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REMPARK System Assessment: Main Results

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9.1 Introduction

In the previous chapters, the REMPARK system has been presented and discussed, along with its usefulness. According to the initial project specifications and some important conclusions obtained from the work carried out during the project, the main characteristics and requirements of the integrating parts and REMPARK sub-systems were initially defined and refined afterwards.

The present chapter will first describe the final system and, then, its overall final assessment. This way, first, a description of the communication flows established in the REMPARK platform (type of information, dataflow and security issues) is given. Secondly, an overview of the final necessary platform, ready to be used in the piloting part of the project is provided.

The assessment process was done through a pilot in which the patients tested the system in ambulatory conditions and during their daily living activities. More than 40 PD patients participated from four countries (Spain, Italy, Israel and Ireland).

9.2 Description of Main Communication Flows

As it has been described in previous chapters, the effectivity of REMPARK system is based on a couple of interaction loops that define specific communication data flows. This way, communication between the different sub-systems of REMPARK is a crucial aspect and the correctness and security of the information flows must be guaranteed. In order to understand and specify the characteristics of the communication flows, it must be considered that the REMPARK system has two differentiated functional parts:

- The first one is related to the **monitoring of PD motor symptoms**, including: movement sensors, actuator, smartphone, the REMPARK server, the Rule Engine, the Disease Management System (DMS) and a patient's web interface.
- The second functional part is related to the **monitoring of non-motor PD symptoms**. This monitoring strategy is mainly based on the use of questionnaires and also includes a simple agenda system to interact with the patient. This part of the system requires the smartphone, the REMPARK server and the DMS to exchange information.

Thus, two different information flows are distinguished in the REMPARK system. This differentiation will be used to specify the system according to either 1) the communication flow due to the monitoring of motor symptoms and the application of the actuation action or 2) the communication flow due to non-motor symptoms.

- The monitoring process of the motor symptoms is mainly done in the immediate loop, around the patient. The mobile phone is acting as the gateway for the communication of the related sub-systems with the REMPARK server and the different channels and data type, according to the definition presented in the next section, are shown in the Figure 9.1:
- The non-motor symptoms mode embraces the communication flows related to patient management issues, e.g. agenda, treatment, questionnaires, etc. Figure 9.2 presents the REMPARK system parts participating in non-motor symptoms monitoring and their communication flow.

9.2.1 Type of Transmitted Information

This section details the general specifications of the different information types sent and received through the communication channels indicated in Figures 9.1 and 9.2. Four different types of information are considered:

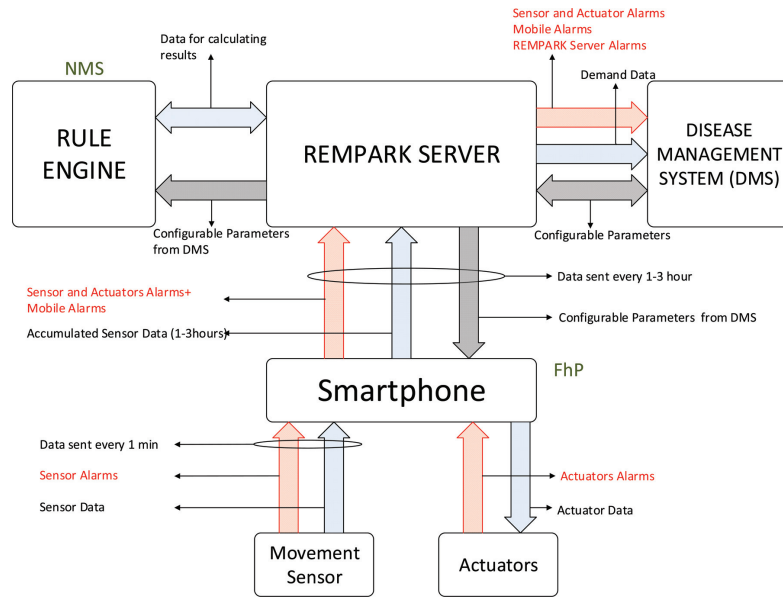


Figure 9.1 Communication flow of motor symptoms detection and actuation in REMPARK system.

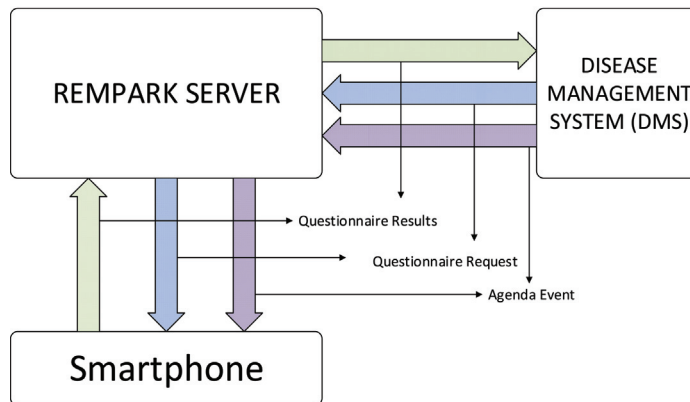


Figure 9.2 Communication flow of non-motor symptoms management and actuation in REMPARK system.

(I) Alarms, (II) Data sent within the closed loop of the REMPARK monitoring system, (III) Configuration parameters in the smartphone and, finally, (IV) Agendas and questionnaires:

- **Alarm specifications**

An alarm is defined as an event detected by the REMPARK system that must be urgently notified to an end-user. For instance, a fall-detection event is the only alarm provided by the REMPARK wearable system. Other alarms can be defined within the DMS as a combination of one or more rules applied to the stored information; for instance, a value from a questionnaire lower than a specific threshold.

In the communication flow, as a general rule, alarms within the REMPARK system will be handled as states. This means, for instance, that when the sensor sends a data packet it will also send the state of all the alarms, a value 1 meaning an activated alarm and a value 0 meaning a deactivated alarm. There should be 3 stages for clinical alarms: red, yellow and green. Therefore, when a low battery level is detected its corresponding alarm will be set to 1, and its value will not become 0 until an optimum charging level is detected.

- **Data sharing between the REMPARK wearable system and the DMS**

The sensor sends data every minute to the smartphone. The smartphone will store the data sent by the movement sensor during a specified time frame, which usually consists in few hours. Once this time frame is reached, the smartphone establishes a connection with the REMPARK server to upload all the data stored since the last connection. The connection between the smartphone and the server will take place every 1–3 hours, except when the data sent by the sensor contains an activated alarm or when an alarm is generated at the smartphone. In this case, an immediate connection with the server is established.

- **Configurable parameters**

All configurable parameters must be stored in the REMPARK server. These parameters are used by the machine learning algorithms and the ACS cueing system, which enable their personalisation to each patient. They are defined in the DMS and their values are transmitted to the smartphone, in which they are applied to the sensor's output provided every minute. These parameters are, for instance, the patient's walking rhythm, the threshold used to detect bradykinesia or the freezing index level necessary to consider an episode of FOG.

