the clinicians' estimates of the total UPDRS score, $p < 0.001$) [493]. Finally, they reduce the scheme to the combination of four features using a kernel support vector machine obtaining a correct classification performance of 91.4% [495].

The studies relied on two principal audio datasets: sustained phonations from people with Parkinson's recorded at home, weekly, over a 6-month period each (50 subjects, 5875 audio samples [493]), and lab-based recordings from healthy controls and people with Parkinson's (43 subjects, 263 audio samples [492], [499]). Other datasets have been used in earlier studies where new dysphonia features were developed [494]–[498]. In terms of detecting the disease, at best they achieved was 98.6% detection accuracy (that is, the percentage of samples that were correctly identified as being either healthy or Parkinson's, averaged over all cross-validation runs) under lab conditions [492]. In terms of the severity of symptoms, the average prediction error is 3,5 points on the 176-point UPDRS scale (approx. 2% mean absolute, cross-validation error) under simulated mobile telephony conditions [499]. Additionally, they found that detection performance appears to level out at around 10 dysphonia features, which include features that measure vocal fold oscillation irregularity, breathiness and noise, and vocal tract resonance fluctuations [492], [493], [499].

4.4.20 REMPARK

REMPARK (Personal Health Device for the Remote and Autonomous Management of Parkinsons Disease) is a research project partially funded by the European Comission. REMPARK project objective was to develop a personal health system with closed loop detection, response and action capabilities for the assessment and possible management of PD patients. The project developed a wearable monitoring system able to identify in real time the motor status of the PD patients and evaluating On, Off and dyskinesia events during ambulatory conditions.

4.4.20.1 Partners involved

- Coordinator: CETpD (Universitat Politècnica de Catalunya)¹³⁰ – Spain
- European Parkinson's disease Association¹³¹ – Belgium
- Neusta mobile solution GmbH¹³² - Germany
- Telefónica Investigación y Desarrollo SA¹³³ - Spain
- Centro Médico Teknon SL¹³⁴ - Spain
- National University of Ireland, Galway¹³⁵ - Ireland
- M&M Qualtech Limited¹³⁶ - Ireland
- Maccabi Healthcare Services¹³⁷ - Israel

¹³⁰ www.epsevg.upc.edu/cetpd/index.php (Last date accessed: December 2015)

¹³¹ www.epda.eu.com (Last date accessed: December 2015)

¹³² www.neusta-ms.de (Last date accessed: December 2015)

¹³³ www.tid.es (Last date accessed: December 2015)

¹³⁴ www.teknon.es (Last date accessed: December 2015)

¹³⁵ www.nuigalway.ie (Last date accessed: December 2015)

¹³⁶ www.mmqualtech.ie (Last date accessed: December 2015)

¹³⁷ www.maccabi4u.co.il (Last date accessed: December 2015)

- Fondazione Santa Lucia¹³⁸ - Italy
- Associação Fraunhofer Portugal Research¹³⁹ - Portugal
- Nordforce Technology AB¹⁴⁰ - Sweden

4.4.20.2 Project description

REMPARK was aimed at building a telemedicine enabled Personal Health System (PHS) for the remote management of mild and advanced PD patients. The PHS is composed by a Body Area Network (BAN) composed by sensors, actuators and a smartphone, which also acts as GPS for providing context-aware information and as an interface for the PD patient, to record their direct feedback especially regarding the non-motor symptoms. Communications among the elements of the BAN are via low energy Bluetooth 4.0 working autonomously constituting a closed and automatic loop. This level of the system is auto-adaptive and customized by means of a constant evaluation of the actuator's effect, auditory and haptic cueing can be used depending on the preferences of each subject. The adjustable drug delivery system is also investigated and tested in REMPARK and the objective is to include it for those patients suffering from unpredictable Off periods. REMPARK offers a second tier designed to act in the medium-long term and constitutes a closed semi-automatic loop, as it allows the intervention of medical professionals. The system allows to send data to the server of the relevant health service provider feeding an intelligent data treatment system that helps to evaluate and predict the evolution of the disease of a particular patient. Artificial intelligence methods are applied to the database information for the automatic detection of motor symptoms [285].

Rodriguez-Martin et al. (2013) characterize basic activities and their transitions using a single sensor located at the waist. Using this postural detection algorithm was able to detect and identify 6 different postural transitions, sit to stand, stand to sit, bending up/down and lying to sit and sit to lying transitions with a sensitivity of 86.5% and specificity of 95%. The algorithm was tested on 31 healthy volunteers and 8 PD patients who performed a total of 545 and 176 transitions respectively [332]. Then, Rodriguez-Martin et al. (2013) built an IMU for long-term monitoring called the "9×2" (contains a triaxial accelerometer, gyroscope, magnetometer and a temperature sensor) which was used to collect movement signals in four different countries from 90 PD patients. The second part of this project consisted in designing intelligent algorithms capable of monitoring different PD symptoms (freezing of gait, dyskinesia, tremor, bradykinesia, falls and gait parameters). The IMU offers the possibility to send inertial data to external devices and the possibility to store it in a microSD card with almost 4 days of data capacity. However, the "9×2" lasts for 36.8 h while continuously storing data without recharging the device. It also includes the possibility to import external data such as another inertial device to compare two different signal sources in real time. Online classifiers have already been tested in a pilot study in which an apomorphine pump was regulated according to the symptoms detected. In that case, a short time Fourier Transform and a Support Vector Machine (SVM) algorithm were computed in real-time and were optimized through a digital signal controller, speeding up the algorithm and saving energy [500].

4.4.21 RESCUE

The RESCUE (Rehabilitation in parkinson's disease: strategies for cueing) project was funded under the PF5 of the EC within the Quality of Life and Management of Living Resources Programme key action. It investigated a physiotherapy technique to improve mobility for people with PD by introducing a rehabilitation programme based around the concept of cueing and focuses mainly on the effects of bradykinesia and akinesia on walking and everyday activity.

¹³⁸ www.hsantalucia.it (Last date accessed: December 2015)

¹³⁹ www.fraunhofer.pt (Last date accessed: December 2015)

¹⁴⁰ www.nordforce.se (Last date accessed: December 2015)

4.4.21.1 Partners involved

- Coordinator: Northumbria's School of Health, Community and Education Studies¹⁴¹ - UK
- Faculty of Physical Education and Physiotherapy at the Katholieke Universiteit Leuven¹⁴² - Belgium
- Medical Centre at the Vrije Universiteit Amsterdam¹⁴³ - The Netherlands

4.4.21.2 Project description

RESCUE investigated the changes induced by auditory and visual cues (rhythmic stimuli) on the walking patterns under various experimental conditions to determine which cues can best improve and sustain functional gait performance. The project successfully tested a home-based physiotherapy programme to train PD patients to use rhythmic cues delivered by a small portable cueing device in a randomised control trial.

Rochester et al. (2005 - 2010) tested the effects of cued training on motor learning in PD. They defined motor learning as acquisition (single task), automaticity (dual task) and retention of single- and dual-task performance (follow-up). 153 subjects with PD received 3 weeks cued gait training as part of a randomised trial. And then, they measured changes in cued gait performance with three external rhythmical cues (auditory, visual and somatosensory) during single and dual tasks after training and 6 weeks follow-up. Accelerometers recorded gait and walking speed, step length and step frequency were determined from raw data. Data were analysed using linear regression models. Walking speed and step length significantly increased with all cues after training during both single- and dual-task gait and these effects were retained. Training effects were not specific to cued gait and were observed in dual-task step length, and walking speed however was more limited in single-task non-cued gait [273], [501]. Multiple regression analysis was used to explore the effect of 12 characteristics representing four domains (personal, motor symptoms, cognitive, affective) on gait outcomes. Thirty-seven percent of variance in single task speed was explained by increased fear of falling, sex, age, disease severity, and depression; 34% of variance in dual task speed was explained by increased fear of falling, disease severity, medication, and depression; 12% of variance in interference scores was explained by greater disease severity and impaired executive function [278], [502]. Finally, they explored the relationship between gait and gait-related activities and fatigue in PD showing that there was no clear association between activity and fatigue in PD subjects [503]. Lim et al. (2004) carried out a study to assess reliability, responsiveness and feasibility of gait and gait related tests in the home of PD patients. The UPDRS, a timed walking test, the TUG test the Berg Balance Scale and the Functional Reach test were applied by three independent observers on 26 PD patients. Moderate to high intraclass correlation coefficients were found, ranging from 0.74 to 0.88 and 0.64 to 0.87 for the intra- and inter-observer reliability, respectively. All test showed reliable change indexes under 11% and the whole test battery was applicable within 30 min [504]. Nieuwboer et al. (2007) ran a single-blind randomised crossover trial including 153 patients with PD who received a 3-week home cueing programme using a prototype cueing device, followed by 3 weeks without training. Posture and gait scores measured at 3, 6 and 12 weeks by blinded testers were the primary outcome measure. Secondary outcomes included specific measures on gait, freezing and balance, functional activities, quality of life and carer strain. Small but significant improvements were found after intervention of 4.2% on the posture and gait scores ($p=0.005$). Severity of freezing was reduced by 5.5% in freezers only ($p=0.007$). Gait speed ($p=0.005$), step length ($p<0.001$) and timed balance tests ($p=0.003$) improved in the full cohort. Effects of intervention had reduced considerably at 6-week follow-up. Cueing training in the home has specific effects on gait, freezing and balance. The decline in effectiveness of intervention effects underscores the need for permanent cueing devices and follow-up treatment [271].

Willems et al. (2006) studied the effect of rhythmic auditory cues on gait in PD subjects with and without freezing and in controls. Freezers and non-freezers showed the same response to rhythmical auditory cues. Within group

¹⁴¹ www.northumbria.ac.uk (Last date accessed: December 2015)

¹⁴² www.kuleuven.be (Last date accessed: December 2015)

¹⁴³ www.vumc.nl (Last date accessed: December 2015)

analysis for stride length showed different cueing effects. Stride length decreased at the +10% condition for freezers ($p < 0.05$), whereas it increased for non-freezers [505]. Later, Nieuwboer et al. (2009) also investigated the effect of different modalities of rhythmic cueing on the duration of a functional turn in freezers and nonfreezers. The effect of 3 different cue modalities on functional turning performance was investigated, involving a 180° turn while picking up a tray. Tests were performed without cues and with auditory, visual, and somatosensory cues delivered in a randomized order at preferred straight-line stepping frequency. Cueing (all types) increased the speed of the turn in all subjects. There was no difference between turn performance of freezers and nonfreezers in cued and noncued conditions. Auditory cues made turning significantly faster than visual cues ($P < .01$) but not compared with somatosensory cues, except in nonfreezers [284]. In a later study, Willems et al. (2007) showed that in contrast to controls, PD patients used a wider turning-arc and took smaller, narrower steps. In addition, they demonstrated a higher coefficient of variation of step duration (6.92%) compared to controls (4.88%, $P < 0.05$). The “wide-arc” turning strategy of PD patients was more prominent in freezers than in nonfreezers. Auditory cues reduced the coefficient of variation of step duration in PD patients (both freezers and nonfreezers) during turning (from 6.92 to 6.00%, $P < 0.05$) [506].

Lim et al. (2008) worked in a multivariate logistic regression model to identify patients susceptible to falls, the final model showed that based on disease duration, freezing symptoms, walking problems, and a prolonged TGUG duration, assessed in the home situation, it was possible to accurately identify 74% of PD patients as fallers [507]. van Wegen et al. (2006) tested an alternative for rhythmic auditory cueing: rhythmic somatosensory cueing (RSC, a miniature vibrating cylinder attached to the wrist). Walking with RSC resulted in lower stride frequencies, and thus larger step lengths (p -values < 0.05), regardless of walking speed. The presence of visual flow did not impair the use of RSC, as evidenced by the lack of differences between conditions 3 and 4 ($p > 0.05$). Rhythmic somatosensory cueing may be a viable alternative for auditory cueing and is robust to changes in walking speed and visual distractors [508].

4.4.22 SENSE-PARK

SENSE-PARK (Supporting and Empowering Parkinson patients in their home environment using a Novel SENSory information system that monitors daily-life-relevant parameters of PARKinson disease and their) is an European funded initiative which aims to address the critical issue of accurate measurement of PD.

4.4.22.1 Partners involved

- Coordinator: Eberhard Karls Universität Tübingen¹⁴⁴ - Germany
- HASOMED Hard- und Software für Medizin Gesellschaft mbH¹⁴⁵ - Germany
- Hahn-Schickard-Gesellschaft für angewandte Forschung e.V.¹⁴⁶ – Germany
- Universitetssykehuset Nord-Norge HF – Norway
- Instituto de Medicina Molecular¹⁴⁷ - Portugal
- The Cure Parkinson's Trust¹⁴⁸ - UK
- AbilityNet¹⁴⁹ - UK

¹⁴⁴ www.uni-tuebingen.de (Last date accessed: December 2015)

¹⁴⁵ www.hasomed.de (Last date accessed: December 2015)

¹⁴⁶ www.hsg-mst.de (Last date accessed: December 2015)

¹⁴⁷ www.imm.fm.ul.pt (Last date accessed: December 2015)

¹⁴⁸ www.cureparkinsons.org.uk (Last date accessed: December 2015)

¹⁴⁹ www.abilitynet.org.uk (Last date accessed: December 2015)

4.4.22.2 Project description

The aim of the SENSE-PARK project was to develop an unobtrusive and empowering information system for use in the home environment to monitor patterns in PD patients, *Figure 44* shows the SENSE-PARK sensor and the collected signals.

Louter et al. (2014) explored the use of a triaxial accelerometer as a tool to identify the risk of developing PD quantifying nocturnal movements. Outcome measurements included mean acceleration, and qualitative axial movement parameters, such as duration and speed. Compared with controls, patients with PD had an overall decreased mean acceleration, as well as smaller and shorter nocturnal axial movements. These changes did not occur in the potential “high risk PD” individuals, suggesting that relevant axial movement alterations during sleep have either not developed or cannot be detected by the means applied in this at-risk cohort [352]. Adema et al. and Al-Jawad et al. (2012) presented a feasibility study of an instrumented TUG test using a wearable inertial sensor unit attached on the lower back of the person. The developed algorithm was based on the Dynamic Time Warping (DTW) for detection and duration assessment of turn state transitions, while a 1-dimensional DTW is used to detect the sit-to-stand and stand-to-sit phases. The feature set was a 3-dimensional vector which consisted of the angular velocity, derived angle and features from Linear Discriminant Analysis (LDA) [333], [334]. Also, using the cost inertial sensors attached on the lower back, Al-Jawad et al. (2013) presented a quaternion-based extended Kalman filter (used as a data fusion algorithm) to characterize the postural steadiness during stance. The orientation of the body based on acceleration and angular rate signals was estimated. In order to get the coordinate of the body's centre of mass (CoM), the height of the sensor was projected on the horizontal plane by using the estimated orientation. Many parameters such as the mean velocity of sway, lateral/anterior-posterior range and others are then obtained from the sway path, which help the clinicians to assess the postural instability [335].

Figure 44 - Sensor system development and data interpretation in SENSE-PARK (Source: project website)

Finally, Serrano et al. (2014) designed, prototyped and tested the integration of the patient diary notes (self-reported) with information gathered from movement sensors (automatic measurement) and a visualization mechanism combining the two [509].

4.4.23 V-time

V-TIME is a project funded by the EU 7th Framework Programme under the Health theme. The consortium brings together world leaders in ageing, neuroscience, rehabilitation and VR technology to test a new therapy that may dramatically reduce the negative costs of falls, financial and other.

4.4.23.1 Partners involved

- Gait & Neurodynamics Laboratory, Department of Neurology, Tel Aviv Sourasky Medical Centre¹⁵⁰ - Israel
- Department of Rehabilitation Sciences, Katholieke Universiteit Leuven¹⁵¹ – Belgium

¹⁵⁰ www.tasmc.org.il (Last date accessed: December 2015)

¹⁵¹ <https://gbiomed.kuleuven.be/english/research/50000743/index.html> (Last date accessed: December 2015)

- Institute for Ageing and Health, Newcastle University¹⁵² - UK
- Department of Neurosciences, University of Genoa¹⁵³ - Italy
- Departments of Geriatrics & Neurology, University Medical Centre St Radboud¹⁵⁴ - Netherlands
- University of Sassari¹⁵⁵ - Italy
- Inition 3D technologies¹⁵⁶ - UK
- Beacon Tech Limited¹⁵⁷ - Israel
- ADDS S.r.o¹⁵⁸ - Czech Republic

4.4.23.2 Project description

The V-TIME project proposes a multi-modal intervention consisting of a treadmill training that promotes walking abilities and physical fitness. It simultaneously uses a virtual reality (VR) environment that challenges, implicitly teaches, and enhances cognitive skills that facilitate the safe execution of many activities of daily living: visual scanning, planning, dual tasking abilities, and obstacle negotiation. V-TIME is aimed to demonstrate the extent to which an intervention that combines treadmill training augmented by virtual reality reduces fall risk, improves mobility and enhances cognitive function in a diverse group of older adults. V-TIME offers task-specific training in a motivating and safe environment that can readily be reproduced and standardized. The major goal of the current proposal is to establish the beneficial effects of V-TIME training in a large (N=300) and diverse group of elderly via a multi-centre, prospective randomized controlled trial. Outcomes include post-training 6 month fall incidence rates (the primary outcome), gait, physical activity (e.g., steps walked in 7 days), cognitive function, quality of life, and neuroimaging measures (fNIRS, fMRI). Assessments will take place before, after, and 1 month and 6 months after the completion of the training. A falls calendar will be kept by each participant for 6 months after completing the training to assess fall incidence (i.e., the number of falls, multiple falls and falls rate). In addition, they will measure gait under usual and dual task conditions, balance, community mobility, health related quality of life, user satisfaction and cognitive function [510].

4.4.24 WalkMate

4.4.24.1 Partners involved

- Department of Computational Intelligence and Systems Science, Tokyo Institute of Technology, Yokohama, Japan¹⁵⁹.
- Max Planck Institute for Human Cognitive and Brain Sciences, Leipzig, Germany¹⁶⁰

4.4.24.2 Project description

WalkMate system features an auditory feedback for people suffering from PD or hemiplegia. The system uses the timing of the walking person as a sensory input for the robot and the sound of a walking rhythm as the robot's output. An algorithm based on travelling wave dynamics is used to control the timing difference between the

¹⁵² www.ncl.ac.uk/biomedicine/iah/ (Last date accessed: December 2015)

¹⁵³ www.unige.it (Last date accessed: December 2015)

¹⁵⁴ www.radboudumc.nl (Last date accessed: December 2015)

¹⁵⁵ www.uniss.it (Last date accessed: December 2015)

¹⁵⁶ www.inition.co.uk (Last date accessed: December 2015)

¹⁵⁷ www.beacontech.eu (Last date accessed: December 2015)

¹⁵⁸ www.adds.com (Last date accessed: December 2015)

¹⁵⁹ www.titech.ac.jp (Last date accessed: December 2015)

¹⁶⁰ www.mpg.de/149614/kognition_neuro (Last date accessed: December 2015)

gathered data and sound signals the device is sending to its wearers. Miyake (2009) demonstrated that the two walking rhythms adapt mutually after the start of interaction indicating the importance of interpersonal mutual entrainment of rhythmic motion for walking support, and new human-robot interaction technologies are expected as an extension of this work [511]. PD patients using WalkMate had healthier looking stride patterns and they achieved a greater stability and synchronization compared to other walking aids that have a fixed rhythm. Hove et al. (2012) run a study with PD patients and healthy participants walked with a) no auditory stimulation, b) fixed-tempo Rhythmic Auditory Stimulation (RAS), and c) *interactive* rhythmic auditory stimulation. Patients consistently synchronized with the interactive system, their fractal scaling returned to levels of healthy participants, and their gait felt more stable to them. Patients and healthy participants rarely synchronized with fixed-tempo RAS, and when they did synchronize their fractal scaling declined from healthy $1/f$ levels. Five minutes after removing the interactive rhythmic stimulation, the PD patients' gait retained high fractal scaling, suggesting that the interaction stabilized the internal rhythm generating system and reintegrated timing networks. The experiment demonstrates that complex interaction is important in the (re)emergence of $1/f$ structure in human behavior and that interactive rhythmic auditory stimulation is a promising therapeutic tool for improving gait of PD patients [512]. Also, it has been showed that mutual entrainment can facilitate gait relearning effectively [513].

Figure 45 - Schematic illustration and components of the WalkMate system (Source: Tokyo Institute of Technology press release [514])

4.4.25 Summary

Project name - Status - Country	Short description	Starting date (dd/mm/yy) - Duration (months)	Funding source & scheme - Budget/ Funding	Web	Keywords	Results	Functionality - Application - Technology
BeatHealth - Ongoing - EU	Health and Wellness on the Beat BeatHealth explores the link between music and movement for boosting individual performance and enhancing health and wellness. It is also aimed at exploring the use of this approach in Parkinson's disease populations.	2013-10-01 - 36	European Commission FP7 ICT Collaborative Project - Project reference: 610633 - 3.8 / 2.9	Project website ¹⁶¹ Cordis ¹⁶²	audio biofeedback, wearable, exergaming, wearable sensors, external cueing	Preelinary results on using external stimulation on movement [406][407]. Preliminary work on PD [282].	Treatment, Rehabilitation - Speciality - (sync, BAN, wireless)
Cupid - Completed - EU	Closed-loop system for personalized and at-home rehabilitation of people with Parkinson's Disease It is aimed to develop an ICT-enabled solution to the rehabilitation of patients with PD in their home setting, tailoring the solution to target mobility, cognitive function and debilitating PD symptoms such as freezing of gait.	01/10/11 - 36	European Commission FP7 ICT Collaborative Project Project reference: 288516 - 3.5 / 2.6	Project website ¹⁶³ Cordis ¹⁶⁴	Monitoring, audio biofeedback, rehabilitation, wearable, exergaming, wearable sensors, virtual reality, external cueing	Audio biofeedback [286], [326]; FoG detection [327], [410]; Exergaming [411] [330]; TUG test [412], [413]	Mentoring, Rehabilitation - Speciality - (async, VPN, wireless)

¹⁶¹ <http://www.euromov.eu/beathealth/publications> (Last date accessed: December 2015)

¹⁶² http://cordis.europa.eu/project/rcn/110990_en.html (Last date accessed: December 2015)

¹⁶³ www.cupid-project.eu (Last date accessed: December 2015)

¹⁶⁴ cordis.europa.eu/projects/rcn/100767_en.html (Last date accessed: December 2015)

<p>DAPHNE</p> <p>- Completed</p> <p>- EU</p>	<p>Detection of Activity Performance for Health with New Equipment</p> <p>Quantitative measurement of neurological and psycho-physical health state. It proposes a portable computerized instrument that measures fundamental parameters of Parkinsonian reactive capabilities.</p>	<p>01/01/2001</p> <p>- 24</p>	<p>European Commission FP5 IST CSC - Cost-sharing contracts</p> <p>Project reference: IST-2000-25107</p> <p>- 1.5 / 0.8</p>	<p>Cordis¹⁶⁵</p>	<p>Neuromotory pathology, Reactive capabilities</p>	<p>Fuzzy logic to diagnose and monitor the neuro-psycho-physical conditions. Measuring reaction time, speed, strength and tremor [416], [417].</p>	<p>Monitoring</p> <p>- Speciality</p> <p>- async-, Open Internet, wire,</p>
<p>DAPHNET</p> <p>- Completed</p> <p>- EU</p>	<p>DAPHNET (Dynamic analysis of physiological Networks)</p> <p>Physiological functions to be studied are the cardio vascular capacities, brain activity (EEG), motor control, gait, posture, sleep and sympathetic and parasympathetic effects. Algorithms to assess the long-term effects and Inter-relations between signals representing these functions are at the core of this proposal.</p>	<p>01/04/2006</p> <p>- 36</p>	<p>European Commission FP6 IST-2004-2.3.4.1 b7</p> <p>IST-2004-2.3.4.1.b7 FET open</p> <p>Project reference: 018474-2</p> <p>- 2.1 / 1.9</p>	<p>Cordis¹⁶⁶</p>	<p>Gait assessment, FoG detection, Auditory cueing</p>	<p>FoG detection and auditory cueing [419]–[423].</p>	<p>Monitoring</p> <p>Mentoring</p> <p>- Speciality</p> <p>- async-, Open Internet, wireless,</p>

¹⁶⁵ cordis.europa.eu/project/rcn/60687_en.html (Last date accessed: December 2015)

¹⁶⁶ http://cordis.europa.eu/project/rcn/80442_en.html (Last date accessed: December 2015)

State of the art

DiPAR - Execution - EU	DiPAR (Diagnosing Parkinson's Disease by neuromuscular function evaluation) The proposed sortium is a new, vertically integrated supply chain, leveraging significant revenues from the sale and licensing of the project end results through collaboration with other innovative SMEs involved in the DiPAR project.	01/12/10 - 94	European Commission FP7 SME Research for SMEs Project reference: 262291 - 1.7 / 1.3	Project website ¹⁶⁷ Cordis ¹⁶⁸	Handwriting assessment, early diagnosis	Handwriting assessment to distinguish PD and healthy subjects [396]	Diagnosis, Monitoring - Speciality - (async-, Internet, wire)
EDUPARK - Completed - EU	EDUPARK (Patient education in Parkinson's disease) The overall objective of this project is to improve the quality o life of people suffering from a chronic degenerative disease, i.e. Parkinson's Disease (PD) through patient education and psychosocial support.	01/01/2003 - 28	European Commission FP5-LIFE QUALITY Cost-sharing contracts Project reference: QLK6-CT-2002-02674 - 0.9 / 0.9	Cordis ¹⁶⁹	Patient and carer education and empowerment	<i>"Patient Education for People with Parkinson's Disease and their Carers: A Manual" [427]</i>	Mentoring - treatment modality - (async-, Open Internet, wireless)

¹⁶⁷ <http://www.dipar.net/> (Last date accessed: December 2015)

¹⁶⁸ http://cordis.europa.eu/projects/rcn/96874_en.html (Last date accessed: December 2015)

¹⁶⁹ http://cordis.europa.eu/projects/rcn/67227_en.html (Last date accessed: December 2015)

State of the art

E-MOTIONS - Completed - Sweden	E-MOTIONS, Decision support in treatment of Parkinson's disease. The research project E-MOTIONS is about developing, applying and evaluating IT-based methods for supporting treatment and evaluation of treatments for Parkinson's disease with motor fluctuations.	01/01/2010 - 36	KK-stiftelsen Abbott Product Operations AG Nordforce Technology AB - NA	Project website ¹⁷⁰	Decision Support System, Parkinson, Levodopa, Duodopa, Motor test, Electronic diary, Web interface, Treatment assessment	Handwriting assessment [398], [399], [430], [431]	Diagnosis, Monitoring - Site of care - (async-, Open Internet, wireless)
FitForAge - Execution - Germany	The scope of the research consortium is to develop technology based solutions which will help elderly people in their future living environment comprising home and workplace as well as in communication and transportation. Eventually not only elderly people but also all social groups should profit from these solutions.	NA - 36	Bavarian Research Foundation - NA/2.5	Project website ¹⁷¹	Development of smart, wearable and washable sensors: trousers, pullover and gloves	FoG detection [435], [436], PD assessment based on gloves [437] and washable accelerometer [433], [434]	Monitoring - Site of care - (async-, Open Internet, wireless)
HELP - Completed - Spain	The HELP Project consortium is designing a Health Monitoring System specifically targeted for the needs of Parkinson Disease (PD) patients. The help system has been specifically designed and implemented as a health monitoring system in order to optimize treatment and improve quality of life of people with Parkinson's.	01/06/09 - 36	Ambient Assisted Living Joint Programme - 11.6 / 1.8	Project website ¹⁷²	Closed loop. Monitoring + intraoral drug delivery	Closed loop [438], [439]	Monitoring Treatment - Site of care, treatment modality - (sync-,-, wireless)

¹⁷⁰ www.du.se/en/Forskning/Forskningsprojekt/?&pid=HDA2010-00041 (Last date accessed: December 2015)

¹⁷¹ www.fit4age.org (Last date accessed: December 2015)

¹⁷² www.aal-europe.eu/projects/help (Last date accessed: December 2015)

State of the art

Mercury	A Wearable Sensor Network Platform for High-Fidelity Motion Analysis	NA - NA	Microsoft, Intel, NSF, IBM, Sun Microsystems, Siemens, ArsLogica, National Instruments, NIH, CIMIT, Institute at Boston University, US Army - NA	Project website ¹⁷³	Accelerometers Dyskinesia, Tremor, Bradykinesia	PD assessment based on wearable accelerometers and machine learning algorithms [441]–[449] Web-based app for home monitoring [450]–[452]	Consultation, Monitoring - Site of care - Technology (sync, Open Internet, Wireless)
MoMoPa - Completed - Spanish Government	MoMoPa (Motor monitoring of Parkinson's disease patients with therapeutic aim)	26/01/2009 - 29	Spanish Instituto Carlos III Ministry of Economy and Competitiveness Strategic Health Actions, National Plan of R&D&I 2008-2011 Project reference: PI08/90756	Project website ¹⁷⁴	Inertial sensors, Monitoring Gait, dyskinesias	Activity detection, gait assessment, dyskinesia detection [453]–[455]	Monitoring - (Speciality, Disease Entity, Site of care, treatment modality) - (async-, Open Internet, wireless)

¹⁷³ <http://fiji.eecs.harvard.edu/Mercury> (Last date accessed: December 2015)

¹⁷⁴ <http://www.fundacioabat.cat/index.php/momopa-2?lang=es> (Last date accessed: December 2015)

State of the art

mPower - Ongoing - NA	mPower is an iPhone app-based study designed to monitor and understand the causes of variations in symptoms of Parkinson disease .	2015 - NA	Study sponsored by Sage Bionetworks with funding from the Robert Wood Johnson Foundation - NA	Project website ¹⁷⁵	mHealth, mobile monitoring, motor symptoms, speech, cognitive	Released the first six months of data from this study donated by more than 9,500 mPower participants on Synapse ¹⁷⁶ .	Monitoring - (Speciality, Disease Entity, Site of care, treatment modality) - (async-, Open Internet, wireless)
NeuroTREMOR - Completed - EU	NeuroTREMOR (A novel concept for support to diagnosis and remote management of tremor) The main objective of the project is to validate technically, functionally and clinically, a novel system for understanding, giving support to diagnosis, and remotely managing tremors.	01/02/2012 - 36	European Commission FP7 ICT Collaborative project Project reference: 287739 - 3.3 / 2.4	Cordis ¹⁷⁷ Project website ¹⁷⁸	Tremor, Neuroprostheses, Neurostimulation Essential tremor; Functional electrical stimulation	Motor unit identification from high-density sEMG [458]–[460]. Neuroprostheses is [461]–[463].	Monitoring Treatment - (Site of care, treatment modality) - (sync-, -, wire)
neuroQWERTY - Execution - Spain	Team neuroQWERTY is developing a new transparent technology capable of detecting early signs of neurodegenerative disorders, i.e. Parkinson's disease, via the finger interaction with electronic devices.	01/01/2013 -	M-Vision Foundation ¹⁷⁹ Michael J. Fox Foundation - -	Project website ¹⁸⁰	Monitoring	-	Diagnosis Monitoring - Site of care - Technology (async-, Open Internet)

¹⁷⁵ <http://parkinsonmpower.org/> (Last date accessed: December 2015)

¹⁷⁶ <https://www.synapse.org/#!Synapse:syn4993293/wiki/247859> (Last date accessed: March 2015)

¹⁷⁷ http://cordis.europa.eu/projects/rcn/100748_en.html (Last date accessed: December 2015)

¹⁷⁸ www.car.upm-csic.es/bioingenieria/neurotremor (Last date accessed: December 2015)

¹⁷⁹ <http://mvisionconsortium.org/> (Last date accessed: December 2015)

¹⁸⁰ <http://neuroqwerty.mit.edu/en/index.php> (Last date accessed: December 2015)

State of the art

PARREHA - Completed - EU	PARREHA (Rehabilitation IT Aid for the Parkinsonians) The project will incorporate virtual reality, visual stimulation, auditory biofeedback and interactive video conferencing technologies with conventional kinematics analysis. Aimed to improve care provision and provide rehabilitation services to Parkinsonians in all kinds of geographical areas including isolated areas.	01/01/2000 - 36	European Comission FP5 IST Cost-sharing contracts Project reference: IST-1999-12552 - 2.8 / 1.6	Cordis ¹⁸¹	Auditory cueing, Visual cueing, gait	Auditory and visual cueing through a portable virtual reality system [465]	Rehabilitation - Site of care, treatment modality - Technology (async-, Open Internet, Wireless)
PAULINA - Ongoing - Sweden	PAULINA (Home-assessment of Parkinson's disease symptoms) A focus of the PAULINA project is to assess speech impairments and integrating it into a tele-monitoring platform.	01/09/2013 - 24	KK-stiftelsen Animech AB Nordforce Technology AB - NA	Project website ¹⁸²	Home-assessment, self-assessment, speech processing, dysarthria, spirometry, tapping	Different methods for PD assessment: a computer-vision for scoring Paced Finger-Tapping (PFT) [471], speech [469][470], spirometry [474], [475]	Monitoring - Site of care, - Technology (async-, Open Internet, Wireless)

¹⁸¹ http://cordis.europa.eu/projects/rcn/58089_en.html (Last date accessed: December 2015)

¹⁸² www.du.se/en/Forskning/Forskningsprojekt/?pid=HDA2013-00032 (Last date accessed: December 2015)

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PD_manager - Ongoing - EU	PD_manager aims to build and evaluate an innovative, mhealth, patient centric ecosystem for Parkinson's disease (PD) management.	2015-01-01 - 36	European Commission H2020 PHC-26-2014 Project reference: 643706 - 4.3/4.3	Project website ¹⁸³ Cordis ¹⁸⁴	mHealth, wearables, monitoring, assessment, motor and non-motor assessment	User needs analysis [20], preeliminary assessment of motor [490] and non-motor symptoms [491]	Monitoring, treatment - Speciality - (sync, BAN, wireless)
PERFORM - Completed - EU	A soPhisticatEd multi-paRametric system FOR the continuous effective assessment and Monitoring of motor status in Parkinson's disease and other neurodegenerative diseases.	01/02/08 - 36	European Commission FP7 ICT Collaborative Project Project reference: 215952 - 9.8 / 6.9	Cordis ¹⁸⁵ Project Web ¹⁸⁶	Motor assessment, monitoring, accelerometert, closed-loop	LID assessment [476], [480], [481]. Gait assessment [5], [6], [482]. Tremor assessment [478], [483], [484] and bradykinesia assessment [9], [477].	Diagnosis, Monitoring, Treatment - Speciality, Site of care, treatment modality - (async-, Open Internet, wireless,)

¹⁸³ <http://www.parkinson-manager.eu/> (Last date accessed: December 2015)

¹⁸⁴ http://cordis.europa.eu/project/rcn/194093_en.html (Last date accessed: December 2015)

¹⁸⁵ http://cordis.europa.eu/project/rcn/85571_en.html (Last date accessed: December 2015)

¹⁸⁶ www.perform-project.eu (Last date accessed: December 2015)

PVI - Execution - US	Parkinson's Voice Initiative it is aimed to develop the technology to test for PD symptoms using voice recordings alone.	01/01/2007 - NA	Private: PatientsLikeMe ¹⁸⁷ The Michael J. Fox Foundation ¹⁸⁸ Twilio ¹⁸⁹ AculabCloud ¹⁹⁰ - NA	Project website ¹⁹¹	Speech assessment	Dysphonia features, extraction and classification [492]–[494], [499]	Diagnosis, Monitoring - Site of care, treatment modality - (async-, network Open Internet/network, wireless)
REMPARK - Execution - EU	REMPARK (Personal Health Device for the Remote and Autonomous Management of Parkinson's Disease) The specific and ultimate goal of the REMPARK project is to develop a PHS with closed loop detection, response and treatment capabilities for management of Parkinson's Disease (PD) patients.	01/11/11 - 42	European Commission FP7 ICT Collaborative Project Project reference: 287677 - 4.7 / 3.2	Project website ¹⁹² Cordis ¹⁹³	Monitoring, Closed loop	Monitoring [332] [500].	Treatment - treatment modality - (sync-, VPM, wireless)

¹⁸⁷ www.patientslikeme.com (Last date accessed: December 2015)

¹⁸⁸ www.michaeljfox.org (Last date accessed: December 2015)

¹⁸⁹ www.twilio.com (Last date accessed: December 2015)

¹⁹⁰ <https://cloud.aculab.com> (Last date accessed: December 2015)

¹⁹¹ www.parkinsonsvoice.org (Last date accessed: December 2015)

¹⁹² www.rempark.eu (Last date accessed: December 2015)

¹⁹³ http://cordis.europa.eu/projects/rcn/100805_en.html (Last date accessed: December 2015)

RESCUE - Completed - EU	RESCUE (Rehabilitation in Parkinson's disease: strategies for cueing) It introduces a rehabilitation programme based around the concept of cueing and focuses mainly on the effects of bradykinesia and akinesia on walking and everyday activity.	01/01/2002 - 39	European Commission FP5 LIFE QUALITY Demonstration contracts Project reference: QLK6-CT-2001-00120 - 1.6 / 1.6	Cordis ¹⁹⁴ Project website ¹⁹⁵	Auditory cueing, Visual cueing	Auditory and visual cueing [271], [273], [278], [284], [501]–[506]	Rehabilitation - treatment modality - (async-, offline, wireless)
SENSE-PARK - Completed - EU	SENSE-PARK: Supporting and Empowering Parkinson patients in their home environment using a Novel SENSory information system that monitors daily-life-relevant parameters of PARKinson disease and their Supporting and Empowering Parkinson patients in their home environment using a novel sensory information system that monitors daily-life-relevant parameters of Parkinson disease and their change	01/10/2011 - 36	European Commission FP7 ICT Collaborative project Project reference: 288557 - 2.7 / 2.1	Cordis ¹⁹⁶ Project website ¹⁹⁷	Closed loop	Instrumented TUG test using a wearable [333], [334] gait assessment [335][509].	Treatment - treatment modality - (sync-, offline, wired)

¹⁹⁴ http://cordis.europa.eu/projects/rcn/60158_en.html (Last date accessed: December 2015)

¹⁹⁵ <http://www.rescueprojects.org> (Last date accessed: December 2015)

¹⁹⁶ http://cordis.europa.eu/projects/rcn/100801_en.html (Last date accessed: December 2015)

¹⁹⁷ www.sense-park.eu (Last date accessed: December 2015)

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V-TIME - Execution - EU	V-TIME (Virtual reality-Treadmill combined Intervention for enhancing Mobility and reducing falls in the Elderly)	01/01/2012 - 48	European Commission FP7-HEALTH-2011-two-stage Project reference: 278169 - 7.4/5.7	Cordis ¹⁹⁸ Project website ¹⁹⁹	Auditory cueing, Virtual reality	Preliminary results [510]	Rehabilitation - treatment modality - (sync-, offline, wireless)
WalkMate - Execution - Japan/Germany	Walk-mate	01/01/2009 - NA	NA	-	Cueing Monitoring	Effect of cueing on gait [511]–[513]	Rehabilitation - treatment modality - (sync-, offline, wired)

Table 11 - Research projects summary

¹⁹⁸ http://cordis.europa.eu/project/rcn/101785_en.html (Last date accessed: December 2015)

¹⁹⁹ www.v-time.eu (Last date accessed: December 2015)

4.5 Serious games

Rego et al. proposed a classification schema towards a taxonomy based on a set of criteria for the design of more effective rehabilitation games [301]. Following a literature review, Rego et al. identified as important the following criteria for the classification of serious games in the rehabilitation area:

- Application area: is the domain application in which game can be applied; despite this domain can be very vast, we may consider however two main applications: cognitive rehabilitation (Cognitive) and physical/motor rehabilitation (Motor).
- Interaction Technology: the technology used by the patient to interact with the system. This can vary from the traditional methods using a mouse or keyboard process to VR based methods. For instance, in VR, interface devices that can be used are: visual interfaces that include head-mounted displays (HMDs) and desktop monitors; haptic interfaces like data gloves; and motion tracking devices.
- Game interface: the interface used in the game. It can be 2D or 3D.
- Number of players: single player / multi-player.
- Game Genre: the games genre can vary in relation with the technology used.
- Adaptability (Yes/No): the system capability to adapt dynamically game difficulty or challenge, according to the patient performance in the game.
- Performance Feedback (Yes/No): this dimension is related with the system capability to transmit to the patient the results of the interaction.
- Progress monitoring: is the capability of the system to allow saving the results of patients' interaction with the system
- Game portability: is related with the capability of the system to be used at home, or at a hospital or clinic.

Some extra considerations extending the Rego et al. taxonomy have been also included:

- Game platform: the platform where the user runs the game, e.g. mobile, PC or a specific platform.
- Mutiplayer: in the case that the game includes support for multiple players not necessarily playing at the same time.
- Patient follow-up: apart from the games inputs and the scoring system the platform could run a parallel assessment of the patient taking into account the historical information.