- **Questionnaires and agendas**

The data associated with the monitoring of non-motor symptoms can be grouped in three broad categories: the request for a specific questionnaire, the generation of an event in the agenda and the completion of a questionnaire. All the questionnaires, including the TAP tests, are stored

locally in the smartphone and in the DMS. The request for a specific questionnaire consists in asking for a specific questionnaire number and a date and time. The results of the questionnaires are sent in an encoded REMPARK format. As an option, the questionnaires could be filled in 3 ways:

1. Using the smartphone
2. Through the Patient's web application
3. By the nurse asking the patient and completing, directly, through the DMS platform

The data from the questionnaires will be sent to the REMPARK server from the smartphone or the DMS respectively, they will be analysed by the Rule Engine and alerts will be then sent to the DMS. The smartphone will send all data filled by the patient and will be presented to the patient also on the Web application. An agenda event is generated by the DMS and sent to the smartphone through the REMPARK server. Even if the event is stored in the server for record purposes, this information will not be accessible by the rest of the subsystems (smartphone or DMS) once the event is transferred to the smartphone. All the data related to the questionnaires and the agendas must be stored in the REMPARK server.

9.2.2 Security Aspects

Security aspects related to the communication are very important in the application of the REMPARK system. The system can be split into two different domains (the BAN and the platform/server), and different considerations should be made possible. In the BAN, security issues are related to the Bluetooth communication between the different sub-systems. In the platform, security aspects come in the communication between the smartphone and the server and the rest of the entities of that domain, the Rule Engine and the DMS. The most relevant security aspects are summarized as follows:

- **BAN:** All the different devices forming the BAN, i.e. the sensor, the smartphone and the cueing system, exchange data using Bluetooth 2.1. Traditionally, using Bluetooth devices was associated to use pin codes for each device in order to establish communication between devices. This method required a manual intervention and security is not very high. REMPARK uses Bluetooth v2.1, which uses SSP. This security approach uses public key cryptography, which gives a lot of advantages. It just works without manual intervention; however, a device may prompt

the user to confirm the pairing process. During the pairing time, if the devices have a screen, numeric comparison is used, which informs the user that a device is trying to connect. The number shown in the screen must be the same as the one in the device. From Bluetooth v2.1 encryption is required and the encryption key is regularly refreshed.

- **Platform/server:** The server is interfaced by three different elements, the Rule Engine, the DMS and the smartphone. Communication with the server fulfils the European Data Protection Directive (Directive 95/46/EC), which embraces the different national laws for data protection.

9.2.3 Final Deployment and Implementation of the REMPARK Platform

With the already presented specifications and characteristics, the REMPARK platform was implemented for its use during the last piloting phase of the project. According to the pilot specification, the system was conceived to be implemented following a distributed approach, and this is how it was tested during an early pre-pilot phase. Many efforts were devoted to ensure the synchronisation, data transmission, processing and representation of the information considering different scenarios like a sudden lack of communication, for instance.

After this early phase, the integration of the Rule Engine into the REMPARK server was decided, obtaining in this way a more efficient management of the communication bandwidth and a mitigation of transmission delays.

The REMPARK system worked steady, secure and with good performance to carry out the scheduled pilots. The Figure 9.3 shows the **final REMPARK functional view** (it was deployed in June 2014 as starting point for the pilots).

In the figure, the Rule Engine is already presented as a part integrated in the REMPARK server and directly accessing to the information generated by the patient's sensor (measures, alerts). All this information is transmitted by patient's smartphone in a secure way using a Transport Layer Security (TLS) channel.

The Rule Engine, then, analyses this information and creates new post-processed measures, which are stored and forwarded to the DMS system in a secure way using a TLS channel. Eventually, the DMS shows all the gathered information to the clinical professionals as well as providing a decision support system that follows the defined clinical protocols. Furthermore, clinical professionals can set up treatments and appointments that are forwarded to patients' mobile phone.

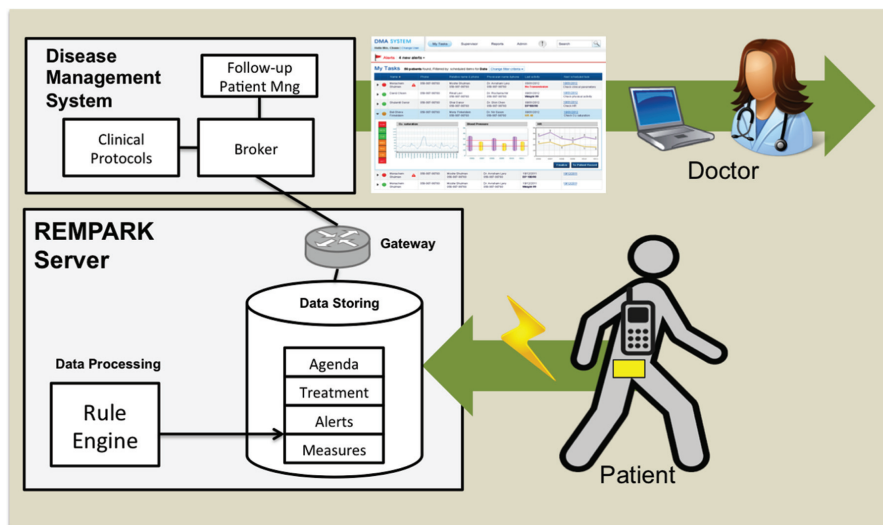


Figure 9.3 Final REMPARK platform (ready for pilots) functional view.

In order to guarantee the execution of the pilot, it was decided to implement four different and equivalent environments. As REMPARK pilot experience must be distributed among four different countries (Spain, Ireland, Italy and Israel), it was entailed the deployment of four different servers, one isolated server per pilot site and the same replica for the DMS system.

In order to guarantee patient's data privacy, pseudonyms and ID's instead of personal information were transmitted. Moreover, to maximise the security of the pilots, external calls to each environment were forwarded through a proxy to an isolated Telefónica's private network which can only be accessed from inside (Telefónica was the responsible partner for the REMPARK platform and communications). The Figure 9.4 shows how it looks like this set up.

In total, four environments were set up assuring this level of security. Furthermore, any external communication with the server, either from patient's mobile phone or the DMS system goes through a TLS channel and each message includes specific credentials according to the type of user/system sending the message (i.e. patient, DMS). Moreover, other security mechanisms have been implemented to assure that there are warning alerts in cases where there are communication problems between the different devices (i.e. alert when the smartphone loses communication with the platform, alert if sensor or actuator connections are lost, presence of a fall detection). Figure 9.5 shows

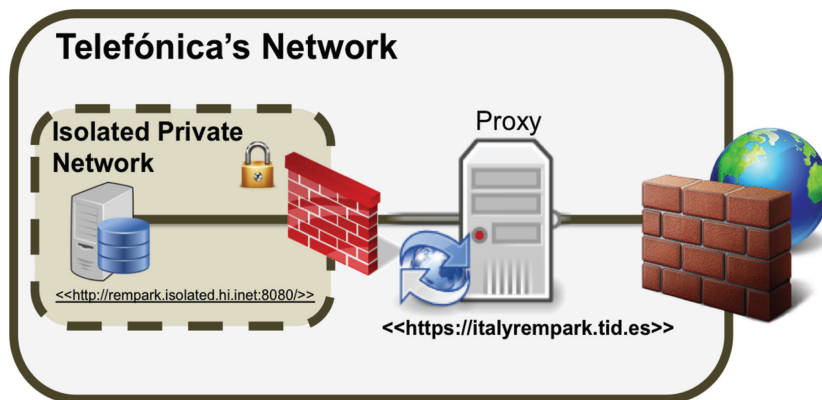


Figure 9.4 REMPARK server in isolated network.