Table 12 shows the classification of serious games found in the literature organized following the extended taxonomy of Rego et al. Assessing and training standing balance in older adults: A novel approach using the 'Nintendo Wii' Balance Board [515]. Using the Nintendo 'Wii Balance Board' (WBB), the authors have developed an interface that allows a user to accurately calculate a subject's centre of pressure (COP) and incorporate it into a virtual environment to create bespoke diagnostic or training programmes that exploit real-time visual feedback of current COP position. Development of a System for Monitoring and Tracking of Physiotherapeutic Movements in Patients with Neurological Diseases [516]. A friendly software application for monitoring the physical therapy movements of patients suffering from severe motor disabilities. Table 1 synthesizes the main features of each solution according to our adapted version of the Rego et al taxonomy.

Also, although most of the games have shown good acceptance among the patients and the results in terms of rehabilitation outcomes are very promising there is still a lot of place to expand the multiplayer/social part of the games. These features have been showing excellent results in the regular video games during the last years.

	[517]	[518]	[519]	[520]	[521]	[515]	[516]
Application	Motor	Motor	Cognitive + motor	Motor	Motor	Motor	Motor
Interaction technology	Webcam	Wii Balance	Webcam	Infrared camera + body markers	Wii Balance	Wii Balance	Microsoft Kinect
Game platform	PC	Nintendo Wii	PC	PC	Nintendo Wii	Nintendo Wii	PC
Game interface	2D	2D/3D	2D/3D	2D	2D	2D	2D
Number of players at the same time	1	1	1	1	1	1	1
Mutiplayer	N/A	N/A	Yes	N/A	N/A	N/A	No
Game Genre	Mini-games	Assorted	Mini-games	Mini-games	Assorted	Mini-games	Assorted
Adaptability	No, but there are different auditory cueing	Yes	No dynamic adaptability . There are different levels	Yes	No	Yes	No
Performance Feedback	Auditory	Visual	Visual + auditory	Visual + auditory	Visual	Yes	No
Patient follow-up	No	Yes	No	No	No	No	No
Game portability	Home + Hospital	Home + Hospital	Home + Hospital	Hospital	Home + Hospital	Home + Hospital	Home + Hospital
Comments	They showed that music improves upper limbs movements.	Increase in the static and dynamic stabilization of the PD patients in respect with the control group.	It is suggested an improvement in the patient motivation to perform the physical activities.	Preliminary assessment with healthy subjects.	Increase in the static and dynamic stabilization of the PD patients in respect with the control group.	It was shown a concentration in the variation of the Center of Pressure (CoP) of the subjects after some sessions.	They show that it was possible the monitoring of movements using this system such as lateral movement and joint flexion.

Table 12 –Serious games for Parkinson’s disease

4.6 Patents and commercial solutions

4.6.1 Patents

E. Wang, L. Verhagen Metman and Emil Jovanov patented in 2013 both a method and a device for treating patients with a movement disorder who experience sudden change in regularity of gait or akinesia. Such device detects the changes in gait regularity or temporary akinesia and automatically issues a cue signal to support the subject restarting the regular movement. The invention claimed is a device comprising: a sensor for sensing an akinetic episodes and a receiver which automatically generates a cueing signal upon the regularity of gait is detected [522]. Previously, in 2005 Metin Akay patented an intelligent wearable monitoring system which includes a Wireless

Personal Area Network (WPAN) for extended monitoring of a patient's motor functions. Such system is based on an accelerometer unit which measures acceleration in real-time and it is transmitted to a personal server to process it by applying linear and non-linear analysis. The results are transmitted to a remote access unit for statistical analysis and formatting into visual representations [523].

4.6.2 Commercial solutions

4.6.2.1 Catsys

Catsys is a portable PC-based test system from Danish Product Development Ltd²⁰⁰ for quantifying human behaviours such as coordination ability, reaction time, tremor and postural stability (balance). It is a portable, Windows-based system consisting of a data logger and four different sensors (tremor pen, touch recording plate, reaction time handle, and force plate for balance recording) for quantification of neuromotor functions. A complete Catsys test takes less than 15 minutes and its measures provide a useful supplement to clinical evaluation. Papapetropoulos et al. (2010) run a study using Catsys for PD monitoring. Forty-four patients with idiopathic PD and 28 healthy controls. Catsys discriminated between PD and controls on measurements of rest/postural tremor, pronation/supination, finger tapping, simple reaction time, and postural sway intensity and velocity. Catsys measurements using the proposed test battery were associated with relevant clinician-rated UPDRS items assessing tremor and bradykinesia [524].

4.6.2.2 GaitAid

The GaitAid from MediGait²⁰¹ consists of a small lightweight control unit and a set of high-tech display glasses. The control unit connects to special display glasses designed to be comfortable and easy to use. The glasses contain a see-through display and built-in earphones, *Figure 46*. The control device creates images and sounds by responding to the patient movements. Stepping over the images of the black and white tiles while listening to the sound cues, improves your stride length and rhythm, helping to restore your normal walking ability. While using the glasses, users can see the tiled floor image and the surroundings at the same time. The usual therapy routine simply means going for a walk while stepping on the virtual tiles displayed on the glasses. The glasses may be detached and the GaitAid can be used with head phones alone.

Figure 46 - GaitAid device (Source: MediGait website)

4.6.2.3 Kinesia™

The Kinesia™ is a device from Great Lakes NeuroTechnologies²⁰², a spin-off company of Cleveland Medical Devices Inc which has acquired the rights to develop, market, and manufacture clinical motor assessment and therapy systems for the movement disorders market as well as physiological monitors for research and education markets.

²⁰⁰ www.catsys.dk (Last date accessed: December 2015)

²⁰¹ medigait.com (Last date accessed: December 2015)

²⁰² <http://glneurotech.com/kinesia/> (Last date accessed: December 2015)

Currently, two different devices are available Kinesia™ One and Kinesia™ 360:

- Kinesia™ ONE uses an app and wireless sensors to objectively measures movement disorders such as PD. The sensor and app measure tremor, bradykinesia, and dyskinesia during specific tasks. The system can be integrated into clinical trials or patient care.
- Kinesia™ 360 uses wearable sensors and a mobile app to continuously measure Parkinson's disease during the day. The medical device measures tremor, dyskinesia, and mobility. The system can be integrated into clinical trials or patient care.

They are the result of a continuous research activity and clinical validation during the last decade. Heldman et al. (2011) and Giuffrida et al. (2009) designed, built and assessed Kinesia™ for automated assessment of PD tremor using the accelerometers and gyroscopes in wearable unit. In this study, PD subjects performed the tremor subset of the UPDRS motor section while wearing Kinesia™, quantitative kinematic features were processed and highly correlated to clinician scores for rest tremor ($R^2 = 0.89$), postural tremor ($R^2 = 0.90$), and kinetic tremor ($R^2 = 0.69$). The quantitative features were used to develop a mathematical model that predicted tremor severity scores for new data with low errors [525], [526]. Later, Pulliam et al. (2013) evaluated the ability of motion sensors to quantify tremor during unconstrained activities at home. 20 ET subjects wore a wireless sensor continuously for up to 10 hours daily on two days and completed hourly standardized tremor assessments involving pre-defined tasks. At home tremor scores from hourly standardized assessments correlated with at home tremor scores estimated during unconstrained activities immediately following the standardized assessments. Both types of tremor ratings (standardized and continuous) showed high day-to-day test-retest reliability with intraclass correlation coefficients ranging from 0.67 to 0.90 for continuous ratings and 0.77 to 0.95 for standardized ratings [527]. Heldman et al. (2012) developed and evaluated the algorithms for quantifying gait and lower extremity bradykinesia using kinematic data recorded on a heel-worn motion sensor unit. Multiple linear regression models were developed and clinician scores and produced outputs highly correlated to clinician scores with an average correlation coefficient of 0.86 [359]. Mera et al. (2011) used a wireless finger-worn motion sensor for automated tremor and bradykinesia severity score assessments. These algorithms were then applied to data collected from the PD subjects who used the Kinesia™ system at home to complete motor exams 3–6 times per day over 3–6 days [528].

4.6.2.4 Meditouch

MediTouch²⁰³ was established in 2004 with the aim of developing and distributing wearable and affordable motion feedback devices for the upper and lower extremity physical rehabilitation market. MediTouch has developed a low cost technological platform that precisely determines the position and speed of motion of human body joints as well as a rehabilitation platform that use exercises and biofeedback to improve patient's lower and upper extremity functional movement ability. MediTouch firstly targeted hand rehabilitation indications and launched its HandTutor™ system with CE and FDA certification in 2008. In 2011 MediTouch launched three new Tutor products. Firstly, the ArmTutor™ allows for evaluation and virtual functional task evaluation of the arm including the shoulder and elbow. Secondly the LegTutor™ was introduced to allow evaluation and virtual functional task treatment of the hip and knee. Finally, the 3DTutor™, a wireless sensor was introduced. The 3DTutor™ can be positioned on several parts of the body and compliments the ArmTutor™ and LegTutor™ to give complete upper and lower extremity evaluation and treatment solutions.

4.6.2.5 Motus Movement Monitor

The Motus Movement Monitor by Motus Bioengineering Inc.²⁰⁴ is a measuring movement disorders system that utilizes a miniature solid state gyroscope (not gravity sensitive accelerometers) to quantify: tremor (resting, posture, kinetic), rapid pronation/supination of the hand, arm swing, lateral truncal sway, leg stride, spasticity

²⁰³ www.meditouch.co.il (Last date accessed: December 2015)

²⁰⁴ www.motusbioengineering.com (Last date accessed: December 2015)

(pendulum drop test), dyskinesia, bradykinesia and alternating dystonia. The sensor signal is processed by a portable computer-based system and data is presented on screen showing a real time strip chart, fast Fourier transform plot and other selected parameters including displacement and peak frequency.

4.6.2.6 MVB - Parkinson

This German company, MVB – Parkinson²⁰⁵ offers a videoconference service specialized on Parkinson's disease. This service allow doctors to carry out a remote visit with the patients at their own homes. , the neurologist from the individual effect of the medication the patient can make an image itself. The medical video accompaniment, patients can benefit of personal medical doctor visits, without leaving their house for a single time. They can send all the information via video recording, from home, right in their neurologist system. On the other side, clinicians can quickly and safely determine the best medication for their patients and react immediately to changes in the clinical picture.

4.6.2.7 ParkAid

The consortium (see 4.4.15 PARREHA) built ParkAid²⁰⁶, a start-up company which aim was to exploit ParkWalker and to build a supporting service around it called ParkService. ParkService is a telemedical service integrating home support with a ground-breaking walking aid for people with PD [529]. It provides a home-based service supporting the clinical management of PD and the social inclusion of patients. Using the television as user interface and an internet connection, it allows people with PD to create videos of themselves, either as messages to others or as a particular record of symptoms for clinicians. Videos are uploaded to a secure server from which the user can control access by other ParkService users, text-messaging and diaries for symptoms are also available.

ParkAid also developed ParkWalker from the PARREHA prototypes, which later took the commercial name of INDIGO (INdependent I GO), is based on a small display which clips on to a normal pair of glasses. Visual stimulation is generated by a small portable device which can also wirelessly connect to a clinician when the user is at home. Using virtual reality glasses and bespoke portable electronics, INDIGO overlays a video of “visual cues” (e.g. scrolling black & white stripes) onto the normal view of the user. In the presence of visual cues suitable subjects break out of freezing phases and walk near-normally.

Figure 47 – Picture of the Parkinson's KinetiGraph™ (Image source: Global Kinetics Corporation website)

4.6.2.8 Parkinson's KinetiGraph™ (PKG™)

Parkinson's KinetiGraph™ belongs to the Global Kinetics Corporation²⁰⁷ established in 2007 to commercialise technology arising from the Howard Florey Institute²⁰⁸, Australia. The Parkinson's KinetiGraph™ (PKG™) movement recording is worn like a wrist watch and features a vibrating reminder when patients should register that they have taken their prescribed medication. It can be worn continuously over 6 to 10 days in the home environment during the activities of daily living. The data collected generates a report showing the kinematics of symptoms of movement disorders, such as Parkinson's Disease.

²⁰⁵ <http://mvb-parkinson.de> (Last date accessed: December 2015)

²⁰⁶ www.parkaid.net (Last date accessed: December 2015)

²⁰⁷ www.globalkineticscorporation.com (Last date accessed: December 2015)

²⁰⁸ www.florey.edu.au (Last date accessed: December 2015)

4.6.2.9 Perfect Posture and Activ8 Physical Activity Monitor

The Perfect Posture²⁰⁹ is a solution that enables and assists PD patients in improving their daily mobility developed by 2M Engineering²¹⁰ from The Netherlands. Perfect Posture (*Figure 48*) corrects posture by alerting patients when their posture deviates excessively from an upright position. Different warning angles can be set by care givers for forwards and sideways posture. The Perfect Posture also improves mobility and reduces freezes using cueing signals (metronome or rhythmic vibration). The cueing frequency (in beats per minute) can be adjusted to the needs of each individual patient. The provided software allows the caregiver to upload the individual patient settings. It is a small lightweight device which can be worn underneath or over normal day to day clothes and is powered by rechargeable batteries. It also provides an option for caregivers to store relevant information, for example a patient's physical activity level or chest angle.

Activ8 Physical Activity Monitor²¹¹ consists of a physical activity monitor combined with the Activ8 personal online dashboard. The user friendly Activ8 activity tracker is a small and lightweight device that reliably recognizes activity patterns and tracks energy consumption.

Figure 48 - Perfect Posture from 2M Engineering (Image source: 2M Engineering website)

4.6.2.10 Lift Labs

Lift Labs²¹² has developed a smart spoon (called Liftware Spoon, *Figure 49*) and two software applications (called Lift Pulse and Lift Stride) aimed at supporting patients who suffer from PD and essential tremor. The Liftware Spoon system is designed for people whose hand tremor interferes with activities of daily living. Sensors in the Liftware handle detect a person's tremor, and the device responds using motors to move the spoon opposite the tremor. The spoon can discern motion from hand tremor from other types of motion, allowing it to respond to just the tremor while preserving the user's intended motion. In contrast to braces, which force a user's hand to be still and can cause patient discomfort, Liftware allows the patient's hand to shake while stabilizing food in the spoon.

Lift Pulse is a mobile application calibrated to measure the tremor frequency and amplitude. To get a reading, the subject must hold his phone in his hand and press record. Then, the application will show the frequency spectrum, it automatically finds the peak and integrates it to calculate the overall tremor amplitude in centimeters. Lift Pulse allows the users to compare their tremor to a pre-set baseline. Lift Stride is an auditory cueing smartphone application for PD patients. It allows the user to adjust the cadence to just above his preferred walking speed and can be used with a headset to move around while the auditory stimuli is playing.

²⁰⁹ www.2mel.nl/products/medical-device-development/parkinson-buddy/ (Last date accessed: December 2015)

²¹⁰ www.2mel.nl (Last date accessed: December 2015)

²¹¹ www.2mel.nl/products/medical-device-development/activ8-physical-activity-monitor/ (Last date accessed: December 2015)

²¹² www.liftlabsdesign.com (Last date accessed: December 2015)

Figure 49 - Liftware Spoon (Image source: Lift Labs website)

4.7 Conclusion

Parkinson's disease disturbs a wide range of the patients' capabilities especially those regarding the motor performance. For that reason, most of the works presented on this chapter and that cover the research activities of the last decades show a special focus on the monitoring, assessment and management of the motor symptoms or signs. In many cases it has been shown that the analysis of motion features could lead to an objective and continuous monitoring of the PD patients. In a first approach, most of the works tried to detect and quantify the cardinal motor symptoms of PD as well as their gait performance. Then, the variation of the severity of the symptoms along the day can be certainly used for the identification of On-Off fluctuations. This information has an important clinical implication since it is an indicator that a medication adjustment is required. A plausible reason for this is that in current clinical practice the assessment of the motor symptoms is probably the main input for the decision-making process and for the clinical management of the disease.

Apart from the systems dealing with the automatic detection and assessment of the motor symptoms a significant amount of works related with the implementation of a telematic visit as a complement or substitute of presential visit to the hospital were found. Also, the use of telematic services were explored to support and facilitate the performance of several kind of clinical tests remotely. In some cases, sensors or devices are included to perform the tests, on that case the outcomes of the sensors are transmitted remotely to the hospital or to the research center, while in other ways the telematic services are used to facilitate the performance of motor tests remotely. Especially relevant is the case of all the sensors that can be used as wearable sensors, like the accelerometers or the inertial sensors which due to their low cost and size have been largely studied for this purpose. Also in this case different approaches have been suggested and studied, in some cases, the sensors have been integrated with other sensors of the same kind conforming Body Area Networks (BAN) able to cover a wider range of symptoms or improving the accuracy in the detection and assessment of symptoms. In other cases, they were integrated with other different sensors or devices conforming more complex systems such as closed-loop system (HELP project [438]), telehealth systems (PERFORM [14]–[16] or SENSE-PARK [333], [334]), platforms to deal with the FoG using cueing (CuPID [408], [409] or REMPARK [453], [455]), complex system for tremor suppression (NEUROTREMOR [463]) and also they have been integrated into a web-based applications enabling home monitoring of patients with (PD) using wearable sensors (Mercury [450], [452]).

A common problem faced in all cases, or at least in a majority of them, is how to deal efficiently with the huge quantity of data generated by a continuous monitoring of patients and how to extract knowledge and clinically relevant information to support the decision-making process. Most of the research works so far, explored the use of both linear and non-linear signal processing methods to transform raw data collected in a way to help the clinicians, the patients and any other stakeholder involved in the process. Normally, and independently of the method used for the signal processing, the typical approach tries to map standard clinical scales such as the UPDRS. The employment of machine learning techniques such as classifiers or regressions has been a common practice improving the initial studies which were more focus on the simple signal and statistical analysis. But, even doing that, the continuous monitoring generates a data avalanche which is not easy to handle, for that reason apart from the classic signal processing (data filtering, normalization, features extraction, etc.) an additional analysis or

processing tier is usually added. This second layer tries to firstly, have a wider view of each particular symptom and then, to extract derived information from the processed signals, for example if the patient is stable or getting worse, the progression of the symptoms or the disease or the correlation between symptoms. Nevertheless, the work on this second layer, and specially on the second part, is incipient and there are still many work to do and to explore. Also, the exploration of the non-motor area, both individually and in correlation with the motor area is another are for future work. In any case, the growing number of mobile and wearable gadgets available in the market represent a valuable opportunity also for the health sector. The familiarity, awareness and knowledge of the technology by the general users will encourage their adoption and acceptability as well as to facilitate the market adoption. The use of WBAN or BAN merging data from the different sensors, devices and tests carried out in a mobile app can cover a wider spectrum of symptoms or improve the characterization of the already known symptoms.

Chapter 5 Hypothesis and objectives

5.1 Hypothesis

PD therapy is based primarily on symptomatic treatment with dopaminergic medication, and this is usually effective in reducing the classical motor features. However, there are drawbacks to current pharmacotherapy in PD. Long-term use of dopaminergic treatment is complicated by development of dose-limiting response fluctuations, including sometimes disabling dyskinesias. Therefore, the primary objective of this thesis is to understand and explore how to improve the management and the treatment of Parkinson's disease in a home setting with respect to the current clinical practice by using appropriate ICT tools and infrastructures. This requires, not only, contribute to the effectiveness, automatic and long-term monitoring of PD but also to study the factors that could contribute to the translation of these tools to the clinical practice. On this regards, the research questions for this thesis can be articulated as follows:

- **Research question 1 (RQ1)** – Is it feasible to perform a continuous monitoring of the motor symptoms of PD patients in a home environment using wearable technologies? Which are the methodologies to carry out such monitoring?
- **Research question 2 (RQ2)** – Is this information clinically relevant for the monitoring and management of PD patients? Could this information contribute to an efficient management of Parkinson's disease patients?
- **Research question 3 (RQ3)** – Which are the key factors for the system acceptance by the PD patients?
- **Research question 4 (RQ4)** – In order to translate this kind of solutions in the current clinical practice, which are the requirements and needs that must be taken into consideration?
- **Research question 5 (RQ5)** – Is it possible to estimate which is the economic impact of a technological solution for PD management? In that case, which is the economic impact of such solution and how does it impact the different stakeholders involved?

5.2 Objectives

Based on the abovementioned research questions, the following research objectives have been defined:

- **Research objective 1 (RO1)** – Design and development of methods for extracting clinically meaningful information, developing a quantitative assessment tool for motor symptoms on PD based on data gathered using wearable and low-cost sensors.
 - **Research objective 1.1** - To design and develop machine learning algorithms for the automatic assessment of bradykinesia and to design and develop an algorithm for the automatic assessment of the gait performance based on the mHealth platform and wearable devices.
 - **Research objective 1.2** - To carry out a feasibility study to implement the automatic assessment methods into a telehealth system located at patients' homes.

- **Research objective 2 (R02)** – To carry out a research study to the compliance of a monitoring system by the final users, i.e. the patients. Identifying potential backwards and direct feedback that will reflect the actual uptake from the final users.
- **Research objective 3 (R03)** – To clearly understand which are the key requirements and needs of the different stakeholders involved in this ecosystem in order to translate this kind of system from a research prototype to the current clinical practice.
 - **Research objective 3.1** – To elicit experts knowledge and user needs to understand which are the key elements for this kind of systems and to build a HTA assessment framework.
 - **Research objective 3.2** – To use the HTA assessment framework to evaluate a telehealth system as study case.
- **Research objective 4 (R04)** – To design and to develop a methodology for the assessment of potential economic impact of a novel technological solution and apply it to a specific tool: PERFORM as a case of study.
 - **Research objective 4.1** – To explore and to identify tools and methods for economic assessment of novel technological solutions.
 - **Research objective 4.2** – To study the potential cost-benefit scenarios of telehealth solutions for PD management.
 - **Research objective 4.3** – Apply such tools to estimate the economic impact and cost-benefit of the PERFORM system.

Chapter 6 Methods and material

This thesis addressed the assessment of the feasibility of telehealth in the context of Parkinson's disease (PD). Aimed at doing that, three research lines were explored, the first one was to explore the technical feasibility of telehealth for PD remote assessment, the second one dealt with the human factors around telehealth and finally, the last one was aimed at providing the appropriate tools to carry out a Health Technology Assessment. This chapter introduces the general framework under which this thesis was carried out. The detailed description of the methods, materials and protocol for data collection used on each of the studies covering the three research topics are detailed on each of the chapters (*Chapter 7 Motor assessment, Chapter 8 Human Factors and Chapter 9 Health Technology Assessment*). Therefore, the next three chapters will present the full description of the studies including methods, materials, results and conclusions.

6.1 General overview

The global objective of this thesis is to explore how novel telehealth solutions could be translated to the clinical practice and support health professionals in the management of this disease. To achieve that, first of all, it is needed to understand which the key elements for a successful innovation process are. On this regards, Eugene Fitzgerald, Andreas Wanknerl and Carl Schramm proposed the MIT model for innovation [530]. According to them:

"We have emphasized (indeed, "reiterated") the fact that a good innovation process is highly iterative. We have further said it requires repeated iteration among three key elements, which we shall now formalize by using capital letters: Technology, Market, and Implementation. These three elements can be seen as the basic "factors of innovation" in much the same way that Land, Labor and Capital were once seen as the factors of production. Before we illustrate the dynamics of iteration, we need to explain more fully what each of the elements consists of. And we can do this by building a bridge of understanding between the old, linear concept of innovation and the new. Keeping in mind that the linear model may have some validity as an after-the-fact recording — but does not depict how innovation actually occurs — we reproduce it here one final time:

discovery→invention→development→product→market→profit

Although the process will rarely take place in such an orderly and stepwise fashion, it certainly seems true that everything described in this model is typically involved in the process: "development" is done, we eventually wind up with a "product", and so forth. It also certainly seems true that the right-hand side of the line describes the desired end result, and that the items there are fundamentally different from those on the left-hand side. So: remembering, as always, that the process unfolds in iterative loops rather than a straight-line progression, we can roughly map our three elements onto the pieces of the linearized model as follows.

- *Technology includes the items on the left-hand side. It encompasses those aspects of the innovative idea that are objectively verifiable, by scientific method: all repeatable constructions, formulations, etc. that will eventually make it possible to have an "idea embodied in the marketplace".*
- *Market includes the items on the right-hand side. It encompasses the people who will use the innovation, the benefits they can expect from it, the behaviors they will change as they benefit from using the innovation — and the profit they are willing to render to the businesses selling the*

innovation. Here we are in the realm of so-called human factors, measurable to a degree, but not nearly so predictable or objectively verifiable.

• Implementation includes all that must happen to connect the two, moving the Technology of the innovative idea into the human realm of the Market. It encompasses everything required to make the innovation functional in reality, from the forms and methods of production to the forms and methods of delivery. No distinctions or definitions are immutably perfect. There will of course be gray areas between the elements as we are describing them. But based upon the authors' long collective experience, these three elements are the categories that best and most usefully capture the many different concerns that innovators must address and balance as they go about their creative endeavors."

Basically, their proposal remarks that innovation occurs through the continuous iteration between technology, implementation and market. These iterations act as a funnel selecting the appropriate elements within each of the three domains and providing feedback to the next element. Following this idea, within this thesis different methodologies have been explored to cover the first iteration of a telehealth system for Parkinson's disease management. To guide this work the research project PERFORM has been used as a case of study.

6.1.1 PERFORM system as a case of study

The research project PERFORM has been used as a case of study. The section 4.4.17 *PERFORM* provided a description of both the functionalities and architecture of the system. Instead, in this section the different phases of the project are described. Also, the details of the system for data collection, designed and developed ad-hoc for the project are described since they will be needed to understand further chapters.

Figure 50 – Different phases of the PERFORM project

The data collected during the phases I and II was used to design and build the different algorithms for motor assessment such as tremor, bradykinesia, LID, gait assessment and On-Off fluctuations. Data collected from the

phases I, II, III and IV was used to design and build the Stability and Worsening modules as well as Medication Change Proposal. This thesis covers the design and development of the bradykinesia and gait automatic assessment in the *Chapter 7 Motor assessment*. Apart of using the data collections for the design and development the pilots, particularly the phase III and IV, were used to study the feasibility and the performance of the wearable platform for the continuous monitoring of PD patients at home. This feasibility studies can be divided in two groups, aiming to the wireless communication integrity and the acceleration measurement accuracy.

The PERFORM system was a research project aimed at producing a platform able to tackle problems associated with the efficient remote health status monitoring, the qualitative and quantitative assessment and the treatment personalization for people suffering from neurodegenerative diseases and movement disorders, such as PD. The system is based on a Body Area Network (BAN) of wearable monitoring devices (accelerometers and gyroscopes) wirelessly connected and seamlessly integrated to produce a user-friendly and patient-customized monitoring tool. The recorded signals are pre-processed and stored at the patient site. At the point of care (hospital centre), the supervising health professionals are able to remotely monitor their patients, personalize their treatment and medication schedules and generate statistical data, so as to study and evaluate the efficacy of medication, based on the patients' specific personal and medical characteristics [15]. The PERFORM system was aimed at supporting the continuous follow-up of patients using wearable devices and extracting the appropriate information from the collected data to optimize and personalize the treatment for each patient and consequently to delay the progression and/or the appearance of symptoms and to improve quality of patients' lives. These improvements could be achieved by providing clinicians with a long-term monitoring and assessment of the motor symptoms improving significantly the current short-term subjective medical practice and allowing the health professionals to assess the disease's progress and evaluation/adaptation of the medical treatment based on the changing symptoms and efficiency of drug intake (type of drug, dose, timing) [14]–[16]. In contrast with other diseases the dosage and the way of medication administration are totally personalized for every patient. When the PD disease appears the treatment seems very simple but in the course of time the treatment becomes complicated and requires more and more the patient's participation. During the short visit of PD patient the clinician must be informed for the patient's day motor status. This is required to configure the treatment strategy, drug time intake, drug doses, intervals between doses, combination of drugs depending on the food intake and other details. The clinician tries to retrieve information for patient's motor status for the previous days or weeks. This is almost impossible since it is difficult for PD patients to describe their symptoms and they cannot assess exactly their reaction to the drug. Consequently, the clinician cannot receive proper information to define realistically the drug administration treatment. The PERFORM system offers daily assistance to the clinician neurologist who tries through conflicting information from the patients and their relatives to determine the optimal therapeutically schema. The PERFORM system is used by the PD patients and in a simple, safe, painless and non-invasive way to record patient motor status for long-time intervals. In this way, the clinician can have a precise, long-term and objective view of patient's motor status in relation to drug and food intake; all the aforementioned factors are directly involved in the drug absorption and action. With the PERFORM system the clinician can remotely receive precise information for the PD patient's motor status on previous days and define the optimal therapeutically treatment [15].

The different phases presented on *Figure 50* reflected the evolution of the project, on each phase the prototype of the system was evolved, both the software and the wearable BAN, each of these evolutions were used to collect data in order to design and develop the algorithms for the automatic motor assessment, but also to explore the feasibility of the system to fulfil the clinical needs. The Phase I was carried out with 20 healthy subjects simulating PD symptoms on sessions of 20-25 min. The second phase was carried out with 36 PD patients at hospital laboratory and following a common protocol of data collection of around 15 min in both ON and OFF states. The phase II was run at patients' homes recording two daily sessions of 4 hours during 3-5 days. The last phase was the final evaluation of PERFORM system at home adapting the PERFORM system for everyday practice (both clinicians & patients) 20 PD patients & 12 patients with Parkinson Plus Symptoms 4 h per recording session twice a day during 7 days.

Patients fulfilling the following criteria were eligible for the study: diagnosed of Parkinson's disease, aged between 40-70 years old, ambulatory, capable of complying with study requirements, receiving stable dopaminergic

treatment, experiencing motor fluctuations and being supported by a responsible caregiver who can cooperate with patient and doctor. Participants suffering from dementia, hallucinations or any significant systemic disease were excluded from the study. Before taking part to the study, patients were provided with a participant information sheet describing the study in their own language as well as an oral explanation of the research expressed in terms that would have the best chance of being understood. The experimental nature of this study, its inherent risks and drawbacks, and its chance of improving the treatment of PD were discussed. Then clinician obtained informed consent and gave a letter with a synopsis of Perform Protocol for family doctor to inform him about main issues of the study.

6.2 The monitoring unit

During the first phase of the project the SHIMMER platform was used for data collection. SHIMMER is a small cordless sensor platform designed for health-sensing applications which provides a 3-axis accelerometer signals large storage, and low-power standards based communication capabilities. They also provide a Bluetooth protocol capability that allow them to stream the data to a computer. The sensor size is similar to that of a matchbox. Sensors on the arms and legs were attached using designed elastic bands, which allow fixation to any wrist or ankle size. Sampling rate was set to 100Hz by default for each signal.

For the Phase II the first version of the ad-hoc system wearable sensors were designed and provided by one of the partners on the consortium project. This platform was a wearable Body Area Network (BAN) consisted of four tri-axial accelerometers (ALA-6g accelerometers) used to record the accelerations of the movements at each patient extremity, one accelerometer/gyroscope on the waist (AGYRO device) used to record body movement accelerations and angular body velocity during body turning, and one data acquisition unit which is called Parkinson Daily Data Set Logger (PDSL-1 logger), receiving all recorded signals. The AGYRO device was permanently attached to the PDSL-1 device by means of a long wire, while the ALA-6g accelerometers communicate wirelessly making up a body sensor network. Two versions of the ALA-6g were provided the first one achieves a 3.5h autonomy having an internal small battery, while the second version achieves an autonomy existing 16h thanks to an external battery compartment, firmly attached at the bottom of the main body of the sensor. In any case, they worked as nodes (terminal units) in an IEEE802.15.4 wireless network at the free ISM radio band of 2.4GHz. Each device, of either type, holds a unique MAC address (network identifier) allowing many such devices to co-exist in the same IEEE802.15.4 wireless network without conflicts. The devices feature an auto channel scan capability, allowing the user to freely choose any available channel in the ISM radio band for the wireless network. The resulting data stream is divided and encapsulated into variable length packets, which are transmitted every 61.44ms (superframe), during a specific time slot. Other nodes on the network are allocated in different time slots, allowing the whole system to embody as many as four wireless sensors transmitting data all together. The only controls available to the user are the push-button power-on switch and two LED indicators. The push-button which turns on the device (it will turn off automatically if an IEEE802.15.4 wireless network cannot be detected after more than a 1min). The red LED indicator flashes in a slow manner as long as the device remains a registered member of an IEEE802.15.4 wireless network or in a fast manner as long as it is searching for one to join with. The yellow LED indicator glints during the battery charging cycle. The acceleration value is captured and measured in the defined sampling rate by an acceleration sensor chip, which communicates with the microcontroller inside the IEEE.802.15.4. This sensor, constructed according to the MEMS technology, offers accurate acceleration measurements in 3-axis (X, Y, Z). A power supply and a battery charging circuit conclude the electronic circuit, managing all the power needs of the device. The charging current for the internal or the external battery is provided via a mini USB connector.

The Body Sensor AGYRO 150/6 is a combination of a 3-axis acceleration and gyroscope sensor measuring his movement characteristics. The two sensors are electrically connected by means of a flexible bunch of wires and must be considered as one system. The measurement of the acceleration is performed by means of 3- axis MEMS (Micro-Electro-Mechanical-System) acceleration sensor. According to this technology, a membrane with a heavy object in the middle forms a capacitor against a solid surface inside the sensor chip. The acceleration applied to the device, pushes the object causing distortion to the membrane, which subsequently changes the capacitance of

the whole construction. This change is used to measure the acceleration magnitude. The MEMS gyroscopes functions almost in the same way, but this time the heavy object is replaced with a tuning fork oscillating at its resonance frequency. Any attempt to rotate this construction creates an opposite force by the tuning fork, which in turn distorts the membrane changing its capacitance. This change is used to measure the angular velocity magnitude. The power supply powers the device with 3.0V and 5.0V obtaining power externally. No power source is placed into this device. A large graphics illuminated display, an audible indicator, three press buttons and 6 LED indicators constitute the interface of the device with the patient. One full speed USB interface allows fast data uploading and device configuration.

Figure 51 – Final version of the Body Area Network (BAN) used in the PERFORM project and the position of the sensors and logger on the body.

6.3 Overview of the methods and material

As it was already mentioned, this work carried out a feasibility study to explore the potential of using telehealth for the remote assessment and management of Parkinson's disease patients on their own homes. The term *holistic* included in the title refers to the necessity of covering this topic with a wider perspective. On this regards, the research included on this thesis covers not only the automatic assessment of the PD symptoms but also it incorporates the study of the human factors as well as a Health Technology Assessment (HTA) study. This means that the methods used on each of those studies are quite different and independent from each other. To facilitate the reading of the document, the full description of the methods and material have been included on the specific chapters covering each topic.

However, this section introduces very briefly the methods used in further chapters. The first part of the research work covers the automatic assessment of bradykinesia and gait performance and the feasibility study of translating this methodology to remote monitoring at patients' homes. Two different approaches have been followed to address the gait and bradykinesia assessment. In the gait case, the inverted pendulum model was used to estimate different gait features such as velocity, step frequency and step length. Other metrics like arm swing and entropy were also extracted. The feasibility study tried to explore whether the proposed BAN was feasible for the implementation of such algorithms. For the bradykinesia case, different a non-linear approach was followed, specifically machine learning has been used exploring diverse configurations in order to find about the best setup for bradykinesia assessment, then a meta-analysis methodology was proposed to improve the outcomes of the machine learning algorithms.

For the second part, a methodological approach has been followed in order to extract and analyse the PD patients feedback regarding the wearability of the PERFORM system. To carry out this wearability assessment different methodologies already validated have been emplaced, specifically the REBA, Borg and CRS scales have been used

in combination with a body map when needed. Further details of these methodologies will be provided later on this document. A total of 32 PD patients have been involved in this study showing an excellent acceptance of the PERFORM system in wearability terms.

Finally, on the last part, is aimed at identifying tools available to carry out an early HTA on telehealth systems for PD management and apply such methodologies to assess the PERFORM system as a case of study. The whole chapter is divided in two parts addressing two complementary works which try to provide two complementary points of view. The first part is aimed at identifying the elements that a telehealth system for PD management should satisfy to be effective and aligned with the users' needs and also to understand if clinicians and technicians share a common opinion when evaluating these systems. Instead, the second part provides a methodology to estimate the potential economic impact, in terms of cost-effectiveness, of a real implementation of telehealth systems for PD management. After the exploration of the available tools for early HTA two methodologies were selected, the first one called Analytic Hierarchy Process (AHP) allows the elicitation of the user needs and the definition of a framework for the evaluation of telehealth solutions for Parkinson's disease patients. 16 experts in the domain both with clinical and technical backgrounds were involved in the study. The second part of the chapter explores the use of Markov models with a minimal number of states were used to perform "what-if" and finally, to simulate and estimate potential scenarios for the economic impact, in terms of cost-effectiveness, of a telehealth platform. Then, this approach was used to estimate the potential cost-effectiveness of the PERFORM project. Finally, a sensitivity analysis will be carried out.

Chapter 7 Motor assessment

Parkinson's disease (PD) patients have severely affected their motor performance, the assessment and evaluation of the motor symptoms and the monitoring of their progression, paying special attention to the detection and characterization of the motor fluctuations. Within the state of the art chapter a detailed description of the different approaches, sensors and devices used in the last years to assess, evaluate or monitor PD patients has been provided and analogized in deep. In the last decades several research works have proposed to automatically evaluate the symptoms of Parkinson's disease and in some cases they also go further by automatically assessing the motor symptoms by providing the severity of the symptoms according to the clinical standards such as the Unified Parkinson's Disease Rating Scale (UPDRS) or any other scale used in the clinical practice. Nevertheless, all those works were designed to work on unsupervised environments, either in the clinical facilities or at patients' home but with the clinical supervision through a telematic supervision. A step forward requires the exploration of performing the assessment of PD patient on unsupervised environments. Part of the work presented in this chapter, including figures and tables, have been already published in Cancela et al. (2014) "*Feasibility Study of a Wearable System Based on a Wireless Body Area Network for Gait Assessment in Parkinson's Disease Patients*" [482] as well as in the proceedings of several international conferences [1], [3], [5], [8]–[10], [12], [14]–[16], [531].

Objectives – Using the work carried out within the PERFORM project as case of study, this chapter presents part of the work done within the project, specifically the works related with the automatic assessment of bradykinesia and gait performance and the feasibility study of translating this methodology to remote monitoring at patients' homes.

Methods and material – Two different approaches have been followed to address the gait and bradykinesia assessment. In the gait case, the inverted pendulum model was used to estimate different gait features such as velocity, step frequency and step length. Other metrics like arm swing and entropy were also extracted. The feasibility study tried to explore whether the proposed BAN was feasible for the implementation of such algorithms. For the bradykinesia case, different a non-linear approach was followed, specifically machine learning has been used exploring diverse configurations in order to find about the best setup for bradykinesia assessment, then a meta-analysis methodology was proposed to improve the outcomes of the machine learning algorithms.

Results – In the case of the bradykinesia assessment the best results were showed taking the signals coming from wrist sensor as input while the subject was performing some hand movement, on this case the accuracy of the classifier achieved up to 86.48% of correct classified instances. The accuracy in the bradykinesia severity detection while the subjects were walking was slightly lower (ranging from 70.83% to 75%). In all the cases, the combination of the rms+range features showed the better performance. Using the proposed meta-analysis method an average of 74.4% of agreement between the clinical examination and the system outcomes was achieved, ranging from 91.9% to a 48.8%. To study the gait performance, SampEn was evaluated as a metric to characterize the degradation of the gait performance confronting PD patients and healthy subjects, the values of SampEn were significantly different and provide useful information especially in the waist sensor ($p < 0.01$) and the left arm ($p < 0.01$), right arm ($p = 0.05$). Regarding the estimation of the gait features for PD, the mean error of Step frequency, Stride Length and Speed, calculated on 30 trials and 10 subjects are respectively: $3.36\% \pm 2.57$, $7.31\% \pm 4.69$, and $7.77\% \pm 5.34$. The average data loss satisfied that in all cases more than 95% of the data is successfully transmitted. Nevertheless, analysing the average burst length and the standard deviation of these values we found burst of up to 143.04 ± 240.10 ms, a burst of these characteristics in the middle of the transmission would compromise seriously the performance and accuracy of the system. Nevertheless, adding the most frequent burst length as an extra measure and observing the raw data we can easily identify that 64ms is the most common

burst in all the cases, moreover the longest burst are always at the beginning of the session i.e. during the start-up process. That means that waiting for all the sensors to be properly connected before start computing the gait features will remove the longest burst errors.

7.1 Bradykinesia and akinesia assessment

This section describes the methodology used to assess the feasibility of using a Body Area Network (BAN) of wearable sensors to assess continuously the severity of the bradykinesia in PD patients, the results of the performance tests and the introduction of a methodology for the meta-analysis of the data provided by the direct assessment of the bradykinesia. Inspecting the review of the state of the art (*Chapter 4 State of the art*) the assessment of bradykinesia followed two different approaches in the previous works, the first one focuses on the use of wearable sensors, typically placed in the limbs of the subjects, and the second one exploits the use of computer peripherals to quantify bradykinesia. Bradykinesia is one of the main symptoms of PD. It is defined as reduced speed when initiating and executing a single movement and a progressive reduction of its amplitude, up to complete cessation during repetitive simple movements. Bradykinesia appears to result from the inability of PD's patients to maximize their movement speed when required to drive internally their motor output, a full description of the bradykinesia and its origin is described in section 3.5.1 *Motor symptoms*. The manifestation or presence of bradykinesia is especially evident in the limbs for that reason, for the assessment of this symptom in the current clinical practice, patients are asked to perform tasks such as the finger tapping, fist open and close, heel tapping and alternate hand movements (for example, some of these tests are also included in the UPDRS). Moreover, by asking the patients to perform these tasks as fast as they can it is easier to identify the limitation and the slowness in the movements of each subject, especially by confronting the performance of the same subject along time. Somehow, by asking the patients to do those specific tasks and by asking them as fast as they can, a framework of evaluation to measure the slowness of movements is defined which other way would be difficult to measure in absolute terms.

One of the first attempts to build a tool for the automatic assessment of bradykinesia was carry out in 1997 by Dunnewold et al. [532], on that work accelerometers were used to quantify hand movements during finger tapping and movement time. The quantification of the bradykinesia severity was estimated with the mean value of the acquired signal and it was correlated with the UPDRS values. Later, two remarkable works using Body Area Networks of wearable sensors were carried out addressing the automatic assessment of bradykinesia. Salarian et al. employed accelerometers and gyroscopes [305], also the laboratory of Paolo Bonato carried out notable progresses using a BAN of between 4 and 6 accelerometer to record patients movements in a controlled environment. Then they process such a data using patterns recognition algorithms [444], [447], [451]. The second category focuses on providing computerised tests that can be used as diagnosis aids. For example, Allen et al, (2007) [396], [533] proposed the use of a force feedback joystick and a steering wheel to perform a pursuit tracking and a step-tracking test on the screen, several methods have been proposed to digitalize and automatize some of the tests frequently used such as the finger tapping test [471], [534].

The work presented within this chapter is aimed at providing at exploring the potential of using a Body Area Network (BAN) of wearable sensors transmitting simultaneously to perform a continuous assessment of the bradykinesia in PD patients at their own homes, therefore

7.1.1 Data collection

The whole process is split in two different phases, the first one was aimed at designing and developing the algorithms for the automatic assessment of this bradykinesia while the second one is a feasibility study to explore the capability to perform a continuous monitoring of bradykinesia in unsupervised environments through the proposed Body Area Network of sensors.

a) Design and development of the bradykinesia classifier

The first phase was focus on the design and development of the algorithms for the detection and assessment of bradykinesia. For this phase, the data were collected on a supervised environment, with the collaboration of the

hospital medical staff. Specifically, the data for the design and development of this algorithm were collected during the Phase II of the PERFORM project (see 6.1.1 *PERFORM system as a case of study* for more details). Patients involved in this phase were required to be aged between 18 and 85 years old, suffering from Parkinson's disease, who were ambulatory patients, capable of complying with study requirements, receiving stable dopaminergic treatment and experiencing motor fluctuations. Dementia, psychosis (simple visual hallucinations excluded) and significant systemic diseases (such as: cancer, hepatic or kidney dysfunction, etc.) were the exclusion criteria applied when selecting the participants. The dataset used in this study includes data from twenty PD patients, *Table 13* summarizes the data collected during this phase. In order to comply with ethical requirements, all procedures were carried with the Clinic Institutional Review Board's permission. Data were collected following a standard clinical protocol in which patients carried out daily basic activities (i.e. walking, lying, sitting, drinking a glass of water, opening and closing a door) during two cycles of On-Off oscillations in response to levodopa during the same day and under the supervision of a clinician. The described protocol were recorded with a video camera and sensors twice a day while the patient was hospitalized. During each recording, patients were evaluated by a neurologist using the UPDRS scale. During each measurement, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS) [240], Appendix I shows. Regarding the bradykinesia, the UPDRS covers it on this point:

UPDRS 31: Body bradykinesia and hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

0: None.

1: Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2: Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3: Moderate slowness, poverty or small amplitude of movement.

4: Marked slowness, poverty or small amplitude of movement.

Patient Number	State	Brad Severity	Duration (min)
1	OFF	4	17
	ON	1	16
	OFF	3	17
	ON	1	14
2	OFF	1	9
3	ON	1	14
4	OFF	0	21
	ON	3	13
	ON	0	8
5	OFF	1	14
	ON	3	14
6	OFF	0	12
	ON	2	16
7	ON	-	15
	ON	-	14
8	OFF	3	11
9	ON	1	15
10	ON	0	10
11	OFF	4	13
12	OFF	1.5	32
	ON	1	40
	OFF	1	41
	ON	1	33

13	OFF	1	52
	ON	0	33
	OFF	0.5	32
	ON	0	31
14	OFF	0	70
	ON	0	29
	OFF	0	24
	ON	0	54
15	OFF	2	38
	ON	1	21
	OFF	1	31
	ON	1	33
16	OFF	2	51
	ON	1	47
	OFF	2	41
	ON	1	27
17	OFF	1	33
	ON	0.5	26
	OFF	1	29
	ON	1	43
18	OFF	2.5	55
	ON	0.5	31
	OFF	2.5	26
	ON	1.5	53
19	OFF	0	27
	ON	0	48
	OFF	0	43
	ON	0	35
20	OFF	3	33
	ON	1	31
	OFF	3	39
	ON	1	25
21	OFF	1	34
	ON	0.5	27
	OFF	1	39
	ON	0.5	71

Table 13 - Subjects involved in the first phase of bradykinesia assessment

b) Bradykinesia event detection on unsupervised environments

The second part of the work was aimed at testing the algorithms previously developed in an uncontrolled environment, i.e. at patients' homes. During this second phase, data was collected in patients' homes and with the collaboration of a caregiver. In order to achieve this goal, the patients were asked to wear the sensors at home during a week. The devices were preprogrammed to continuously monitor the patient for 8 hours every day. The patient had to wear the devices in the morning, and had to switch them on 10 minutes before the start of the pre-scheduled monitor session. Then, the participant patients were asked to move free and to carry out his/her usual daily activities. Moreover, the patients were asked to introduce the information about the medication intake and the meal intake along the day, to do that, they were provided with a computer with a touch-screen which was setup at their homes. A special Graphic User Interface (GUI) and a software for the medication and meals was installed. At the end of the day, patients with the help of the caregiver must connect the device to the PC, where the signal processing started automatically.

Two daily visits from the clinician took place in order to evaluate each patient. Six patients were involved in this phase (2 women and 4 men, average age was 64.63 ± 2.25 years). During the visit of the neurologist patients were asked to perform the same protocol than in the previous phase, these protocol was video recorded. At the end of

the day, data was processed using the training set computed in the previous phase and the output were checked with the results provided by the clinician, as a result of the evaluation of the standard clinical protocol. Once all signals are processed, the output is compared with the clinician annotation in order to define the accuracy of the classifiers, expressed as the percentage of epochs that matches with the clinician annotation during the test.

7.1.2 Methods and material

a) Design and development of the bradykinesia classifier

Figure 52 - Diagram of the signal processing used for the bradykinesia assessment

The scheme followed for signal processing quantification of the bradykinesia symptom is described in Figure 52. Firstly, data was collected using a Body Area Network composed by 6 accelerometer sensors placed in the waist, belt and limbs. Once the signals had been acquired, the resultant vector for each sample was calculated, based on the expression, where x, y and z are the 3 axis values provided by the accelerometer sensor (4).

$$|Acc(t)| = \sqrt{Acc(t)_x^2 + Acc(t)_y^2 + Acc(t)_z^2} \quad (4)$$

Afterwards, the resultant signal is filtered with a Band-Pass IIR Butterworth 4th order (1-3 Hz) filter to cut off continues components. The underlying idea is that the filtered signals contain only the low frequencies, useful to calculate the slowest movements of the patients, this procedure was implemented taking into account the previous works available in the literature. The next phase, is called epoch segmentation and it requires splitting the whole signal in smaller pieces, this a necessary step to work with machine learning, the underlying idea is to split a continuous signal in smaller pieces that can be labelled and that can be used as inputs in a machine learning algorithm. In this, case and following the available literature – particularly, the works of Paolo Bonato and his

group [295], [447] – the length of the epoch segmentation was fixed on 5 seconds length using a 50% overlap between them in order to not lose information. After the segmentation, a set of features is calculated for each epoch, moreover, each epoch is tagged with the clinical evaluation provided by the clinicians with the UPDRS value for bradykinesia. The features extracted are:

- Range – difference between the maximum and minimum value of the signal within each epoch
- Root Mean Square (RMS) (5)

$$x_{rms} = \sqrt{\frac{1}{N} \sum_{i=1}^n x_i^2} \quad (5)$$

- Cross Correlation
- Sample Entropy (SampEn) and Approximation Entropy (ApEn)

There are many techniques to calculate the function of entropy of information on time series. The techniques most used are Sample Entropy and Approximation Entropy [535]–[537]. Both techniques quantify the regularity of a given time series by comparing subsections of the signal with the rest of the signal and provide a useful estimation of the signal disorder or anarchy. For their definition let's consider a time series of N points, $\{x(1), x(2), \dots, x(N)\}$ which could be split into N-m vectors (6).

$$x_m(i) = \{x_i, x_{i+1}, \dots, x_{i+m-1}\} \quad (6)$$

Such time series is defined as a “template” for $1 < i < N+m$. Then, a match occurs if the distance between two vectors, $x_m(i), x_m(j)$ verifies that it is smaller than a specified tolerance level “r” (7).

$$d(x_m(i), x_m(j)) = \max\{|x_{i+k} - x_{j+k}|, 0 \leq k \leq m-1\} \quad (7)$$

In this study “ $r=0.2\sigma$ ” has been chosen, being σ the standard deviation. Let $n_i^m(r)$ be the number of vectors that match at tolerance level “r”, then (8) represents the probability represents the probability that any two vector $x_m(i)$ and $x_m(j)$ match between them and the average value is calculated as (9).

$$C_i^m(r) = \frac{n_i^m(r)}{(N-m-1)} \quad (8)$$

$$C_i^m(r), C(r) = (N-m)^{-1} \sum_{i=1}^{N-m} C_i^m(r) \quad (9)$$

Based on the definition of the average value, SampEn is defined as (10):

$$SampEn(m, r) = \lim_{N \rightarrow \infty} \left[-\ln \frac{C^{m+1}(r)}{C^m(r)} \right] \quad (10)$$

which is estimated by the statistics (11):

$$SampEn(m, r) = -\ln \frac{C^{m+1}(r)}{C^m(r)} \quad (11)$$

So, $\text{SampEn}(m,r)$ is the negative of the natural logarithm of the conditional probability that two sequences that are close within a tolerance $r\sigma$ from m consecutive points remain close at next point [538]. Therefore, SampEn quantifies the regularity of a time series. It reflects the conditional probability that two series of “ m ” consecutive data points which are similar to each other will remain similar when one more consecutive point is included [535]–[537].

Finally, the definition of the Approximate Entropy presents a different formulation (12) and (13):

$$\phi^m(r) = (N - m + 1)^{-1} \sum_{i=1}^{N-m+1} C_i^m(r) \quad (12)$$

$$\text{ApEn}(m,r) = \phi^m(r) - \phi^{m+1}(r) \quad (13)$$

The features were used in 12 different combinations: $\text{SampEn}+\text{Range}$, $\text{rms}+\text{ApEn}+\text{Range}$, $\text{xcorr}+\text{SampEn}+\text{Range}$, $\text{xcorr}+\text{ApEn}+\text{range}$, $\text{rms}+\text{range}$, $\text{xcorr}+\text{range}$, $\text{rms}+\text{ApEn}$, $\text{rms}+\text{SampEn}$, $\text{xcorr}+\text{ApEn}$, $\text{xcorr}+\text{SampEn}$, $\text{range}+\text{ApEn}$ and $\text{Range}+\text{SampEn}$. Once the features were calculated each epoch was tagged with the clinical assessment (in this case the question 31 of the UPRDS was used as gold standard for the assessment of the bradykinesia in PD patients) and finally these tagged epochs were used to train and test different classifiers. In this study, the performance of six classifiers has been examined: *k-Nearest Neighbours (kNN)*, *Support Vector Machines (SVM)* and *Kernel Density Estimation (or Parzen Windows)* were tested. The implemented method gives, as output, the severity level of Bradykinesia symptom, according to the UDPRS, where 0 describes the absence of the symptom and 4 describes the highest possible value.

b) Bradykinesia event detection on unsupervised environments

As it has been already mentioned, bradykinesia is a symptom associated with movement, more specifically slowness in the movements, therefore the module for automatic detection and quantification of the bradykinesia in unsupervised environments should work - and actually it has been designed to work on - the specific times where the subject is performing to particular actions: 1) when the subject is walking, 2) when the subject is moving one or both arms. Based on this requirement and in the results achieved in the previous entry, for the first case, when the patient is walking, the algorithm could use 5 sensors and measures the level of bradykinesia of each limb plus the trunk. In the second situation, hand movement, the algorithm is limited to the measurements on the arms. To achieve that, the first step is the detection of the times of the day where the classifier should be run, to do that, the PERFORM system implemented an “activity recognition” module that provides the periods of the day where the subject has been walking and/or moving his hand. With that information, the PERFORM system splits the whole signal according to the information provided by the activity recognizer and run the bradykinesia classifier with two different configurations:

- Walking case: In this case the module handles signals coming from 5 signals. It creates a list containing the epochs classified as “walking” by the precedent module.
- Upper Limb movements: In this case, the module creates a list containing only the signals coming from the upper limbs and the trunk/belt.

Table 14 shows an example of the classifier outcome. The data provided includes the severity of the bradykinesia, computed in the interval between start time and end time as the result of the classification as well as the confidence in that value. This value for certainty or uncertainty in the outcome of the classifier is a combination between the classifier probability and the movement certainty. The last column contains the overlap value, in this case 50%.

At this point the challenge is to use all the information calculated every five seconds, and with an overlapping of the 50%, to assess the severity of the bradykinesia along the day. At this point is where this approach could improve the performance of traditional bradykinesia tests. Contrasting with that approach, which usually only includes one punctual test, this methodology allows the continuous collection of data and the continuous assessment of the symptom. The integration all this data could contribute to provide a more accurate and detailed characterization of the symptom in the patient. For example, by providing information about the daily fluctuations

of the symptom along the day as well as its correlation with different events such as food or drug intakes.

Start Time	End Time	Severity	Confidence	Overlapping
2011-02-08 15:42:33:658	2011-02-08 15:42:38:633	1	66.77%	50%
2011-02-08 15:42:36:154	2011-02-08 15:42:41:129	1	89.47%	50%

Table 14 – Example of the bradykinesia classifier outcomes

Therefore, at this point, we have a stream of 5-length epochs with the severity of the bradykinesia and the confidence on that value provided by the classifier, moreover this stream of data is overlapped at 50%. The next step consist on carry out a meta-analysis to detect symptoms events based on this information. The underlying idea is to use the confidence in the results, the continuous data and the redundant information to aggregate data and achieve a better understanding of the bradykinesia behaviour.

Figure 53 shows the scheme of processing for the outcomes provided by the bradykinesia classifier. The top stream shows the raw outcome of the classifier, due to the overlapping between the epochs for each time slot there are two severity values with their associated confidences. As it has been mentioned, these confidences values and this redundancy can be used to improve the results. Particularly, two questions must be answered:

- How to find out the new UPDRS
- How to find out the confidence in the new value

The approach followed calculates the new severity by merging the information from two epochs using a weighted sum; the new value will take the information from the UPDRS values and confidence values, according to the expression reflected in Figure 53 (A). Then, the timeslot will be assigned with the closest UPDRS value. Therefore this method uses the confidence in each value as the weight the value itself has in the output. A confidence value is assigned to that UPDRS value depending on the distance between the weighted sum result and the actual value assigned to the time slot Figure 53 (B). For example, if we have 1.65 as output of the weighted sum and the assigned value was 2 (the closest one), the distance between our output and the final value is 0.35 with leads us to a confidence in this result of 70% if only UPDRS integer values are considered. Finally, the length of the new epochs are calculated taking into account the original epoch length and the overlapping value. According to that, and unless the overlapping is 50%, this length will be different for odd and even epochs as reflected in the Figure 53 (C) formulation.

Up to this point each time slot has been analysing individually and a UPDRS and a confidence values have been assigned depending on the values in the given time slot. The next step is to study the signal from a broadened view trying to figure out the big picture of the symptom and taking advantage of the continuous monitoring and the vast quantity of data available. At the end, the final goal is to achieve a better and clearer view of the bradykinesia symptom on each patient and a better knowledge of its progression. That involves that, given an epoch, their neighbours are studied to decide if the value assigned makes sense in its environment. The aim of this step is to remove noise from the signal generated as outcome of the classifier. The clinicians provided crucial clues on the bradykinesia symptom behaviour and how much the symptom could change in an epoch length time (in about three seconds). In this case there are five seconds long epochs and an overlapping of 50%; hence time slots are of 2.5 seconds. Concluding that bradykinesia should not change from one time slot to the next, it could be also used the information of the neighbours to confirm that the value is correct and to fix some errors generated by the classifiers. Again the technique used is the weighted sum: the value of a given epoch will take into account the value of the following and previous epochs. Initially, the weight is the same for the three epochs involved in the calculation and the weight of each one only depends on the confidence of each epoch but it will be updated after the tests performed in the pilot, for instance to give more weight to the current epoch. The aim of these algorithm is to fix a possible error of the classifier or noise of the signal. Figure 53 (D) shows the implementation of this concept, again a weighted sum is used to aggregate data from contiguous epochs. In this case, each severity value is weighted by two elements, the first one is the confidence calculated in the previous step and the second one is

the length of the epoch in form of overlapping percentage.

Figure 53 – Processing of the bradykinesia classifier outcome

Finally, the last phase is defined as the event detection, in this step the main purpose is to detect contiguous epochs with the same value and with a time length clinically significant, that is fifteen seconds according to the clinicians involved in the PERFORM consortium. This algorithm groups all contiguous epochs with the same severity value, in events and assign a confidence depending on the number of epochs within the group which has the same value that the event, as example in *Figure 54*, case (a) we have eight epochs of value four that generate the first event with a confidence of 100% (all the epochs have value four), then the nine following epochs conforming a second event of value three and confidence 100% and finally the last eleven epochs generate an event of value two, although in this case the confidence is only 72,23% because the algorithm find that within this event there are epochs of different value than two although they do not conform an event by themselves since their extension is smaller than the clinically relevant and the previous and following epochs have the same value. Instead in *Figure 54* case (b) the previous and following epochs have different values therefore the algorithm labelled the epochs of the middle as “transition epochs” and generate two events, the first one of UPDRS value two and the second one with UPDRS value three. The following table shows the list of events generated in both cases. At the end this module provides a list with the event of the day, for the example show here it should generate this *Table 15* for the case (a) and this other table, Table, for the case (b). Finally, after generating the events, the last step in the profiling process is the calculation of clinically relevant statistics for the physicians.

Figure 54 – Example of event generation

Event	UPDRS value	Start time	End time	Confidence (%)
1	4	9:45:05.000	9:45:25.000	100
2	3	9:45:25.000	9:45:47.500	100
3	2	9:45:47.500	9:46:15.000	72.23

Table 15 – Example of event generation case (a)

Event	UPDRS value	Start time	End time	Confidence (%)
1	4	9:45:05.000	9:45:25.000	100
2	3	9:45:25.000	9:45:47.500	100
3	2	9:45:47.500	9:46:15.000	100
4	T	9:45:57.500	9:46:05.000	-
5	3	9:46:05.000	9:46:15.000	100

Table 16 - Example of event generation case (b)

7.1.3 Results

a) Design and development of the bradykinesia classifier

Table 17 shows the best results in terms of accuracy in the classification of the bradykinesia severity achieved by the different classifiers and using different combinations of sensors and features.

#	Sensors	Number of features	Classifier			
			KNN	SVM	Parzen	Random Forest
1	Chest + Limbs	3	73.44%	70.83%	68.23%	61.98%
2	Waist + Limbs	3	72.92%	73.96%	70.83%	59.90%
3	Chest + Limbs	2	66.15%	70.84%	66.67%	63.54%
4	Waist + Limbs	2	70.83%	75%	66.15%	62.50%
5	2 arms	3	71.35%	-	67.71%	58.85%
6	2 arms	2	70.31%	70.83%	68.75%	61.46%
7	2 legs	3	68.75%	70.83%	66.15%	61.98%

8	2 legs	2	70.83%	70.83%	66.67%	58.85%
9	Chest	2	70.31%	70.83%	73.44%	57.81%
10	Chest	3	70.83%	-	70.83%	59.38%
11	Waist	2	70.83%	70.83%	73.44%	57.81%
12	Waist	3	70.83%	-	71.35%	55.73%
13	1 arm	3	85.85%	86.48%	84.91%	79.87%
14	1 arm	2	86.79%	-	85.53%	79.56%
		Average	72%	74%	70%	62%

Table 17 – Accuracy in the classification of the bradykinesia severity by different classifiers and using different combinations of sensors and devices

In general terms, the best performance is achieved using Support Vector Classifier, more in detail (Table 18). As expected the best results are showed in the wrist sensor while the subject was performing some hand movement (86.48%). The accuracy in the detection while the subjects were walking is slightly lower (ranging from 70.83% to 75%). In all the cases, rms+range showed the better performance.

Sensor combination	Features	Features	Classification accuracy
Walking			
4 + 1 trunk	rms+range	SVN	70.83%
4 + 1 belt	rms+range	SVN	75%
2 sensors arms	rms+range	SVN	70.83%
2 sensors legs	rms+range	SVN	70.83%
1 trunk	rms+range	SVN	70.83%
1 belt	rms+range	SVN	70.83%
Hand movements			
1 sensor	rms+range	SVN	86.48%

Table 18 – Accuracy in the quantification of the bradykinesia severity detailed for the SVM

b) Bradykinesia event detection on unsupervised environments

For this study PERFORM system was installed at six patients homes for one week. Clinicians visited patients twice a week and evaluated the bradykinesia severity. The portion of the signal recorded during the evaluation was used to the comparison between clinician evaluation and the output of the classifier. Table 19 shows the results of this evaluation with six patients. The first three columns show the average accuracy – match between the classifier outcome and the clinician evaluation – as well as the maximum and minimum accuracy values. The last three columns show the results after the meta-analysis.

Patient Id	Direct analysis			Meta-analysis		
	Accuracy [Mean±Std.Dev]	Max Accuracy	Min Accuracy	Accuracy [Mean±Std.Dev]	Max Accuracy	Min Accuracy
1	[53.4±17.9]%	86.7%	37.5%	[48.8±30.3]%	92.9%	20.0%
2	[65.7±9.4]%	80.9%	58.3%	[83.5±3.2]%	85.7%	81.3%
3	[70.93±16.3]%	100%	52.9%	[78.1±17.6]%	100%	50%
4	[68.1±16.2]%	87.5%	56.3%	[70.9±23.3]%	100%	57.1%
5	[78.1±20.3]%	100%	42.9%	[82.1±22.3]%	100%	42.9%
6	[76.5±4.9]%	83.3%	69.4%	[91.9±6.7]%	100%	75.0%
TOTAL	[68.3±8.9]%	78.1%	53.4%	[74.4±14.9]%	91.9%	48.8%

Table 19 – Bradykinesia event detection accuracy

The results show that the global outputs of the bradykinesia classifier are in agreement with the medical evaluation. The accuracy of the classifier outputs increases when the meta-analysis algorithm is applied in around 6 percentage points when the average values of the 6 patients are considered. Using the proposed meta-analysis methodology an average of 74.4% of agreement is achieved, ranging from 91.9% to a 48.8%. The mean accuracy

value only decrease in the case of Patient 1, this could be caused by the variability of the bradykinesia symptom in the patient. However the results show that the bradykinesia classifier reaches a highest value of maximum accuracy when the meta-analysis algorithm is applied.

7.2 Gait assessment

People suffering from PD are unable to move fluently, that has direct implications in the gait performance modifying the walking pattern and generating a more complex and entropic signal. The movements of Parkinsonian patients become slower and present a typical “gear effect” as the disease evolves due to the appearance of the rigidity and bradykinesia but also for the dysregulation of the dopaminergic pathways, a full description of the gait impairments in PD population has been described in the section 3.5.1 *Motor symptoms*. Another characteristic of PD progression is that many patients present a “shuffling walking”, characterised by short and rush steps. In other words, the complexity of the movement decreases. Visual exploration of an accelerometer signal collected with a sensors placed in the belt of a PD patient and a healthy subject provide initial insights to overcome their analysis [5], [482]. *Figure 55* and *Figure 56* show the acceleration in the belt sensor for each axis in a healthy subject and in a PD’s patient and the Fourier transformation of each signal. It is possible to verify that x-axis (the axis along the body) and z-axis (the perpendicular axis to the thorax) contain most of the information related with the walking movement. During forward movement and as consequence of each step the z-axis is suffering acceleration, although the result is the subject moving in constant velocity. Also as consequence of the forward movement, when the subject impulses himself, the x-axis suffers the acceleration in the sagittal plane. Both x-axis and z-axis show these accelerations periodic pattern related with the normal walking process, while the y-axis reflects the movements within the coronal plane. Acceleration in this plane appears when the subject turns, although there is also a periodic component due to the cadence during walking. By contrast, motor signals from PD patients show an important distance with the aforementioned pattern. Essentially, the presence of bradykinesia and rigidity in PD patients lead to a complication in the walking process. Patients are unable to move correctly and that modifies the healthy walking pattern in a more complex and entropic signal. This approach constitutes an important tool for the detection of a PD walking pattern. Performing some methods of signal processing it is possible obtain a wide range of features which can be linked with a healthy pattern gait. In addition, the analysis of the movement pattern in healthy subjects helps to establish a comparison with the output of the PD’s patient recording. The intuitive conclusions extracted from the visual inspection of the temporal signal can be confirmed by exploring the outcome of the Fourier transformation. Taking the whole signal of a healthy subject and transforming it in the frequency space a signal with a significant peak around 1.5Hz - 2Hz is obtained, where more than the 90% of the signal power is accumulated. This peak represents the step frequency. Performing the same proceeding in the PD signal a different pattern is obtained. The power spectrum is wider in this case and the power in the main peak has moved to different frequency bands, generating new peaks with a significant power. Thus, measuring this degradation of the signal could be used as an index of abnormal gait. Besides this also implies that the capacity of the system for the extraction of features of the gait, such as: step frequency or speed will be strongly affected by the poor quality of signal and in some cases the values obtained from this kind of signal could be far away from reality. The aim of the gait assessment is to provide a set of features that can inform physicians about the gait degradation and its fluctuations along the day.

Figure 55 - Signals from the belt sensor in a healthy subject. From top to bottom the figure shows the x-axis, y-axis and z-axis. Values on the horizontal axis are samples and vertical axis is the normalized output of the accelerometers [5], [482]. Figure on the right represents the spectrum of the same signal.

Figure 56 - Signals from the belt sensor in a PD patient. From top to bottom the figure shows the x-axis, y-axis and z-axis. Values on the horizontal axis are samples and vertical axis is directly is the normalized output of the accelerometers [5], [482]. Figure on the right represents the spectrum of the same signal.

7.2.1 Data collection

Two different phases were carried out to address the gait assessment and to design and develop the appropriate algorithms.

a) First iteration

This first part was carried out within the Phase I and II of the PERFORM study. At this point, data collected was used to design and develop the algorithms to perform the gait assessment. Data was collected on 10 subjects, 5 healthy subjects (mean age 28 ± 2.4) and 5 PD patients (mean age 62 ± 2.9 , mean leg's length measured on right trochanter major femoris 0.96 ± 0.07). The subjects walked through a well-lit corridor for a distance of 20 m. Each subject was asked to walk three times with different speeds: slow, normal, quickly. During the test the following parameters were measured: number of steps, time and leg's length of the subject. PD patients were asked to take their medication shortly before the testing sessions. The symptoms were rated by a professional neurologist with more than 20 years of experience with PD patients. Four accelerometers were placed on the right and left forearms, and on the right and left calves with a fifth accelerometer being placed on the trunk, just at the base of the sternum. The study took place in a control environment, in which subjects walked in three trials. In the first trial, the subject walked in a straight line for 4 meters, turned back towards the left and returned in the same straight line to the starting position. In the second trial, the subject turned back towards the right and in the third trial the subject

only walked the initial 4 meters and ended in a standing position.

b) Feasibility study

This part was carry out during the Phase III of the PERFORM project. At this point the PERFORM system was installed at patients' homes. All patients were asked to wear the system in their homes and to move freely carrying out their daily activities. The patients were using the system between 5 and 7 days, running 2 sessions of 4 hours each per day, *Figure 57* shows an example of raw data collected during these sessions. During the first day, they and their caregivers received a training session about how to use properly the system and the sensors. Moreover, a printed manual was left at their homes and a telephone line was available for questions during the whole time as well. *Table 20* shows the assessment of bradykinesia, gait and limbs' rigidity according to the Unified Parkinson's Disease Rating Scale (UPDRS) [240], this evaluation was done by a clinician on the first day of the test. During the experiment step frequency, stride length, entropy and arm swing were calculated from the 642 walking events coming from 10 PD patients. For each patient the features extracted from the recordings in OFF and ON state were confronted.

Figure 57 – Example of data collected during the protocol in the hospital

The example of the *Figure 57* illustrates the raw data coming from the four accelerometers in the limbs. The module of the 3-axis sensors is plotted to show how each of these signals change when the subject perform different daily tasks. Signals RW (right wrist) and LW (left wrist) show the acceleration in the wrists and RL (right leg) and LL (left leg) acceleration in the legs. Panel a) shows the subject opening a door with her left hand and the arrow links this moment with the raw data signal. Panel b) shows the subject moving her right hand to drink water and the corresponding raw signal. Panel c) shows a moment where the patient was walking. The arrows relate the tasks with the response in the signals. The PERFORM system has its own activity recognizer module which is based on analysis of these signals as explained in [539]. In the present work, these measures have been compared from the same patient in OFF state and ON state. Identifying which of them characterized both states more accurately in an unsupervised environment. Next paragraphs explain each measure and the procedure carried out to implement them. PD affects severely the motor status of the patients. In particular, the loss of dopaminergic neurons compromises the speed and fluidity of movements.

Id	Sex (Age)	Status	Gait	Brad.	Left Leg Rigidity	Right Leg Rigidity	Left Wrist Rigidity	Right Wrist Rigidity
1	F (71)	OFF	0	1	1	1	1	1
		ON	0	1	1	0	1	0
2	M (68)	OFF	0	0-1	1-2	0-1	1	0-1
		ON	0	0	0	0	0	0
3	M (63)	OFF	0	0	1	1	1	1
		ON	0	0	0	0-1	0	1
4	F (67)	OFF	3	2	2	2	1	2
		ON	1	1	1	1	1	1
5	M (63)	OFF	0	0	0	1	0	2
		ON	0	0	0	1	0	2
6	M (68)	OFF	0	3	0	0	1	1
		ON	0	1	1	2	1	1
7	M (76)	OFF	0	1	1	0	0	1-2
		ON	0	0	1	0	1	2
8	M (52)	OFF	4	3	4	4	4	4
		ON	1	1	1	1	1	1
9	F (56)	OFF	2	3	3	2	3	2
		ON	1	0	1	0	1	0
10	M (58)	OFF	2	3	3	3	3	3
		ON	1	1	1	1	1	1
11	F (79)	OFF	0	2	1	1	1	1
		ON	0	0	0	0	0	0

Table 20 - Details of the patients enrolled in the feasibility study. Table shows the sex, age and clinical evaluation of the patients during their ON and OFF states according to the UPDRS scale

7.2.2 Methods and material

Two different types of analysis are performed; the first one using intrinsic features of the signal, specifically entropy, which by definition is a direct measure of complexity. Entropy is the measure of the uncertainty or unpredictability associated to a specific variable, or in other words, it is a measure of the disorder. Former works [5], [6], [8] have shown how to use the technique “Sample Entropy” to calculate the variability and complexity of gait in PD disease. Sample entropy quantifies the regularity of a time series. It reflects the conditional probability that two series of “m” consecutive data points which are similar to each other will remain similar when one more consecutive point is included [537]. Two data series are considered similar if the value of a specific measure of distance is less than a parameter “r”.

The algorithm is based on the analysis of the signal coming from an accelerometer attached on the belt (the same algorithm has been proved to be valid for sensors attached on the trunk). The algorithm calibrates the signals and normalizes them to gravity’s acceleration. Then, the row signal is low-pass filtered before further analysis (minimum order zero-lag Butterworth filter at 20 Hz). The algorithm calculates the main frequency of the signal coming from the sensors attached on the trunk/belt. The assessment of the main frequency of gait is performed calculating the main frequency of “unbiased” auto-correlation function of the z axis [8]. Figure 58 shows the overview of the scheme followed to extract the gait features.

The algorithm is based on the “inverted pendulum model of human walking” [540], Figure 59. This model was used to estimate the length of the steps during walking. The algorithm measures the distance between two “toe off” using the signal coming from the trunk/belt accelerometer and the length of the subject’s leg. The present algorithm has been previously used in several studies. However, PERFORM’s version of the algorithm has been designed to reduce the drift of “numeric integration” using different pre-processing filters. Indeed, the signal is band-pass filtered (minimum order zero-lag Butterworth filter at 1-6 Hz). Furthermore, to reduce the error of the measurement it is recommended to reset the double integration on each step to avoid the drift error.

Finally, it is necessary to point out that a segmentation module was developed within PERFORM in order to analyse

when the patient was actually walking [539] and run the gait characterization algorithms only at that times. This work has proved that even 2 accelerometers are enough to classify walking activities with accuracy higher than 99%. The inclination of trunk is also a relevant indicator of gait impairment and it might be a useful clinical indicator for the medical doctor to assess the status of the patients and the evolution of motor degradation.

Figure 58 – General scheme for the gait assessment

The “inverted pendulum” was originally proposed by Cavagna in 1976 to estimate the stride length by analysing the vertical displacement of a sensor placed close to the human Centre of Mass (CoM), particularly close to the L-3 vertebra [541]. Later, Zijlstra et al. 1997 explored the use of an accelerometer to implement this model [542]. According to this model the human gait can be analysed by splitting the gait cycle in two different phases. In this model, the first phase of the cycle is modelled as an inverted pendulum and the second part is estimated with a constant value. Therefore, by measuring the acceleration of a sensor placed in the L-3 vertebra and using the formulations of the classic mechanic it can be calculated the vertical displacement and finally the estimation of the stride by applying the model [543]. The original method as well as different evolutions which have been proposed in the last years have been largely used in to estimate gait parameters [349], [540], [544], [545].

The model, represented in the *Figure 59* and the stride length is calculated according to the following expression (14), taking into account that K is a constant which has to be calibrated for each individual based on experimental data. The calibration procedure is as follows: for each individual K is the ratio between the real and the estimated walked distance for a given trial.

$$S = 2\sqrt{l * h * h^2} \quad (14)$$

Figure 59 – Inverted pendulum (Image source: Alvarez et al. 2006 [540])

7.2.3 Results

a) First iteration

Figure 60 – SampEn comparison between the control group and the PD group on the different sensors of the Body Area Network (BAN)

Figure 60 shows the values of SampEn for each sensor on the Body Area Network (BAN) confronting the PD group and the control group. As shown, the entropy measured in all the sensors while walking is higher in the PD group than in the control group. The subjects affected by PD progressively lose complexity in their movements and, consequently, their gait parameters become more irregular. As a consequence of this increase in variability, the entropy of the time series acquired from the PD patient accelerometers raises substantially. The values of SampEn evaluated in real patients and healthy subjects differed significantly. Though the standard deviation in the cases of left leg and right arm does not allow for a statistical separation the two groups of subjects, in others cases the values of SampEn are significantly different and provide useful information. Waist sensor ($p < 0.01$) and the left arm ($p < 0.01$), right arm ($p = 0.05$) and right leg ($p < 0.05$). Nevertheless, left leg did not show a significant difference ($p = 0.313$). Regarding the estimation of the gait features for PD, the mean error of Step frequency, Stride Length and Speed, calculated on 30 trials and 10 subjects are respectively: $3.36\% \pm 2.57$, $7.31\% \pm 4.69$, and $7.77\% \pm 5.34$.

Subject	Subject	Step frequency error (%) (mean $\pm$ std)	Stride length error (%) (mean $\pm$ std)	Speed error (%) (mean $\pm$ std)
1	PD	4.94 $\pm$ 1.45	2.55 $\pm$ 2.66	6.19 $\pm$ 3.73
2	PD	1.32 $\pm$ 2.79	2.87 $\pm$ 2.27	3.09 $\pm$ 2.90
3	PD	0.66 $\pm$ 1.46	5.78 $\pm$ 6.94	6.46 $\pm$ 6.40
4	PD	4.41 $\pm$ 3.05	9.28 $\pm$ 2.15	3.75 $\pm$ 3.65
5	PD	2.12 $\pm$ 0.28	1.34 $\pm$ 3.72	1.97 $\pm$ 2.09
6	Control	1.01 $\pm$ 1.14	7.70 $\pm$ 7.23	5.12 $\pm$ 7.95
7	Control	1.67 $\pm$ 3.62	6.29 $\pm$ 1.67	3.60 $\pm$ 4.44
8	Control	2.39 $\pm$ 2.72	6.14 $\pm$ 4.23	9.38 $\pm$ 5.09
9	Control	5.11 $\pm$ 3.74	9.63 $\pm$ 2.58	15.26 $\pm$ 0.99
10	Control	1.73 $\pm$ 2.11	12.09 $\pm$ 4.03	10.63 $\pm$ 5.06
Aggregated		2.13 $\pm$ 2.57	5.20 $\pm$ 4.69	5.53 $\pm$ 5.34

Table 21 – Results of the gait features estimation

b) Feasibility study

Step frequency, stride length, entropy and arm swing present a significant variation between the OFF and ON in all the patients. Nevertheless, arm swing and entropy show a significant better performance. The entropy variation (lower values in the ON phase) reflects the predictability of the signals coming from the ON phase in contrast with ones from the OFF phase. Finally, step frequency and stride length show higher values in the ON phase as it was expected. Additionally, parallel experiments indicated that it is not possible to create a generalization for all the patients. There is not a direct correlation between variation in the magnitudes and variation in the UPDRS, i.e. a specific variation between ON and OFF does not necessarily imply a direct variation of UPDRS. That means the system needs to be calibrated for each patient, indicating how are the specific parameters during the OFF and ON states of the patient. Finally, *Figure 61* shows an example of output events for a specific patient. The first part of the figure (11:30:00 – 11:31:20) shows the events generated during the ON state. The right side (13:50:00 – 13:51:48) is the OFF state. In both states the arm swing and entropy were evaluated while the subject was walking. The averages of the three values were calculated for ON and OFF and are plotted with wider and darker lines. The three features followed the expected evolution in the change from ON to OFF i.e. decreased of the arm swing and increase of the entropy. The reduction of the step frequency, number of steps in time, and the shortening of stride length are a common symptom of PD gait alteration. Therefore studying variations in these features along the day will help to detect an abnormality of the motion. To measure the step frequency algorithms based on the autocorrelation have been implemented. Autocorrelation is the cross-correlation of a signal with itself. Informally, it represents the similarity between observations as a function of the time separation between them. It is a mathematical tool for finding repeating patterns, such as the presence of a periodic signal which has been buried under noise, or identifying the missing fundamental frequency in a signal implied by its harmonic frequencies. The algorithm calculates the main frequency of the signal coming from the sensor attached on the belt.

Figure 61 – Example of gait features and entropy fluctuations from On and Off for a patient in the study

Table 22 shows the average data loss and standard deviation, the average length of data loss burst and standard deviation and the most frequent length of data loss burst. The average data loss satisfied that in all cases more than 95% of the data is successfully transmitted. Nevertheless, analysing the average burst length and the standard deviation of these values we found burst of up to 143.04 ± 240.10 ms, a burst of these characteristics in the middle of the transmission would compromise seriously the performance and accuracy of the system. Nevertheless, adding the most frequent burst length as an extra measure and observing the raw data we can easily identify that

64ms is the most common burst in all the cases, moreover the longest burst are always at the beginning of the session i.e. during the start-up process. That means that waiting for all the sensors to be properly connected before start computing the gait features will remove the longest burst errors. Then, we will still keep sporadic disconnections of 64ms (the minimum time of the data logger to reconnect with the accelerometer) which still will guarantees an average data loss much more acceptable.