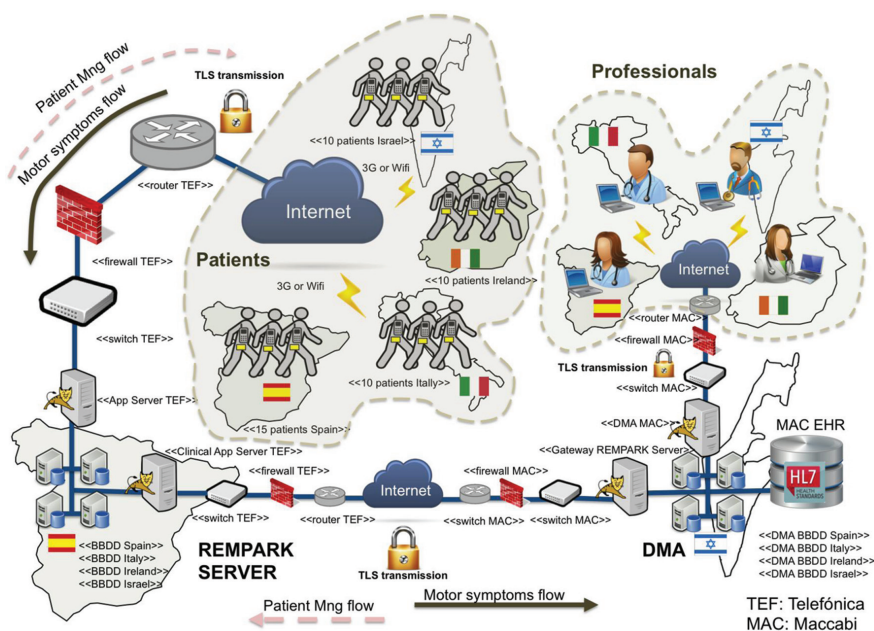


Figure 9.5 Final REMPARK system deployment and used for the pilots.

the final set-up implemented and used for REMPARK's pilots. The secure connections between the REMPARK server and other external sub-systems, like the DMS and the smartphones used by the patients are indicated. As a

proof of concept, the DMS was integrated with the information systems used by Maccabi in Israel through HL7 protocol.

9.3 Pilot for the REMPARK System Assessment: Description

This section introduces the details and the execution of the distributed pilot, executed in REMPARK. The main objective of this pilot was the global assessment of the system in terms of ON and OFF detection. As a previous activity, before starting the main pilot, an early pre-pilot was organized with very few volunteers in order to test the stability and the validity of the overall system.

In this section, the experimental protocol is described first, followed by some conclusions after the early trial (pre-pilot experience). Finally, the analysis of the REMPARK system during the pilots is fully provided, with the main conclusions regarding the obtained results.

9.3.1 Definition of the Pilots' Objectives and Eligibility Criteria

The objectives of the pilot activity were divided into primary and secondary. The complete list to be covered is following:

Primary objectives

- To study the performance and reliability of the REMPARK system under real conditions on a significant group of patients.
- To study the validity of the ON/OFF motor phase detection by the system on a significant group of patients.

Secondary objectives

- To study the functionality of cognitive tests administered through the smartphone in detecting ON/OFF states on a pilot group of patients.
- To check the operation of an auditory cueing system, activated by the output of an algorithm, in improving the gait on a pilot group of patients.
- To assess both usability and user's satisfaction referring to the REMPARK system under real daily living conditions on a pilot group of patients.
- To study the validity of the fall detection algorithm of the REMPARK's system on a pilot group of patients.

- To verify the safety of the REMPARK in individuals with Parkinson's disease on a pilot group of patients.

Population and eligibility criteria

The reference population is that formed by a pilot group of patients with moderate to severe Parkinson's Disease, presenting ON/OFF phases, FOG or dyskinesia (Hoehn and Yahr greater than 2 in ON phases and lower than 5 in OFF phases). Candidates found to be eligible to participate in the study immediately were provided with the Patient Information Sheet and the Informed Consent Form. The Principal Investigator or a co-investigator met the subjects and explained the study purpose, procedures, possible risks and benefits and subject responsibilities to the potential participants. The subjects had the opportunity to evaluate these documents in detail and were allowed to ask the investigators any question regarding the study. The subject's willingness and ability to meet the follow-up requirements were determined.

Patients fulfilling the following criteria were candidates to be included in the study:

- Clinical diagnosis of Idiopathic Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank [1].
- Disease in moderate-severe phase, with a Hoehn and Yahr greater than 2 in ON phases and lower than 5 in OFF phases, or with a scale greater or equal to 2.5 (in ON state) with motor fluctuations comprising bradykinesia, FOG and/or dyskinesia [2].
- Able to walk unaided in OFF state.
- Age between 50 and 80 years.
- Sufficient literacy capacity to answer questionnaires.
- Willing to participate in the study (in writing-sign informed consent) and wanting to co-operate in all its parts, accepting the performance regulations and procedures provided by the researchers. The patients' family members and responsible doctors should fulfil, also, this inclusion criteria.

Patients fulfilling the following criteria were excluded from the study:

- Other health problems that hamper physical activity and gait: rheumatologic, neuromuscular, respiratory, cardiologic problems other neurological disorders- (Post stroke, Polio), mental disorders, significant pain.
- Alcohol and/or drug abuse.

- Being treated with duodopa or apomorphine pump, or deep brain stimulator.
- Patients who are participating in another clinical trial.
- Dementia according to clinical criteria -DSM-IV-TR [3].
- Unable to fully understand the potential risks and benefits of the study and give informed consent.
- Unable to recognize the ON and OFF fluctuations, after proper training.
- Subjects who are unable or unwilling to cooperate with study procedures (for example- unwilling to carry the sensors during the study hours).

All participants in the pilot presented motor fluctuations, according with the inclusion criteria, and at least 25% of the total of the sample had FOG problems. Family members and responsible doctors of the participants were included in the study and they were allowed to consult patient’s health data through the web information system.

9.3.2 Design of the Study

The REMPARK pilot was designed as a longitudinal pilot study in which each participant was using the REMPARK system under real conditions (ambulatory conditions) during 4 consecutive days. An additional pre-trial day (day 0) is necessary for customizing the system to the user, and a day 1, to train the user in the system’s use. This pre-trial day was scheduled at least 1 week prior to the trial start. The organization of the study design is shown in Figure 9.6.

In the pre-trial day (day 0), the thresholds for the bradykinesia detection algorithm, the FOG detection algorithm and the TAP test parameters were adjusted for each individual participant. For doing so, three short specific experiments were conducted: walk in OFF, walk in ON, FOG provocation test and TAP test. During the trial days (day 1–day 4), patients were wearing and using the REMPARK system under real conditions. The system was recording

DAY -1	DAY 0		DAY 1	DAY 2	DAY 3	DAY 4
Inclusion visit	Testing for thresholds	Customization of algorithms	Cueing testing; Patient’s training & Real conditions use	Real conditions use	Real conditions use	Real conditions use
Sign informed consent						Satisfaction & usability

Figure 9.6 Timing of the methodological study design.

motor and non-motor symptoms, which were also video recorded by standard means (video cameras or smartphones).