Id	Data loss (%)	Average burst error length (ms)	Most frequent burst error length (ms)
1	0.95±0.77%	111.55±532.89	64
2	0.97±0.55%	92.07±242.97	64
3	2.02±0.78%	104.22±531.12	64
4	1.14±1.12%	101.25±532.89	64
5	1.51±1.17%	114.85±529.04	64
6	0.32±0.37%	143.04±240.10	64
7	1.83±1.04%	139.44±542.15	64
8	1.25±1.26%	123.64±242.97	64
9	1.31±1.02%	174.26±527.90	64
10	1.27±1.07%	115.10±542.15	64
11	1.84±1.11%	106.55±542.59	64

Table 22 - Data loss measures for the accelerometer network working on a real environment

7.3 Discussion

This chapter addressed the automatic assessment of bradykinesia and gait performance on PD patients and their feasibility to be translated and integrated into a telehealth platform for the continuous monitoring of PD patients at their our homes. In the two cases presented here, the whole process has been split into two parts, the first one to design and implement the algorithms using data from a supervised environment. The second one to explore their feasibility on the patients' homes. Regarding the bradykinesia, the proposed system provides a useful tool for the analysis of the bradykinesia in PD's patients. Physiological signals are outputs of the human body, i.e. they are outcomes of one of the most complex systems, they are typically nonlinear and no stationary, and much information is hidden in the dynamics of their fluctuations. Moreover, the large variability and the unpredictability of the movement may be the cause of classification errors. In fact it is complicated to find a common pattern in different PD's patients in an unsupervised environment. The results of the second phase of testing are satisfactory, reaching a high level of accuracy, taking in account that evaluation of the status of the patient by clinicians presents a statistical error of 5% due to the subjective characteristics of the UPDRS scale. To improve these initial results, not only the testing phase will continue on a larger sample of patients, but the classification method will also need to be personalized, in order to achieve a higher level of accuracy, for example introducing special classifier trained for each patient in order to adjust the parameters. Thus, this work represents an innovation approach tool for quantifying bradykinesia severity without requiring standard motor tests such as finger tapping. In contrast with that traditional approach this methodology shows a slightly lower classification accuracy of individual epochs although on the other hand it could take advantage of the redundant information available to automatically increase the accuracy in the detection of the symptoms, for example by using the proposed meta-analysis. Nevertheless, as expected the best results in the automatic assessment of the bradykinesia severity was achieved in the sensors placed in the hands. This is an important limitation for the unsupervised scenario since there are very limited situations along the day where the subjects perform continues movements with their hands for more than five seconds (as we could verify during the study at patients' homes within the PERFORM project). Moreover, both approaches could be combined to achieve a more robust implementation. A continuous monitoring of the bradykinesia symptom using wearable sensors enhanced with the punctual performance of standard test, measuring their performance either with the same wearable sensors or another devices providing a more accurate results by contextualizing the measuring in the standard tests framework. As for the bradykinesia profiling component of the system, the structure of the method so far is meaningful in that it allows physicians to monitor and detect changes in the symptomatic behaviour as quickly as the changes appear. A remotely installed system,

at the patient's home, with such capabilities could eventually redefine the paradigm of taking care of motor neurodegenerative disease patients, providing far more and richer information to be used by doctors at the time of making decisions or designing treatments.

On the other hand, the gait analysis module implemented provides useful information about the motor status of a PD's patient. It has been shown that data collected by accelerometers can be used to measure parameters like stride length, speed of locomotion, step frequency and to evaluate the complexity of locomotion. Furthermore, preliminary results are promising, showing that the Sample Entropy metric is valid to assess the decrement of gait complexity in PD. However, these initial results need to be confirmed on a larger and age-matched sample. It was found that age could probably be a factor affecting the gait pattern and causing the differences in sample Entropy. Regarding the correlation between SampEn and the UPDRS scale, trials with real PD's patients are still needed.

The feasibility study explores the use of only one accelerometer in the belt together with the "inverted pendulous" model and using entropy as an index of degradation of the gait performance. Nevertheless, it is important to highlight that this approach estimates the gait features, thus it is an indirect measure and it is user dependent. The algorithm should be personalized with a constant depending on every subject in order to provide an accurate output. Moreover, the model uses the leg length as input parameter measured with shoes; this value will change according to the kind of shoe that the patient is wearing. Nevertheless, all these inaccuracies are relevant when looking for an exact value of velocity and stride length, but we are more interested in studying the same day variation of the patient. These systems can provide us with a detailed and accurate status of the impairment. Every patient walks following a different pattern, two patients can walk with different step frequency not because of the disease itself but because they are different. Besides, even the same subject walk differently depending on the situations. Working in unsupervised environments, parameters related with the walking analysis are not very representative and the use of alternative measures like entropy or the measure of the arm swing are a better choice. These features fluctuate according to the status of the patient during the day. Therefore, it is possible to develop a continuous monitoring system able to identify the different phases of the disease within the day. This system could easily alert the professionals when the patient faces an OFF phase indicating that a reschedule in the medication intake is needed. It is also important have in mind that dyskinetic movements will alter the entropy patterns.

Working in an unsupervised and wireless environment achieving a low data loss rate became essential. In the last release of the PERFORM platform, the four accelerometers in the limbs work simultaneously and transmit data in separate time slots avoiding most of the packet loss. Nevertheless sometimes there could be something between the sensor and the receiver i.e. when patient is walking the body is between the sensor and the receiver and that could generate some packet loss. Furthermore, the module provides physicians with information about gait degradation throughout the evolution of the disease. The assessment of gait degradation is based on a comparison of PD patients vs. controls through entropy analysis. Entropy of information allows evaluating the complexity of the human gait and it is useful to assess the level of symmetry of limb movements during walking. The limitation of these features in an unsupervised environment is that they can change not necessarily because of a worsening on the patient status but for the willingness of the patient i.e. the patient at home can walk slowly or run depending on the situation. For this reason including other measures able to estimate the worsening of the walking pattern independently of the patient activities, the measure of the entropy of the accelerometer signal has been proved to be one the best indicators to discriminate between a "healthy" pattern and a walking pattern coming from a PD patient.

Chapter 8 Human Factors

During the last decade, we have witnessed tremendous progress in the development of wearable technologies for health monitoring and long-term monitoring of patients, and healthy subjects, in their daily lives. This progress has been benefit by the development of new communication standards for low-power wireless communication, smaller size of the sensors, lower battery consumption and at the same time an evolution in the computational capabilities of these devices. Health monitoring applications of wearable systems most often employ multiple sensors that are typically integrated into a sensor network either limited to body-worn sensors or integrating body-worn sensors and ambient sensors. In the PERFORM case a Body Area Network was designed in order to cover all the major symptoms of the Parkinson's Disease (PD) and it will be described in detail in the next section. The use of these systems could be highly intrusive and uncomfortable for the patients and this could lead the project to fail even when it has been proved the benefits for the patient's health. Therefore, the wearability assessment should be taken into serious consideration during the development of any wearable system in order to identify weak points in the adoption of the systems by the final users.

Objectives – On this chapter a methodological approach has been followed in order to extract and analyse the PD patients feedback regarding the wearability of the PERFORM system.

Methods and material – To carry out this wearability assessment different methodologies already validated have been emplaced, specifically the REBA, Borg and CRS scales have been used in combination with a body map when needed. Further details of these methodologies will be provided later on this document. A total of 32 PD patients have been involved in this study showing an excellent acceptance of the PERFORM system in wearability terms.

Results - The overall result of the evaluation can be break down in the subsequent marks: average perceived exertion score (0.71 on the Borg CR-10 scale), average posture score (0 based on the REBA scale), average localized pain/discomfort score (0.11 on the Borg CR-10 scale), average emotion score (1.4 on the CRS scale), average attachment score (2.5 on the CRS scale), average harm score (0.15 on the CRS scale), average perceived change score (0.67 on the CRS scale), average movement score (0.59 on the CRS scale) and average anxiety score (1.63 on the CRS scale). Each individual component of the wearability assessment can be labelled as low level of effect according to the guidelines provided by each of the methodologies.

8.1 Human factors

In short and plain words, Human Factors (HF) is a scientific branch concerned about the interaction between humans and technology. Its roots can be found in the 70s and 80s, when doubts about the safe use of complex technology became manifest in industrial environments and aviation. The safe use of complex systems requires a reliable performance of such systems but also a full understanding of the interaction between humans and computers, as well as the appropriate training of the final users. Human cognition and cognitive psychology can provide a conceptual framework for a safe approach to systems development [546]. From the study of aviation accidents four strategies were suggested to reduce risks and to increase safety in complex systems: a better design of technology, a better workplace design, introduce guidelines and protocols for tasks that need to be executed and to design and execute educational programs for users to improve their performance. Current clinical and healthcare system are also complex system involving an continuous interplay of stakeholders, systems and processes, particularly the gradual introduction of technologies in healthcare has led to a gradual increase of the complexity in this environment with a high risk of impairing patient safety. Traditionally, attention to accidents

and risk factors has been experienced in places where the patient is most at risk, such as the operating room, the emergency room and the intensive care unit [546]. One of the original objectives of medical informatics was the development of decision support system aimed at improving medical decision making based on the assumption that humans are fallible decision makers because they can not possibly oversee the breadth of medical knowledge and to efficiently manage the increasing quantity of data available [546]. Interest HF and usability applied to medical informatics kept constantly growing, with the raising of telehealth, eHealth and mHealth systems the final users are not only the clinicians or health professionals instead patients and caregivers are also now active users of these systems [546]. Considering these new final users, it is important to note that HF is not only related with the safety use of technology, but also final adoption and acceptance of the new technologies by the healthcare professionals and the patients are closely related to the usability of these technologies and to the training of the users with [547]. The challenge is to design systems that are powerful enough not only to handle the volume of information and the complexity of medical data, but also to support both professionals in doing their work and to engage professionals and patients in the continuous use of the system [548]. Usability factors could be a major barrier to the adoption of health technologies. It is evident that novel health informatics solutions can offer tremendous benefits for the healthcare system. Nevertheless, there is also the risk that they can also interrupt the workflow, cause delays, and introduce errors, at least in the initial phases and depending on the learning curve of the system. For that reason, lack of attention to the evaluation of HF with the final users of these novel solutions may result in dissatisfied users, decreased effectiveness, and increases in error costs [549].

More formally, HF could be defined as the scientific discipline concerned with the understanding of interactions among humans and other elements of a system. HF also involves the enhancement and optimization of the relationship between technology and the people and their activities. HF requires the integration of human sciences and engineering in systematic applications, considering cognitive and socio-technical aspects [547] [546]. The system represents the physical, cognitive and organizational artefacts that people interact with and in this contexts the word system refers in fact to the socio-technical system involving the people, their tasks, and the physical-technical environment in which they work [547]. Therefore in healthcare, HF could contribute to optimize the relationship between healthcare professionals and patients and their working activities (the healthcare process), with the aim of optimizing human performances [547].

According to the International Standard Organization (ISO 9241) [550] usability is the “effectiveness, efficiency and satisfaction with which a specified set of users can achieve a specified set of tasks in a particular environment”. Effectiveness refers to the accuracy and completeness with which users achieve specific goals, efficiency to the resources expended in relation with effectiveness, satisfaction to the comfort and acceptability of use as subjectively experienced by the end-users, context of use to the users, goals, tasks, equipment, physical and social environment, and work system to the set and organization of users, equipment, tasks environment, in which a product is used. The task can be defined as a goal (what’s to be done) and the conditions (constraints) to reach the goal, while the activity refers to the set of actions (mental and behavioural) carried out by the user to perform the task [547].

Usability is a quality of the product, but it is defined in the terms of the people and a relevant consideration is that it is not possible to add usability to a system after it is designed. This means, it is needed to pay attention to usability from the beginning of a project. In order to achieve the maximum benefits and effectiveness from a novel telehealth system it is essential to be attentive to usability, keeping in mind its intended users, task and environment. Usability evaluation is a method for identifying specific problems with IT products and specifically focuses on the interaction between the user and task in a defined environment. Effective usability evaluation improves predictability of products and saves development time and cost [549]. In the field of human-computer interaction, this process is often called user-centred design (UCD). This process begins with an understanding of the context of use and incorporates evaluation of design solutions as a way to modify the design until it meets the needs of users [548]. But also, there methods of evaluation based on systematic analysis of the usability features by expert, for example the Heuristic Evaluation is carried out with a reduced group usability experts following the recommendations of the 10 Nielsen Heuristics and ranking each of the issue founded [551]:

- *H1 - Visibility of system status - The system should always keep users informed about what is going on,*

through appropriate feedback within reasonable time.

- *H2 - Match between system and the real world - The system should speak the user's language, with words, phrases and concepts familiar to the user, rather than system-oriented terms. Follow real-world conventions, making information appear in a natural and logical order.*
- *H3 - User control and freedom - Users often choose system functions by mistake and will need a clearly marked "emergency exit" to leave the unwanted state without having to go through an extended dialogue. Support undo and redo.*
- *H4 - Consistency and standards - Users should not have to wonder whether different words, situations, or actions mean the same thing. Follow platform conventions.*
- *H5 - Error prevention - Even better than good error messages is a careful design which prevents a problem from occurring in the first place. Either eliminate error-prone conditions or check for them and present users with a confirmation option before they commit to the action.*
- *H6 - Recognition rather than recall - Minimize the user's memory load by making objects, actions, and options visible. The user should not have to remember information from one part of the dialogue to another. Instructions for use of the system should be visible or easily retrievable whenever appropriate.*
- *H7 - Flexibility and efficiency of use - Accelerators—unseen by the novice user—may often speed up the interaction for the expert user such that the system can cater to both inexperienced and experienced users. Allow users to tailor frequent actions.*
- *H8 - Aesthetic and minimalist design - Dialogues should not contain information which is irrelevant or rarely needed. Every extra unit of information in a dialogue competes with the relevant units of information and diminishes their relative visibility.*
- *H9 - Help users recognize, diagnose, and recover from errors - Error messages should be expressed in plain language (no codes), precisely indicate the problem, and constructively suggest a solution.*
- *H10 - Help and documentation - Even though it is better if the system can be used without documentation, it may be necessary to provide help and documentation. Any such information should be easy to search, focused on the user's task, list concrete steps to be carried out, and not be too large.*

8.2 Human Factors in PERFORM

The PERFORM system followed a User-Centred Design approach, both patients and clinicians were asked and involved in the design process of the system. To do achieve that, an iterative approach was followed, patients and clinicians were asked on each iteration their opinion about the PERFORM platform and data regarding the interaction with the system was collected on each of the phases of the PERFORM trials (see 6.1.1 *PERFORM system as a case of study*). To address the Human Factors in the PERFORM system two different approaches were followed, first of all, a traditional usability evaluation was carry out on each of the phases with the final users in order to re-design the interfaces of the system according to their feedback. As an example, *Figure 62 and Figure 63* show some examples of how the interfaces evolved within the project. The second part was aimed at covering the human factors regarding the wearable Body Area Network (BAN) used for patient monitoring. To accomplish this study a methodology for the wearability evaluation of a BAN was defined and used to assess the PERFORM system. This study is described in the next section and has been published in the journal Cancela et al. (2014) "*Wearability Assessment of a Wearable System for Parkinson's Disease Remote Monitoring Based on a Body Area Network of Sensors*" [13].

Figure 62 – Evolution of the PERFORM interface for food intake

Figure 63 - Evolution of the PERFORM interface for the healthcare professional

8.3 Wearability assessment

In defining what a wearable computer is, Bass stated that wearable computers should be designed to exist within the corporeal envelope of the user [552]. And according to Mann definition, wearable computers should be situated in a manner that makes it part of what the user considers himself or herself [553]. These definitions give a philosophical notion to the concept of having an intimate interaction with the wearable computer, but they do not necessarily highlight the physicality of wearing a computer. In differentiating wearable technology from portable technology, three criteria have been proposed by Knight et al. [554]:

- The device is attached to the body and does not require muscular effort to remain in contact with the body (i.e. you do not have to hold it, which would require muscular grip force).
- The device remains attached to the body regardless of the body's orientation or activity (i.e. you do not have to take it off to perform a task specific action, even when not using the computer).
- The device does not have to be detached to be interacted with (i.e. the first two criteria are not violated when the device is in use).

With these criteria, wearable systems differ from portable technologies, such as mobile phones, which are designed to be carried. Even mobile phones, 'worn' in a holster attached to a belt, are often detached and held in the hand when dialling or texting, and as such are merely being carried until they are used [554]. For wearable computer systems, the term "wearability" has been defined as the use of the human body as a support system for some product [555]. Extending this definition, the term 'dynamic wearability', includes the notion of the device being wearable while the body is in motion [555]. These definitions address the physicality of wearing computer equipment. They highlight the need for any such device to be designed with the wearer as the focus of the design, by ensuring that in the first instance, it is safe to wear, and in the second, that it is usable [556]. Wearability directly impacts on the usability of a wearable computer system. If the wearer is uncomfortable or placed under too much stress then the usability of the system will be reduced. Wearability evaluations can highlight areas for concern and indicate needs for improvement in product design [554]. They may also help generate guidelines for use. Usability is not simply a product of the device but a consequence of the interaction between person and device in the pursuit of some goal [557].

The first step in order to plan the wearability evaluation of the PERFORM wearable device, was to establish the desired outcomes of this evaluation. One obvious goal is to identify if the device is acceptable by the end users and how the design could be improved. However, since the design of a wearable device is clearly a multi-criteria optimization problem, it was decided to adopt a tested methodology that could provide useful insights on the problematic areas and will enable the optimization of the design. A wearability assessment can be used to ensure that wearing the system is not physically demanding, does not inhibit performance (i.e. it is physically usable), is not uncomfortable, and ultimately ensure that it is safe to wear. And finally, since PERFORM wearable is intended to be used by PD patients, it is essential to take into account the characteristics of the disease for the final selection of assessment methods. The research performed confirmed that the wearability evaluation of a device is a multifaceted problem; the wearable devices affect the wearer in different ways and thus there are several effects that should be taken into account when assessing the wearability of the device. These effects are ranging from physiological effects due to attachment of extra load to the human body to comfort related effects. Given that each wearable device is designed and manufactured in order to provide a sophisticated functionality and to be used in several usage scenarios is adding more dimensions to the problem. Furthermore, there are a number of methods for measuring physiological and biomechanical variables that could be employed for an evaluation of wearable computers. However, these methods usually employ expensive equipment that requires technical expertise and are often limited in their applicability in real world settings due to issues of the size of equipment, portability and calibration. These methods are therefore, preferred for lab-based experiments, rather than user trials and specially trials in patients' homes. For this kind of trials, methods are required that are non-invasive and non-restrictive, relatively quick and easy to implement, and require minimal interference with the user during data acquisition. Therefore, observation and questionnaire-based methods are preferred, for methodology selected for the wearability evaluation of PERFORM device is mostly based on the work of Knight and Baber [554]. Attaching a load to the body, as it does any wearable computer equipment, can have a number of physical effects that should be assessed to ascertain its wearability. These effects include [554]:

Figure 64 - Wearability assessment scheme

- **Physiological** – this refers to the level of energy expended when performing a specific activity, which may include perceptions of exertion and physical fatigue. An attached load to the body will have a direct effect on the energy expended by the body, as the muscles burn more energy to generate force to counteract the weight of the load. This situation sees a wearer of a wearable computer potentially increase their overall energy expenditure to overcome inertial changes. In addition, energy expenditure may also increase due to movement and posture alteration [554]. For measuring the physiological effects monitoring the heart rate is perhaps the most common method of estimating energy expenditure. Since this is not one of the parameters measured by the PERFORM wearable, it was decided not to be used as an extra sensor would be needed. The method selected is through the BORG CR-10 scales for perceived exertion which is also proposed by Knight et al. [554].

The Borg CR-10 scale can be used to measure overall physiological effort and is usually employed to measure the perceived exertion while exercising [558]. In PERFORM the user will need to point out the extra exertion he/she has given due to the fact that he/she was wearing the PERFORM wearable while carrying out daily activities. The Borg scale will be analysed in detail in the following section.

- **Biomechanical** – this refers to musculoskeletal loading, which may be localised and may result in perceptions of muscle fatigue. It also refers to changes in movement patterns and posture. For measuring the biomechanical effects several studies have been carried out in order to define how we can assess if a wearable device predisposes the wearer to excessive musculoskeletal loading. Knight and Baber recommended assessing the postures adopted when interacting with the wearable device to determine the level of postural loading [554]. They also recommended measuring the effect

of adding load to the body in the form of a wearable device.

Since in PERFORM the wearers are must wear the device while performing daily activities, this study did not intend to emphasize on specific postures but rather making sure that the device does not obstruct the users in any of the normal postures. The study of the biomechanical component has been broken down into two subsections:

- Posture and movement, which have been asses through the Rapid Entire Body Assessment (REBA) described later in this document [559].
- Musculoskeletal loading, specifically with regard to the weight of the wearable, need to be undertaken. Measurements of loading can be made by modelling of electromyography to measure levels of muscular exertion. However, these methods are best applied in controlled experimental conditions, rather than user trials. An alternative method is to use rating scales, such as the Borg CR-10 used in conjunction with body maps [558].
- Comfort – this refers to localised discomfort due to musculoskeletal loading, as well as a general sense of well-being. It may also include discomfort due to stresses placed on specific physiological systems (e.g. head mounted displays and the visual system). The comfort assessment of the device needs to take into account several dimensions. Knight and Baber developed a tool for the comfort assessment of wearable devices called the Comfort Rating Scales [556] which break down the comfort analysis into six different components. This tool will also be introduced in the following paragraphs.

Assessing the wearability of a given wearable computer could thus involve an evaluation of the physiological, biomechanical and comfort effects. For each category of effects, the selected methods and scales are synthetized in the *Figure 64* according to previous research [554].

			Level of effect				
	Metric	Units	Low	Moderate	Large	Very Large	Extreme
Energy cost	Relative perceived exertion	Borg CR-10 score	0-1	2-3	4-5	6-7	8-10
Biomechanical	Posture	REBA score + body map	1	2-3	4-7	8-10	11-15
	Localised pain and discomfort	Borg CR-10 score	0-1	2-3	4-5	6-7	8-10
Comfort	General wearable	CRS score	0-4	5-8	9-12	13-16	17-20

Table 23 - Level of effect of the different scales in the wearability of a system [554]

So far, a set of measures and tools have been proposed but the determination of this evaluation requires the convergence of the measures of the three axes (comfort, biomechanical and physiological) and their nine branches into one wearability score. To determine that value a set of criteria have been developed using the methods discussed above [554]. These criteria are shown in *Table 23*. For each measure, the value obtained from an assessment can be associated to a level of effect ranging from 'Low' to 'Extreme'. These levels were determined from values published for the descriptors used on the CR-10 scales [558], the action levels published with the REBA method [559]. For the comfort scales the levels of effect were determined by proportioning the scales into equal parts [554], [556].

From the levels of effect, five Wearability Levels (WL) have been proposed by Knight and Baber, as shown in *Table 24* [554]. This table allow the homogenous interpretation of the different metrics and scales in an easy and direct way providing a final score rating the wearability of the system under study.

Level of effect	Wearability Level	Outcome
Low	WL1	System is wearable
Moderate	WL2	System is wearable, but changes may be necessary, further investigation is needed
Large	WL3	System is wearable, but changes are advised. Uncomfortable
Very Large	WL4	System is not wearable, fatiguing, very uncomfortable
Extreme	WPL5	System is not wearable, extremely stressful and potential harmful

Table 24 - Level of effects and corresponding wearability levels [554]

8.4 Methods

The aim of this section is the description of each of the scales abovementioned, their aim, and explanation of how they should be used in the context of the wearability assessment.

8.4.1 Rapid Entire Body Assessment (REBA)

Changes in posture and movement can result in perceptions of physiological exertion, muscle exertion and discomfort. Over a short time these can develop into perceptions of fatigue and pain, and in the long term have been associated with chronic musculoskeletal problems. Posture and movement can be assessed using opto-electronic devices or digitising video or cine images [554]. However, these methods are often expensive and time consuming in setting up and analysing the data. Alternatively, posture and movement can be assessed using observational methods. An example of these methods is the REBA method developed by Hignett and McAtamney [559]. This method requires that the observer categorise the posture of individual body segments as to its level of angular displacement from neutral. For example, the upper arm can be categorised as being flexed by less than 30 degrees, less than 45 degrees or less than 90 degrees. This method has previously been used to assess changes in working postures of wearers of wearable technology. Initially the REBA method can be used to measure differences in postures between different conditions. Furthermore, it can also be used to rate any specific posture as to the level of stress it places on the body. With this REBA score, an assessment of the appropriateness of the posture adopted by the wearable wearer can be made. The REBA method has been developed to fill a perceived need for a practitioner's field tool, specifically designed to be sensitive to the type of unpredictable working postures found in health care and other service industries [559]. A multidisciplinary team of ergonomists, physiotherapists, occupational therapists and nurses collected and individually coded over 600 postural examples to produce a tool incorporating dynamic and static postural loading factors, human-load interface (coupling), and a concept of a gravity-assisted upper limb position.

Most postural analysis techniques have two, usually contradictory, qualities of generality and sensitivity [560]. High generality in a postural analysis method may be compensated by low sensitivity [559]. A need was perceived within the spectrum of postural analysis tools, specifically with sensitivity to the type of unpredictable working postures found in health care (e.g. animate load handling) and other service industries. This led to the development of the following postural analysis tool: Rapid Entire Body Assessment, REBA [559] which is aimed to:

- Develop a postural analysis system sensitive to musculoskeletal risks in a variety of tasks.
- Divide the body into segments to be coded individually, with reference to movement planes.
- Provide a scoring system for muscle activity caused by static, dynamic, rapid changing or unstable postures.
- Reflect that coupling is important in the handling of loads but may not always be via the hands.
- Give an action level with an indication of urgency.

- Require minimal equipment – pen and paper method.

For each region, there is a posture scoring scale and additional adjustments which need to be considered and accounted for in the score. To carry out the REBA assessment the evaluator is provided with a scoring card showing some schemes to help the evaluator to understand some of the questions and the tables *Table 25 to Table 35* where the criteria for the REBA assessment. Figure 3 shows an example of evaluation performed during the PERFORM assessment.

Movement	Score	Change score
Upright	1	+1 if twisting or side flexed
0 ⁰ - 20 ⁰ flexion	2	
0 ⁰ - 20 ⁰ extension		
20 ⁰ - 60 ⁰ flexion	3	
> 60 ⁰ extension		
> 60 ⁰ flexion	4	

Table 25 - REBA trunk scoring table [559]

Movement	Score	Change score:
0° - 20° flexion	1	+1 if twisting or side flexed
> 20° flexion or in extension	2	

Table 26 - REBA neck scoring table [559]

Position	Score	Change score:
Bilateral weight bearing, walking or sitting	1	+1 if the knee(s) between 30° and 60° flexion. +2 if the knee(s) >60° flexion (n.b. not for sitting)
Unilateral weight bearing. Feather weight bearing or an unstable posture.	2	

Table 27 - REBA legs scoring table [559]

Position	Score	Change score:
20 ⁰ extension to 20 ⁰ flexion	1	+1 if arm is: <ul style="list-style-type: none">• Abducted• Rotated +1 if shoulder is raised -1 if leaning, supporting weight of arm or if posture is gravity assisted
>20 ⁰ extension	2	
20 ⁰ - 45 ⁰ flexion	3	
45 ⁰ - 90 ⁰ flexion		
>90 ⁰ flexion	4	

Table 28 - REBA upper arms scoring table [559]

Movement	Score
60° - 100° flexion	1
<60° flexion or >100° flexion	2

Table 29 - REBA lower arms scoring table [559]

Movement	Score	Change score:
0° - 15° flexion/extension	1	+1 if wrists is deviated or twisted
>15° flexion/extension	2	

Table 30 - REBA wrists scoring table [559]

Score	0	1	2	Change score:
	< 5 kg	5 - 10 kg	+ 10 kg	+1 if shock or rapid build-up of force

Table 31 - REBA Load/Force scoring table [559]

Score	0 - Good	1 - Fair	2- Poor	3 - Unacceptable
	Well-fitting handle and a mid-range, power grip.	Hand hold acceptable but not ideal or coupling is acceptable via another part of the body.	Hand hold not acceptable although possible.	Awkward, unsafe grip, no handleless. Coupling is unacceptable using other parts of the body.

Table 32 - REBA coupling scoring table [559]

		Neck											
		1				2				3			
Trunk Posture Score	Legs	1	2	3	4	1	2	3	4	1	2	3	4
	1	1	2	3	4	1	2	3	4	3	3	5	6
	2	2	3	4	5	3	4	5	6	4	5	6	7
	3	2	4	5	6	4	5	6	7	5	6	7	8
	4	3	5	6	7	5	6	7	8	6	7	8	9
	5	4	6	7	8	6	7	8	9	7	8	9	9

Table 33 - REBA score Table A [559]

		Lower arm					
		1			2		
Upper arm score	Wrist	1	2	3	1	2	3
	1	1	2	2	1	2	3
	2	1	2	3	2	3	4
	3	3	4	5	4	5	5
	4	4	5	5	5	6	7
	5	6	7	8	7	8	8
	6	7	8	8	8	9	9

Table 34 - REBA Table B for scoring [559]

Score A	Score B											
	1	2	3	4	5	6	7	8	9	10	11	12
1	1	1	1	2	3	3	4	5	6	7	7	7
2	1	2	2	3	4	4	5	6	6	7	7	8
3	2	3	3	3	4	5	6	7	7	8	8	8
4	3	4	4	4	5	6	7	8	8	9	9	9
5	4	4	4	5	6	7	8	8	9	9	9	9
6	6	6	6	7	8	8	9	9	10	10	10	10
7	7	7	7	8	9	9	9	10	10	11	11	11
8	8	8	8	9	10	10	10	10	10	11	11	11
9	9	9	9	10	10	10	11	11	11	12	12	12
10	10	10	10	11	11	11	11	12	12	12	12	12
11	11	11	11	11	12	12	12	12	12	12	12	12
12	12	12	12	12	12	12	12	12	12	12	12	12

Table 35 - REBA Table C for scoring [559]

The steps to carry out the REBA assessment are as follows:

- Step 1: Perform the trunk (*Table 25*), neck (*Table 26*) and leg analysis (*Table 27*).
- Steps 2: Calculate the score for Load/Force following the *Table 31* instructions.
- Step 3: Using values from steps 1 and 2, locate the, so called, Score A using the *Table 33* (named Table A according to the REBA nomenclature).
- Step 4: Perform the upper arm (*Table 28*), lower arm (*Table 29*) and wrist (*Table 30*).
- Step 5: Calculate the score for coupling following the *Table 32* instructions.
- Step 6: Using values from steps 4 and 5, locate the, so called, Score B using the *Table 34* (named Table B according to the REBA nomenclature).
- Step 7: Using values from steps 3 (Score A) and 6 (Score B), locate the REBA using the *Table 35* (named Table C according to the REBA nomenclature).

8.4.2 Borg scales

The Borg Relative Perceived Exertion (RPE) scale is used to measure overall physiological effort [554]. The RPE Scale is a common method for determining exercise intensity levels. It is used in some research studies for that purpose, but may also be used in training programs to describe the intensity of training sessions. The scale of perceived exertion is how hard you feel your body is working, and therefore is a subjective measurement. The commonly used scale is based on the research of Gunnar Borg, and is therefore also called the Borg Scale [561]. There are different versions of this scale, the two best well-known are:

- Borg 6-20 - the original scale as developed by Borg, with the ratings between 6-20 which correspond to 1/10 of the exercise heart rate.
- Borg CR-10 - an updated combined category and ration scale by Borg with the ratings between 0 (nothing at all) and 10 (very hard) [558].

The original scale introduced by Gunnar Borg rated exertion on a scale of 6-20. Borg then constructed a category (C) ratio (R) scale, the Borg CR-10 Scale. This is especially used in clinical diagnosis of breathlessness and dyspnoea, chest pain, angina and muscle-skeletal pain. The CR-10 scale is best suited when there is an overriding sensation arising either from a specific area of the body, for example, muscle pain. In these cases, the scale is used together with a body map, in this way the user can self-assess the perceived exertion on each body part (*Figure 65*).

Figure 65 - Example of the REBA scoring card used during PEFORM pilots based on the Hignett and McAtamney scheme [559].

8.4.3 Comfort Rating Scales (CRSs)

When wearing something, the level of comfort can be affected by a multiple number of things, such as the device's size and weight, how it affects movement, and pain, whether direct (e.g., friction, knocking, heat) or indirect (e.g., muscle fatigue) [556]. In addition to physical factors, comfort may be affected by psychological responses such as embarrassment, especially in the case of medical devices where wearing a device could disclosure that the subject is suffering a certain pathology. Therefore, simply knowing that when wearing the device the wearer has a certain level of discomfort does not help in determining what aspect of the device makes the wearer feel uncomfortable. Consequently, Knight and Baber proposed that comfort should be measured across a number of dimensions and for such task they developed the Comfort Rating Scales (CRSs) [556].

Figure 66 - Borg CR-10 Scale and body map

The CRSs have been developed to provide a quick and easy-to-use tool to assess the comfort of wearable computers. Using the scales may assist researchers and designers of wearable computers in measuring total wearer comfort and highlight factors that should be addressed to improve comfort. The CRSs can be used to measure the level of comfort specific to the comfort dimension and device or to make comparisons between devices. The CRSs can also be used to assess the effectiveness of modifications to wearable computer design and thus determine whether or not the changes have improved comfort. The CRSs attempt to gain a comprehensive

assessment of the comfort status of the wearer of any item of technology by measuring comfort across six dimensions. These dimensions are:

- Emotion – concerns about appearance and relaxation.
- Attachment – comfort related to non-harmful physical sensation of the device on the body (e.g. the feel of the device either directly as pressing on the body or indirectly as it pulls on clothing or moves in relation to the body).
- Harm – physical sensation conveying pain.
- Perceived change – non-harmful indirect physical sensation making the wearer feel different overall with perceptions such as being awkward or uncoordinated, may result in making conscious compensations to movement or actions.
- Movement – conscious awareness of modification to posture or movement due to direct impedance or inhibition by the device.
- Anxiety – worries as to the safety of wearing the device and concerns as to whether the wearer is using it correctly or it is working appropriately.

The CRSs are 21-point scales anchored at each end with the labels low and high (*Figure 67*). A 21-point scale was used so that scoring on the scale would range from 0 at the far left to 20 at the far right [556]. According to Knight and Baber this range was considered large enough to elicit a range of responses that could be used for detailed analysis. In rating perceptions of comfort, the scorer simply marks on the scale his or her level of agreement, from low to high, with the statements made in the “description” column of Table 14. These statements were devised based on the interpretation of the aspect of comfort each group conveyed.

Figure 67 – 21-point scales for CRS evaluation

Using the CRSs initially gives a score for the level of discomfort for each of the six dimensions. These can be used to highlight which factors cause perceptions of discomfort and which do not. These may then be used to direct focus for modifications of design. Subsequently using the CRSs on the modified product will determine whether the modifications improved the level of comfort. One limitation of the CRSs is that they give a score for comfort on six dimensions but do not give a reason for the comfort score [556] (they were developed to be a quick and easy to use method) They generate scores that can highlight areas on which subsequent analysis can focus. This analysis may then use more focused and detailed methods. For this reason, and as it will be mentioned later, it was decided to complement the study with an informal interview with the users where they were asked to freely express their concerning and/or questions regarding the device.

Furthermore, the previous comment does not mean that the scales cannot be used to indicate possible reasons for the scores. By using the statements used to generate the CRS score, it is possible to figure out what may have caused a specific score [556]. As it is shown in the results analysis section the interpretation of the obtained data provided us with a useful feedback about the comfort of the system, its weak points and the areas of improvement.

For all technologies assessed in the studies, the attachment dimension scored highest. However, if the aim is for the technology to be likened to items of clothing, then it should feel like clothing. Just as wearers hardly notice the physical sensation of wearing everyday items such as clothing, jewellery, spectacles, and so forth, so it should be with wearable technology. The measurement of attachment comfort thus determines how noticeable the physical feel of the device on the body is [556].

8.5 Participants

Subjects fulfilling the following criteria were eligible for the study: diagnosis of PD, aged between 40 and 70 years old, ambulatory, capable of complying with study requirements, experiencing motor fluctuations, receiving stable dopaminergic treatment and with the support of a caregiver who can cooperate with the patient and the doctor. Participants suffering from dementia, hallucinations or any significant systemic disease were excluded from our study.

Figure 68 -Age distribution of participants in our study.

Before the enrolment of the patients in the study, they were provided with a detailed document describing the study in plain language as well as an oral explanation of the research expressed in terms that would have the best chance of being understood. The experimental nature of this study, its inherent risks and drawbacks, and its chance of improving the treatment of PD were discussed. Then the clinician obtained informed consent and gave a letter with a synopsis of the study protocol for the family doctor to inform him about main issues of the study. A total of 32 participants with the age and gender distribution shown in *Figure 68* were involved in our study.

8.6 Data collection

Based on the above methods of assessment, a wearability questionnaire was elaborated to be used during wearability evaluation and it is composed of six sections ().

Section	Name	Description
1	Personal information	Age, Sex
2	Posture Analysis	To be completed by an observer & includes all the material related to the REBA score chart
3	Energy Cost Analysis	To be completed by the patient according to his perception of extra energy used in order to perform daily activities
4	Pain/Discomfort Analysis	To be completed by the patient according to his perception of pain or discomfort to specific body areas (using the body maps)
5	Pain/Discomfort Analysis	To be completed by the patient in order to provide his/her thoughts and feelings with regard to several issues related to comfort (emotions, anxieties & harm caused)
6	Interview and complementary questions	Includes both some complementary questions that are related to allergic reactions, excess heat & sweat caused by the device Enables the user to provide his/her own suggestions on how the system being improved

Table 36 - The main sections of the wearability analysis

It should be noted that each section is preceded by short guidelines for the interviewer. The evaluation procedure starts with the Posture Analysis, based on REBA evaluation.

- All patients were asked to stand up and stay still for a couple of minutes, while an observer

completed the scoring card of REBA evaluation based on the posture of trunk, neck, legs and arms. Photographs were also taken to capture their current posture (prior to wearing the PERFORM device).

- Then the patients were asked to wear the prototype device and the same procedure was followed. This second posture evaluation had similar results for every single body part of each patient respectively; obviously resulting to similar REBA scores.
- As it was previously mentioned, the REBA evaluation in Parkinson patients is meaningful if the observer differentiates between the postural changes caused by the disease and any postural changes caused by the wearable itself. Thus, in order to identify these changes in PERFORM we use as score for our evaluation the difference between the REBA scores the patient gained i) without and ii) with the wearable device. This helps us to concentrate the posture analysis on the effects imposed by the wearable itself.

In the second step of the evaluation process the patients were asked to make a self-assessment of their own perceived energy cost due to the load of the wearable device, using the Borg CR-10 scale for energy cost. In the third step of the evaluation process the patients were asked to provide a rating from 0 to 10 representing their own feeling of pain/discomfort for each body part (Borg CR-10 scale for pain/discomfort). Finally, in the last section of the evaluation the patients were asked to read a number of statements and to provide a rating between Low (0) and High (20) corresponding to their level of agreement with each statement. The patients' responses are indicated in the following sections.

8.7 Results

For better comprehension of the results all the perceived exertion and emotion were translated into a homogenous five-level scale following the criteria of *Table 23*.

Figure 69 - Results for the perceived exertion evaluation

8.7.1 Physiological

As it was already mentioned a wearable device is an extra load that gets attached to the human body. Thus, it could have a direct effect both on the energy consumed by the body as the muscles need more energy in order to produce the force to counteract the weight of the device and the resulting movement and posture changes. The physiological effects study focused on the analysis of the self-assessment perceived exertion by the patients.

8.7.1.1 Perceived Exertion

As indicated in Figure 6, the majority of patients did not feel any exertion caused by the device. A moderate feeling of physical stress was reported by only one 71 year old female patient.

8.7.2 Biomechanical

Apart from the extra energy needed in order the muscles to perform the necessary movements, the device can cause musculoskeletal loading. In some cases, the loading might be localised and result to perceptions of muscle fatigue. In this case the results presented here are the posture and movement analysis based on the REBA score with and without wearing the device and the musculoskeletal loading based on the self-assessment of the patients with a Borg CR-10 scale and a body map.

8.7.2.1 Posture and Movement

As indicated in *Figure 70*, the interpretation of this outcome is that the wearable device did not have any impact on the patients' posture.

Figure 70 - Posture analysis results using REBA scale.

8.7.2.2 Musculoskeletal Loading

The responses reported in Table 5 reveal that the majority of the patients did not feel any discomfort/pain on almost any parts of their body. Only a few patients (eight out of 32 patients) felt extremely weak discomfort/pain at the overall assessment of their body and at some parts of their body such as: Mid Torso–Waist, Mid and Lower Back, Right and Left Wrist, Right and Left ankle. According to Level of effect described in *Table 23*, all the affected areas are coded as “Low”. The most remarkable effects in the Mid Torso–Waist, Mid Back and Lower Back are a direct consequence of the data logger impact (the heaviest and largest device of the BAN).

Body Segment	Average	Body Segment	Average	Body Segment	Average
1 Head	0	9 Lower Back	0.17	17 Left wrist	0.07
2 Face	0	10 Right Shoulder	0	18 Right Upper Leg	0
3 Neck	0	11 Left Shoulder	0	19 Left Upper Leg	0
4 Chest	0	12 Right Upper Arm	0	20 Right Lower Leg	0
5 Mid Torso–Waist	0.29	13 Left Upper Arm	0	21 Left Lower Leg	0
6 Lower Torso	0	14 Right Lower Arm	0	22 Right ankle	0.04
7 Upper Back	0	15 Left Lower Arm	0	23 Left ankle	0.06
8 Mid Back	0.03	16 Right Wrist	0.09	24 Overall (of the affected areas)	0.11

Table 37: Pain-discomfort results using Borg-CR10 scale.

8.7.3 Comfort

Apart from muscle fatigue, the musculoskeletal loading might could also lead to discomfort or affect the general

sense of well-being. It may also lead to discomfort due to stresses placed on specific physiological systems. All the results are expressed as perceptual values ranging from 0–1 and grouped according to *Table 23*.

8.7.3.1 Emotion

The graphs in *Figure 71* are indicative of the patients' responses on the emotion-related questions of the Comfort Rating Scale questionnaire. The social impact from wearing the sensors and being seen by other people is a sensible concern for the PD patients involved in the study. The majority of the patients did not feel very tense wearing the device. However, most of the participants agree that they would not mind wearing the device if it was invisible as depicted in the *Figure 71* (e1.3). As it was mentioned above, part of this concern could come from the public disclosure of suffering a disease only by wearing a device.

Figure 71 - Comfort results regarding the emotion factor. The questions asked to the users were: e1.1 "I feel worried and embarrassed."; e1.2 "I feel tense." and e1.3 "I would wear the device if it was invisible.".

8.7.3.2 Attachment

The graphs in *Figure 72* indicate that patients have some difficulties related to the attachment of the device to their body. Some of them tried to be careful with their movements out of fear of dropping or disconnecting any sensor, also the attachment method, and the requirement of tighten the straps to ensure a good technical performance of the system, has a moderate impact in the comfort of the patients (*Figure 72* a2.1). Also, the straps methods led to some difficult to wear the device without a care giver help. Finally, the answer to the (*Figure 72* a2.3) question shows that the system does not restrict the daily movement and activities of the patients.

Figure 72 - Comfort results regarding the attachment factors, the questions asked to the users were: a2.1 "I feel the device on the body."; a2.2 "I feel the device moving."; a2.3 "I was not able to move as usual." and a2.4 "I have difficult in putting on the device.".

8.7.3.3 Harm

Results regarding the Harm (indicative of the subjects' perception of any kind of harm e.g., headache, pain, itching, irritation, etc.) caused by the device are shown in the Figure 73. The feedback received is that none of the patients had such a concern, ranging in their answers from Not at all and Not very much.

Figure 73 - Comfort results regarding the harm factor, the question asked to the users was: h3.1 "The attached device causes me some kind of harm.".

8.7.3.4 Perceived Change

Figure 74 shows the results for the Perceived change questions. Again the social component appears again since some patient expressed their concerns about what other people could think about them (Figure 74 pc4.2).

Figure 74 - Comfort results regarding the perceived change factors, the questions asked to the users were: pc4.1 "I feel more bulky." and a4.2 "I feel change in the way people look at me."

8.7.3.5 Movement

As far as the impedance of movements is concerned, the received feedback is depicted in Figure 75. In general, all participants in the study agree that the system did not obstruct or block them in everyday activities neither limit their activities.

Figure 75 - Comfort results regarding the movement factor, the question asked to the users was: m5.1 "The device obstructs my movements."

8.7.3.6 Anxiety

A constant moderate concerning is shown in all the questions regarding the Anxiety space (Figure 76). The anxiety caused to patients by the device is generated by a lack of feedback to patient about the correct placement and functioning of the device.

Figure 76 - Comfort results regarding the perceived change factors, the questions asked to the users were: an6.1 "I do not feel secure with the device.", an6.2 "I feel that I do not have the device properly attached." and an6.3 "I feel that the device is not working properly."

8.7.4 Interview and complementary questions

The last section of the wearability study was an informal interview with the patients where they were allowed to freely express their concerns and feelings about the device. The meeting with the users raised some appearance and emotional issues among a substantial group of patients (six out of 32). This subset of patients had some concerns about others' opinions when wearing the device. They would feel much more comfortable wearing an invisible device or if the wearing time were limited to the home environment. Apart from appearance aspects, they experienced no particular problem with the device.

As far as the rest of the patients are concerned, most of them had absolutely no substantial problem with the device. In fact they have forgotten of wearing it after a while. There were also patients who wouldn't mind wearing it both in and outside their home. We hereby present some statements as given by patients:

- "The device created a little bit of stress and nervousness"
- "I felt weird due to the presence of other persons in the same space"
- "I felt embarrassment because I thought that everybody was looking at me"
- "I encountered some problems to wear the device at home"
- "My only concern is that I may encounter some difficulties in attaching properly the device if I am in OFF state; the same problem I have also for dressing up."
- "I experienced no problem at all while wearing the device."
- "After some rehearsals I will be able to attach the device myself without help."

As far as the ability to wear and attach the device properly on their own, most patients replied that they would need some help from their caregivers. On the other hand, the device would not prevent them from doing their daily tasks.

Also, a common concern raised during the interview was if the devices were waterproof since some daily and very common activities could wet the devices, especially the ones on the wrists, for example when washing the hands and washing dishes. Afterwards all patients responded to a number of questions related to allergic reactions, excess heat and sweat caused by the device. Table 38 summarizes the number of positive and negative responses to the allergic reaction received by the total number of patients. As it is shown no problem was encountered by any of the participants.

Problem Encountered	(No)	(Yes)	If Yes, Any Comments?
User's allergy to the materials of the device	32	0	-
User's allergy to the materials used for the attachment	32	0	-
Materials caused sweating	32	0	-
Materials did not let the body "breath"	32	0	-
Materials absorbed water and took a long time to dry	32	0	-
The attachment of the device was too tight	24	12	-Straps were too short
The device generated additional heat leading to excess sweating	32	0	-

Table 38 - Complementary questions asked to the patient during the informal interview.

8.7.5 Overall evaluation

The overall level of effect of the device on patients is summarized in *Table 39*. To calculate the average CRS score of the e1.3 value in the emotion section the answers of the patients were transformed in to mirror image over the CRS scale, e.g., an answer of 19 was transformed to 1 and vice-versa. This was needed to make the e1.3 homogeneous with all the other comfort values, where the lowest the value the better in terms of wearability. After this change, it was possible to calculate the average value of the emotion section.

	Metric	Units	Average	Level of Effect
Energy cost	Perceived Exertion	Borg CR-10 score	0.71	Low
Biomechanical	Posture	REBA score	0	Low
	Localized pain/discomfort	Borg CR-10 score	0.11	Low
Comfort	Emotion	Average CRS score	1.4	Low
	Attachment	Average CRS score	2.5	Low
	Harm	Average CRS score	0.15	Low
	Perceived change	Average CRS score	0.67	Low
	Movement	Average CRS score	0.59	Low
	Anxiety	Average CRS score	1.63	Low

Table 39 - Overall wearability results.

8.8 Discussion

In this work we have performed a wearability analysis of a particular system, which is used for the monitoring of patients with Parkinson's disease. The system is based on a set of sensors and analysis of the acquired signals using intelligent algorithms. The analysis performed can be extended to the wearability analysis of similar systems for movement disorders monitoring or other diseases which require the use of sensors for the continuous monitoring of physiological parameters. The proposed methodology is not applicable when implanted or invasive sensors are used, since other parameters must be taken into account. The approach can be based on a similar methodology, but it differs since other sensors used present different features that must be evaluated, such as weight, battery operation, placement, *etc.*

The evaluation of the system will be benefited from extending the analysis to a larger number of patients. To our knowledge the number of patients used in our study is large enough compared to other wearability studies [562]–[565] and evaluation of monitoring systems for the Parkinson's disease and other movement disorder diseases.

The results of the wearability assessment are summarized in *Table 39* and indicate that the general level of effect of the system is "Low" since all scores are "Low" for each category of assessment. Nevertheless, analysing the charts results in detail, it is possible to extract some weak points and areas of improvement for the system under assessment.

Starting this analysis with the energy cost and the biomechanical spaces the low scores for the perceived exertion and the posture values suggest that even the prototype is larger and heavier than a commercial device it does suppose a substantial physical load for the users. The results of the localized pain/discomfort confirm this suggestion. The moderate scores in the mid torso-waist, mid back and lower back lead to identify the weight of the data logger device as the part of the BAN more penalized by the users in terms of physical impact and energy cost. A direct action to palliate this is to reduce the weight and size of the data logger device. Another option could be to modify the attachment method. Using a strap as attachment of the data logger device to the subject makes that all the force generated by the logger weight is applied in the subject's waist. Transforming the data logger into portable device to wear in the pocket could improve this and, at the same time, and thanks to the advances in the smartphone devices, currently the data logger device could be integrated into a commercial smartphone.

Regarding the comfort analysis, both the emotion and anxiety results suggest a significant concern of the patients about their privacy, most of the patients do not like what other people could think about them when they wear the device, especially in public spaces. Feelings of anxiety indicate levels of discomfort arising from concerns about safety and reliability and from feelings of insecurity [556]. One method to reduce this apprehension could be to make the device less noticeable by reducing the size of the device, hiding it within clothing or camouflaging it as an everyday item of clothing. Ankle sensors could be hidden under the clothes and the wrist sensors could be modified to imitate bracelets. Regarding the logger device, again, a good option could be to substitute it by a portable device that could be carried in a pocket. Ultimately, levels of both emotion and anxiety may be reduced with time and experience as the wearer becomes accustomed to the device [556].

About the attachment which according to the users is the weakest point of the system, it has been confirmed with the informal interviews that the use of the straps lead to some unpleasant feelings in terms of comfort but also, it makes very difficult to users the self-wearing of the device, especially the wrist sensors. The way that patients wear and attach the devices or sensors properly on their own is difficult and uncomfortable and they might need some help from their caregivers.

Likewise, the moderate impact of the perceived change results suggests that the users expect to receive more feedback from the system about the correct functioning or at least a procedure to know if the system is working properly. In general a better understanding of the device and how it works could address the anxiety of the patients, therefore providing better training material in a friendly way could help to reduce this concern, but the system should also be improved to provide an easy to understand feedback to the patients at any time, and in the case some error is risen a clear message must be provided with the proper instructions to overcome or to report such a problem.

Finally, it is also important to ensure waterproofing of the sensors, or at least for the wrist sensors. Although, this should not be a restrictive requirement, since the goal is not to dip the sensors, for example to take a bath, but to allow the user to carry out daily activities such as washing the hands and washing the dishes, activities where the sensors could eventually get wet.

To summarize, the data logger device should be transformed into a portable device or even integrated into a currently available smartphone platform. The wrists sensor should be evolved to make it more imperceptible either by reducing the size or by imitating some item of clothing and waterproof. Also, the attachment method should be enhanced to facilitate the self-wearing of the device. Finally, the ankle sensors have not received any special critique but the attachment method could be also improved. And, in any case, it seems important to design sensor devices or sensors that could not be easily spotted by other persons.

Chapter 9 Health Technology Assessment

Healthcare systems throughout the world are struggling with the challenge of how to manage healthcare delivery in conditions of resource constraint [566], this challenge requires to reduce costs of healthcare delivery without dropping the quality on the outcomes. Assessing health technologies in an objective and methodological way becomes fundamental to provide a clear picture to healthcare managers and policy makers regarding the adoption of a novel technology. Health Technology Assessment (HTA) is not a simple task, it is a multidisciplinary and multidimensional process which, by definition, requires a complex analysis involving the consideration and the convergence of different stakeholders into a common decision. Actually, as it was pointed out in the section 2.2 healthcare systems usually fail to measure their economic impact. Fragmentation plays an important role on this but also the fact that most systems measure their impact by the quantity of services offered and they do not pay attention to measure the outcomes of their services. HTA is even harder when the assessment of the new technology should be done at an early stage of development (early HTA). At such point, the maturity of the technology does not always allow to conduct an extended pilot and consequently the available data to evaluate the cost effectiveness using classic methods is scarce and very limited. At the same time, this lack of economic information may diminish the interest of policy-makers, decision-makers, healthcare managers and in general from the market on such technology. Accordingly, it may limit future development iterations and the actual deployment in the clinical practice. Part of this chapter has been published on Cancela et al. 2015 *“Using the Analytic Hierarchy Process (AHP) to understand the most important factors to design and evaluate a telehealth system for Parkinson's disease”* on the Journal *BMC medical informatics and decision making* [567] as well as in the proceedings of a few international conferences [18], [19].

Objectives – This chapter is aimed at identifying tools are available and feasible to carry out an early HTA on telehealth systems for Parkinson's disease (PD) management and apply such methodologies to assess the PERFORM system as a case of study. The whole chapter is divide in two parts addressing two complementary works which try to provide two complementary point of view. The first part is aimed at identifying the elements that a telehealth system for PD management should satisfy to be effective and aligned with the users' needs and also to understand if clinicians and technicians share a common opinion when evaluating these systems. Instead, the second part provides a methodology to estimate the potential economic impact, in terms of cost-effectiveness, of a real implementation of telehealth systems for PD management.

Methods and material – After the exploration of the available tools for early HTA two methodologies were selected, the first one called Analytic Hierarchy Process (AHP) allows the elicitation of the user needs and the definition of a framework for the evaluation of telehealth solutions for Parkinson's disease patients. 16 experts in the domain both with clinical and technical backgrounds were involved in the study. The second part of the chapter explores the use of Markov models with a minimal number of states were used to perform “what-if” and finally, to simulate and estimate potential scenarios for the economic impact, in terms of cost-effectiveness, of a telehealth platform. Then, this approach was used to estimate the potential cost-effectiveness of the PERFORM project. Finally, a sensitivity analysis will be carried out.

Results - According to the results of the responders, the three most important user needs are *Increase the wearability acceptance* (0.102), *Increase the self-management support* (0.093) and *On/Off fluctuations detection* (0.085), based on the values from the Global Weights (GW). In a second level of importance it was found *Increase patient & carers knowledge* (0.080), *Assist care givers* (0.070), *User-friendly interfaces* (0.068), *Motor symptoms assessment* (0.064) and *Increase patient Quality of Life* (0.063). The agreements between the responders of the technical and clinical groups showed a significant correlation between both, $\rho = 0.590$ ($p=0.012$).

Regarding the use of Markov modelling, six general “what-if” scenarios were simulated providing a general overview of how inputs variations could impact the ICER values. These scenarios provide a quantitative reference framework for any health technology related to Parkinson’s disease and could be useful to understand and to orientate the research, particularly in early stage of development, towards an efficient cost-effectiveness path. Then, the PERFORM system was used as case of study with the market analysis. It was confronted with the base case and the cumulative costs and QALYs were calculated for each one and the ICER was calculated at year 5. The ICER values estimated by the model are 6,397.36 for the societal perspective and 8,977.20 for the third party perspective. These values suggest that PERFORM will not be a cost-saving technology (positive ICER) but these values are below most of the ICER thresholds commonly accepted worldwide (10,000€/QALY). Finally, by placing the PERFORM innovation from the societal and third party perspective in the Δ QALY- Δ C plane it was possible to see the margin in incremental cost to the different ICER thresholds. Taking the 30,000€/QALY as reference, the PERFORM system has a margin of 20,855.28€ incremental costs in the societal perspective and 18,575.73€ incremental cost in the third party perspective. A sensitivity analysis was also performed to explore the robustness of the results and the limitations of this approach were properly identified.

9.1 Health Technology Assessment

There is a general perception that most telehealth applications are not as widely used as might be expected. Telehealth, in its more general sense, enables the delivery of healthcare services directly to the home environment of the patients, extending and enhancing the level of care [291]. Actually, in the last decades several works have showed that using Information Technologies (IT) on health domain reached positive conclusions [134]. For chronic and long-term disease management telehealth offers a broad range of potential tools that can enhance the health outcomes and effectiveness of the care delivery. Unfortunately, much of the evidence, is fragmented and based on limited proof-of-concept applications, lacking information on large-scale performance and economic impact on real scenarios [121], [568]. Assuming that all medical products need to be adopted by the heavily regulated healthcare market at one point in time [569], the lack of large-scale validation and performance information on that kind of scenarios could be a barrier for its adoption on the current clinical practice [121]. Likewise, many policy-makers and healthcare managers are not aware of its potential or they were not provided with enough information – further than a proof-of-concept study – to really understand the potential benefits of implementing a novel health technology within their institutions. Deployment of safer and more effective health technologies relies on policies for selection and management based on scientific evidence and best practice for organization of their management and use [104], [121]. Healthcare policy and regulation should prevent the uptake of unsafe or lack-of-evidence technologies but the same time it should allow the systems to progress in order to maximize the positive impact of health-care interventions on population health, while maximizing the value from the cost of providing the interventions [566]. That means that innovation in healthcare is - as always - aimed at enhancing life expectancy, quality of life, and diagnostic and treatment options. But also, in the last decades it has been required to look for efficiency and cost effectiveness without decrease the quality of the health outcomes [134]. In the particular case of chronic diseases, advancements in their treatment have resulted in reduced length of hospital stay, and in some cases, the avoidance of hospital visits. The World Health Organization (WHO) published on 2011 a report entitled “Health technology assessment of medical devices” where they stated:

“HTA is the systematic evaluation of properties, effects, and/or impacts of health technology. Its main purpose is to inform technology-related policy-making in health care, and thus improve the uptake of cost-effective new technologies and prevent the uptake of technologies that are of doubtful value for the health system. It is one of three complementary functions to ensure the appropriate introduction and use of health technology. The other two components are regulation, which is concerned with safety and efficacy, and assessment of all significant intended as well as unintended consequences of technology use; and management, which is concerned with the procurement and maintenance of the technology during its life cycle. The performance of health systems is strengthened when the linkages and exchange among these elements are clearly differentiated but mutually supportive [566]”.

Considering health technology as “any intervention that may be used to promote health, to prevent, diagnose or

treat disease or for rehabilitation or long-term care” it covers elements ranging from biomedical devices to procedures, healthcare processes and procedures. HTAs can take different forms depending on the issues involved, the time frame of decision-making, and the availability of resources and it may be carried out from different perspectives from the high level (government or health system perspective) to the low level (the hospital or department views). Economic analysis is often, but not always, part of an HTA. The economic dimensions may include cost-benefit analysis, cost-utility analysis, cost-effectiveness analysis, cost-minimization analysis, and also budget impact analysis and other forms of economic assessments.

HTA started in the early 1970s as response to the innovations in the field of the biomedical imaging and it is still very much used to inform the decision-making process concerning the introduction of new technologies to a health system along their natural life-cycle, as show in the *Figure 77* [566]. The processes of HTA and innovation are intertwined. However, the innovation process goes beyond the development of a new device for regulatory approval. Innovation comprises a continuous iteration process between technology, market and implementation [530]. In this sense, a novel technology requires to be adopted into the market through a proper implementation to be considered as an innovation. When any of these three elements fail there is no innovation. Actually, it should exist a continuous iteration between then to redefine the final product. Talking about telehealth, to transfer from a research scenario to the market it is required to cover the user needs that stakeholders and market demands. But, at the same time, it is required that technologist and researchers do not only focus on proving the clinical validation of the system but also, its technical and economic feasibility for implementation. Finally, the market should feedback the technologists and researchers closing the loop of innovation. HTA is aimed at improving the uptake of cost-effective new technologies, preventing the uptake of technologies that are of doubtful value for the health system, and slowing the uptake of technologies that seem promising but have persistent uncertainties [566].

Figure 77 - Health Technology assessment and diffusion of health technologies (Figure source: WHO 2011 [566])

9.1.1 Early Health Technology Assessment

Going back to *Figure 77*, usually the first HTA studies are carried out at the end of the *Experimental Technology* stage, therefore during the *Research and development* and the *Experimental technology* phases there is no information available about the HTA that can feedback the researchers and medical technology developers. Moreover, most of the HTA methods are primarily envisioned to support governments and regulators in making decisions and they do not inform biomedical product developers on the probability of return on investment or market needs [569]. At the same time, policy-makers and potential beneficiaries such as healthcare managers do not have enough information to evaluate the potential of these novel technologies, not only regarding its effectiveness but also its cost, limiting the uptake of such systems in the clinical practice. Nevertheless, the increasing pressure on healthcare budgets has tried to shift the assessment to early stages of development in order to discard unviable technologies as soon as possible focusing investments on promising technologies. It could be

said that there is a gap at the end of the *Research and development* phase that some technologies are not able to overcome due to this lack of HTA information. But measuring health outcomes, costs, and organizational and societal impact requires long-term and rigorous clinical trials. The data requirements and logistics for such long-term economic assessment are likely to be demanding [568].

Figure 78 – The pyramid of clinical evidence (Figure source: HLWIKI International [570])

The pyramid of evidence, represented in the Figure 78 is the gold standard for the assessment of clinical evidence. The bottom of the pyramid is integrated by background information and the opinion coming from experts. Over this base there are different unfiltered sources are such as studies, reports or trials covering a particular topic. Then, these unfiltered sources are synthesized as filtered information (or secondary data), via systematic reviews of literature. At the top of the evidence pyramid are the systematic reviews of Randomized Controlled Trials (RCTs) with meta-analyses. These studies, after individuating relevant literature using well defined research strategies and scientific databases, pool together RCT outcomes, overcoming contextual limitations, which otherwise reduce their evidence (e.g. limited number of patients, single centre patient enrolment, limited time of enrolment) [571]. Due to the rapid velocity of the technical development, especially on the case of mobile technologies or wearable devices, most of the research are works placed at the bottom of the pyramid, or at least very close to it. Also, when developing a new technology, not always it is available in its early stages to be applicable on a RTC study. Thus, it can be difficult to apply this methodology on the telehealth context, particularly in the early stages. Actually, most of the HTA methodologies were designed having in mind drug assessment as the target. Nevertheless, there are some remarkable differences between drugs and medical devices, which impact severely on HTA (Table 40) as it was pointed out by Craven in 2006 [572]. Moreover, classic HTA methods fail to properly feedback the developers as it was already discussed in this section [571]. Established in 2003, the Multidisciplinary Assessment of Technology Centre for Healthcare (MATCH²¹³) is a long-term research collaboration between four UK universities (Birmingham, Brunel, and Nottingham & Ulster) and a cohort of industrial partners, also supported by stakeholders from the National Health System (NHS) in the UK and other public sector organizations. The MATCH experience shows that it is possible to develop specific methods to assess biomedical devices at an early stage. In particular, the Analytical Hierarchy Process (AHP) proved to be an effective method to elicit user needs (9.2.2 AHP) in complex environments and Markov models with a minimal number of states can be used to perform “what-if” analyses at an early stage (9.2.3 Markov Model) [571].

²¹³ www.match.ac.uk (Last date accessed: January 2015)

	Devices	Drugs
Principal action	Other than principally drugs	Pharmaco./Immunologic/Metabolic
	Mechanical/Electromagnetic/Materials	Chemical based
Product life cycle	Short life cycle	Long life cycle
	Constantly evolving components/parts	Unchanging compound
Clinical evaluation	Difficult to blind (no placebo)	Easy to blind
	Multiple end users	Usually one end users
	Long learning curve	Short learning curve
	Strongly dependent by settings/users	Less dependent by settings/users
	Complex to standardize for RCT	Easy to standardize for RCT
Use issues	User-dependent efficacy	Efficacy is less user-dependent
	Often require intensive training	Usually do not require training
	Complication decrease with use	Complication increase with use
Diversity	Mainly small companies/few large co.	Mainly large multinationals
	Diagnostic or therapeutic	Therapeutic
Costs	Varying overheads/slow return	High overheads with quicker return
	Higher distribution costs	Lower distribution costs
	Higher maintenance/installation costs	No maintenance/installation

Table 40 - Main differences among drugs and devices impacting on HTA (Table source: Craven 2006 [572])

As it was discussed the innovation process in the healthcare field requires improving the health outcomes, although it should be done at a rational cost, or it should reduce the costs keeping the same health outcomes. An analysis of the economic impact of home telehealth must focus on the incremental costs and health benefits associated with the application of the program to a population of patients, rather than to an individual patient [291]. This consideration is especially relevant in a telehealth scenario, since even it could be proved that a telehealth mechanism can benefit patients and provide a better diagnosis, assessment or follow-up of the disease it also involves a significant initial cost for the set-up as well as additional regular cost associated with the maintenance of telehealth system. It could even require a significant fixed costs in new personnel [573]. Another limitation in many works is the few number of published studies concerning the longer-term economic impact of telemedicine [568]. Most studies agree that telemedicine could lead to a reduced use of health services such as physician office visits, emergency department visits, number of hospitalizations, hospital readmissions, home visits, length of hospital stay, use of ambulance services, number of referrals, duration of consultations, number of laboratory tests, and avoided transfers/evacuations [382]–[385], [573]. Moreover, in many of these studies a reduced use of healthcare resources is interpreted as an evidence of improved outcomes. Nevertheless, analysing the impact of a health technology requires an assessment of incremental costs and incremental outcomes of each healthcare program evaluated. Thus, the majority of published studies are not economic evaluations of home telehealth and cannot assist in determining whether a treatment is justifiable based on the impact on costs and treatment outcomes [291]. Usually a telemedicine program evolves through a known number of stages [568]: a) Pilot or introductory phase, focus on demonstrate the feasibility of the system (limited numbers of patients); b) a routine telemedicine service and c) deploy of the telemedicine application across an entire health system or expanded network. Each of these stages in the life of a telemedicine program requires a specific assessment, in order to analyse its feasibility, but the kind of assessment changes as the application matures, including changes in the focus of evaluation and the sources of information [568].

9.1.2 Health economics

Health economics is a branch of economics concerned with issues related to efficiency, effectiveness, value and behaviour in the production and consumption of health and health care. Health economics theories and methodologies are widely used in the healthcare for the evaluation of new interventions (i.e. new drugs, devices or procedures) in order to evaluate them in terms of costs and benefits and provide policy makers and program

administrators with enough information to make decisions, nevertheless, economic evaluations of telemedicine remain rare [568], [573]. Health gains must be valued monetarily, ideally through the assessment of the willingness to pay for health gains. *Figure 79* shows a schematic representation with the components of an economic evaluation in healthcare proposed by Drummond et al. [574]. Basically, an economic evaluation is a constrained optimization where it should be decided what allocation of resources will achieve the greatest gain in health that is attainable without exceeding the budget or from the other point of view, what allocation of resources will minimize the expenditures, subject to the requirement of achieving at least some target level of health gain.

Figure 79 – Components of economic evaluation in healthcare (Source: Drummond et al. [574])

The requirements change as the application matures, including changes in the focus of evaluation and the sources of information. There are four principal analytic techniques for economic evaluation [575]:

- Cost-Minimization Analysis (CMA), this methodology is simply a comparison of costs of comparator therapies. CMA is only appropriate if the effects associated with all therapies are identical [576].
- Cost-Effectiveness Analysis (CEA). In most of the cases the clinical outcomes associated with treatments will differ and CMA would not be feasible. In a CEA, the cost effectiveness of a therapy is assessed in terms of the incremental cost per outcome gained [577].
- Cost-Utility Analysis (CUA) is a form of CEA which incorporates all effects of treatment (i.e. morbidity and mortality). Outcome is expressed as QALY, a standard unit for this kind of measures that will be detailed later. By adopting a common outcome measure, CUA allows the assessment of the cost effectiveness of therapy relative to treatments for other diseases [578], [579].
- Cost-Benefit Analysis (CBA). It is the most comprehensive type of economic evaluation and allows the study of interventions with multiple outcomes [573]. However, there are measurements difficulties within CBA which has limited its adoption. Few telemedicine evaluations have conducted BCAs because this type of evaluation is data intensive and technically sophisticated [573]. A true CBA requires that all outcomes are expressed in monetary values [580].

9.1.3 Quality-Adjusted Life Year (QALY) vs. Daily Adjusted Live Years (DALY)

Quality-Adjusted Life Year (QALY) is a measure including both the quality and the quantity of life lived and it is a metric typically used for assessing the economic impact medical intervention or health technologies [581]. The QALY is based on the number of years of life that would be added by an intervention. The intuitive idea is that two years lived at 50% are as good as 1 year at 100%. Thus, each year living in perfect health is assigned with the maximum value, i.e. 1.0, while the minimum value, 0.0, is assigned for death. For the years not lived in full health a value between 0 and 1 is assigned. This utility score is obtained from a structured set of questions to patients

using a Visual Analog Scale (VAS) or structured questionnaires like the EQ-5D where patients self-assess five different perceptions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) using three levels (no problem, some problems, severe problems). By combining this quality values with the duration of the benefit in years or the expected remaining years of life it is possible to convert health outcomes into a quality-of-life score and ultimately into monetary values.

DALY instead can be thought of as one year of healthy life lost, and the overall disease burden can be thought of as a measure of the gap between current health status and the ideal health status, where the individual lives to old age free from disease and disability (see 3.4 *Burden of Parkinson's disease* for more details).

9.1.4 Discounting and age-weighting modulation

When working with economic evaluation prolonged on it is necessary to adjust cost and utilities using the discounting methods. In other words, cost and utilities values change with time progression – or in Markov context, they change on each cycle. The concept of discounting involves a preference by the benefits today rather than in the future. Additionally a euro today would be a higher value than one in the future. Usually it is preferred to defer costs to the future than incur them now and, on the other hand, benefits are preferred now rather than in the future [582]. A similar approach is considered when the age variable is included in the economic analysis where an age-weighting modulation factor (K) is usually applied. The age-weighting modulation factor quantifies the perception that a year of healthy life has greater social value during early adulthood ($K = 1$) than during earlier or later life ($K = 0$ when healthy life values equally) [19], [582].

9.1.5 Cost of Parkinson disease

Whilst burden of disease studies are interesting and relevant to understand the impact of a given disease from a macro level (see section 3.4 *Burden of Parkinson's disease*), they do not detail the costs of the disease and where those costs occur. Thus, burden analysis are useful for some specific task and research at a macro or epidemiological but, to explore the cost-effectiveness of a new health technology a cost analysis is needed in order to compare how health care resources are used, how they can be optimized and to support the decision making process for healthcare managers and policy makers [583]. Both of them can work together as complementary views of the same problem. Basically, a cost analysis requires to provide in giving a monetary value to each resource used in the process of care. Nevertheless, due to the fragmentation and specialization of the health care system this is not a simple tasks. Moreover, many resources vary according to pathology evolution, the probability to have exacerbations and the levels of exacerbation [571]. As PD progresses, patients are more likely to develop comorbid conditions and their quality of life and family relationships suffer. Economic costs escalate as the disease becomes more severe and patients use more healthcare resources. Ultimately, many patients require expensive institutional care increase sing with age and with Hoehn and Yahr stage [159].

9.1.5.1 Measuring costs in health care

A cost-of-illness analysis can be conducted from several different perspectives e.g. an individual hospital, insurance company, societal, healthcare system, third-party or government [19], [291], [583]. For example, the societal perspective implies that all costs, whether incurred by individuals, employers, or government, should be taken into account. Another important consideration is that boundaries around healthcare are different between countries so that what is called healthcare in one system is called social care in another system and consistency of estimation would require a comprehensive measure [583]. The first step to measure the cost of a given disease is to identify and understand the different costs around such disease. Typically, in healthcare the cost can be classify in the following categories:

- **Indirect costs** are defined as the value of the output that is lost because people with a certain illness, disease or disorder are impaired and too ill to work, either short-term or long-term [584]. Some examples are costs of loss of production due to short-term absence from work, early retirement or reduced productivity at work due to illness [583]. The analysis of indirect cost is highly variable

depending on the considerations made [159].

- **Intangible costs**, which include pain, psychosocial suffering, and changes in social functioning and activities of daily living. Intangible costs are in general not included in many cost of illness studies due to difficulties in quantifying these costs. However, the intangible costs are probably far from insignificant for many diseases.
- **Direct healthcare costs**, are costs for goods and services used in the prevention, diagnosis, treatment and rehabilitation of the illness, disease or disorder in question, e.g. costs for medical visits, hospitalization and pharmaceuticals. Telehealth specific direct costs [291]: Cost of program administration, program delivery, and program capital costs (i.e., costs of technology required for the delivery of home telehealth). The costs of technology used over a period of time must be amortized over the technology's useful life. Also, the volume of nursing and other homecare visits should be considered. Moreover, the potential financial impact on patients and their families and caregivers must be also measured (travel, medication costs, and family caregiver time).
 - **Direct non-medical costs**, include all other resource use related to a disease, for example transportation, adaptations, social services, etc. [583].
 - Direct medical costs,
 - Fixed costs
 - Capital costs, for setting up the service.
 - Labour costs, e.g. salary of pharmacists.
 - Overhead costs, for running the services e.g. lighting, heating, cleaning
 - Semi-fixed costs, e.g. salaries
 - Variable/Material costs, e.g. drugs, consumables, fuel, food.
 - Steeped, they have the same behaviour as the fixed costs until the level of activity reaches a threshold, when they step to a higher level

The complexity of the different costs around a specific disease, due to their different nature and source, leads to misclassification problems and consequently makes almost impossible to compare different cost analysis carried out in different countries or even in different institutions within the same country [583]. For example, it is common that the accountability of a specific disease is spread across different departments or administrations, depending also from different accountability departments which do not exchange data or knowledge to evaluate the cost of a specific disease or disorder. Moreover, there is no consensus about which costs should be included in a costs analysis and how, thus it is not always possible to combine the results coming from different cost studies. Additionally, brain disorders have impacts across a wide range of personal dimensions (e.g. one's health, quality of life, ability to work, social relations, income) and hence it would be falsely constraining to only look at the healthcare consequences [583].

9.1.5.2 Cost of Parkinson's disease

PD affects significantly both motor and non-motor complications leading to a significant deterioration in the physical, cognitive, social and emotional domains as the disease progresses. Despite the progressive decline and comorbidity associated with PD, the lifespan or mortality rates do not differ radically from subjects without PD thanks to modern drug therapy (see 3.3 *Incidence and prevalence* for further details). Thus, PD patients may live up for 20 or more years with PD, generating serious implications for the cost of treating PD. The relatively high prevalence of the disease, its degenerative component, and the associated social and family implications have led most researchers to agree that the economic impact of PD is significant health care systems, patients and their families and society in general [254]. Andlin-Sobocki et al. [583] conducted an interesting work analysing the cost of brain disorders in Europe. Direct healthcare cost due to brain disorders in Europe, according to their estimations

the total cost of this kind of diseases amounted to €135 billion, corresponding to 35% of the total. The cost for hospital care is the dominating healthcare cost, reaching €78 billion in 2004 (20% of the total cost and 57% of the healthcare cost). The cost of outpatient care amounted to a total of €45 billion and drug cost totalled €13 billion (3% of the total cost). Direct non-medical costs (i.e. community care, transportation, adaptations and informal care) totalled €72 billion in Europe. The largest non-medical resource component was cost of social services, €52 billion (13% of total cost) also closely related with the informal care. It refers to the unpaid care provided by family members, friends or voluntary workers to disabled and impaired individuals in the community [238]. The indirect cost was estimated to €179 billion, 46% of the total cost. The majority of the indirect cost of brain disorders was caused by sick leave, €124 billion (33% of the total cost). The cost of lost workdays due to early retirement and premature death each amounted to €27 billion [583]. In the neurological diseases, the direct cost is the dominating resource, comprising 63% of the total cost. In the neurosurgical diseases (brain tumour and trauma) indirect costs are predominant, making up 42% of the total cost. Informal care is the unpaid care provided by family members, friends or voluntary workers to disabled and impaired individuals in the community. This kind of care is especially relevant for elderly patients as well as for long-term or chronic conditions. Besides, there is an important cultural component since it is especially relevant on those European countries where there is a tradition of caring for the elderly at home. Finally, the chronic nature of most brain disorders means that informal care is not punctual but instead it is needed over a long period of time. Still, find accurate cost estimates for informal care is not easy.

The published literature about PD costs also reflects that following the pattern presented by Andlin-Sobocki et al. as this is a costly disease with remarkable pressures on either the patient and the society and in general terms, the progression of the disease leads to higher costs [238]. As it was already stated, measuring accurately the cost of a specific disease is not a simple task, neither the aggregation of different already available cost studies nor the comparison of their results. They depend on the data sources available (e.g. based on insurance claims or surveys), the type of data considered (direct, indirect, medical, no-medical, etc.), the type of patients included (early, mild or advanced PD) and the number of patients considered in the study. As an example, Findley et al. 2007 analysed the annual direct cost of PD from 10 previous cost analyses studies. Annual costs per patient ranged from \$1750 in Canada to \$17,560 in Germany. Even considering studies only from the US the annual cost per patient ranged from \$2706 to \$12,397 due to the differences in the methodology [159]. Furthermore, it is not easy to disassociate the component due to PD to the other conditions of the individual or the natural aging process. One of the most relevant studies, Huse et al. 2005 used a retrospective analysis of health insurance claims data to compare the cost between a cohort of patients with PD (N = 20016) and cohort without PD (N = 20016) who were matched for age, sex, insurance type and period of eligibility for benefits [160]. The total annual direct cost per patient was \$11,247 for those without PD and \$23,101 for those with PD. This represents an incremental cost of \$10,349 annually (adjusted for demographics, comorbidity and type of insurance coverage) for each patient with PD. The largest component of the cost was inpatient care and nursing home costs (almost half of the direct costs). Moreover, the presence of comorbidities had a relevant impact on the cost of PD. Neuropsychiatric disorders (dementia, delirium and depression) were three times more frequent, falls and injuries were 57% more frequent, and autonomic nervous dysfunction (constipation, urinary problems and dysphagia) were doubled in the PD group compared with the control cohort. Prescription drugs were the smallest contributor to the cost of PD (incremental cost of \$1646 per patient per year). Annual indirect costs were estimated at \$25,326 per patient. Productivity losses accounted for almost half of this cost and uncompensated care was approximately 19% of the total. Thus, indirect costs accounted for more than two-thirds of the entire burden [159], [160]. Another study carried out in the UK by Findely et al. 2003 completed a cross-sectional, survey-based approach to evaluate the total economic impact of PD on both healthcare providers and patients including the NHS costs, social service and private costs [159], [585]. Also, indirect costs (loss of earnings, loss of leisure time and carer replacement costs) were also considered. The authors broke down the cost results by age, *Figure 80*, and according to Hoehn and Yahr stage, *Figure 81*. According to this study total direct cost of care accounted for £5993 per patient per year, composed by NHS costs (38%), social services costs (35%) and private expenditure (27%). The NHS costs component is especially relevant in younger age groups (65% of the total) as shown in *Figure 80*. Accordingly, social services costs and private expenditures components increased with age. Patients at Hoehn and Yahr stage V had costs that were six times higher than patients at stage 0 or I (£2971 vs. £18,358 per patient per year). Institutional care (cost of participants receiving institutional care were more than 4.5 times higher than for patients who remained at home) was one of

the most significant components and interestingly, drug costs did not change with increasing disease severity.

Figure 80 - Direct cost of PD in the UK according to age (N=423) (Figure source: Findely et al. 2003 [585]).

Different scenarios of indirect costs were explored within this work, if lost productivity for the patient was considered, the indirect costs are relatively low at £1668 per patient per year (most of the patient are close to retirement). Using the lost leisure time approach, costs increased to £5829. And, if the cost of replacing the care given by a family member with a professional carer was considered, the indirect cost increased to over £27,000 per patient per year. According to the same study, the overall cost of PD in the UK ranges from £449 million to £3.3 billion annually, depending on the prevalence used or if a different model is used to estimate the indirect costs, Figure 82 [159], [585]. While the total annual burden of PD in the US in 2002 was estimated in \$23 billion [159], [160].

Figure 81 - Direct cost of PD in the UK according to Hoehn and Yahr scale (N=423) (Figure source: Findely et al. 2003 [585]).

Figure 82 - Total cost of PD in the UK based on three indirect cost models (Figure source: Findely et al. 2003 [585]).

For the estimation of economic benefits, it is necessary to analyse the most commonly measured outcomes in the evaluation of telemedicine programs followed by an analysis on how to obtain or derive monetary conversion factors to convert those same outcomes to dollar values. Telemedicine programs, diverse as they are, have distinct

applications and objectives depending on the specialty, target population, location, etc. [573]. Dávalos et al. [573] propose a wide range of outcomes that can be monitored to analyse the outcome of the telemedicine system such as: increased access to healthcare (reduced length of consultations), increased health knowledge/ability for self-care (increased medication adherence), faster/accurate diagnosis and treatment (increased knowledge transfer among practitioners), reduced waiting and/or consultation time (increased accuracy and faster diagnosis and treatment), increased medication adherence (increased patient satisfaction), decreased travel (decreased travel and/or home visits for staff), Increased employment/leisure/classroom time - increased employment time (productivity) [19].