The pilot study started after getting the approval of the corresponding Ethics Committees and the competent authorities in the four countries (i.e., in Spain the Spanish Agency for Drugs and Medical Devices, AEMPS gave the corresponding permission). The following data and records from each participant were obtained and integrated into the pilot database:

- **Personal identification data:** name, address, phone number.
- **Socio-demographic variables:** date of birth, gender, educational level, cohabitation.
- **Clinical assessment questionnaires:**
 - **Parkinson's diagnosis:** according Brain Bank criteria by Hughes et al. [1].
 - **Parkinson's severity:** measured by Hoehn and Yahr scale [2].
 - **Questionnaire assessment of motor fluctuations, FOGs, and dyskinesia.**
 - **Basal health status:** list of chronic conditions, list of current medications.
 - **ON/OFF current phase:** The current motor phase was established by using three different instruments. 1) Patient's report: patients who were previously trained for recognizing their ON/OFF phases 2) report whether they are in ON or OFF phase every 60 minutes, or 3) when they detect a change.
 - **Unified Parkinson's Disease Rating Scale (UPDRS)** [4], which was administered by a trained researcher to participants several times during the pilot.
 - **Video recording** and posterior analysis by an expert was used for confirming the motor phase of the patient.
 - **TAP-test:** This test was designed to objectively assess changes in movement, such as slowing and rigidity which are effects commonly related to the OFF state. In this test the subject is requested to repeatedly press a button on the touch screen of the smartphone representing a white arrow in order to fill up a vessel as soon as possible according to ten predefined levels (each target level is marked by a green bar). The ten levels represent the number of button presses needed for the level to be fulfilled. The subject has to press the button by using his forefinger of the dominant hand (i.e., right hand).

- **Cognitive status:** Assessed by Folstein Mini-Mental [5] and applying the criteria of DSM-IV TR dementia.
- **Freezing of Gait (FOG) episodes and severity**, measured by two different standard methods:
 - Video recording and subsequent analysis by a trained observer, was used for identifying the section of the sensor signal's corresponding to FOG episodes.
 - Freezing of Gait Questionnaire (FOG-Q) [6]: This instrument was used for establishing the basal (over the last 4 days week) severity of freezing of gait in the participants, and also its severity during the 4 days of the REMPARK's system use.
- **Gait quality:**
 - Video recorded timed Up & Go test [7]: This instrument is a timed test of standing and walking. It is a gait-speed test used to assess a person's mobility and requires both static and dynamic balance.
- **Non-motor symptoms:**
 - Non-Motor Symptom Questionnaire: NMSQuest [8].
- **Usability:** The usability instruments were used to assess separately the usability of each device, and also the whole system.
 - System Usability Scale (SUS) [9].
 - Quebec User Evaluation of Satisfaction with Assistive Technologies (QUEST) [10].

The REMPARK system for these pilots included all the already described sub-systems:

- Sensor sub-system (located in the waist). μ SD cards were used on day 0 to collect the raw data from the sensor in order to perform the user particularization. The remaining days, the sensor shared the results of the algorithms with the smartphone once per minute.
- Smartphone: The smartphone used in the experiments is the Samsung Galaxy Nexus. The specific software running in the smartphone was developed within the framework of the REMPARK project.
- Headset for auditory cueing: The headset chosen for the REMPARK experiments was the Samsung HM3500 Bluetooth earphone.
- REMPARK Platform (according the description in precedent text).
- Web Server – Disease Management System (application for managing the patient's health by the medical staff).

9.3.3 Pre-Pilot Conclusions

As it has been mentioned, a preliminary pre-pilot activity was scheduled with the participation of a limited number of patients, and with the objective of checking the stability of the overall REMPARK system to be used. It was also intended to evaluate its performance in terms of correct detection of the motor state of few PD patients in ambulatory conditions.

During the pre-pilot, regarding the system stability, it must be noted that the data gathered by the REMPARK sensor were correctly sent through the different communication layers so that no information loss due to communication errors were detected. Although some packet losses were observed during the experiment, they were due to the fact that the user didn't remember to have the smartphone always in coverage range of the sensor. In this respect, it was concluded that, during the user training session, emphasis to keep both devices as close as possible during the whole duration of the experiments had to be done.

It was also found with these pre-pilot tests that the performance of the REMPARK system when detecting the motor state of a patient is in line with the original specifications, even if the gold standard available to validate the results is not always accurate enough. The existing issue is the fact that the only available gold standard is the self-reporting of the patients using a diary. Figure 9.7 presents the diary filled by one of the participants in the pre-pilot experience, during the first day of experimentation (day 1). It can be observed that the patient, as it is commonly done in motor states self-reporting, writes down the motor state for each hour of the day.

Reporting the motor state in this manner presents the following two issues:

- The time in which the motor state is reported has been shown to be inaccurate in some cases. More specifically, it is unclear when exactly changes among motor states occur. In contrast, the information obtained by REMPARK system is known with seconds' accuracy.

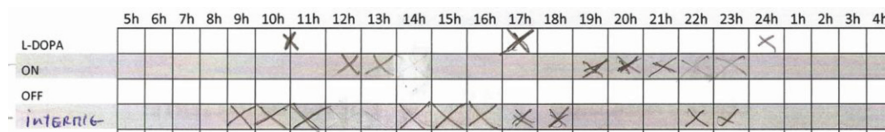


Figure 9.7 Motor states section of the diary filled by one patient during the first day of experimentation. Third row corresponds to the 'intermediate state'.

- Some PD patients are not able to recognize their motor state. This risk could be mitigated in the recruitment phase, since neurologists only should select those patients able to recognize ON and OFF states.

In order to evaluate the ability of the REMPARK system for the detection of ON and OFF motor states, a set of three main performance measures are used: specificity, sensitivity and correlation with a gold standard. These measures can be severely affected by the two inaccuracy issues presented above:

- Concerning specificity and sensitivity measurements: These measurements may be strongly affected by the described issues, since the REMPARK system provides an estimation of the motor state once every 10 minutes. First, given a patient who constantly switches among different motor states, a big difference between the time assumed in self-reporting and the time provided by the REMPARK system could lead to very low specificity and sensitivity values. Second, if the patient does not correctly recognize the motor state, a similar effect would be obtained.
- Concerning the correlation between REMPARK system output and patient diary (used as gold-standard), it must be pointed out that these measurements would be affected similarly to the specificity and sensitivity ones.

Two possible options appear when comparing the self-reported motor state of a patient and the REMPARK system output:

- It is possible to consider the correct REMPARK system output as the output that is closest to the time of the self-reported motor state by the patient. Results for this option were presented as ‘*exact time*’.
- It is possible to consider the correct REMPARK system output as the mode (most frequent value) among the outputs obtained within the one-hour period that corresponds to the self-reported motor state. Results for this option were presented as ‘*mode*’.

Finally, it should be noted that patients can report to be in ON, OFF or intermediate state (see Figure 9.7). However, REMPARK system only provides ON and OFF predictions. In consequence, those periods in which intermediate state was reported will not be included in the performance analysis.

Table 9.1 shows results for two patients, who participated in the pre-pilot. No valid conclusions can be extracted from this pre-pilot phase, but the identification of the discussed issues and the technical validation of the system. In the results of the first patient, it can be observed that only 8 hours were analysed, given that most of the reported states correspond to the ‘intermediate state’.

Table 9.1 Pre-pilot results on motor state detection

Patient	REMPARK System Output	Specificity	Sensitivity	VPP	VPN	Correlation	Number of Hours Analysed
	Selection						
1	Mode	0.6	0.3	0.33	0.6	-0.07	8
	Exact time	1	1	1	1	1	8
2	Mode	0.91	0.71	0.71	0.90	0.62	29
	Exact time	0.73	1	1	0.54	0.7	29

9.4 REMPAK Pilots' Execution and Obtained Results

Pilots with REMPAK system were conducted in accordance with the protocol presented above. It must be remembered that the main objectives of the study were to analyse the performance and reliability of the REMPAK system under real conditions, and to study the validity of the ON/OFF detection by the system. A list of secondary objectives was also focused (see Section 9.3.1).

The recruitment was carried out following a convenience sampling among patients assisted in the different centres participating in the study, following the methodology described in the above Section 9.3.1. Fifty-four (54) patients were initially contacted, 44 of them met inclusion criteria and agreed to participate. Three of the included patient did not complete the study days. One of them discontinued participation voluntarily. Two patients were removed from the study by the researchers, the first of them due to lack of adherence to the study protocol, the second patient was removed due to a health condition, which required hospitalization, apparently not related to study devices or procedures. Finally, 41 patients completed all study days and evaluations.

Table 9.2 shows recruitment and follow-up data by participant entity.

Table 9.2 Recruitment and follow-up data by participant entity

Medical Partner	Contacted Patients	Included Patients	Lost-Dropout Patients	Completed Protocol
NUI Galway (Ireland)	7	7	1	6
TEKNON (Spain)	18	15	0	15
FSL (Italy)	16	10	0	10
MACCABI (Israel)	13	12	2	10
Total	54	44	3	41

Concerning the socio-demographic and health data of the participants, twenty-eight participant patients were men (68.3%) and 13 were women (31,7%). The average age of participants was 71.3 years (SD 7.3; range 56–84).

All the participants had been diagnosed of Parkinson's Disease according to the UK Parkinson's Disease Society Brain Bank [1]. The average time from diagnosis was 11.3 years (range 2–26). As per inclusion criteria, all participants had a Hoehn and Yahr scale equal or greater than 2.5 [2], being median stage of the sample 3 (range 2.5–4). The motor section of the Unified Parkinson's Disease Rating Scale (UPDRS) was in average 28.2 (SD 1.7) [3], when the patients were in OFF phase and 12.2 (SD 1.5) when the patients were in ON phase. The median of the Freezing of Gait (FOG) questionnaire of all participants was 13 (IQR 6) [4], this scale explores gait disturbances of the patients and ranges from 0 through 24, being the higher scores related to worse gait disturbances.

Participants with dementia and acute medical conditions were not included in the study. Mini-Mental State Examination (MMSE) [5] results of the participants are shown in Table 9.3, along with other medical chronic conditions of participants.

Table 9.3 Mental and chronic disease condition of the participants

Condition	Number of Participants (n)	%
High blood pressure	15	36,6
Heart conditions	3	7,3
Arthritis, osteoarthritis or rheumatic conditions	11	26,8
Back ache	13	31,7
Asthma or COPD	1	2,4
Diabetes	10	24,4
Urinary incontinence	14	35
High cholesterol	12	29,3
Depression	9	22,5
Anxiety disorder	3	7,3
Stroke, cerebral embolism, cerebral infarct or cerebral bleeding in the past	0	0
Cancer (malignant tumours)	5	12,2
Osteoporosis	2	5
Thyroid disease	1	2,4
Cognition (MMSE)	29 (Median)	5 (IQR)

9.4.1 Performance of the System

The assessment of the system performance was done considering and analysing the data received and stored in the REMPARK server.

One of the main problems that was detected in the system and that was widely repeated in many users is related to the communication structure of the BAN and the usage received from patients. REMPARK wearable system is composed of a smartphone, a wireless headset and the waist-worn movement sensor. Bluetooth is employed among them to communicate. More concretely, the movement sensor and smartphone communicate once per minute (every 60 seconds). In consequence, given the short-range reached by this type of communication, whenever patients placed the sensor and smartphone at a certain distance (e.g. in different rooms) communication could be lost. Some measures would not be received by the smartphone which, then, would not be received by the server. These periods of lost information were mainly addressed and analysed as an objective measurement of the system performance.

In order to distinguish them from those in which the sensor is turned off, it was used the first packet after the communication between the smartphone and the sensor is established, which contains specific values that make this situation recognisable.

The performance analysis process of the REMPARK system was organized according the following procedure. First, presenting a summary of the most relevant data sent and stored in the server during the pilots, distinguishing them according to the different sources and types of information. Then, data received in each day of the pilot were analysed in order to evaluate the performance of the system communications. In ideal conditions, in every minute during which the patient wore the system, the corresponding set of samples should be stored in the server.

Table 9.4 shows just a summary example of the kind of data stored in the REMPARK server. This table includes the source of the information (in this example, only data corresponding to the sensor and the smartphone are shown), a description of the variable (between parentheses, the internal code assigned to the variable in the database is appearing) and the amount of data samples for each variable stored in the server.

Along the complete pilot execution, a total of 949 hours of raw data were stored in the system. This assumes that an average of 6.6 hours of raw data per user per day were collected. It is noted that this average number of monitoring hours is obtained on a minute basis, that is, the number of values in which the movement sensor sent information, meaning that missing values are not included.

Table 9.4 Example of data stored in the REMPARK server

Information Source	Information Variable	Quantity
Movement sensor	BRADYKINESIA – NUM STEPS (106)	56955
	BRADYKINESIA – BRADY MEAN (107)	56955
	BRADYKINESIA – BRADY STD (108)	56955
	DYSKINESIA – DISK PROBABILITY (110)	56955
	DYSKINESIA – DISK CONFIDENCE (111)	56955
	FOG – MAX_FI (112)	56955
	ACTIVITY – SMA (901)	56955
	ACTIVITY – CADENCE (902)	56955
Smartphone	BRADYKINESIA (201)	56955
	FREEZING OF GAIT (202)	56955
	DYSKINESIA (203)	56955
	TAP RESPONSE TIME MEAN (204)	99
	TAP RESPONSE TIME STD (205)	99
	LAST TAP RESPONSE TIME MEAN (206)	99
	LAST TAP RESPONSE TIME STD (207)	99
	TAP TEST RESULT DECISION (208)	99

In order to estimate the amount of missed data, it must be considered that if the sensor did not communicate with the smartphone during a given period of usage, missing packets are reflected with time intervals higher than 60 seconds. More concretely, it is considered that some packets have been missed when two consecutive movement-sensor measurements were received by the smartphone with more than 100 seconds of difference.