9.2 Methods

9.2.1 Methodology introduction

HTA is a multidisciplinary and multidimensional process useful for evaluating alternative and competing medical technologies. Nonetheless, HTA methods can be difficult to apply to biomedical devices and health technologies particularly in early stage assessment [571]. In this context, and based in the abovementioned MATCH project, two different tools have been selected to carry out an early HTA of telehealth technologies for Parkinson's disease (PD) as a particular use case they will be used to assess the *PERFORM* system (section 4.4.17).

The first tool is the Analytic Hierarchy process (AHP) which has been used to elicit user needs using a panel of experts with clinical and technical backgrounds. The elicitation of user's needs by using the AHP led to the elaboration of a framework of evaluation for telehealth for PD systems which was further employed to assess the *PERFORM* system as case of study. The second one, is the use of Markov Models to estimate the cost-effectiveness of telehealth for PD and in particular the case of the *PERFORM* system. Moreover, Markov modelling allows researcher to easily explore different scenarios and hypothesis ("what-if" scenarios), even in an early stage of the technology. For example, apart from the cost-effectiveness analysis it allows to estimate the range of costs where a novel technology could move and still remain cost-effective.

The Analytic Hierarchy Process (AHP) is a method for decision-making, aiming at solving complex problems. This method allows quantifying opinions and transforming them into a coherent decision model. A hierarchy of elements, grouped into categories, is defined through this method. Elements and categories are then ranked, via questionnaires, through pair-wise comparisons. Moreover, it is possible to assess the coherence of respondent judgments and ask the experts to refine incoherent answers. Once questionnaires are finalized, it is possible to extract the relative importance of each need per category (local weights, LW), the relative importance of each category (category weights, CW), and the importance of each need compared to all the others (Global weights, GW) [586], [587]. AHP allows to elicit and prioritize user requirements and it could facilitate a wide range of decisions related to the design, selection and purchasing of new health technologies. Also, the application of AHP could help to identify the differences between opinions of the different experts and stakeholders. The result of AHP conform a framework that can be used lately for the evaluation of different systems. Basically, thanks to this tool it is possible to identify which aspect should be maximized in order to actually improve the health outcomes [20], [588].

9.2.2 AHP for User Needs Elicitation

The complexities of medical device decision making require to collect and organise a spectrum of qualitative and quantitative information in a systematic way [589]. The first step to analyse the potential impact of novel health technology, is to quantitatively assess his potential impact and how well it is able to deal with the necessities of the final users. As it was stated by Pecchia et al. (2014) [589]:

"It is widely accepted that if devices are to be used effectively they must meet the requirements of their users [590]; however, capturing user requirements for healthcare technology is extremely complex [571]. Although clinical effectiveness and safety are the primary concerns in medicine, many other aspects must also be considered including training needs, storage, labelling, servicing

and cleaning [591]. [...] Research has shown that collecting and considering this information is challenging; a lack of time and resources may preclude rigorous work into requirements [592], as can a lack of knowledge of appropriate methods for data collection and analysis [593]. This can result in the collection of data that are incomplete, difficult to interpret or that fail to address the questions of interest [594]. Finally, the complex nature of telehealth user requirements resides in the large number of possible users and stakeholders, including professional and lay users, all with differing specialties, skills and abilities. This information must not only be collected and considered, but differences and conflicts between them must also be balanced. This is a critical issue for the developers of medical technology but also for healthcare providers when making purchasing decisions. It is a particular issue for publically funded healthcare providers who must demonstrate that the purchasing decisions about high-cost equipment are transparent and are to be based on the best possible evidence available at that time [571], [589]."

It is widely accepted that medical devices, or in general health technologies can be used only if they cover the needs of end-users [590]. Nevertheless, achieving this goal can be quite complex and challenging, identical requirements (e.g. safety, efficacy) can be evaluated differently for the same technology and technique, depending on the clinical problem, the medical and organizational skills and procedures of a practice team, on patient's attitudes and health status [589], [591]. Even within apparently homogeneous user groups, individuals may count with different backgrounds, different training and different working guidelines. Thus, receiving opinions and views from different stakeholders must be considered and balanced taking into consideration the differences and conflicts that may arise. This kind of approach is relevant for the professionals with the design, production, evaluation and purchase of health technology [589]. Actually, the healthcare industry has been increasingly adopting and making use of user needs elicitation methods and seeking for quantified and objective information that allow them to define strategies for improving their services and products [595]. Unfortunately, the lack of time, resources or knowledge could compromise the correct elicitation of these requirements [592], [593], resulting in an analysis that could be fragmented or inconsistent and therefore not enough to answer the desired questions, or even worse, to guide them in the wrong direction [589], [594]. The AHP is a multidimensional, multi-level and multifactorial decision making method based on the idea that it is possible to prioritize elements by grouping them into meaningful categories and sub-categories and performing pairwise comparisons between individual elements, i.e. by breaking down a global and complex problem into smaller and simpler decisions. Following this approach, AHP allows the definition of a coherent framework of quantitative and qualitative knowledge allowing the measuring of intangible domains [589]. In general terms, an AHP study is composed of the different phases:

1. Identification of the user needs. This step requires domain experts and a literature review to extract all the potential user's needs.
2. Elaboration of the hierarchy or tree of needs, organizing the user needs identified in the previous step in nodes (categories) and leaves (needs). This phase requires also the involvement of domain experts and an AHP expert.
3. Generation of the questionnaires and submission to the experts.
4. Pairwise comparisons. This involves "n" domain experts.
5. Analysis of AHP results and elaboration of the framework of evaluation.

The real value of using AHP arrives when the domain experts are asked to perform the pairwise comparisons. The mathematics behind the AHP method allow to automatically feedback the expert about the consistency of his responses on real time and to suggest him with changes that could be more consistent based on their own responses. It is important to highlight that AHP is typically applied in complex systems and therefore it is common that even domain experts could fail to directly rank (quantify) all the user's needs. For each pair of needs (i, j) in a pairwise comparison responders answered by choosing which one of the options was more important. Then, in accordance with the Saaty natural scale [586], [587], an integer numerical value is given to each pairwise comparison, from 1 (both options are equally important) to 9 (the selected elements is much more important). The reciprocal values were given to the remaining judgments. The participants are asked to respond firstly the

comparisons between the elements of each node and then the evaluation between the nodes. Once this process is finished, a matrix containing the relative importance of each user need is built. This matrix is known as judgment matrix and it is an $A_{n \times n}$ matrix where “n” is the number of needs in the specific category or the number of categories in the case of categories pairwise comparison. According to Saaty theory [586], [587], [589], each matrix has the following properties:

1. The generic element (a_{ij}) referred to the ratio between the relative importances of the need “i” (N_i) and “j” (N_j).
2. The element a_{ji} was the reciprocal of a_{ij} , assuming the reciprocity of judgment (if N_i was 5 times more important than N_j , then N_j should be 1/5 of N_i).
3. The element a_{ii} was equal to 1;
4. The matrix A was assumed to be a transitive matrix, which means that “ $\forall i, j, k \in (1; n)$, $a_{ij} = a_{ik} * a_{kj}$ by definition of a_{ij} (15)

$$a_{ij} = \frac{N_i}{N_j} = \frac{N_i}{N_k} * \frac{N_k}{N_j} = a_{ik} * a_{kj} \quad (15)$$

If a matrix A satisfies the properties described it is possible to define some measures that can be calculated based on the properties of the matrix itself that can be used to understand and to interpret the responses of the participants.

- Local weights (LW)

Local weights defined as the relative importance of needs within each category. It has been proved [586] that, if a matrix A satisfies the properties described in the previous section then each column is proportional to the others and only one real eigenvalue (λ) exists, which is equal to “n”. The eigenvector associated with this eigenvalue is again proportional to each column, and represents the relative importance of each need compared to each of the other needs in the same category. The relative importance or weight of a particular need i within the category m will be further recalled as LW_i^m or local weight. In cases where the judgments are not fully consistent, the columns of the matrix are not proportional to one another. In addition, the matrix has more eigenvectors and none are proportional to all the columns. In this case, the main eigenvector, which is the one corresponding to the largest eigenvalue (λ_{max}), is chosen. Its normalized components represent the relative importance of each need [586], [587], [589].

- Category importance per responder

By applying the same algorithm to the categories it was possible to evaluate their relative importance. The relative importance of a category m will be further recalled as category importance (weight) or Categorical Weight (CW_m) [589].

- Global-importance of each need per responder

Finally, the relative importance of a need i compared to all the others (not only those in the same category) is defined as global-importance (Global-Weight) of the need i (GW_i). GWs are calculated by multiplying the local (within category) importance of the need by the importance of the root element (category) into the Hierarchy. For instance the global-weight of the need i, which is in the category m, was calculated as the product of the local importance of the need (LW_i^k) and the importance of its category m (CW^m) (16) [589].

$$GW_i = LW_i^k * CW^m \quad (16)$$

- Consistency estimation

The advantage of using AHP is that inconsistencies can be detected and measured as the responders are taking the questionnaire and, even more, it is possible to identify which comparisons are generating the inconsistencies. As

it was already mentioned, if the transitivity property is not respected, an inconsistency will be generated. This inconsistency was estimated by posing some redundant questions. Considering three needs (i, j, and k) the respondent was asked to perform the pair comparisons i-j and j-k, and then the redundant comparison i-k. The answer to the redundant question was compared with the one deduced from the first two, assuming the transitivity of judgment. The difference between the real answer and the transitive one represents the degree of inconsistency. The global effect of this inconsistency was estimated by measuring the difference between the major eigenvalue $\lambda_{\max}$ and “n”. The error is zero when the framework is completely consistent. Inconsistency is, in the majority of cases, due to loss of interest or distraction. Also, due to the complex nature of the system under analysis, it is pretty common that eventually some inconsistencies are generated [589]. At each node, the responders’ consistence was estimated measuring the difference of the eigenvalue $\lambda_{\max}$ from “n” (number of elements in the node), normalized to “n”. This is defined as the consistency index (CI) [587], and is zero when the framework is completely consistent ($\lambda_{\max}=n$). According to literature, the CI is divided by the Random Consistency Index (R.I.), which is a tabled [587] value changing for n from 1 to 9. This ratio is called Consistency Ratio (CR=CI/CR) and a threshold of $CR \leq 0.1$ is generally considered appropriate, although some authors have proved that it is possible to increase this threshold to 0.2 when the hierarchy is complex and it is not feasible for the responders to discuss the questionnaire results [596], [597].

- Correlations among responders’ preferences

In order to analyse the consistency of the responses between the different participants, two different measures have been used. The first one is the Spearman rank correlation (ρ or RHO), commonly used for AHP-based studies [589], [597], [598], to show how much two sets of elements are ranked in the same order [599]. The p-value was used ($p < 0.05$) to identify which values should be considered as significant. Furthermore, the BPMSG AHP Online System automatically provides a measure of consensus group (both for the general hierarchy as well as for the responses of every individual category), defined as a diversity index for the distribution of priorities among criteria [600]. The diversity index is then used to build a relative index of homogeneity S, which can be used as a consensus indicator; it is zero, when the priorities are completely distinct and unity when the priorities of all are identical.

9.2.3 Markov Modelling

Country/Region	ICER Threshold
Australia	24,700€ – 44,700€ per life year
Canada	12,700€ - 63,300€ per QALY
England and Wales	22,800€ - 34,100€ per QALY
Netherlands	20,000€ - 80,000€ per QALY
New Zealand	1,400€ - 7,200 per QALY
Scotland	22,800€ - 34,100 per QALY
United States	34,400€ per QALY

Table 41 - Threshold ICER values in a selection of countries (Table source: [601])

When a new technology proves to be less effective and more costly than the benchmark, it is directly rejected. Instead, a good candidate for technology adoption should prove to be more effective and less costly than the current clinical practice. Real scenarios are often not so clear and they are in a halfway point where achieving more effectiveness bring along additional costs. This particularly evident in health technologies where usually an initial investment is required (technology setup, new equipment acquisition, staff training for operating and maintenance, new personnel, etc.) also, behind a new technology there are design and prototyping costs together with low volume productions [571]. With this picture, the cost-effectiveness analysis is not so straightforward. A wide extended measure to overcome this kind of situations is the Incremental Cost Effectiveness (or Utility) Ratio (respectively ICER or ICUR). An ICER value over a given threshold may suggest that the new technology is more cost-effective, and therefore its adoption is justified since the expected outcomes are considered to be worth the costs incurred [571]. These threshold express as the maximum cost that a decision-maker is willing to pay per unit of QALY gained and they vary on each decision-maker and there is no uniform consensus about which is the optimal threshold, Table 41. Markov chains are a modelling technique that allows the analysis and recreation of a

random process over time by splitting the whole process into discrete states called “Markov states” and the transition between them with transition probabilities. In the case of health care, these probabilities define in a stochastic way how the disease progresses in a demarcated time (or “cycle length”) defined as “Markov cycle” and for a specific temporal duration called “time horizon”. To complete the model, each state of the model is characterized by a health utility and cost. For its characteristics, Markov modelling is a practical tool for the modelling and simulation of a disease progression, and is particularly appropriate for chronic, recursive and long-term diseases. However, it is important to keep in mind that this is a modelling approach and might be low in validity compared with clinical trials or cohort studies, actually it is intended to work on an early scenario with incomplete and restricted data available. Some of the weakness of this approach are the limitation in the quality of the input data and the limited capacity of the model to cover all the potential complexities of the real world. Nevertheless, it is useful for early HTA since it is relatively quick and easy to apply and it works with finite input data [571]. Moreover, it makes possible to enhance the model and the simulation as the technology progresses. According to Xin (2007) the benefits of modelling are recognised, at least, in the following aspects [602]:

- *“To extend the results of a clinical trial, Markov modelling can be used to extend short-term data into the future (extending the outcomes and costs into longer-term ones), and translating efficacy outcomes into health economic outcomes.”*
- *“To extrapolate intermediate clinical results of trials to long-term consequences.”*
- *“Combining evidence into head-to-head comparisons. Frequently, drugs effectiveness are compared with placebo, while policy-makers and regulators are more interested in the comparative efficiency with existing, effective medicines in the same therapeutic class. Modelling can be used to artificially carry out head-to-head comparisons between them.”*

Thus, through Markov modelling it is possible to carry out a cost-effectiveness analysis from very early stages of the design process. By populating the model with state-of-the-art values and refining it as technology matures and more specific information about costs, performance and health outcomes are collected. Actually, during the development of a new health technology it may be difficult to obtain data that fully considers stratification of patients and their costs and outcomes. Nonetheless, it may be sufficient at an early stage to consider the main outcomes, limit stratification to one or two groups and to build the model with the minimum number of states and transitions [571]. Another recurrent use of Markov modelling is to estimate the maximum cost that a new technology should have in order to be considered by the policy-makers and healthcare managers as a potential candidate for its real adoption in the clinical practice.

More formally a Markov model (it is called model when the probabilities of transition are constant over time) should verify the “Markovian assumption” i.e. the transition probability depends exclusively on the current state and not on the history [540] and when it is applied in the health care field it is composed of the following elements:

- Each state of the model defines a state of the disease and it is associated with a marginal cost (δC_k) and a marginal outcomes, which may be effectiveness (δE_k) or utility (δU_k) [571]. Due to the fragmentation and the way health care is delivered the total costs and utilities of a given state for a specific disease is not always easy to obtain and the values can range significantly depending on the data source consulted (for example, some studies include social services as part of the cost while others do not consider this cost since they are provided by a different organism).
- Then, transitions between states are modelled as a transition probability. Such value indicates the likelihood of transition from one state to another – or the probability to stay in the same state – at the end of a given cycle. Also, there are some special states that patients cannot leave, known as “absorbing state” (e.g. death). For a same disease different Markov models can be available, since modelling implies a simplification of the real world, the chosen model should cover the clinical and/or economically events that are relevant for each particular study. Transition probabilities, states definition and cycle length are defined based on the clinical prognosis or natural history of the disease [571].

- Markov models can be evaluated dynamically by matrix algebra, as a cohort simulation, or as a Monte Carlo simulation, these methods will be analysed more in deep in the next section.

The typical scenario in health technology assessment is the contrast of cost-effectiveness between the new technology performance and a benchmark (i.e. current clinical practice). In this case, the Markov modelling is repeated using the same model, but with different probabilities, costs and consequences in order to calculate differential costs and consequences among the two scenarios. Thus, the cost-consequence plane has as x-axis the differences in consequences (ΔE or ΔU) and on the y-axis the differences in costs (ΔC), finally it is possible to include the threshold boundary defined as a $y=\alpha x$, where α is the relevant ICER [571]. Markov modelling has been largely used in the field of health economics to carry out estimations of the economic impact of different drugs and health technologies, the case of Parkinson's disease is not an exception [244], [254], [575], [603]–[607].

$$ICER = \frac{C_{innovation} - C_{base}}{E_{innovation} - E_{base}} \quad (17)$$

9.2.3.1 Cohort simulation vs Montecarlo simulation

Once the Markov model is built there are two alternative – or complementary – ways to evaluate it. The first option is to run a Markov Cohort Simulation, this is the most straightforward way to use it, and it is widely appreciated by healthcare decision-makers and policy-makers. Essentially, in the cohort simulation a hypothetical cohort of patients (e.g. 1000 persons individuals) and pre-distributed in the different states, transit from one state to another on each cycle and according to the transition probabilities. Thus, the distribution of patients among the states evolved on each cycle and utilities and costs are evaluated according to the population on each state. Per cycle this process is repeated for an enough number of cycles to cover the time horizon of study. As an additional consideration, it is assumed that transitions happen at the end of each cycle. Nevertheless, in the real world patient transition from state to state is a continuous process happening at any time within the cycle. To correct this issue, a half-cycle correction could be used, which assumes that state transitions occur, on average, half way through the cycle [571], [602]. In the Markov Monte Carlo approach the simulation is performed individually, one by one each individual patient moves through the states in a random manner according to the transition probabilities. In this case, it will be a probabilistically execution of the model and the result is a distribution of answers around a mean (this mean is the result of the Cohort execution). The interesting results of this approach is that it provides a “distribution profiles” of patients around the states as well as the deviation of the average costs and QALYs, reflecting the uncertainty of the estimated results. However, such uncertainty is just a representation of the random nature of the model structure. The methods for attaching utilities and cost differ also in both methods, in cohort simulation, the patients stay at the different health states in a cycle, and their health outcomes and costs are calculated separately of the states in that cycle and total values are obtained by summing the values of the different health states. In Monte Carlo simulation, the total health outcomes and costs of an individual are weighted by the probability of being in that state at a given cycle and final values are obtained by summing the health outcomes and costs of all patients [571], [602].

9.2.3.2 Sensitivity

Sensitivity analysis is conducted to examine the robustness of results and to explore the variation of the results based on the uncertainty of the model structure. Generally speaking four types of uncertainty can be identified in Markov modelling [602], parameter uncertainty (on probabilities, health consequences and resources use), analytical uncertainty (such as time preference and the methods to evaluate costing and outcomes), generalisability of results and finally structure uncertainty (whether the developed structure can actually simulate the disease progression). Sensitivity analysis can be classified as deterministic and stochastic in nature. In deterministic analysis, simple sensitivity analysis, extreme analysis and threshold analysis can be applied to explore the effect of variables inputs on the outcomes. Probabilistic analysis (Monte Carlo simulation) incorporates the probability distribution of key variables to produce the distribution of expected results [602]. The most extended probabilistic sensitivity analysis – as it is known – is the second-order simulation which reflects the random features of parameters, and thus the estimated outcomes (for example ICER statistic). On this approach

the parameters are characterized with a probability distribution and therefore the outcomes are also affected by this uncertainty.

9.2.3.3 Markov modelling for early Health Technology Assessment

Health technology companies, researchers and developers in the health technology fields are increasingly being challenged to justify the economic value of their innovation at an early stage, in a manner that is acceptable to the health technology assessment community. On this regards, Markov modelling has been proposed as a useful tool to generate a common understanding of value between innovator and assessors [571]. The advantages of this approach is that it allows the simulation of different scenarios from an early stage of the technology development and the progressive refinement of the model as the technology evolves and more, and better, data is available, including both data on the real cost of implementation and maintenance as well as on the effectiveness and health outcomes. Therefore, Markov modelling allows the simulation of cost-effectiveness under given hypothesis of cost and outcomes, in other words, it allows to perform different “what-if” analysis. Actually, it has been suggested to use Markov models that use a minimum number of states and transitions since during the early development of a new health technology it may be difficult to obtain data that fully considers stratification of patients, outcomes and costs [571]. Also, performing this kind of studies helps to minimise uncertainty in early stage decision-making within development and adoption processes can be achieved by the use of formal methods, models and tools and also it should foster mutual understanding of cost-effectiveness by suppliers, evaluators and buyers. This approach has been already used to perform an early HTA of a total knee replacements [608] and to explore a device aimed at promoting healing in diabetic foot ulcer [609]. Literature and state-of-the-art works is the starting point to identify the key health states and the transitions for the model which may include mortality rates or healing rates as well as the utilities for each state. All the input values should be converted to the appropriate time period. Costs may be found from databases, from manufacturers or from estimations [609].

Finally, Markov modelling can be used to stimulate another scenario, given a certain ICER it is possible to use the model to estimate the maximum cost that a technology should cos according to the willingness to pay of the decision-makers. On this regards, Markov modelling could be seeing as a warning system, especially for the early stages of development.

9.3 AHP study

This section presents the work done to define a hierarchy for AHP based on the expertise of a focus group of clinical and technical experts, how this hierarchy was distributed to a group of experts to rate each of the user needs previously identified, how the a evaluation framework was built based on the results collected and analysed and finally how this framework was utilized to lead a part of the Health Technology Assessment of the PERFORM project.

9.3.1 Objectives

This research work aims at identifying and ranking the key user needs that a telehealth system for the management of Parkinson’s disease should cover, in order to be useful and effective. Additionally to the identification, a quantitative evaluation of the importance of each need compared to the others is provided. The Analytic Hierarchy Process (AHP) was chosen to perform this work. This methodology has been already used in healthcare, with different goals and objectives, such as user needs elicitation [589], [610], [611], medical decision-making [612], budget allocation [613] and medical device purchasing [614]. A group of experts was involved to identify and prioritize these needs. Two types of expertise have been required as inclusion criteria for the expert selection. On the one hand, participants with a clinical background, and with experience and knowledge of the eHealth field; on the other hand, participants with a technical background as well as experience in the design and development of telehealth and/or eHealth systems. In both cases, the selection of the participants required at least a basic knowledge of the Parkinson’s disease symptoms and progression. The analysis of the results allowed to identify, rank and quantify the views from both technical and clinical experts, and finally, to understand in which cases their opinion is similar and in which cases there are discrepancies in their points of view. As a case study, the results

this process have been used for the assessment of the PERFORM system (see 4.4.17 PERFORM).

9.3.2 Ethical consideration

This was an interview study with experts and without patient involvement. A participant information sheet was presented informing about the purpose of study and a detailed description of the tasks that they must perform. Participants gave informed consent to participate in the study. The data collected was associated to the participant profile and background in order to analyse the results properly. The name or any other personal detail has not be disclosed at any time. The full letter sent to the experts asking them to join this study can be found at Appendix III. The following excerpt has been extracting from it:

"You have been selected to be part of this study as expert in the field. The data collected will be associated to your profile and background in order to analyse your opinion as expert but your name or any other personal detail will not be disclosed at any time. Your opinion will only be used for research purposes. By taking part of this study and submitting your response you will agree with these conditions."

9.3.3 Hierarchy definition

The first step in the AHP is the elaboration of a hierarchy as initial step to complete an Analytic Hierarchy Process (AHP). The identification of the user needs play a central role in the Health Technology Assessment (HTA) practice. In order to identify elements of the hierarchy a systematic literature was performed and then a focus group with experts was consulted to organize these factors in the nodes and leafs. This focus group identified a total of 29 different clinical needs that must be satisfied by a telehealth system for effective PD monitoring and management. This focus group involved 2 clinicians and 5 biomedical engineers with extensive experience of the design. JC acted as the facilitator and designed the first version of the hierarchy, based on his own experience, the facilitator input and the work of Dávalos et al. [573], who proposed a wide range of outcomes that can be monitoring to analyse the outcome of the telemedicine system and how to convert them into monetary units. Then, the hierarchy was distributed among the other experts and reviewed with the other participants to check that it was accurate and comprehensive. Finally, it was updated according to the feedback received from all of them. The 29 needs were organized into five meaningful categories [18], this hierarchy is showed in the *Table 42*.

Nodes	Leafs
Technical	On/Off fluctuations detection.
	Bradykinesia severity assessment.
	Tremor severity assessment.
	Dyskinesias severity assessment.
	Gait assessment.
	Freezing of gait / Festination detection.
	Rigidity assessment
	Other motor symptoms detection and quantification.
	Cognitive and behavioural assessment.
	Merging current assessment with historical patient data.
	Building a patient profile and a disease trend.
Wearability and assessment	Wearability acceptance by the users.
	Use the minimum number of sensors.
	Minimum time of sensors wearing.
	Friendly interfaces.
Clinical practice	Increase the adherence to treatment.
	Self-management support.
	Data mining for automatic data interpretation.
	Increase patient and care giver health knowledge.
	Improve patient-professional interaction.

Economic	Reduction of informal care giver effort.
	Reduction of patient visits to the hospital.
	Reduction of nights in the hospital.
	Increase the patient Quality of Life.
	Faster and more reliable diagnosis.
Technical issues	Reduction of waiting and/or consultation time.
	24/7 user support to solve unexpected problems.
	Scalability.
	Security and privacy.
	Maintenance.
	Data interoperability.

Table 42 - Initial table with the hierarchy of user needs

Then, the hierarchy was distributed among the other experts and reviewed with the other participants to check that it was accurate and comprehensive. Finally, it was updated according to the feedback received from all of them. The 29 needs were re-organized into five meaningful nodes and 17 leafs. The final tree was designed which each node represented a category, and each leaf represented a need (Table 43).

Nodes	Elements
Performance	Motor symptoms assessment
	ON/OFF fluctuations detection
	Cognitive & behavioural assessment
	Data mining & disease modelling
User experience	↑ wearability acceptance
	User-friendly interfaces
	Seamlessly integration
Clinical practice	↑ patient-clinician bond
	↑ patient & carers knowledge
	↑ self-management support
	↑ assist care givers
Economic	↓ visits and stays in hospital
	↑ patient Quality of Life
	Faster and more reliable diagnosis
Technical issues	Scalability and interoperability
	Security and privacy
	↓ maintenance and support cost

Table 43 – Definitive hierarchy for the AHP study

9.3.4 Questionnaires

Once the tree was finalized, questionnaires were prepared to compare the relative importance of each need with all of the other needs within the same category. For each pair of needs, the following question was asked: “In a technological solution for Parkinson’s disease monitoring, assessment and/or management, from your point of view and according to your experience, which is the most important element and how much important it is with respect to the other?”. Responders answered by choosing which one of the options was more important, by selecting an integer numerical value from 1 (both options are equally important) to 9 (the selected element is much more important). The application used for creating the hierarchy and collecting answers is the BPMSG AHP Online System²¹⁴. This system automatically calculates the Consistency Rate (CR) and shows some options to improve the consistency when the value is higher than 10%.

²¹⁴ <http://bpmsg.com/> (Last date accessed: January 2015)

9.3.5 Participants

Table 44 shows the profile of the different experts involved in this study.

Code	Profile	Sex	Years of working experience	Years of experience with PD	Years of experience with eHealth
1	Technical	Female	26	5	26
2	Technical	Male	20	11	20
3	Technical	Male	8	7	8
4	Technical	Male	12	6	12
5	Technical	Male	7	5	6
6	Technical	Male	7	5	6
7	Technical	Male	10	1	8
8	Technical	Male	10	2	8
9	Technical	Male	5	4	5
10	Technical	Male	7	5	6
11	Clinical	Female	8	4	5
12	Clinical	Female	12	10	4
13	Clinical	Male	19	11	5
14	Clinical	Male	25	25	15
15	Clinical	Female	26	12	0
16	Clinical	Female	4	4	2

Table 44 – Profile of the participants in the AHP study

9.3.6 Grouping experts judgements

One of the aims of this work was to explore the differences between the two groups of experts. Different actions were done to study the different perspectives of both groups. The first one was to graphically represent the GW of each user needs using a boxplot chart with data from all the participants (*Figure 84*) and another one was to aggregate the GW with the technical and clinical participants (*Figure 85*). Boxplots plot the median values (central marks), the 25th and the 75th percentiles (the blue range) and the outliers (crosses). Then, on the different results tables (*Table 45 and Table 46*) the median values of the GW, LW and CW for each group are included in a numerical way.

9.3.7 Correlations among responders' preferences and group consensus

In order to analyse the consistency of the responses between the different participants, two different measures have been used. The first one is the Spearman rank correlation (ρ or RHO), commonly used for AHP-based studies [589], [597], [598], to show how much two sets of elements are ranked in the same order [599]. The p-value was used ($p < 0.05$) to identify which values should be considered as significant. Furthermore, the BPMSG AHP Online System automatically provides a measure of consensus group (both for the general hierarchy as well as for the responses of every individual category), defined as a diversity index for the distribution of priorities among criteria [600]. The diversity index is then used to build a relative index of homogeneity S, which can be used as a consensus indicator; it is zero, when the priorities are completely distinct and unity when the priorities of all are identical.

9.3.8 Results of the AHP study

Figure 83 shows the global picture of the AHP results and Table 45 summarizes the results of the AHP questionnaire. The second column shows for each element of the hierarchy the Global Weights (GW) and the Local

Weights (LW) resulted from the AHP analysis. These results are based on the AHP method and take into account the responses from all the participants. The third and fourth columns show the median of the GW and LW values, grouped according to the profile of the responders (clinical and technical). The last column show the t-test comparing the responses of the two groups of responders. The information of the median values is also provided in the *Figure 84*, where the boxplots show, for each element of the hierarchy, the median value (central mark), the 25th and the 75th percentiles.

Table 46 contains the Categorical Weights (CW) obtained from the responses of all the participants (second column); the third and fourth columns show the median values obtained for the technical and clinical groups. The last column shows the t-test between the CW between clinical and technical groups.

Table 47 shows the group consensus within each category, within categories and integrated group consensus based on the GW values.

Figure 83 - Group results of the user needs

Figure 84 - Boxplot with the result of all the responders. Central mark is the median, the edges of the box are the 25th and 75th percentiles, the whiskers extend to the most extreme data points not considered outliers, and outliers are plotted individually

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Figure 85 - Boxplot with the result of the responders grouped by technicians and clinicians profiles

	Group results GW (LW)	Median Technical GW (LW)	Median Clinical GW (LW)	GW t-test (LW t-test)
1 Performance				
1.1 Motor symptoms assessment	0.064 (0.292)	0.064 (0.304)	0.032 (0.231)	0.522 (0.486)
1.2 ON/OFF fluctuations detection	0.085 (0.388)	0.099 (0.392)	0.078 (0.288)	0.269 (0.24)
1.3 Cognitive & behavioural assessment	0.042 (0.197)	0.030 (0.127)	0.041 (0.305)	0.844 (0.032)
1.4 Data mining & disease modelling	0.028 (0.129)	0.027 (0.090)	0.024 (0.120)	0.448 (0.664)
2. User experience				
2.1 ↑wearability acceptance	0.102 (0.457)	0.077 (0.388)	0.068 (0.461)	0.782 (0.494)
2.2 User-friendly interfaces	0.068 (0.305)	0.077 (0.281)	0.047 (0.310)	0.849 (0.408)
2.3 Seamlessly integration	0.053 (0.237)	0.038 (0.322)	0.026 (0.169)	0.099 (0.107)
3 Clinical practice				
3.1 ↑patient-clinician bond	0.054 (0.181)	0.041 (0.203)	0.048 (0.139)	0.695 (0.736)
3.2 ↑patient & carers knowledge	0.080 (0.270)	0.054 (0.25)	0.063 (0.245)	0.761 (0.593)
3.3 ↑self-management support	0.093 (0.314)	0.058 (0.290)	0.089 (0.284)	0.880 (0.849)
3.4 assist care givers	0.070 (0.235)	0.051 (0.201)	0.062 (0.259)	0.482 (0.814)
4 Economic				
4.1 ↓visits and stays in hospital	0.022 (0.175)	0.015 (0.169)	0.027 (0.162)	0.313 (0.588)
4.2 ↑patient Quality of Life	0.063 (0.511)	0.051 (0.468)	0.035 (0.376)	0.826 (0.197)
4.3 Faster and more reliable diagnosis	0.039 (0.313)	0.029 (0.299)	0.050 (0.323)	0.189 (0.428)
5 Technical issues				
5.1 Scalability and interoperability	0.040 (0.293)	0.039 (0.310)	0.026 (0.281)	0.472 (0.615)
5.2 Security and privacy	0.059 (0.430)	0.041 (0.464)	0.029 (0.396)	0.563 (0.600)
5.3 ↓maintenance and support cost	0.038 (0.277)	0.024 (0.177)	0.049 (0.367)	0.092 (0.341)

Table 45 - Local and global weights of needs (CR<0.1), median of the Local and global weights for the clinical and technical groups and t-test between the two groups

	CW	Technical	Clinical	t-test
1 Performance	0.219	0.207	0.200	0.375
2 User experience	0.222	0.216	0.159	0.560
3 Clinical practice	0.297	0.233	0.278	0.573
4 Economic	0.124	0.110	0.104	0.520
5 Technical issues	0.137	0.103	0.140	0.337

Table 46 - Categorical weights, median of the weights for the clinical and technical groups and t-test between the two groups

	Group consensus
1 Performance elements	0.720
2 User experience elements	0.867
3 Clinical practice elements	0.773
4 Economic elements	0.762
5 Technical issues elements	0.784
Between categories elements	0.709
AHP Group consensus (rel. homogeneity)	0.736 (0.734)

Table 47 - Group consensus

9.3.8.1 Discussion

This work has two main goals: firstly, to identify the elements that a telehealth system for PD management should fulfil in order to be effective and, secondly, to understand if clinicians and technicians share a common opinion when evaluating these systems.

According to the results of the responders, the three most important user needs are *Increase the wearability acceptance* (0.102), *Increase the self-management support* (0.093) and *On/Off fluctuations detection* (0.085), based on the values from the Global Weights (GW). In a second level of importance we found *Increase patient & carers knowledge* (0.080), *Assist care givers* (0.070), *User-friendly interfaces* (0.068), *Motor symptoms assessment* (0.064) and *Increase patient Quality of Life* (0.063).

The analysis of the Categorical Weights (CW) provides information about the importance of the different categories. The *Clinical Practice* category has been highlighted as the most relevant category by all the responders (0.297), followed by the *Performance* and *User experience* categories which scored very similarly (0.219 and 0.222). Finally, the *Economic* and *Technical Issues* categories were the less relevant according to these results (0.124 and 0.137). As regards the differences between the clinical and the technical groups, in both cases the *Clinical practice* category has the highest relevance. *Performance* and the *User experience* categories as the following categories, while *Economic* and *Technical issues* as the less relevant ones. Nevertheless, there are some differences: for the technical group the *User experience* is the second most important category and the *Technical issues* the less important; for the clinical group it is the opposite: *Performance* is the second most important, while the *Economic* category the less one. However, no significant difference between the responses of the clinical and technical groups has been found. Regarding the GW and LW of all the elements (Table 45), a similar scenario has been found. In this case, the only statistically significant difference is found in the LW of the *Cognitive & behavioural assessment* element. The clinical group has rated this issue significantly higher than the technical group. In all the other cases, the differences are not significant. Besides, in the clinical group the three top GW of the clinical group match the aggregated top three GW; in the case of the technical group, *On/Off fluctuations detection*, *Increase wearability acceptance*, and *User-friendly interfaces* have been considered as the most relevant elements. It is also important to highlight that some of those requirements such as wearability, usability have a huge impact, not only on the user experience but also on the effectiveness and safety of health technologies.

As regards the relevance of the different elements given a specific category: in the *Performance* category *On/Off fluctuations detection* (0.388) is the most important element, followed by the *Motor symptoms assessment* (0.292), *Cognitive & behavioural assessment* (0.197) and *Data mining & disease modelling* (0.129). Regarding the *User experience* category, *Increasing the wearability acceptance* (0.457) is considered the most important need, followed by *User-friendly interfaces* (0.305) and *Seamlessly integration* (0.237). According to these results, when working with wearable devices, the User Experience (UX) is strongly affected by the experience of the user interacting with the physical devices. This effect is due to not only to the physical features of the devices (i.e. size, weight, comfort) but also to a social component implicit in wearing a medical device (i.e. what other people could think when I wear this device) [615]. This issue may also be linked with the privacy of the patient.

In the third category, *Clinical practice*, the need *Increase self-management support* (0.314) obtained the highest LW, followed by *Increase patient & carers knowledge* (0.270) and *Assist care givers* (0.235). Finally, *Increase patient-clinician bond* (0.181) scored the lowest weight. These results reflect a clear demand in providing both patients

and carers with tools that improve the management of the disease and increase the effectiveness of healthcare interventions.

As regards the fourth category, *Economic aspects*, *Increase patient Quality of Life* (0.511) is considered as the most important element; the second one is *Faster and more reliable diagnosis* (0.313), while *Decreasing visits and stays in the hospital* (0.175) is considered as less important. This last result was expected since most of the PD patients do not suffer acute episodes requiring long stays in the hospital. Instead, the main economic benefit could be achieved by improving the QoL. Actually, this could also be expected since PD has an enormous impact on the QoL by limiting their mobility and independence. Additionally, improving in diagnosis could also generate an economical benefit due to a most effective use of the resources.

Finally, within the last category, *Technical issues*, the *Security and privacy* (0.430) aspects are ranked as the most relevant user needs, followed by *Scalability and interoperability* (0.293) and *Decrease maintenance and support cost* (0.277). As expected in a healthcare scenario, security and privacy issues are the most relevant needs, while other Information Technology (IT) issues are considered as secondary.

Usually, clinical effectiveness and safety are the primary concerns in medicine [591], in this case, the impact of a telehealth system for disease management and monitoring in the safety of the patient is very limited and this fact is reflected in the opinion of the experts that did not include these issues among the most relevant ones.

Additionally to the t-test performed between the median values for the CW, GW and LW calculated for the clinical and technical groups, the Spearman correlation (ρ) and the associated p-value (p) were also calculated taking into consideration the median values of the GW for the clinical and technical groups. This measure is intended to quantify the similarity between the responses of both groups. The result is $\rho = 0.590$ ($p=0.012$) showing a significant correlation between both groups. This fact is reinforced by the measures of the group consensus on *Table 47*. These values show a high degree of consensus between all the participants, especially within the elements of the *User experience* category (0.867).

9.3.9 Evaluation of the PERFORM system

At this point, and based on the defined framework for evaluation built with the AHP methodology, it is possible to use it to assess qualitatively and quantitatively telehealth system for PD, specifically in the case the PERFORM system will be used as case of study. On this regards, two different approaches have been followed, the first one is the qualitative discussion of each of the user needs and how well (or bad) the case under study fulfils them, taking into account the specific weight of each of these user needs. On the other hand, and in order to assess quantitatively the system, three experts with a complete knowledge of the platform were asked to rate from 0 to 10 how much the system under study fulfil each of the user's needs. *Table 48* summarizes these results, the second column shows the GW, i.e. the weight of each user need, the third column shows the average score of the three experts evaluation, the forth column is the weighted score of the experts evaluation – i.e. the weight of the need multiplied by the score – and the last column is the quantitative evaluation of the user need. Finally, *Figure 86* shows graphically the quantitative assessment of the system by plotting together the weights of the user needs and the weighted scores of the experts.

As regards the most relevant elements, *On/Off fluctuations detection*, *Increase wearability acceptance*, *Increase patient & carers knowledge* and *Increase self-management support*, it is possible to appreciate that the PERFORM system fulfilled reasonably the *On/Off fluctuations detection* and *Increase wearability acceptance*. It partially complies with the *Increase self-management support*. Nevertheless, it failed in reaching the *Increase patient & carers knowledge* element: even though the system provides enough information about patients' symptoms and their evolution, it does not give support in understanding their own status. According to the experts, it is not enough to monitor and assess the patient seamlessly but it is also crucial to advise and guide him/her, by customizing and personalizing guidelines according to the current status that the system allows to assess. Another important issue where PERFORM fails and that it was highlighted as important, is to assist care givers. According to the experts consulted in the study, the role of caregivers is remarkably important – this stakeholder is also included in the *Increase patient & carers knowledge* – and was not considered in the current version of the system.

Moreover, PERFORM did not incorporate the monitoring of no-motor systems, being especially relevant the *Cognitive & behavioural assessment* one. The incorporation of these user needs and the jointly assessment of motor and cognitive components would significantly enrich and benefit the modelling of the disease according to the experts' opinion.