It was observed that some packets were lost in most patients (only in 5 patients there were not any missed packets). Moreover, it was calculated that the average number of missed packets was only of 6 minutes. Finally, the error rate was considered in terms of missed packets vs. total number of measurements received. According to this, it was observed that less than 4% of the packets were missed among all patients.

These missed short periods are not relevant since motor symptoms algorithms, require sensor measurements on a time interval of 60 minutes, allowing to have missing values in the analysed period, which means that these short-time missed packets do not influence the information provided to clinicians.

Given these considerations, Table 9.5 provides the performance analysis of REMPARK system related to a very few patients participating in the pilot (shown patients are randomly selected from the complete set and must be considered only as an illustrative example).

Table 9.5 Performance analysis of the REMPARK system (some examples)

Patient Number	ID	Number of Time Intervals of Missing Packets	Average Number of Missing Packets Per Time Interval	Number of Time Intervals > 10 min.
1	TEKNON 1	1	2,67	0
2	TEKNON 2	18	10,55	6
16	MACC 1	37	19,74	8
24	FSL 1	6	3,28	0
25	FSL 2	11	7,64	2
34	NUIG 1	21	20,11	10
Total pilot average	–	8,64	6,70	2,16

9.4.2 Validity of the ON-OFF Detection Algorithm

REMPARK system would be very useful enabling neurologists to adjust the medication regime based on detailed information of ON/OFF states fluctuations, which is provided in real-time by the wearable sensor subsystem (a waist-worn inertial sensor), with the concurrency of a smartphone. Final adjustment is then performed with the help of the specifically designed Disease Management System (DMS), which is a server-based service that allows neurologists, patients and caregivers to follow the disease evolution and communicate among them. This section presents the validation of the main objective of the REMPARK: the monitoring of ON/OFF motor fluctuations. The presented validation consists in the evaluation of the REMPARK system in detecting motor states in PD patients, who used the system over 4 consecutive days, as part of the described pilot.

9.4.2.1 The methodology

The system assesses, in real-time, objective ON/OFF motor states based on the inertial signals given by the waist-worn device, treated with different machine learning algorithms that provide the presence or absence of specific symptoms, from which PD motor states are then determined. In the following part, the ON/OFF detection methodology is described.

Accelerometer measurements obtained by the waist-sensor are analysed with two different algorithms: a bradykinetic-gait detector [11] and a dyskinesia (choreic-dyskinesia) detector [12]. The bradykinetic-gait detector is based on the patients' strides analyses, only after identifying that the patient is walking. Each stride is characterized by a measure of its fluidity: high

fluidity measurements correspond to non-bradykinetic gait and vice-versa. On the other hand, the dyskinesia algorithm has two main outcomes: first, a probability value that represents the chances of having obtained the signals from a patient suffering dyskinesia and, second, a confidence value that represents the degree of certainty on such probability. The outputs of both algorithms on a period of T minutes are then processed.

The inferred motor state is ON when bradykinesia is not present in gait or when dyskinesia output is present. This is due to, on the one hand, a lack of symptomatic gait in ON states and, on the other hand, because of peak-dose dyskinesia detection, also is associated to ON states. OFF state is determined as the detection of bradykinesia and the absence of dyskinesia. Finally, the intermediate state is defined by an intermediate detection of the bradykinesia algorithm and lack of dyskinesia. A not evaluated (NE) state is provided in case of not detecting dyskinesia and if the patient did not walk in the period under analysis.

A final refinement is performed to the sequence of ON-OFF detections obtained from the evaluation of 10 consecutive 1-minute periods. Those periods determined as not NE are changed according to the following rules:

- If a NE period is found between two periods whose states are equal (either ON or OFF), that period is set to be the same state as adjacent periods.
- If adjacent periods of an empty period correspond to different motor states, an intermediate state is then inserted.

9.4.2.2 Validation of the ON-OFF diaries: available data

As it was introduced in above Section 9.3.3, the only possible and available gold-standard for the validation of the ON and OFF states detection algorithms are the patients' diaries with the self-reported states and all the inherent and already described inaccuracies. In order to establish a methodology, two strategies were followed to ensure the validity of the gold-standard:

- First, the validity of motor state diaries was evaluated based on clinicians' expertise through UPDRS. In each scale that clinicians administered, it was annotated the state in which the patient perceived to be. As it has been described in many works devoted to study the factors involved in UPDRS, scores obtained in OFF state are higher than the scores obtained in ON states [13]. Thus, the validity of the gold-standard has been evaluated based on an objective measure consisting in the correlation between UPDRS scores and motor states provided by patients at the moment of administration. Motor state is represented with 2 = OFF, 1 = Intermediate

and 0 = ON, so positive correlations are expected. It is noted that, in some cases, negative correlations have been obtained. In order to also avoid those situations in which there is not any relation between UPDRS and the annotated motor state (i.e. nearly-zero correlation), patients whose correlation was lower than 0.20 were not included in the study since their ON/OFF diaries were considered not reliable enough to be used as gold-standard.

- A second aspect taken into account is the timeframe during which annotations are valid. More concretely, in order to consider a motor state annotation to be valid, this motor state has to appear two consecutive times in the diary, being the time interval of 1 hour between both annotations its corresponding valid timeframe. In case the motor state changes between two consecutive annotations, both annotations are excluded from the analysis since the time in which the motor state changed cannot be established. Although this strategy reduces the number of annotations used from patients, it ensures that the annotations employed to validate the system are temporally reliable. Results obtained when this procedure is applied are presented under the name *Strict diary*. On the other hand, when this procedure is not applied, results obtained are reported as *Original diary*.

The complete validation of the ON/OFF detection algorithm requires the usage of the data stored in REMPARK server during the pilots, the ON/OFF diaries filled in by patients and the CRF's administered by clinicians. Finally used and useful data for these purposes were obtained from a total of 36 patients, after two drop-outs and the exclusion of 5 diaries due to incoherencies (15 patients administered by Teknon in Spain, 10 patients from Italy administered by FSL, 8 patients from Israel under the supervision of Maccabi and 3 patients from Ireland administered by NUIG).

9.4.2.3 Results of the ON/OFF state detection

Among the initial 36 patients, data from 3 of them were removed due to a low correlation between UPDRS scores and the movement state reported by the patient (correlations were -0.62 , 0.06 and 0.2 , respectively), as discussed in the previous section.

Table 9.6 presents the average results of REMPARK system in detecting motor states in the 33 patients under real-life conditions, being the system adjusted without using data from artificially induced OFF states. The average specificity and sensitivity achieved by the system in recognizing

Table 9.6 Average results according to the Original diary method and time-ensured method (Strict)

Validation Method	Average Specificity Per Patient	Average Sensitivity Per Patient	Average Number of Validated Hours Per Patient	Average Number of ON/OFF Monitoring Hours Per Patient
Original diary	82%	57%	9.73	81.25
Strict diary	89%	98%	6.42	81.25

ON/OFF motor states is 89% and 98%, respectively. These values dramatically decrease when the described time ensuring is removed: specificity is 82% and sensitivity falls to 57%.

In overall, the system generates an average of 35.3 hourly-based motor state detections per patient over the 4 days (11.8 hours in ON, 4.9 hours in OFF and 18.6 hours in an intermediate state). Thus, in average, for each of the four days, almost 9 hours of monitoring per day have been provided by the system.

Performance obtained by the system provides excellent results (sensitivity of 98% and specificity of 89%). Although the minimum sensitivity achieved is 75%, some specificity values are presented in the range of 50–70%. The lowest values are obtained due to a very low number of validated estimations for some of the participating patients. It must be noted that in some cases validation was not possible due to a lack of annotations, which is noted with NE in both Specificity and Sensitivity (main reason was because patients did not fill in the diary).

Regarding the method used to set the thresholds of the bradykinetic-gait measurement algorithm, the distribution-based approach reveals to suitably set the algorithm parameters, according to the excellent results obtained. The novelty of this approach relies on the fact that the approach does not require any OFF-induced data. In contrast, other works such as [14] employ OFF-induced states, obtained by skipping medication intakes, to train machine learning algorithms. Following the method described here, patients would not be required to skip medication intakes to adjust the algorithms. Moreover, patients do not have to follow any specific set of scripted activities as in [14], either at home or in a lab, to particularize the detection method.

One of the main limitations of the system is that, in order to estimate the motor state, it requires the patient either to walk or to present choreic-dyskinesia. However, this is compensated by a reasonable high number of

monitored hours with enough number of correct detections and a correct selection done for the kind of patients recruited (H&Y greater than 2 and lower than 5 in OFF state). On the other hand, one of the main advantages of the motor states detection offered by REMPARK system is in the fact that the evaluation method only requires patients to wear a single sensor.

9.4.3 Non-Motor Symptoms Descriptive Analysis

The REMPARK system was designed for the administration of questionnaires to the participants in the pilots [15], through the mobile phone interface. One of these questionnaires was a patient-based 30-points, used to determine the non-motor symptoms experienced by the patient during the past month. It had thirty items answered by the patient with a dichotomous answer: yes or no.

The following two questions were added to enquiry other non-motor symptoms:

- Difficulty to speak.
- Have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop (Such gambling, cleaning, use the computer, obsessing about food or sex)?

In addition to the standard dichotomous answers (yes or no), the REMPARK system was given the option of rating each symptom by using an analogical 10-points scale (0–10).

All the 41 patients answered the non-motor symptoms questionnaire (NMSQ). Among them, 63.4% presented mild non-motor symptoms, 36.6% presented moderated non-motor symptoms and no patient had a result within the “severe” range of the questionnaire. The median of the questionnaire answers was 8 (over the 30 points) and IQR was 9.0.

Table 9.7 shows a random selection of answers (five of them) with the most frequent positive answer. In addition, the two new introduced questions are also shown.

9.4.4 Efficacy and Effectiveness of the Cueing System

The efficacy of the cueing system to improve walk was tested by comparing the timed UP and GO test [16] with and without the cueing system activated, according the protocol of the study established in REMPARK.

The average time performing the timed UP & GO (TUG) test with the cueing system activated was 25.8 seconds, and without the cueing system was 25.7 seconds. Thus, no significant or clinical difference was found.

Table 9.7 Non-motor symptoms selected answers sorted by frequency

Question Number	Question Text	Positive (n)	Positive (%)
8	A sense of urgency to pass urine makes you rush to the toilet	27	69,5
9	Getting up regularly at night to pass urine	27	69,5
5	Constipation (less than 3 bowel movements a week) or having to strain to pass a stool (faeces)	17	41,5
12	Problems remembering things that have happened recently or forgetting to do things	17	41,5
15	Difficulty concentrating or staying focused	17	41,5
Added	Difficult to speech	26	63,4
Added	Have you had unusually strong urges that are hard to control? Do you feel driven to do or think about something and find it hard to stop (Such gambling, cleaning, use the computer, obsessing about food or sex)?	2	4,9

Several sub-analyses selecting participants were performed with severe gait problems according their FOG questionnaire. Some improvement in the average time in completing the timed UP and GO test was found then, but it was still no significant from a statistical point of view. Results of these sub-analyses are shown in Table 9.8.

The effectiveness of the ACS cueing system to improve walking problems was tested by comparing the results of two administered FOG questionnaires (before and after the REMPARK system testing). At the beginning of the pilots, participants answered the FOG questionnaire [6], which measures walking related problems (higher values in the results of this questionnaire means more

Table 9.8 Results of the cueing systems for participants with severe gait problems

FOG Questionnaire Filter*	n	TUG with Cueing: Average Seconds	TUG without Cueing: Average Seconds	Mean Differences (seconds)	Comment
Questions 4 > 2	11	24,7	27,0	-2,4	Ns
Questions 5 & 6 > 2	9	26,9	29,5	-2,5	Ns
Questions 4 or 5 or 6 > 2	16	24,5	26,0	-1,5	Ns

*FOG questionnaire question 4 > 2: longest FOG episodes lasting > 10 seconds

*FOG questionnaire question 5 > 2: starting hesitation episodes lasting > 10 seconds

*FOG questionnaire question 6 > 2: turning hesitation episodes lasting > 10 seconds

Ns: no significant.

severe gait problems), regarding the last 4–5 days. After the pilot experiments, the participants answered again the same questionnaire, regarding the pilot days.

The mean of the FOG questionnaire before using the REMPARK system was 12.8 and after the use of REMPARK system was 12.3, not being the difference clinical or statistically significant. The results did not significantly change in the sub-group of patients with worse walking problems. Thus, we cannot conclude with the data obtained in the study that the cueing system of the REMPARK system helped the patients to reduce their walking problems in real conditions.

9.5 Health-Safety of the REMPARK System

In all health interventions, there is a risk that intervention entailing unexpected negative effects that counteract the possible benefits from it. It is important to notice that, according to the operative definition, and adverse event is “*any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device*”.

During the experimental time, 7 participants presented health “adverse events”, one of them had a “serious adverse event” consisting in condition deterioration that led to hospitalization. The most frequent adverse events were limbs pain (three cases) and depressive symptoms (3 cases); cervical pain was also reported (1 case). All adverse events, including the serious adverse event, were considered as “*unrelated to the investigational device*”.

In conclusion, we can't identify special health-risk associated with the use of the REMPARK system in this pilot, although the study timeline and the lack of comparison group makes difficult to detect any health-risk associated with the use of the system. Further studies on safety are warranted.

9.6 Usability and User Satisfaction of the REMPARK System

The usability and user satisfaction with the system were measured by using two standard instruments: the System Usability Scale (SUS) [17] and the Assistive Device sub-scale of the Quebec User Evaluation of Satisfaction with Assistive Technologies (QUEST) [18].

The SUS is a 10 items Likert scale in which the respondent indicates the degree of agreement or disagreement with the statement on a 5-point scale (Figure 9.8). To calculate the SUS score, first the score contributions from each item are summed. Each item’s score contribution ranges from 0 to 4. For items 1, 3, 5, 7 and 9 the score contribution is the scale position minus 1. For items 2, 4, 6, 8 and 10, the contribution is 5 minus the scale position. Finally, the sum of the scores is multiplied by 2.5 to obtain the overall value of SUS. SUS scores have a range of 0 to 100.