User needs	GW	Experts score	Weighted Experts score	PERFORM
1 Performance				
1.1 Motor symptoms assessment	0.064	10	0.064	<p>One of the main objectives of the PERFORM system was the automatic detection and assessment of the different PD symptoms. Specific algorithms were developed in order to assess bradykinesia, dyskinesias, freezing of gait, gait performance and tremors.</p> <p>About the technical performance of the system it shows an accuracy of up to 93.73% of accuracy for the classification of Levodopa Induced Dyskinesias (LID) severity [476], an 86% for the classification of bradykinesia severity [477] and 87% for tremor severity [478]. Also, a specific module was developed for the assessment of gait [5].</p>
1.2 ON/OFF fluctuations detection	0.085	9.33	0.079	The detection of the On and Off phases was a main goal for the project. A detection system was designed based on the fluctuations of the motor symptoms previously assessed. This module showed an average accuracy of 88.2% classifying the time that the patient spend on the different On and Off phases [12].
1.3 Cognitive & behavioural assessment	0.042	0	0	Cognitive and behavioural assessment was not included in the PERFORM system
1.4 Data mining & disease modelling	0.028	7	0.020	PERFORM also included a platform for the clinicians and for the healthcare professionals where all the information coming from the continuous monitoring of the patients is used to build a tailored model of the disease and generate alerts when a remarkable event was detected [15]. This rule-based system takes not only the motor assessment but also other information provided by the PERFORM system such as food and medication intakes [489].
2. User experience				
2.1 ↑wearability acceptance	0.102	9	0.091	The wearability acceptance of the system was seriously taking into account during the project. Actually, this issue was also raised during the evolution of the project, external reviewers suggested that a specific strategy to study and address this topic would benefit enormously the project, for this reason a wearability study was carried out [13]. In this study most of the patients showed their positive compliance with the wearable devices and only some subject reported issues regarding the size and shape of the

				sensors [15]. A variety of methodologies (REBA, Borg and CRS scales in combination with a body map) has been used to study the comfort, biomechanical and physiological effects of the system. The acceptance of the system was eventually satisfactory and user-friendly, over the desired threshold. Moreover, useful insights and guidance to improve the system design were gathered in this phase.
2.2 User-friendly interfaces	0.068	8.33	0.57	PERFORM followed a User-Centred design approach both with clinicians and patients. Several redesigns of the Graphic User Interfaces (GUI) were done following the feedback of the users on each iteration [15].
2.3 Seamlessly integration	0.053	9	0.050	The PERFORM system was designed following seamlessly integration as one of the technical requirements. Download of data from sensors to the patient computer, processing of data and transmission of data to the hospital works seamlessly. Nevertheless switch on the monitoring sensors require some effort by the users [15].
3 Clinical practice				
3.1 ↑patient-clinician bond	0.054	6.66	0.036	PERFORM facilitates the continuous monitoring and the data transmission from the patient to the clinician, as well as it enables and facilitates a better knowledge of the patient by the clinician and healthcare professionals. Nevertheless, in the opposite direction it only allows the clinician to request a new appointment but does not allow them to establish a richer communication [15].
3.2 ↑patient & carers knowledge	0.080	4	0.032	PERFORM system was designed to perform a seamlessly monitoring and, since one the aims of the projects was the validation of such assessment methodologies, it was decided to do that without providing a specific feedback to the patients about their assessment or the evolution of the disease. Instead, all the monitoring data was sent directly to the hospital where a rule-based Decision Support System (DSS) alert the clinicians in the case of the symptoms fluctuated excessively.
3.3 ↑self-management support	0.093	4.66	0.043	Using PERFORM the patient takes a more active role in the assessment and monitoring of his own disease – for example by reporting medication and food intakes. They were also trained to use the wearable sensors for the daily monitoring. In this sense, the patients take an active role in the self-monitoring of their own disease – still, it is insufficient. More feedback and a clear and tailored management guidelines may be generated and presented to the patient in order to support him on this process [15].
3.4 assist care givers	0.070	0.66	0.004	Care givers have not been included as potential stakeholders in the design of the PERFORM project. In this sense, most of the user needs of the care givers are not covered.

4 Economic				
4.1↓visits and stays in hospital	0.022	4.33	0.009	The automatic detection of motor symptoms and On-Off fluctuations allows the adjustment of the medication and the reduction of Off periods without the necessity of a visit to the hospital. Also, the continuous monitoring of motor symptoms and the automatic generation of a report enable the remote monitoring and follow-up of the patients [15]. On the other hand, even if visits and stays may be reduced PERFORM will require a trained professional working on the tool continuously.
4.2↑patient Quality of Life	0.063	6.66	0.004	The actual impact patient QoL it is needed to keep the patient on the On state during as much time as possible during the day. The automatic detection of motor symptoms and On-Off fluctuations allows the adjustment of the medication and the reduction of Off periods and consequently the increase of patient QoL.
4.3Faster and more reliable diagnosis	0.039	9.33	0.036	As it was abovementioned PERFORM allow the continuous monitoring and assessment of the motor symptoms of PD patients. Therefore, it provides clinicians with an objective tool for the diagnosis of PD patients.
5 Technical issues				
5.1 Scalability and interoperability	0.040	6.333	0.025	The last prototype of PERFORM was developed based on market standards. The patient application was developed on .NET, the sensors download information to the LBU application through a USB and the clinicians' application is on the cloud working as a web application from any browser. This need can be improved by the adoption of healthcare standards (e.g. HL7).
5.2 Security and privacy	0.059	7	0.041	PERFORM was designed following security and privacy guidelines for healthcare applications. SSL was used for the transmission of data between the patients' home and the hospital solutions.
5.3↓maintenance and support cost	0.038	4.33	0.016	No specific actions were taking on this regards. A large pilot is required to accurately measure the technical maintenance and the support cost of the PERFORM system and to compare it with the current clinical practice.

Table 48 – Assessment of the PERFORM system based on the AHP framework developed.

Based on the above mentioned analysis, it is possible to see that the PERFORM system fulfilled reasonably the *On/Off fluctuations detection* and *Increase wearability acceptance*. It also fulfil partially the *Increase self-management support*. Nevertheless, it failed in the *Increase patient & carers knowledge*, even if the system achieves a good knowledge of the symptoms in the patient and their evolution, it does not provide the patients with this information in way that could benefit the patient in the understanding of their own status. In this sense, the areas of improvement should focus on the education and training of patients and caregivers, providing them with tailored guidelines based on the assessment.

Figure 86 – Graphical representation of the PERFORM assessment taking into account the AHP framework

9.4 Markov modelling for early HTA study

9.4.1 Objectives

As it was previously stated, within this work Markov modelling will be used to explore the potential economic impact of a telehealth system for PD management and to advice developers about the maximum cost of the technology according to the willingness to pay of the decision makers. Markov modelling will be used in different ways from generalist to a more specific scenarios:

- 1) In the first place, Markov model will be used assuming a constant ICER value, with this assumption in mind the model will be run to explore how changes in the utilities and in the transitions probabilities of the model impact in the cost outcomes. This first approach offers a general picture, a global picture that could be used as a general advice framework for a new telehealth system for PD management.

- 2) In the second step, PERFORM system (see section 4.4.17) will be used as a particular case of study. The cost of this system will be used to run a Markov model and the ICER will be calculated analytically using the cohort method and probabilistically using a monte carlo simulation.
- 3) Finally, a sensitivity analysis will be carried out.

9.4.2 State of the art

As an initial step, a state-of-the-art study was carried out looking for already validated Markov models for Parkinson's disease that could provide a validated model to be used in the context of early HTA for telehealth. *Table 49* summarizes the works that have been found. A total number of eight cost-effectiveness studies have been found in which Markov modelling has been used as tool to explore the economic impact of drugs ([254], [575], [603]) as well as medical devices ([244], [604]–[607]). Also, many of these works have been used aimed at extending the results of a time-limited clinical trial. For that reason, they have collected their own data regarding costs and utilities to build the Markov model of the innovation while they are based on literature and available data to build the benchmark Markov model. Essentially, three Markov models were found, Nuijten et al. (2001) [603], Palmer et al. (2002) [254] and Coyle et al. (2003) [575] used a three state model proposed by Dodel et al. (1998) [616].

Then, Antonini et al. [604] (2008) employed a 8-state Markov model, although in this case the technology under study is novel screening technique for PD and not a drug or medical device. Finally, Lowin et al. (2011) [244], Dams et al. (2013) [605], Eggington et al. (2014) [571] and Walter and Odin 2015 [572] use different variations of a common model based on the evolution of PD according to the Hoehn and Yahr scale.

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	Nuijten et al. 2001 [603]	Palmer et al. 2002 [254]	Coyle et al. 2003 [575]	Antonini et al. 2008 [604]	Lowin et al. 2011 [244]	Dams et al. 2013 [605]	Eggington et al. 2014 [606]	Walter and Odin 2015 [607]
Definition	Cost-effectiveness of complementary treatment with entacampone versus standard treatment	Cost-effectiveness of complementary treatment with entacampone versus standard treatment	Cost-effectiveness of complementary treatment with entacampone versus standard treatment	123I-FP-CIT SPECT (DaTSCAN1) vs. clinical judgment differentiating ET from PD	Cost-effectiveness of LCIG vs. standard care in patients with aPD.	Cost-effectiveness of DBS compared with long-term medical treatment.	Cost-effectiveness to compare interventions in aPD, based on patient-level RCT data.	Cost-effectiveness of CSAI vs. LCIG, DBS and standard care.
Number of states	3 health states Severe: ≤25% "off time per day"; Moderate: >25% off time per day and Dead	3 health states Severe: ≤25% "off time per day"; Moderate: >25% off time per day and Dead	3 health states Severe: ≤25% "off time per day"; Moderate: >25% off time per day and Dead	8 health states	4 health states: H&Y 3, 4, 5 and Dead + 4 sub-states per H&Y states: 0-25%, 26-50%, 51-75% and 76-100% of waking day Off.	6 health states: H&Y 1, 2, 3, 4, 5 and Dead + 2 sub-states per state: On and Off	6 health states: H&Y 1, 2, 3, 4, 5 and Dead + 4 sub-states per H&Y states: 0-25%, 26-50%, 51-75% and 76-100% of waking day Off.	12 health states: H&Y 3, 4, 5, Complications, AE and Dead + 4 sub-states per H&Y states: 0-25%, 26-50%, 51-75% and 76-100% of waking day Off.
Country	Netherlands	US	Canada	Italy	UK	Germany	UK	UK, Germany
Time cycle	6 months	6 months	6 months	6 months	6 months	1 year	6 months	6 months
Time horizon	5 years	5 years	5 years	5 years	5 years	5 Years	5 years	5 years
Type of analysis	Societal perspective	Societal perspective. Secondary analysis with third party perspective (only direct medical costs)	Societal perspective. Secondary analysis with third party perspective (only direct medical costs)	Italian National Health Service perspective, with 2005 as the base year.	Perspective of the UK NHS including social services.	German health care provider perspective.	UK NHS perspective.	The perspective of the analysis is that of the national healthcare providers.
Data sources	Entacampone clinical trials (randomised, double-blind), literature and	Entacampone clinical trials (randomised, double-blind), literature and	Entacampone clinical trials (randomised, double-blind), literature and	Published data and results of a double-round Delphi panel of 12 specialists	Data was based on an intern Abbott study some data was re-calculated	Clinical studies, published reports, or meta-analyses. Costs were	Patient-level data from 6-month RCT.	Literature review

	cross sectional observational studies.	cross sectional observational studies.	cross sectional observational studies adjusted for Canadian practice.		based on a series of extrapolation calculations.	assessed from the German health care provider perspective.		
Utilities	Prospectively collected data from a utility study (proportion of off-time/day)	PD disability was assessed using the proportion of off-time/day and the Hoehn and Yahr scale scores.	Study carried out in conjunction with the modelling study (proportion of off-time/day)	Projected Years on Potentially Beneficial Therapy (PBTs).	Based on the EuroQol Group 5-Dimension Self-report Questionnaire (EQ-5D).	Health utilities were evaluated using the EQ-5D	Health utilities were evaluated using the EQ-5D	Utility values were mainly derived from the publication of Lowin et al.
Costs	Direct medical costs (outpatient and inpatient care for the treatment of PD) and direct nonmedical costs were derived from official lists.	Unit costs were obtained from standard national sources. Paid and unpaid caregiver costs were based on an assumption that their value per hour was equal to the home service worker's wage.	Societal perspective Medical care costs + non-medical care costs. Loss of productivity was not included.	Giofil database for drugs and official tariffs were used for tests, exams and for hospitalization costs.	Health state costs were estimated from the results of an observational study of PD	Disease-specific direct costs were calculated depending on HY-on state from the health care provider perspective.	Individual patient-level data on the effect of DBS on PD symptom progression from a large 6-month RCT	Cost of aPD and related costs including the AE and complication costs in the UK and Germany, direct costs were included in the analysis.
Discounting	4% per year	3% per year	5% per year (Canadian guidelines)	5% per year	3.5% per year	3% per year	3.5% (UK guidelines)	3.5% (UK gui.) 3% (Germany gui)

Table 49 - State of the art of works using Markov modelling for cost-effectiveness in Parkinson's disease

9.4.3 Markov model for early HTA in Parkinson's disease

Finally, the Markov model chosen for this work was the one proposed by Dodel et al. 1998 [616] and used on Nuijten et al. 2001 [603], Palmer et al. 2002 [254] and Coyle et al. 2003 [575] as model to study the cost-effectiveness of drug therapies in different countries. The reason to select this model were: 1) it was the most used in the literature works and 2) it is the model with the minimum number of states and transitions, according to previous experiences such features are recommend for carrying out a HTA study on early stages [540]. This model sets a cut-off point at of 25% off time as the indicator to classify a patient as moderate or severe PD patient. Dodel et al. showed that significant levels of decrease in utility values were reached when patients had >25% off time an increase in costs was found if patients had >25% off time. Regarding the probability of transitions between the states they were defined as improvement (short-term improvement, moving the patient from > 25% off time to ≤25% off time) and progression (long-term disease progression moving the patient from ≤25% off time to > 25% off time). In the model, all patients started in the health state > 25% off time and the usual care is defined as a first cycle with no improvement from > 25% off time to ≤25% off time. Hence, these patients remained in the health state for > 25% off time for the entire time horizon unless they died [254], [575], [603], [616].

Figure 87 – Markov model proposed by Dodel et al. 1998 [616] and used within this work

- Model considerations
 - To build the model, data coming from the Nuijten et al. 2001 [603], Palmer et al. 2002 [254] and Coyle et al. 2003 [575] studies were used. As it was already mentioned, to calculate cost and utilities in health care is not always a simple task, for that reason, all the cost-effectiveness studies usually take an average value to perform a base study and then, explores a range of values according to the data available (sensitivity study). In this case, for the utilities, probabilities of transitions, mortalities rates, discounting rates and costs have been taken from the three mentioned studies. Specifically, the average value from the base case of the three studies has be used as base case in this study, for the minimum and maximum values of the ranges the absolute minimum and maximum values have be used to define the range values of this study.

- The case of the costs linked with each of the states was slightly different. Before to calculate the average value for the base study and the range with the minimum and maximum values, two operations were carried out, the first of them was the transformation of all the costs from their currency to US dollars using the exchange rate of the time of the study (AONDA website was used²¹⁵ since it offers a currency exchange tool with historical information), then an inflation calculator was used to transform the cost values to their costs nowadays (the Inflation calculator of the Bank of Canada was used²¹⁶), finally US dollars were transformed to Euros (AONDA).
 - To carry out the study the Markov Chain Simulation for Health Economics²¹⁷ tool developed by the University of Nottingham under the Match framework²¹³ was used.
 - The analysis was done under a societal perspective by incorporating direct medical and non-medical care costs associated with PD progression.
 - To conduct the threshold analysis the maximum value that the decision maker is willing to spend for each unit of outcome gained (QALY) will be used to calculate the correspondent input value and cost associated with that outcome.
 - One-way sensitivity analyses was undertaken to investigate the robustness of the base case analysis to certain intrinsic values of the model (progression and mortality rates, discounting rates and utilities) as well as hypothesis of the innovation performance (probability of progression from moderate to severe state and the increase in the utilities values). On the one-way sensitivity analyses the model is re-evaluated ranging the input variables above and below the base case.
 - Additional key assumptions were that: (i) patients receiving therapy continued their initial therapy for the duration of the model, regardless of improvement or disease progression; and (ii) clinical events during the first cycle occurred at the middle of this cycle, hence, a half-cycle correction was applied to all clinical and economic outcomes. A half-cycle correction was applied to all clinical and economic outcomes. Clinical events during the first cycle (e.g. improvements or worsening of off-time) occurred at the middle of the cycle.
- Assumptions of the PERFORM system:

As a general rule, neurological conditions such as PD are monitored in the course of a short visit to the hospital, on this circumstances obtaining an unambiguous depiction of the patient's status and disease progress is usually difficult. The available methods of recording daily symptoms and critical events (such as a patient diary) often lack objectivity and they depend on the capacity of the patients to understand and properly identify their own symptoms. The PERFORM platform successfully overcomes both of the above drawbacks and provides a powerful and objective decision support tool to health professionals. As it was already discussed (see 3.6 Progression and 3.8.1.1 Dyskinesias and wearing-off) typical treatment on PD is based on levodopa which after some time starts to loss efficacy and patients start to show motor fluctuations. PERFORM system was focus on increase the performance of the medication through a better and more objective monitoring of the patients' symptoms. There are different strategies to improve the medication performance, for example the simply re-schedule of the drug intakes, more intakes along the day making lower dosage each time. Another alternative is to incorporate additional pharmacotherapy to improve the performance of the treatment and, at the same time, reduce some of the side effects. As an example, entacapone is often used together with levodopa, allowing a 10% to 12% which leads to a substantially reduced off time by 17%-22% depending on the study. To ensure best value in outcomes and resource utilisation, clinicians should focus on management strategies that maximise quality of life while

²¹⁵ www.oanda.com (Last date accessed: December 2015)

²¹⁶ www.bankofcanada.ca/rates/related/inflation-calculator (Last date accessed: December 2015)

²¹⁷ www.nottingham.ac.uk/match/research/tools/markovtoolmain.html (Last date accessed: December 2015)

minimising the impact of disease progression as well as to delay the move to more expensive institutional care. This can be achieved by optimising therapies to treat motor symptoms and recommending interventions for non-motor complications, such as depression, where appropriate [159]. The most relevant features of PERFORM for this model are its ability for the detection and assessment of LID ranges from 85.4% to 93.73% and the accuracy in the On-Off detection 88.2 ± 3.7 % (best, 93.7% and worst 87%). Regarding the cost of the system, within the exploitation plan of the project it was calculated the costs of the system per patient, as well as the cost of maintenance and licence per patient, reported in Table 51. To estimate the impact in the QoL of PD patients, Hechtnera et al. (2014) run a cross-sectional study 817 PD patients in France, Germany, Italy, Spain, and the UK. QoL was measured with the generic EuroQoL 5-Dimension questionnaire (EQ-5D) and the disease-specific Parkinson's Disease Questionnaire-39 (PDQ-39) where they found that On-Off fluctuations were associated with a 7.1 percentage point decrease in the EQ-5D ($p < 0.001$) and a 3.6 percentage point deterioration in the PDQ-39 ($p = 0.01$) [617]. Dyskinesias were not seen to affect global QoL scores, but had detrimental effects on the PDQ-39 dimensions activities of daily living, cognitions, stigma, and bodily discomfort. Nevertheless, during the Phase IV of the PERFORM project, 23 PD patients were asked about this fact with a VAS. An increase of 0.083 points were reported. Taking into account this information, the percentage of patients showing motor fluctuations and the accuracy of the PERFORM system to detect these events the incremental utility of each state were calculated Table 51. Patients on the moderate state will benefit of a better management of the disease, in the case of patients in the severe state, part due to an increase in the utility value (better dyskinesias management and less On-Off fluctuations) as well as a potential change in the probability of improvement (moving from severe to moderate) to a value higher than zero (standard treatment).

Parameters		Source (base case, min, max)			Base case	Range	
		Nuijten et al. (2001) [603]	Palmer et al. (2002) [254]	Coyle et al. (2003) [575]		Min	Max
Transition probabilities	Progression	(0.183, 0.09, 0.28)	(0.179, 0.179, 0.474)	(0.179, 0.09, 0.281)	0.180	0.09	0.474
	Mortality rate	(0.032, 0.027, 0.035)	(0.032, 0.027, 0.035)	(0.032, 0.027, 0.035)	0.032	0.027	0.035
Utilities	Moderate	(0.75,-,-)	(0.79, 0.75, 0.82)	(0.79, 0.75, 0.086)	0.78	0.75	0.86
	Severe	(0.64,-,-)	(0.63, 0.62, 0.64)	(0.65, 0.55, 0.76)	0.64	0.55	0.76
Time horizon		5	5	5	5		
Discounting	(%)	(5, 0, 5)	(3, 0, 5)	(4, 0, 5)	4	0	5
Cost - Moderate (€ 2015)	Direct medical	1744.05	1507.77	1441.68	1559.67	1441.68	1744.05
	Direct non-medical	762.891	661.548	1108.93	824.09	661.55	1108.93
	Total	2506.94	2169.32	2550.61	2383.36	2103.22	2852.98
Cost - Severe (€ 2015)	Direct medical	4800.9	5201.21	6371.45	5418.61	4800.90	6371.45
	Direct non-medical	2475.07	2262.82	1620.46	2085.89	1620.46	2475.07
	Total	7275.97	7464.03	7991.91	7504.50	6421.36	8846.52

Table 50 – Input variables for building the Markov model of the base case

Parameters		Source	Base case	Range	
				Min	Max
Patients with motor complications	Percentage (%)	[252]	0.65	0.5	0.8
On-Off management	On-Off detection accuracy	PERFORM	0.88	0.88	0.98
	Percentage of QoL increase (QALY)	[617]	0.035	0.024	0.035
Dyskinesias management	Dyskinesias detection accuracy	PERFORM	0.85	0.85	0.93
	Percentage QoL increase (QALY)	PERFORM	0.046	0.035	0.062
PERFORM cost	Device and setup cost (€)	PERFORM	2,597	2,597	2,597
	6-month cost (€)	PERFORM	500+120	500+120	500+120
Transition probabilities	Improvement (entacapone)	[254], [575], [603]	0.332	0.208	0.464

Table 51 – PERFORM inputs for the Markov model

- Limitations of the model:

The results of any modelling study must be interpreted with caution, particularly in an early stage of the development. Universally, decision analytic techniques such as the Markov model are subject to inherent structural weaknesses [254].

- First, this model was build taken into account different data sources from former studies, some of this data were obtained from clinical trials which not necessarily represent actual clinical practice. The data collected under clinical trial was constricted to a protocol of data collection and to specific conditions that may not be easily replicated outside the trial setting [254]. Additionally, as it was already discussed measuring health care costs of a specific disease is not a simple task and there is a high degree of inconsistency in the values but also in the measurement from country to country and even from region to region. Thus, the data used could not represent the specific treatment patterns and/or specific costs, for example lost productivity is not considered in many studies arguing that is a non relevant cost for PD patients, since many researchers links PD and elderly. However, the Markov model adopted conservative assumptions wherever possible, the most important of these being the assumption that beyond 6 months, no further improvement in off-time is experienced by patients receiving entacapone.
- Second, progression of the disease is only characterized by two levels based on off-time: $\leq 25\%$ and $>25\%$. The use of a model with a reduced number of states and transitions makes evident its limitations in modelling the nature of a complex problem and in its scope. Nevertheless, the use of this kind of model is recommend for early HTA studies, the simplicity of the model facilitates its universality both in its behaviour and in the data used to build it. The main restriction is that due to its simplicity the analysis could not go further in terms of specific details e.g. which is the profile of patients incurring in specific costs, which kind of costs constraint the most the cost-effectiveness of the technology, which process limited the economic viability of the technology, etc. Nevertheless, as technology matures and more data is available more specific models can be used, actually, depending on the evolution of the technology only specific parts of available models could be used for a deep analysis of the technology target, i.e. PD population on stages 1 and 2 in the H&Y scale.
- Third, the model focuses on the optimization of drug therapy, nevertheless, telehealth might potentially result in increased productivity through the reduction of work absences (from hospitalizations, consultations, emergency room visits, etc.) both regarding the patients

when the disease and caregivers. It could also prevent and mitigate lack of adherence to treatment as well as prevent falls and complications related to falls [573]. In the professional side, remote monitoring can prevent unnecessary face-to-face visits and the availability of more accurate and objective assessment of severity of the disease could increase the quality of the service and the therapy. But also, it has been proved in a wide range of works that telemedicine has the ability to reduce or avoid costs by utilizing communications technology, which eliminates the need for transportation, reduces the waiting and/or consultation time can be reduced via telemedicine consultations [573]. The big challenge to measure from the economic point of view PERFORM project and related systems is that its potential to reduce the time required to diagnose efficiently and accurately, and increase access to healthcare as well as to reduce healthcare utilization through early detection of a condition, timely treatment, and the avoided need for further tests [573]. The medication change proposal and the stability and worsening modules of the PERFORM system are intended to work as a Decision Support System (DSS) for the neurologist aimed at saving time, increasing efficiency and reducing errors. Also, the digitalization of the monitoring information, food and drug intakes opens a many future improvements in the abovementioned areas. Future works should focus on the collection of this kind of information in order to transform them in economic terms and include their effects in the Markov model.

9.4.4 Results

9.4.4.1 General scenarios

The primary study carried out was the simulation of different general “what-if” general scenarios. This first approach was aimed at exploring the potential maximum incremental cost that the novel technology should cost under different scenarios, such as changes in the probabilities of disease progression and improvement and variations in the utilities associated with each of the states. To simulate these scenarios, a threshold analysis was carried out, on this approach the parameters under study were modified and the incremental cost was adjusted to achieve the desired ICER outcome. Six different “what-if” scenarios were evaluated:

- The first two scenarios considered the variation of the probability of disease progression, from moderate to severe state. The results were the maximum cost increase in the moderate state (*Figure 88*) and in the severe state (*Figure 89*).
- Third “what-if” scenario analysed the maximum incremental cost of moderate state by increasing the utility of that state (*Figure 90*).
- Forth “what-if” scenario analysed the maximum incremental cost of severe state by increasing the utility of that state (*Figure 91*).
- Finally, the last two “what-if” scenarios explored the maximum incremental cost of the severe state (*Figure 92*) and the moderate state (*Figure 93*) by changing the improvement probability.

These six scenarios provided a general overview of the potential effect that the different model parameters have in the ICER values. They provide a quantitative reference for any health technology related to Parkinson’s disease and could be useful to understand and to orientate the research, particularly in early stage of development, towards an efficient cost-effectiveness path. Regarding the increasing of the disease progression, lower values led to higher incremental costs (*Figure 89*, *Figure 90*). Keeping patients in the moderate state is more cost-effective since the quality of life of patients is higher in that state and the cost associated is lower. Although this general trend is common in both scenarios, they response is slightly different. While the behaviour in the moderate state is almost linear, the lower the probability of progression the higher the incremental costs, in the case of the severe case shows a non-linear response with a threshold value around 0.120. Thus, any improvement from the base case value (0.180) to the threshold value (0.120) does not allow any additional incremental cost in a cost-effective way.

Regarding the values, due to the high cost and low utility of the severe state, by reducing the progression of the disease allows a higher incremental margin in the severe state than in the moderate state. On the utility cases (Figure 90, Figure 91) both the behaviour and the margins in both cases are quite similar, a linear response to a utility increase achieving similar values (slightly higher in the severe state). Finally, the response to an increasing improvement probability showed a linear response for the case incremental cost in the severe state (Figure 92) and a non-linear response in the case of the moderate state (Figure 93). Since the base case does not contemplate a natural improvement of the patient, this scenario showed the higher range of improvement, and the severe case reflected the higher incremental margin cost, at least in the theory.

Figure 88 – Maximum incremental cost in the moderate state according to the progression probability value

Figure 89 – Maximum incremental cost in the severe state according to the progression probability value

Figure 90 - Maximum incremental cost in the moderate state according to the utility in the moderate state

Figure 91 – Maximum incremental cost in the severe state according to the utility in the severe state

Figure 92 - Maximum incremental cost in the severe state according to the improvement probability

Figure 93 - Maximum incremental cost in the moderate state according to the improvement probability

9.4.4.2 PERFORM evaluation

In the second part of the Markov analysis, the innovation model was built based on the information detailed in *Table 51* regarding the performance and cost of the PERFORM system. Then, it was confronted with the base case and the cumulative costs and QALYs were calculated for each one and the ICER was calculated at year 5. Finally, incremental costs and QALYs at year five were plotted in a Δ QALY- Δ C chart together with different ICER thresholds. Moreover, this analysis was carried out both from the societal perspective (*Figure 94*, *Figure 95* and *Figure 96*) and from the third party perspective (*Figure 97*, *Figure 98* and *Figure 99*). The ICER values estimated by the model are 6,397.36 for the societal perspective and 8,977.20 for the third party perspective. These values suggest that PERFORM will not be a cost-saving technology (positive ICER) but these values are below most of the ICER thresholds commonly accepted worldwide (*Table 52*). By examining the cumulative cost charts, both from the societal and third party perspectives (*Figure 94* and *Figure 97*), it can be seen that the base case lines and the PERFORM lines get closer by the end of the simulation. These trends are explaining for the huge initial inversion that a telehealth system requires for the start-up of the system. This initial investment necessarily requires a long-term vision, with this perspective in mind, the increasing cumulative QALYs achieved by the PERFORM (*Figure 95* and *Figure 98*) overcome the initial investment, which on the other hand gets amortized over time. Then, by placing the PERFORM innovation from the societal and third party perspective in the Δ QALY- Δ C plane it is possible to see the margin in incremental cost to the different ICER thresholds (*Figure 96* and *Figure 99*), these values are detailed in *Table 52*. For example, taking the 30,000€/QALY as reference, the PERFORM system has a margin of 20,855.28€ incremental costs in the societal perspective and 18,575.73€ incremental cost in the third party perspective.

Finally, as it was already discussed, it is always highly recommended to carry out a sensitivity analysis to understand the robustness of the model to the uncertainty of the model parameters. The sensitivity analysis is a good indicator of which one of these parameters makes the estimation weaker. In this case, the sensitivity analysis was carried out both with model parameters (probability of disease progression, discounting, costs and utilities) and innovation performance (management of dyskinesias and On-Off). The results are reported in *Figure 100*, according to them, the model is insensible to all the ranges tested, i.e. in all cases the ICER values are under the 20,000€/QALY threshold, and only the worst case of the progression probability is above the 10,000€/QALY threshold. Also, this parameter shows the wider range of fluctuations from the higher ICER to a negative ICER

value. Except the Utilities case, all the model parameters are the ones that produces the higher fluctuations. On the other hand, the variations regarding the PERFORM performance are more constraint.

Figure 94- Cumulative costs for PERFORM and for the base case from the societal perspective

Figure 95 - Cumulative QALYs for PERFORM and for the base case from the societal perspective

Figure 96 – PERFORM in the $\Delta QALY$ - ΔC plane from the societal perspective

Figure 97 - Cumulative costs for PERFORM and for the base case from the third party perspective

Figure 98 - Cumulative QALYs for PERFORM and for the base case from the societal perspective

Figure 99 - PERFORM in the $\Delta QALY$ - ΔC plane from the third party perspective

Threshold	Margin cost (€)	
	Societal perspective	Third party perspective
10,000 €/QALY	3183.28	903.73
20,000 €/QALY	12019.28	9739.73
30,000 €/QALY	20855.28	18575.73
40,000 €/QALY	29691.28	27411.73

Table 52 – Margin between ICER values and the different thresholds

Figure 100 – Sensitivity analysis for the PERFORM analysis

9.5 Discussion

Telehealth systems have been claiming for a long time that the implementation of this kind of systems in clinical practice may improve the efficiency and effectiveness of the healthcare delivery. Nevertheless further proofs are required in order to provide policy makers and healthcare providers of the necessity of the deployment of telemedicine systems and their potential benefits, not only their technical or clinical validation, but their cost-effectiveness and practicability to be deployed on clinical practice. A closer collaboration with the health

economics field is required in order to translate the already known methodologies for the economic evaluation of drugs and medical devices to the telehealth area i.e. translate the system outcomes into monetary values both for the individual/patient, hospital/healthcare provider or societal/policy makers perspectives [19]. Within this chapter two different types of methodologies have been proposed and used to perform an early HTA study of a novel telehealth platform for PD management in an initial stage of development. The first of them, the AHP methodology (see 9.3 *AHP study*), was aimed at identifying which were the user needs and the requirements for this kind of systems. AHP provides not only a qualitative information but also, it provides a rank with the importance – or weight – of each of these requirements. Thus, AHP defines a framework that can be used for the quantitative assessment of telehealth systems. Instead, the second methodology proposed, Markov models for early HTA (see 9.4 *Markov modelling for early HTA study*), was focused on estimate the economic impact of the telehealth platform by exploring different “what-if” scenarios which allow to speculate with diverse settings and the economic impact that they could generate.

First of all, AHP contributed to the elaboration of a common hierarchy, integrating user needs from different stakeholders and promoting the discussion and the agreement into a common framework. Moreover, AHP effectively supported the user need elicitation as well as the assignment of different weights and priorities to each need and consequently, it helped in the elaboration of common framework of assessment of telehealth systems for PD management and monitoring. It has been used to clearly identify the key user needs that a telehealth system for the remote monitoring and management of PD should fulfil, specifically, the *On-Off fluctuations detection*, *Increase wearability acceptance*, *Increase self-management support* and *Increase self-management support* have been identified as the most relevant by a group of clinicians and engineers with experience in the field.

Thus, this work offers a validated framework of evaluation for researchers and developers working in the field of telehealth for PD management and assessment a useful tool for the identification of improvement areas. In the case of the PERFORM system three areas of future improvement were identified: 1) the involvement of the carers in the loop was strongly recommended according to the AHP results, 2) the telehealth system and the information from the monitoring and assessment should be used to educate and feedback patient and carers according to their specific needs in order to make the platform actually useful and 3) the incorporation of cognitive and behavioural analysis to the motor assessment may significantly enhance the modelling of the disease. These elements have been considered for the design of a new research project, the PD Manager project, in which the role of the caregivers, behavioural and cognitive monitoring and patient education have been included as important pillars for a new generation of mHealth services for Parkinson disease. A second conclusion is that no significant differences were found between the clinician and technical groups. Moreover, AHP proved to be a useful tool to improve the communication and promote the discussion among the different stakeholders and the different professionals involved in the design of telehealth systems. In this case a clear agreement between both groups were found and only one of the seventeen user needs show a slight discrepancy between these groups (only at a LW level). Moreover, the high levels of correlation within the answers and of group consensus confirm that this framework could be useful for future evaluation of technologies in PD and thus support the decision-making process in their adoption.

Regarding the results provided by the Markov modelling, first of all, a set of generic “what-if” scenarios have been provided, this could be useful for any researcher or developer approaching the field of telehealth for PD management. The results provided by these simulations provide a quick overview of the potential effects, in economic terms, according to the expected results of the system performance. This information could also be very valuable for the decision maker process both at the level of health care managers and policy makers. The picture provided by these scenarios could be useful designing cost-effective strategic lines and policies starting with very limited input data. The second part, where the PERFORM system is under analysis showed an early HTA of this system presenting results that suggest that PERFORM could be cost-effective. At least, the data aims at take the system to next stage and to collect new data to improve the model and the evaluation of the cost-effectiveness of the system. On this regards, a direct measure of the incremental utility due to the use of the PERFORM could significantly improve the accuracy of the results. Also, an area of improvement and with no data available in the current moment is the cost savings generated by a better efficiency in the management of the PD related to the use of novel technologies. In any case, PERFORM is a large and complex system requiring training and integration

followed by an initial period of commissioning and behaviour change. Even if the simulation carried out with the Markov model showed that the investment could be returned quickly (the ICER is cost-effective in the fifth year) and the trend reflects that it could be even cost saving after that, the set-up of the system will required a significant investment and effort by the uptaking institution. PERFORM is defined as a “long hauls” innovation characterized by a slow, phased user adoption on both supply and the demand side, implying significant effort in order to achieve adoption on a satisfactory scale and move the product upwards towards an extensive adoption.

Chapter 10 Conclusion and discussion

10.1 Research objectives evaluation

Based on the work carried out in this thesis, the *Table 53* compiles the results and conclusions of the previous sections the answer the research objectives, then the research questions have been addressed.

Research objective		
Research objective 1 (R01) – Design and development of methods for extracting clinically meaningful information, developing a quantitative assessment tool for motor symptoms on PD based on data gathered using wearable and low-cost sensors.	Research objective 1.1 - To design and develop machine learning algorithms for the automatic assessment of bradykinesia and to design and develop an algorithm for the automatic assessment of the gait performance based on the mHealth platform and wearable devices.	Sections <i>7.1 Bradykinesia and akinesia assessment</i> and <i>7.2 Gait assessment</i> shows the feasibility of using wearable accelerometers to properly assess bradykinesia and gait in PD populations. Bradykinesia accuracy (using UPDRS as reference) ranges from 70% in walking activities to 87% in hand movements. These results have improved using a meta-analysis of the epochs using the redundant information provided by the continuous monitoring and the overlapping between the epochs to enhance the final results. Regarding the estimation of the gait features for PD, the implemented methods offer an estimation of the step frequency, stride length and speed with a mean error of $3.36\% \pm 2.57$, $7.31\% \pm 4.69$, and $7.77\% \pm 5.34$ respectively, using only an accelerometer placed in the patient's belt. Moreover, SampEn has been suggested as a valid method for the gait quality.
	Research objective 1.2 - To carry out a feasibility study to implement the automatic assessment methods into a telehealth system located at patients' homes.	Sections <i>7.1 Bradykinesia and akinesia assessment</i> and <i>7.2 Gait assessment</i> explored also the feasibility of translating the abovementioned methods in an unsupervised environment. The results obtained by the gait assessment suggest that it is feasible to use it in an unsupervised environment for continuous monitoring of gait performance. Regarding the bradykinesia assessment an important limitation has been found, the best results were obtained while patients were

		moving his hand. At least 5 seconds length are required in order to calculate the bradykinesia, which is a serious limitation since in real environments it is not frequent to find these kind of events.
Research objective 2 (R02) – To carry out a research study to the compliance of a monitoring system by the final users, i.e. the patients. Identifying potential backwards and direct feedback that will reflect the actual uptake from the final users.		<i>Chapter 8 Human Factors</i> studied the human factors of the PERFORM project. Particularly, it covered the wearability and patient acceptance of the Body Area Network (BAN). Generally speaking, patients rated the system positively, and in some cases they reported to feel more comfortable knowing that a clinical team was following them. The main complaints were related with the attachment method (especially for self-wearing the devices) and the limitation on some daily activities such as washing their hands or the dishes as a consequence of not wearing a waterproof device. Finally, some of the results suggest that eventually some patients could show some kind of social stigma by wearing a visible device that could point them as a PD patients.
Research objective 3 (R03) – To clearly understand which are the key requirements and needs of the different stakeholders involved in this ecosystem in order to translate this kind of system from a research prototype to the current clinical practice.	Research objective 3.1 – To elicit experts knowledge and user needs to understand which the key elements are for this kind of systems and to build a HTA assessment framework.	On the section 9.3.9 <i>Evaluation of the PERFORM system</i> the key user needs for the implementation of a telehealth system for PD manager were elicited using the Analytic Hierarchy Process with a group of domain experts. The result was the identification of 17 user needs grouped in five categories and weighted according to their importance, both globally and locally within each category. This result provides a useful guide for the design of new telehealth systems as well as a framework for the evaluation of already existing ones.
	Research objective 3.2 – To use the HTA assessment framework to evaluate a telehealth system as a study case.	At this point the PERFORM system was evaluated according to the AHP framework previously developed. Results reported in 9.3.8 <i>Results of the AHP study</i> , and summarized in the <i>Figure 86</i> show that this system does not cover important user needs such as increasing the self-management of the patients, involving the caregivers in the loop and increasing the knowledge of patients and carers.
Research objective 4 (R04) – To design and to develop a	Research objective 4.1 – To explore and to identify tools	Within the <i>Chapter 9 Health Technology Assessment</i> , different methodologies for early

methodology for the assessment of potential economic impact of a novel technological solution and apply it to a specific tool: PERFORM as a case of study.	and methods for the economic assessment of novel technological solutions.	Health Technology Assessment in eHealth and telehealth have been explored. Finally, two methodologies (AHP and Markov modelling) have been suggested and applied to the particular case of telehealth for PD management. These results can be used for any developer or research working on telehealth for PD management, but also, the methodology can be extrapolated to any other telehealth system.
	Research objective 4.2 – To study the potential cost-benefit scenarios of telehealth solutions for PD management.	<p>Within the <i>9.4 Markov modelling for early HTA study</i> section, Markov modelling was used to simulate different “what-if” scenarios, exploring the potential cost-effectiveness implications of using telehealth for PD management. These results, summarized in <i>Figure 88, Figure 89, Figure 90</i></p> <p><i>Figure 90 - Maximum incremental cost in the moderate state according to the utility in the moderate state</i></p> <p>, <i>Figure 91, Figure 92 and Figure 93</i>, offer a valuable tool for all the researchers and developers in the field in order to understand the potential cost-benefit implications of their work. They can also be useful to advice and support the decision making process of policy-makers and healthcare managers regarding the uptake of new technologies in clinical practice and to design and guide future strategic decisions.</p>
	Research objective 4.3 – Apply such tools to estimate the economic impact and cost-benefit of the PERFORM system.	In the second part of the <i>9.4 Markov modelling for early HTA study</i> section, the Markov model simulation was used to explore the potential cost-benefit of the PERFORM system. The results suggest that the deployment of a telehealth system such as PERFORM could be effective under acceptable cost.

Table 53 - Evaluation of the research objectives

Based on the results achieved for the research objectives it is possible now to answer the research questions presented:

- **Research question 1 (RQ1)** – Is it feasible to perform a continuous monitoring of the motor symptoms of PD patients in a home environment using wearable technologies? Which are the methodologies to carry out such monitoring? The results provided on the RQ1 reflect the feasibility of using machine learning as a valid tool for the assessment of the bradykinesia and the use of the accelerometer data for the assessment of the gait performance.

- **Research question 2 (RQ2)** – Is this information clinically relevant for the monitoring and management of PD patients? Could this information contribute to an efficient management of Parkinson's disease patients? Again, the results provided on the R01 showed that the methods explored within this work provide a useful tool for the continuous monitoring of the symptoms offering as well information clinically relevant for the management of the disease. Results also showed that these methods could be implemented as well in the context of a telehealth system at patients' homes.
- **Research question 3 (RQ3)** – Which are the key factors for the system acceptance by the PD patients? Results from the R02 provided an analysis of the factors regarding the acceptance of the system for the patients.
- **Research question 4 (RQ4)** – In order to translate this kind of solutions in the current clinical practice, which are the requirements and needs that must be taken into consideration? Results from the R03.1 provide a list of key elements for the implementation of a telehealth system for PD management. Moreover, the elements of such list were sorted according to their importance. This framework was then used to evaluate the PERFORM system as a case of study (R03.2)
- **Research question 5 (RQ5)** – Is it possible to estimate which is the economic impact of a technological solution for PD management? In that case, which is the economic impact of such solution and how does it impact the different stakeholders involved? Results of the R04.1 provide a set of tools and methods for economic assessment of novel technological solutions which were used to study the potential cost-benefit scenarios of telehealth solutions for PD management (R04.2) and finally were used to estimate the economic impact and cost-benefit of the PERFORM system as a case of study (R04.3).

10.2 Discussion

Telehealth is more than using wearable sensors at patients' homes, particularly when talking about chronic disease management. It requires to transform the role of patients and caregivers in the care path, shifting their position from passive to active and therefore, to move them to the centre of the healthcare process. The first and most obvious reason is that home telehealth systems need the participation and cooperation of patients and caregivers in order to work efficiently, actually, just to work. Even if telehealth systems are designed to work seamlessly during the day, patient acceptance and cooperation are essential for a real adoption of the technology. In the PERFORM context the algorithms developed have proved their feasibility to be integrated into a home telehealth system, although some areas of improvement have been also identified and suggested. Nevertheless, in order to achieve a good understanding of the disease in the patient and to build a rigorous profile of the patient, context information (i.e. food and medication intakes) is required. That means it is needed to invest time and effort in the patients and caregiver training, in order to provide them with the adequate skills to use the system properly as well as follow the best practices for GUI design. Moreover, it is critical to make them aware of the importance of the self-assessment, not only for a reliable remote monitoring but also for an improvement of their disease management. It is crucial to keep in mind that different subjects can perform different walking patterns and even the same subject can walk differently depending on the situation. The lack of contextual information makes working on unsupervised environments a very challenging task. Parameters related to the walking analysis are not fully representative (speed and stride length are features which need to be in a context, we need to be aware of the fact that sometimes the patient could walk slower than usual because he wants e.g. because he is relaxed at home) and the use of alternative measures like entropy can be a better choice. As a general recommendation, the involvement of an active patient becomes crucial in order to contextualize as much as possible the raw biomedical signal. From this experience, it is also relevant to remark the importance of working on more accurate activity recognizers, as well as on affective recognizers which are able to segment the activities and moods of the subject during their daily life. Studying the walking pattern on PD patients is a promising tool in order to develop a continuous monitoring system capable of identifying the different phases of the disease within the day (OFF-ON). This system could easily alert the professionals when the patient faces an OFF phase, measuring the degradation

of the walking pattern, indicating that a reschedule in the medication treatment is needed. Contextual data is crucial in order to be able to interpret and contextualize the patient gait performance. The use of a patient diary provides excellent information to correlate with the movement assessment, and the new generation of smartphones is a convenient platform to integrate the patient diary and the data collection coming from the limbs' sensors. The future of this technology will likely move to the use of these platforms.

Education of both patients and care givers is also a key element for the transformation and technology adoption. Providing them with the appropriate information about self-management and the importance of taking an active role, intervention adherence and so on is critical. The PERFORM system focuses on the needs of patients (seen as the demand side of health care) and clinicians (seen as the supply side of health care, but also part of the health market demand). As far as healthcare demand is concerned, the crucial question is patient adoption, whereas on the healthcare supply side issues to be examined concern adoption from physicians- neurologists, nurses, care takers and hospitals. Examining the demand side and the patient adoption, the Human Factors study suggests that, apart from design limitation, some of them due to be working with a research prototype, patients willingness adoption is high. However, it is important to highlight again that some patients involved in the study suggested that they would suffer a moderate social stigma were they wearing a device that pointed them as a PD patients. On this regard, the integration of the monitoring devices into commercial wearables could be a good solution that could also increase the willingness of adoption from the patients. Regarding the adoption by the professional side, two interesting tools have been generated within this work. The first one, a result of the AHP study, provides an objective framework for the evaluation of telehealth technologies for PD management, but also a useful tool to guide the design of future systems. On the other hand, the results of the Markov simulations provide an objective tool to the cost-benefit estimation of such technologies. These results can be useful both for the evaluation of already existing system and for the decision support of new technology developments, policies or strategic decisions. It is important to highlight that the European health market presents a very heterogeneous environment. Healthcare funding has followed different trajectories in each state with some countries using mainly public funding for healthcare (e.g. UK, Ireland, Portugal) and others mainly financed through social insurance (e.g. France, Germany). In states such as Germany, complete private health insurance is available as an alternative to the public health service, whereas in Austria and France private insurance is only available as a supplement to the public health service. Studies suggest the adoption of new technology within a European Health System is a multifactorial process which is affected by i) doctors willingness to champion the technology, ii) demand from the public or Media, iii) perception by hospital managers of the effect on reputation iv) attractiveness to staff and v) inducements from manufacturers. The uptake of technologies is strongly influenced by hospital structure, with relatively rapid diffusion through large private hospitals and slower diffusion through health systems with centralised hospital budgets. Decisions about the adoption of new technology should be based on clinical trials and economic analysis.

Finally, the incorporation of the automatic assessment of non-motor symptoms has been emerged as one potential area of improvement for telehealth systems. The collection of data such as cognitive skills and sleep quality and their systematic study and correlation with the disease progression and motor degradation could be extremely beneficial for a better understanding and managing of the disease. So far, only a few works have analysed these issues systematically on PD patients and almost none of the system analysed in the state of the art cover these topics. Moreover, telehealth could contribute to enhance the current clinical practice not only by providing more data and information about these signs and symptoms and their progression but also by improving the management of them enabling multidisciplinary teams working together.

Resume

Jorge Cancela received the B.S. in Telecommunications Engineering and the M.Sc. degree in Telemedicine and Biomedical engineering from Universidad Politecnica de Madrid, Spain, in 2009. Currently, he is a PhD candidate on biomedical engineering at Universidad Politecnica de Madrid. He received a grant to conduct his research from the Campus de Excelencia Internacional CEI Moncloa, Universidad Politecnica de Madrid (UPM) and Universidad Complutense de Madrid (UCM). He was visiting researcher at the Motion Analysis Laboratory at Spaulding Rehabilitation Hospital (USA) in 2011, at the Duke-National University of Singapore (Singapore) in 2012 and at the Politecnico di Milano (Italy) in 2015. Since 2009 he has worked with the Life Supporting Technologies group at UPM where he has been involved in several R&D projects dealing with information and communication technologies (ICT) in the healthcare field. In 2015, he received the IDEA² Madrid Awardee from the Madrid-MIT M+Visión Consortium and a merit prize at the Young Investigator Award 2015 from the International Federation for Medical and Biological Engineering. His research interests involve the design, development and evaluation of eHealth, mHealth and telehealth systems, including the evaluation of human factors, interaction and health technology assessment as well as the used of machine learning in this field.

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Appendix I. Unified Parkinson's disease rating scale

Section I. MENTATION, BEHAVIOR AND MOOD

1. Intellectual impairment:

0	None.
1	Mild. Consistent forgetfulness with partial recollection of events and no other difficulties.
2	Moderate memory loss, with disorientation and moderate difficulty handling complex problems. Mild but definite impairment of function at home with need of occasional prompting.
3	Severe memory loss with disorientation for time and often to place. Severe impairment in handling problems.
4	Severe memory loss with orientation preserved to person only. Unable to make judgments or solve problems. Requires much help with personal care. Cannot be left alone at all.

2. Thought disorder: (DUE TO DEMENTIA OR DRUG INTOXICATION)

0	None.
1	Vivid dreaming.
2	"Benign" hallucinations with insight retained.
3	Occasional to frequent hallucinations or delusions; without insight; could interfere with daily activities.
4	Persistent hallucinations, delusions, or florid psychosis. Not able to care for self.

3. Depression:

0	Not present.
1	Periods of sadness or guilt greater than normal, never sustained for days or weeks.
2	Sustained depression (1 week or more).
3	Sustained depression with vegetative symptoms (insomnia, anorexia, weight loss, loss of interest).
4	Sustained depression with vegetative symptoms and suicidal thoughts or intent.

4. Motivation' Initiative:

0	Normal.
1	Less assertive than usual; more passive.

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2	Loss of initiative or disinterest in elective (no routine) activities.
3	Loss of initiative or disinterest in day-to-day (routine) activities.
4	Withdrawn, complete loss of motivation.

Section II. ACTIVITIES OF DAILY LIVING (DETERMINE FOR "ON/OFF")

5. Speech:

0	Normal.
1	Mildly affected. No difficulty being understood.
2	Moderately affected. Sometimes asked to repeat statements.
3	Severely affected. Frequently asked to repeat statements.
4	Unintelligible most of the time.

6. Salivation:

0	Normal.
1	Slight but definite excess of saliva in mouth; may have night-time drooling.
2	Moderately excessive saliva; may have minimal drooling.
3	Marked excess of saliva with some drooling.
4	Marked drooling, requires constant tissue or handkerchief.

7. Swallowing:

0	Normal.
1	Rare choking.
2	Occasional choking.
3	Requires soft food.
4	Requires NG tube or gastrostomy feeding.

8. Handwriting:

0	Normal.
1	Slightly slow or small.
2	Moderately slow or small; all words are legible.

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3	Severely affected; not all words are legible.
4	The majority of words are not legible.

9. Cutting food and handling utensils:

0	Normal.
1	Somewhat slow and clumsy, but no help needed.
2	Can cut most foods, although clumsy and slow; some help needed.
3	Food must be cut by someone, but can still feed slowly.
4	Needs to be fed.

10. Dressing:

0	Normal.
1	Somewhat slow, but no help needed.
2	Occasional assistance with buttoning, getting arms in sleeves.
3	Considerable help required, but can do some things alone.
4	Helpless.

11. Hygiene:

0	Normal.
1	Somewhat slow, but no help needed.
2	Needs help to shower or bathe; or very slow in hygienic care.
3	Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4	Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bedclothes:

0	Normal.
1	Somewhat slow, but no help needed.
2	Can turn alone or adjust sheets, but with great difficulty.
3	Can initiate, but not turn or adjust sheets alone.
4	Helpless.

13. Falling (unrelated to freezing):

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0	None.
1	Rare falling.
2	Occasionally falls, less than once per day.
3	Falls an average of once daily.
4	Falls more than once daily.

14. Freezing when walking:

0	None.
1	Rare freezing when walking; may have start-hesitation.
2	Occasional freezing when walking.
3	Frequent freezing. Occasionally falls from freezing.
4	Frequent falls from freezing.

15. Walking:

0	Normal.
1	Mild difficulty. May not swing arms or may tend to drag leg.
2	Moderate difficulty, but requires little or no assistance.
3	Severe disturbance of walking, requiring assistance.
4	Cannot walk at all, even with assistance.

16. Tremor:

0	Absent.
1	Slight and infrequently present.
2	Moderate; bothersome to patient.
3	Severe; interferes with many activities.
4	Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism:

0	Normal.
1	Occasionally has numbness, tingling, or mild aching.

Appendix I

2	Frequently has numbness, tingling, or aching; not distressing.
3	Frequent painful sensations.
4	Excruciating pain.

Section III. MOTOR EXAMINATION

18. Speech:

0	Normal.
1	Slight loss of expression, diction and/ or volume.
2	Monotone, slurred but understandable; moderately impaired.
3	Marked impairment, difficult to understand.
4	Unintelligible.

19. Facial expression:

0	Normal.
1	Minimal hypomimia, could be normal "Poker Face".
2	Slight but definitely abnormal diminution of facial expression.
3	Moderate hypomimia; lips parted some of the time.
4	Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest:

0	Absent.
1	Slight and infrequently present.
2	Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.
3	Moderate in amplitude and present most of the time.
4	Marked in amplitude and present most of the time.

21. Action or postural tremor of hands:

0	Absent.
1	Slight; present with action.
2	Moderate in amplitude, present with action.

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3	Moderate in amplitude with posture holding as well as action.
4	Marked in amplitude; interferes with feeding.

22. Rigidity: (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0	Absent.
1	Slight or detectable only when activated by mirror or other movements.
2	Mild to moderate.
3	Marked, but full range of motion easily achieved.
4	Severe, range of motion achieved with difficulty.

23. Finger taps: (Patient taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.)

0	Normal.
1	Mild slowing and/or reduction in amplitude.
2	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4	Can barely perform the task.

24. Hand movements: (Patient opens and closes hands in rapid succession with widest amplitude possible, each hand separately.)

0	Normal.
1	Mild slowing and/or reduction in amplitude.
2	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4	Can barely perform the task.

25. Rapid alternating movements of hands: (Pronation-supination movements of hands, vertically or horizontally, with as large an amplitude as possible, both hands simultaneously.)

0	Normal.
1	Mild slowing and/or reduction in amplitude.
2	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

Appendix I

3	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4	Can barely perform the task.

26. Leg agility: (Patient taps heel on ground in rapid succession, picking up entire leg. Amplitude should be about 3 inches.)

0	Normal.
1	Mild slowing and/or reduction in amplitude.
2	Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.
3	Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.
4	Can barely perform the task.

27. Arising from chair: (Patient attempts to arise from a straight-back wood or metal chair with arms folded across chest.)

0	Normal.
1	Slow; or may need more than one attempt.
2	Pushes self-up from arms of seat.
3	Tends to fall back and may have to try more than one time, but can get up without help.
4	Unable to arise without help.

28. Posture:

0	Normal erect.
1	Not quite erect, slightly stooped posture; could be normal for older person.
2	Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.
3	Severely stooped posture with kyphosis; can be moderately leaning to one side.
4	Marked flexion with extreme abnormality of posture.

29. Gait:

0	Normal.
1	Walks slowly, may shuffle with short steps. But no festination or propulsion.
2	Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.
3	Severe disturbance of gait, requiring assistance.

Appendix I

4	Cannot walk at all, even with assistance.
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30. Postural stability: (Response to sudden posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0	Normal.
1	Retropulsion, but recovers unaided.
2	Absence of postural response; would fall if not caught by examiner.
3	Very unstable, tends to lose balance spontaneously.
4	Unable to stand without assistance.

31. Body bradykinesia and hypokinesia: (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

0	Normal.
1	Possibly reduced amplitude.
2	Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.
3	Moderate slowness, poverty or small amplitude of movement
4	Marked slowness, poverty or small amplitude of movement.

Section IV. COMPLICATIONS OF THERAPY (In the past week)

32. Dyskinesias. Duration: What proportion of the waking day are dyskinesias present? (Historical information)

0	Normal.
1	1-25% of day.
2	26-50% of day.
3	51-75% of day.
4	76-100% of day.

33. Disability: How disabling are the dyskinesias? (Historical information; may be modified by office examination.)

0	Not disabling.
1	Mildly disabling.
2	Moderately disabling.

Appendix I

3	Severely disabling.
4	Completely disabled.

34. Painful dyskinesias: How painful are the dyskinesias?

0	No painful dyskinesias.
1	Slight.
2	Moderate.
3	Severe.
4	Marked.

35. Presence of early morning dystonia: (Historical information)

0	No.
1	Yes.

36. Are any "off" periods predictable as to timing after a dose of medication?

0	No.
1	Yes.

37. Are any "off" period's unpredictable as to timing after a dose of medication?

0	No.
1	Yes.

38. Do any of the "off periods come on suddenly, e.g., over a few seconds?

0	No.
1	Yes.

38. What proportion of the waking day is the patient "off" on average?

0	None.
1	1-25% of day.
2	26-50% of day.
3	51-75% of day.
4	76-100% of day.

40. Does the patient have anorexia, nausea, or vomiting?

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0	No.
1	Yes.

41. Does the patient have any sleep disturbances, e.g., insomnia or hyper-somnolence?

0	No.
1	Yes.

42. Does the patient have symptomatic orthostasis?

0	No.
1	Yes.

Appendix II. Glossary of terms by TeleScope

Term	Definition
Ageing	The process by which minor impairment multiply (e.g. in relation to sight, hearing, dexterity, mobility and cognition), potentially leading to disability and dependency.
Ambient Assisted Living (AAL)	Independent living supported by unobtrusive systems, services and devices within the home.
Ambient Intelligence (Aml)	The intelligence, derived from systems and devices in built into environments that support Ambient Assisted Living (AAL).
Assistive Technology	Any item, piece of equipment, or product system that is used to increase, maintain, or improve the functional capabilities of individuals with disabilities.
eHealth	eHealth describes the application of information and communication technologies across the whole range of functions that affect the health sector. It aims to improve significantly the quality, access and efficacy of healthcare for all.
eInclusion	The policy direction of the EC that affirms the priority given to the social inclusion of citizens in ways furthered through the appropriate use of methods of electronic communication.
Electronic Health Record (EHR)	An electronic record that can be maintained directly by users / patients that securely holds information and data relating to their health history, medication and care received. Includes Personal Health Records.
Electronic Patient Record (EPR)	An electronic record regarding information and data of users / patients by which clinical decisions regarding their treatment can be made.
Empowerment	A process through which people gain or are afforded greater control over decisions and actions affecting their lives.
Health Coaching	see Health Training
Health Record	see Electronic Health Record
Home Telehealth	see Telehealth
Lifestyle Monitoring	The monitoring of environmental conditions, activity (movement or interaction with the environment) and physiology in order to identify situations or circumstances that reflect adverse changes in or threats to personal well-being. Represents an extension of Activity Monitoring.
Medical model of disability	The model of disability and ageing implies that people are disabled as a consequence of their own condition, and seeks to either remedy the impairment through medication, rehabilitation and surgery, or through adaptive aids and equipment.
mHealth	Mobile communications and network technologies for healthcare.
Mobile Telehealth	The provision of health care services with the assistance of a mobile unit that can be located at a distance from normal medical facilities.
Monitoring Centre	A monitoring centre includes call centre functions but carries additional responsibility for people, buildings, equipment, vehicles, etc. that can relate to the operation of services concerned for personal health and wellbeing. See Call Centre.
Motivational Coaching	see Health Training
Patient / User Encounters	A patient / user encounter occurs where there is real time personal communication with a service provider (who may be a health practitioner) on the basis of which decisions may be agreed regarding care, support and treatment.
Personal Health Record	see Electronic Health Record
Personalisation	The design and development of services in ways that respond to the expressed wishes and needs of the people who seek access to them.

Appendix II

Remote Monitoring	The use of devices that collect patient / user vital sign and other data and effect its transmission, in real-time or periodically, to a monitoring centre.
Remote Patient Management (RPM)	Remote evaluation and non-operative treatment of a user / patient, using communications technology.
Self-Monitoring	The periodic use of a device by the patient/user to obtain measures relating to his/her health and wellbeing.
Sensor	Any device that receives a signal or stimulus and responds to it in a distinctive manner.
Service Provider Site	The place, at a distance, where the service provider is located and receives information and/or communicates with the user/patient. Otherwise known as the Hub, Referral or Consulting Site.
Smart Home	A home with installed technologies the use, or automatic operation, of which can assist the resident to live with e.g. greater comfort or safety. Also known as Intelligent Home.
Tele-assistance	The assistance given when a health professional or other person, at the location of the user/patient (the originating site), assists the carrying out of a medical act guided by a doctor or other health professional at the service provider site.
Telecare	The means by which technologies and related services at a distance are accessed by or provided for people and/or their carers at home or in the wider community, in order to facilitate empowerment or the provision of care and/or support in relation to needs associated with their health and well-being.
Teleconferencing	Interactive electronic communication between multiple users at two or more sites which facilitates real time voice, video, and/or data transmission.
Teleconsultation	The means by which clinicians and other healthcare practitioners use telephone or video-telephony to consult with users/patients and/or their carers.
Telehealth	The means by which technologies and related services at a distance are accessed by or provided for people and/or their carers at home or in the wider community, in order to facilitate their empowerment, assessment or the provision of care and/or support in relation to needs associated with their health (including clinical health) and well-being.
Telehealth nursing	Telehealth nursing is the practice of nursing over distance using telecommunications technology.
Tele-Intervention	Tele-intervention is a therapeutic medical act which is performed remotely by a physician on a patient, without or with the local presence of other healthcare professional (e.g. telesurgery).
Telematics	The use of information processing based on a computer in telecommunications, and the use of telecommunications to permit computers to transfer programmes and data to one another.
Telemedicine	The delivery of medical care at a distance by clinicians and other health care staff, via telecommunications technologies. Telemedicine will sometimes involve and include the service user / patient.
Telementoring	The use of audio, video, and other telecommunications technologies to provide guidance or direction.
Telemonitoring	The use of communications technologies to remotely collect/send data relevant to the health and well-being of a user / patient to a monitoring centre to assist in diagnosis and monitoring.
Telepresence	The use of robotic and other instruments that enable a clinician to perform a procedure at a remote location by which he/she receives feedback or sensory information that contributes to his/her sense of presence.
Telesurgery	Surgical procedures carried out remotely with the assistance of robotic devices and a real-time video and audio connection.
uHealth	The notion by which services such as those under the rubric of telehealth offer ubiquitous (u) access.

Appendix III. Usability Questionnaire

Personal Information

In this section we are trying to gather some personal info about the patient that could help us produce some statistical results. In the case the patient wishes to maintain his/her anonymity, the interviewer should pick a code name.

Patient_ID:	
Name:	Age:
Sex:	Disease Stage(Hoehn & Yarn):

Energy cost

0	Nothing at all	Nothing at all means that you don't feel any surplus exertion whatsoever. E.g. no muscle fatigue, no breathlessness or difficulties breathing
0.5	Extremely weak	
1	Very Weak	Very weak means very light. The extra exertion caused by the device is compared to taking a shorter walk at your own pace
2	Weak	
3	Moderate	Moderate is somewhat but not especially hard. It feels good and not difficult to go on.
4	Somewhat strong	
5	Strong	The activity has become hard and tiring but continuing isn't terribly difficult. The effort and exertion is about as half as maximal.
6		
7	Very strong	Very strong is quite strenuous. You can go on but you really have to push yourself and you are very tired.
8		
9		
10	Very, very strong	Is an extremely strenuous level. The use of the device makes it impossible for you to perform this activity.

Based on the above, please indicate in the box the number reflecting your feeling of exertion:

Pain/Discomfort

0	Nothing at all	Nothing at all means that you don't feel any discomfort at all – like you have not been wearing anything. E.g. no muscle fatigue.
0.5	Extremely weak	
1	Very Weak	Very weak means very light discomfort. As carrying around a light shopping bag for a long period of time.
2	Weak	
3	Moderate	Moderate is somewhat but not especially intense. It feels a little annoying but it is not difficult to go on wearing the device.
4	Somewhat strong	
5	Strong	The pain is intense but you would still wear the device for some time longer if needed.
6		
7	Very strong	The pain is very intense and it needs a lot of effort to wear the device for any longer
8		
9		
10	Very, very strong	Is an extremely painful level. For most people this is the most severe pain they have ever experienced. You cannot wear the device any longer.

Based on the above scale and the body map in XXXXX, please indicate the number reflecting your feeling of pain/discomfort per body part. Please complete this value in the pink boxes beside the different body parts. At the end please provide an overall score.

Appendix III

1 Head	0	9 Lower Back	0	17 Left wrist	0
2 Face	0	10 Right Shoulder	0	18 Right Upper Leg	0
3 Neck	0	11 Left Shoulder	0	19 Left Upper Leg	0
4 Chest	0	12 Right Upper Arm	0	20 Right Lower Leg	0
5 Mid Torso -Waist	0	13 Left Upper Arm	0	21Left Lower Leg	0
6 Lower Torso	0	14 Right Lower Arm	0	22 Right ankle	0
7Upper Back	0	15 Left Lower Arm	0	23 Left ankle	0
8 Mid Back	0	16 Right Wrist	0	24 Overall	0

Comfort Rating Scales

e.1. Emotion

e.1.1. I am worried about what people think when I wear this device or I am embarrassed about how I look when I wear this device

e.1.2. I feel tense because I am wearing the device

e.1.3. I wouldn't mind wearing the device if it was not visible

e.2. Attachment

e.2.1. I can feel the device on my body

e.2.2 I can feel the device moving

e.2.3. I am not able to move as usual as I am afraid that I might detach one of the sensors or I might break parts of the device

e.2.4. I cannot put on the device as easily as I can dress myself

e.3. Harm

e.3.1. The device is causing me some harm (e.g. headache, pain, itching, irritation, etc)

e.4. Perceived Change

e.4.1. Wearing the device makes me feel more bulky

e.4.2 I think that the device is changing the way I look

e.5. Movement

e.5.1 The device affects badly the way I move or slows down or obstruct my movements

e.6. Anxiety

e.6.1 I do not feel secure wearing the device

e.6.2 I do not feel that I have attached the device properly

e.6.3. I am afraid that the device is not working properly

Interview and complementary questions

Did the device or the materials used for the attachment cause any skin irritations? If yes, identify what caused the irritation (can be more than one):

Problem encountered	Yes / No	If yes, any comments?
User's allergy to the materials of the device		
User's allergy to the materials used for the attachment		
Materials caused sweating		
Materials did not let the body "breath"		
Materials absorbed water and took a long time to dry		
The attachment of the device was too tight		
The device generated additional heat leading to excess sweating		

Appendix IV. AHP study

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Health Technology Assessment (HTA) study of technological solutions for Parkinson's disease monitoring, assessment and/or management based on Analytic Hierarchy Process (AHP)

First of all, thank you for your time and for taking part of this study aimed at evaluating the key aspects of the new technological solutions for PD monitoring and management. This document contains a detailed description of the study as well as a step-by-step guide about how to carry out the questionnaire.

Introduction

It is widely accepted that if devices are to be used effectively they must meet the requirements of their users [590]; however, capturing user requirements for healthcare technology is extremely complex [571]. Although clinical effectiveness and safety are the primary concerns in medicine, many other aspects must also be considered [591]. Research has shown that collecting and considering this information is challenging (lack of time and resources and the use of inappropriate methods for data collection and analysis [593]). This can result in the collection of data that are incomplete, difficult to interpret or that fail to address the questions of interest [594]. Finally, the complex nature of telehealth user requirements resides in the large number of possible users with differing specialities, skills and abilities. This information must not only be collected and considered, but differences and conflicts between users must also be balanced [571], [589].

Consent form

You have been selected to be part of this study as expert in the field. The data collected will be associated to your profile and background in order to analyze your opinion as expert but your name or any other personal detail will not be disclosed at any time. Your opinion will only be used for research purposes. By taking part of this study and submitting your response you will agree with these conditions.

Objective

To understand which are the real needs and challenges in the development and deployment of novel technological solutions for the monitoring and management of PD patients. One each pairwise comparison you should always follow this criteria: “In a technological solution for Parkinson’s disease monitoring, assessment and/or management, and from your point of view and according to your experience, on each pairwise comparison which is the most important element and how much important it is (from 1, equally important to 9 much more important)”

The Analytic Hierarchy Process (AHP)

The analytic hierarchy process (AHP) is a structured technique for organizing and analysing complex decisions or systems. It was developed by Thomas L. Saaty in the 1970s and has been extensively studied and refined since then and applied in a wide variety of decision situations, in fields such as government, business, industry, healthcare, and education. Rather than prescribing a "correct" version, the AHP helps decision makers find one that best suits their goal and their understanding of the problem. In this context the AHP has been proposed to elicit user needs [589] and to assess the medical technologies in their early stages. The complexities of medical device decision making require to collect and organise a spectrum of qualitative and quantitative information in a systematic way [589]. Users of the AHP first decompose their decision problem into a hierarchy of more easily comprehended sub-problems, each of which can be analysed independently. And, once the hierarchy is built, experts in the field can use it to systematically evaluate its various elements by comparing them to one another two at a time, with respect to their impact on an element above them in the hierarchy. The AHP converts these evaluations to numerical values that can be processed and compared over the entire range of the problem. This hierarchical approach allows the construction of a consistent framework for step-by-step decision-making, breaking a complex problem into many small less-complex ones that decision-makers can more easily deal with [589].

How this works

Basically, and to sum up the methodology, AHP breaks down complex system in “smaller parts” and then asks an expert group to compare and rate these elements in several pairwise comparisons. The mathematics behind AHP allows us to calculate the “Consistency ratio” which measures how coherent are your responses. To illustrate what this, take a look at the following example, let’s say that you state:

(Criteria A > Criteria B) AND (Criteria B > Criteria D)

Then Criteria A >> Criteria D, nevertheless, as we said at the beginning we are analysing complex systems and consequently it is very difficult to rank properly all the Criteria. So, it is possible and common that later in the evaluation the user states that Criteria A > Criteria D or even Criteria A < Criteria D. In this case, and thanks to the AHP method we can quantify the inconsistencies (usually values under 10% are accepted) and suggest the evaluator to modify some decisions to improve the consistency.

The hierarchy

The first step in AHP is the definition of the criteria or hierarchy that you as expert should evaluate. In order to identify elements of the hierarchy a literature review was performed and then a focus group with experts was consulted to organize these factors (this group involved 2 clinicians and 5 biomedical engineers with extensive experience of the design, assessment and management of medical devices). The focus group identified a total of 29 different clinical needs that must be satisfied by a telehealth system for PD management [18]. Then, they were redefined in order to group all the common needs and to avoid misunderstandings, repetitions and overlapping. The table below shows the final criteria list.

Nodes	Elements
Performance	Motor symptoms assessment
	ON/OFF fluctuations detection
	Cognitive & behavioural assessment
	Data mining & disease modelling
User experience	↑ wearability acceptance
	User-friendly interfaces
	Seamlessly integration
Clinical practice	↑ patient-clinician bond
	↑ patient & carers knowledge
	↑ self-management support
	↑ assist care givers
Economic	↓ visits and stays in hospital
	↑ patient Quality of Life
	Faster and more reliable diagnosis
Technical issues	Scalability and interoperability
	Security and privacy
	↓ maintenance and support cost

Step by Step guide

Now, to take the test click on the following link or Copy&Paste this link in the navigation bar of your web browser:

<http://bpmsg.com/academic/ahp-hiergini.php?sc=masAva&pn=htas0001>

The first screen should show a Session Code and personal identifier in the field Your Name. In the case these fields are empty please introduce the following details.

Session code: YYYYYYYY

Your name: XXXXXX

Click “Check input” button, after that, click on the “Go” button.

AHP Group Session

Rational Decision Making Made Easy

[AHP-OS home](#) Version 2014-05-14 (c) by Klaus D. Goepel.

AHP OS is an online tool to support rational decision making based on the *Analytic Hierarchy Process* (AHP). Criteria weights and ranking of alternatives for a decision problem are calculated based on pairwise comparisons. As a participant in one of the AHP projects kindly **enter your session code and name, work through the questionnaire and submit your input for group evaluation**. This will help to reflect your inputs in the final decision. Thank you!

Input Session Data

Session Code:
eqepYz
Participants need this session code to log into the AHP group session

Your Name:
Jorge Cancela
As reflected in the group session (3 - 25 alpha num char)

Please provide name.

At this point the tool shows you the hierarchy, organized in 5 nodes and 15 elements within these nodes. From here you should rate the elements in the nodes, and also the nodes themselves. To do that, click on the “AHP” buttons (in total you should carry out 6 evaluations).

BPMSG AHP Online System

Rational Decision Making Made Easy

[AHP-OS home](#) Version 2014-05-18 (c) by Klaus D. Goepel - You are not logged in. For full functionality please [register](#) and [login](#).

Project: Telehealth tool for PD assessment a

"In a telehealth tool for Parkinson's disease assessment and management, and from your point of view and according to your experience, on each pairwise comparison which is the most important element and how much important it is (from 1, equally important to 9 much more important)"

Level 1	Level 2	Global Priorities
Telehealth tool for PD assessment (AHP)	Performance (AHP)	Motor symptoms assessment (0.3333) 6.7%
	User experience (AHP)	ON/OFF fluctuations detection (0.3333) 6.7%
	Clinical practice (AHP)	Cognitive & behavioral assessment (0.3333) 6.7%
	Economics (AHP)	Wearability acceptance 0.5 10.0%
	Technical issues (AHP)	User-friendly interface 0.5 10.0%
		Self-management support 0.2 4.0%
		Data mining & disease modelling 0.2 4.0%
		1 patient & carers knowledge 0.2 4.0%
		1 patient-clinician relation 0.2 4.0%
		1 assist care giver work 0.2 4.0%
		1 visits & stays in hospital 0.3333 6.7%
		1 patient Quality of Life 0.3333 6.7%
		Faster and more reliable diagnosis 0.3333 6.7%
		Scalability and interoperability 0.5 10.0%
		Security and privacy 0.5 10.0%
		1.0

Group Input Session

Mode: Hierarchy evaluation

Group Session Menu:

Session code: Utopias Session Chair: jorgecancela. Group has 1 participants. You are participating as John Smith

The procedure is the same in all the cases

Each row shows you a pairwise comparison that you should evaluate. You have to choose which one of the two criteria showed per row is more important and then rate it from 1 (equal important) to 9 (much more important). “In a telehealth tool for Parkinson’s disease assessment and management, and from your point of view and according to your experience, on each pairwise comparison which is the most important element and how much important it is (from 1, equally important to 9 much more important)”

AHP Online System

Telehealth tool for PD assessment a: Pairwise Comparison Performance

Please do the pairwise comparison of all criteria. When completed, click **Calculate Result** to get the priorities.

Scale: 1 - Equal Importance, 3 - Moderate importance, 5 - Strong importance, 7 - Very strong importance, 9 - Extreme importance (2,4,6,8 values in-between).

With respect to **Performance**, which criterion is more important, and how much more on a scale 1 to 9 for Telehealth tool for PD assessment a?

A - vs Performance - or B?	Equal	How much more?
1 Motor symptoms assessment or ON/OFF fluctuations detection	1	2 3 4 5 6 7 8 9
2 Motor symptoms assessment or Cognitive & behavioral assessment	1	2 3 4 5 6 7 8 9
3 ON/OFF fluctuations detection or Cognitive & behavioral assessment	1	2 3 4 5 6 7 8 9

CR = 0% Please start pairwise comparison

Calculate Result ☒ AHP ☐ Balanced scale

When you finish the evaluation of all the pairwise comparisons click on the “Calculate Result” button and it will evaluate the Consistency Rate and it will show you the result.

If the Consistency Rate is higher than 10% the tool will advise you that the rate is too high and even it will suggest you with some possible modification that can lead to improve the CR.

To fix it, this tool shows you some recommendations to improve the consistency.

It will highlight in green its suggestions.

Of course, this is only a recommendation, taking into account the valuation of the other pairwise comparisons. You are free to adjust the comparisons as you better estimate.

AHP Online System

Telehealth tool for PD assessment a: Pairwise Comparison Performance

Please do the pairwise comparison of all criteria. When completed, click **Calculate Result** to get the priorities.

To improve consistency, slightly adjust highlighted judgments by plus or minus one or two points in the scale.

Scale: 1 - Equal Importance, 3 - Moderate importance, 5 - Strong importance, 7 - Very strong importance, 9 - Extreme importance (2,4,6,8 values in-between).

With respect to **Performance**, which criterion is more important, and how much more on a scale 1 to 9 for Telehealth tool for PD assessment a?

A - vs Performance - or B?	Equal	How much more?
1 Motor symptoms assessment or ON/OFF fluctuations detection	1	2 3 4 5 6 7 8 9
2 Motor symptoms assessment or Cognitive & behavioral assessment	1	2 3 4 5 6 7 8 9
3 ON/OFF fluctuations detection or Cognitive & behavioral assessment	1	2 3 4 5 6 7 8 9

CR = 18.5% Adjust highlighted judgments to improve consistency

Calculate Result ☒ AHP ☐ Balanced scale **Submit_Priorities**

Resulting Priorities

Category	Priority	Rank
1 Motor symptoms assessment	14.0%	3
2 ON/OFF fluctuations detection	21.3%	2
3 Cognitive & behavioral assessment	64.7%	1

When the Consistency rate is under 10% click on the Submit_Priorities button.

Appendix IV

102 * ↑ patient Quality of Life or Security and privacy 1 2 3 4 5 6 7 8 9

103 * Faster and more reliable diagnosis or Scalability and interoperability 1 2 3 4 5 6 7 8 9

104 * Faster and more reliable diagnosis or Security and privacy 1 2 3 4 5 6 7 8 9

105 * Scalability and interoperability or Security and privacy 1 2 3 4 5 6 7 8 9

CR = 7.4% OK

Calculate Result AHP Balanced Scale Submit_Priorities

Resulting Priorities

Category	Priority	Rank
1 Motor symptoms assessment	14.5%	1
2 ON/OFF fluctuations detection	5.2%	13
3 Cognitive & behavioral assessment	6.0%	6
4 Wearability acceptance	6.0%	6
5 User-friendly interfaces	5.3%	12
6 Self-management support	5.2%	13
7 Data mining & disease modelling	6.0%	6
8 ↑ patient & carers knowledge	5.3%	11
9 ↑ patient-clinician relation	6.0%	6

Repeat this action with all the AHP buttons and once you are done with all of them, click on the “Submit for group eval” button.

BMSG AHP Online System

Rational Decision Making Made Easy

AHP_OS home Version 2014-05-18 (c) by Klaus D. Goepel - You are not logged in. For full functionality please register and login.

Project: Telehealth tool for PD assessment a

"In a telehealth tool for Parkinson's disease assessment and management, and from your point of view and according to your experience, on each pairwise comparison which is the most important element and how much important it is (from 1, equally important to 9 much more important)"

Decision Hierarchy

Level 0	Level 1	Level 2	Global Priorities
Telehealth tool for PD assessment a	Performance: 0.4871 [AHP]	Motor symptoms assessment: 0.1918	9.3%
		ON/OFF fluctuations detection: 0.1744	8.5%
	User experience: 0.1095 [AHP]	Cognitive & behavioral assessment: 0.6337	30.9%
		Wearability acceptance: 0.5	5.5%
	Clinical practice: 0.1095 [AHP]	User-friendly interfaces: 0.5	5.5%
		Self-management support: 0.1713	1.9%
	Economic: 0.1095 [AHP]	Data mining & disease modelling: 0.2866	4.2%
		↑ patient & carers knowledge: 0.1508	1.7%
	Technical issues: 0.1844 [AHP]	↑ patient-clinician relation: 0.1124	1.2%
		↑ assist care giver work: 0.1788	2.0%
		↓ visits & stays in hospital: 0.4997	5.5%
		↑ patient Quality of Life: 0.4274	4.7%
		Faster and more reliable diagnosis: 0.0731	0.8%
		Scalability and interoperability: 0.0711	15.4%
		Security and privacy: 0.1429	2.6%
			1.0

Group Input Session

Mode: Hierarchy evaluation

Group Session Menu Submit for group eval Leave group mode

That's all, thank you again for taking part of this study and for your time.

Best regards,

Jorge Cancela

jcancela@lst.tfo.upm.es