Results over 50 are considered acceptable, and over 68–70 are considered good [19, 20]. The median SUS score of the REMPARK system in the pilots was 70 (IQR 25).

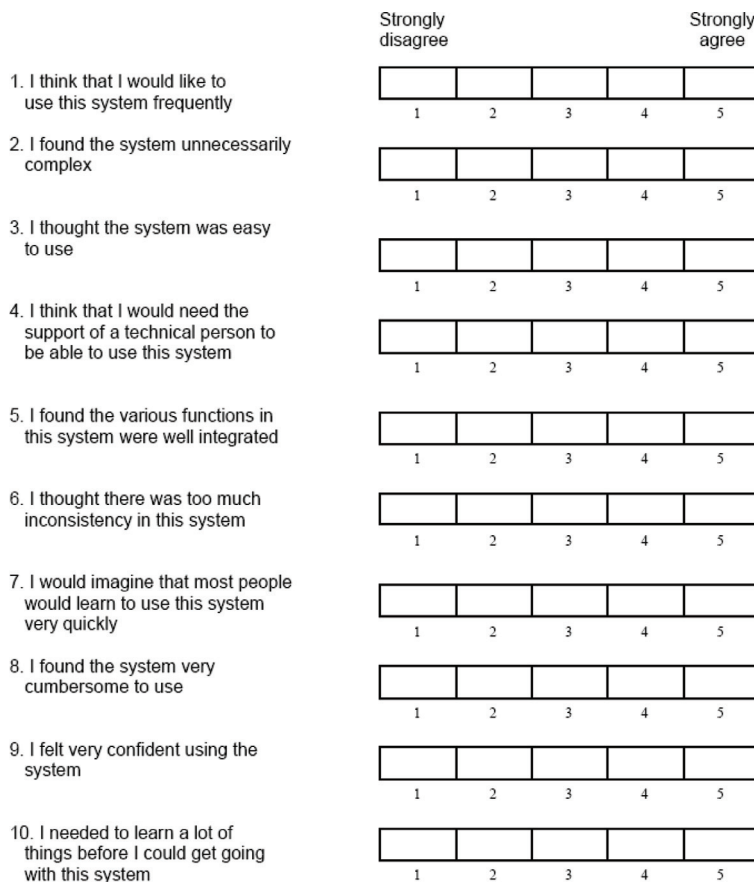


Figure 9.8 System Usability Scale.

The results can be considered good, according with standard interpretations of the scale. However, the results must be interpreted with caution, as the researchers administered themselves the SUS to the participants, who knew that the answers were not anonymous. This could have biased the results, because participants could have tried to please the researchers, offering a more positive vision of the usability than they would have given under anonymous circumstances.

Concerning the evaluation of user satisfaction, a subset of the QUEST questionnaire was used. The QUEST scale as it is described in [18] contains a number of items related to device characteristics and several questions related to the service characteristics. All the answers must be done according the following scale:

1. not satisfied at all
2. not very satisfied
3. more or less satisfied
4. quite satisfied
5. very satisfied

For evaluating REMPARK system, the 6 following items of the device subscale were used, together with a general question (number 7):

1. The dimensions (size, height, length, width) of your assistive device?
2. The weight of your assistive device?
3. The ease in adjusting (fixing, fastening) the parts of your assistive device?
4. How safe and secure your assistive device is?
5. The ease in using your assistive device?
6. The comfort of your assistive device?
7. What is your overall satisfaction with the assistive device?

Obtained results are shown in Table 9.9. The results can be considered good, being comfort the worst rated item and safety the best rated item. Overall satisfaction is good, being not satisfied 5% of the participants, and quite satisfied or very satisfied 75% of the users.

9.7 Summary and Conclusions

Forty-one (41) Parkinson Disease patients, under real conditions, participated in the test of the REMPARK system. Overall results show that the system has a good performance and reliability, with few data loss (4% of data), which does not impact the main information provided by the system, as it comes from several data slots, grouped and presented in 60 minutes' periods.

Table 9.9 Results for the QUEST questionnaire

	Not Satisfied		Not Very Satisfied		More or Less Satisfied		Quite Satisfied		Very Satisfied	
	At All		n	%	n	%	n	%	n	%
	n	%								
Dimensions	0	0	3	7,3	10	24,4	13	32	15	36,6
Weight	0	0	2	4,9	6	14,6	14	34	19	46,3
Ease in adjusting	1	2,4	1	2,4	15	36,6	11	27	13	31,7
Safe	0	0	0	0	7	17,1	22	54	12	29,3
Ease in using	0	0	2	4,9	8	19,5	22	54	9	22
Comfort	3	7,3	2	4,9	11	26,3	18	44	7	17,1
Overall satisfaction	0	0	2	4,9	8	19,5	19	46	12	29,3

The validity of the REMPARK system to detect motor fluctuations is very good. When all possible errors of the gold-standard timeline (the diary completed by the user) are excluded, by using the so called “*strict method*”, the sensitivity reaches 89% and specificity reaches 98%. These seem very good results, given the fact that they have been achieved in real life conditions, which are very demanding; in real life, there are many situations which could cause false positive or false negative detections. We consider this an important outcome, as it opens the door to a possible clinical use of the REMPARK system in the future.

The study has also demonstrated how difficult it is for patient to fill their diaries. In this respect, the REMPARK system constitutes a promising candidate to evaluate the correlation between the medication intake and the motor state in real life conditions. This can also constitute an invaluable help as a quantitative assessment instrument in clinical trials.

Additionally, during the REMPARK pilots, users could answer non-motor symptoms questionnaires using the mobile-phone interface. We did not measure the validity of this way of administration of questionnaires, but we really didn’t expect a decrease in validity of the questionnaires when administered in this electronically way. This, again, suggested that the REMPARK system could be successfully used by clinicians, to remotely gather non-motor symptoms information from their patients.

Although the usefulness of the cueing system to improve gait in PD patients have been previously demonstrated by other groups, we failed to show any benefit of the REMPARK system in improving gait, during this specific pilot. No benefit was noticed when performing the timed Up and Go test under

controlled conditions (efficacy), though a tendency to improvement was shown in the subgroup of patients with severe gait problems. These results did not reach statistical significance, possibly due to the small sample size, which pose problems of statistical power. In addition, the FOG questionnaire did not improve after using the system during the testing days (effectiveness). We think these results are inconclusive, as they were secondary outcomes of the pilot, which was not specifically designed to address these issues. If REMPARK system can improve gait problems or not, should be tested in longer experiments, specifically designed for measuring the effectiveness of the ACS sub-system.

The REMPARK system appeared to be safe, as no health adverse events were noticed, which could be related to the system. However, this result has to be interpreted with caution, as the small sample size and short observation period, pose again problems of power to detected adverse events. Safety of the system should be tested in additional research studies.

Finally, REMPARK system appears to be usable and participants seem to be satisfied with the system. Although this is a very encouraging conclusion, a possible bias in the usability results has to be taken into account, as the participants' answers were not anonymous and the researchers where not blind to their answers.

Overall, we consider that the REMPARK system piloting was successful, demonstrating good performance and validity to detect motor fluctuations, and good usability characteristics. The system is prepared for further testing in its way to commercialization and medical use.

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