3

The REMPARK System

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3.1 Introduction

As it has been presented and described in previous chapters, Parkinson's Disease is a progressive neurological condition. Unfortunately, there is no known cure for the disease and only treatments focused to the management and mitigation of the different symptoms are available to patients.

A well-designed and adapted technological approach (mainly based on WT and machine learning, as suggested in Chapter 2) can help both, the patients and their neurologists, for a better management and follow-up of the disease evolution. This will open the possibility to more effective therapies in order to improve patients' daily activities. From the beginning, with this specific aim, REMPARK project proposed four main objectives to be covered:

Objective 1: **Real-time motor status identification**.

To develop a minimum set of wearable inertial, electronic, intelligent sensors, to register in real-time the ambulatory movements of the patient and to clearly identify the relevant number of parameters, or types of motor disorders associated with Parkinson's Disease.

Objective 2: **Gait improvement system**.

To develop a self-calibrating gait guidance system to prevent the gait impairments and therefore minimize the appearance of FOG episodes and falls. The development will be mainly focused on auditory cueing, based on a system able to generate an auditory or acustic signal when necessary (Auditory Cueing System ACS), in order to help patients to improve their gait.

Objective 3: **User interface to get patient's feedback**.

To develop and implement a specific user interface on a smartphone to collect feedback directly from the patient. This feedback provided by the patient must have, at least, the following functionalities:

- Introduction of routine information such as the medications' intake time, quantity and quality of the sleep and other NMS.
- Answer to specific prompts to validate some situations detected by the REMPARK system. For instance, periodically completing medical tailored tests designed by the doctors (based on the UPDRS scale) in order to assess the evolution of the patient with time regarding the non-motor symptoms.

Objective 4: **REMPARK service for remote management of the disease**.

A central server service (REMPARK Server) organized to act as a repository of the processed ambulatory data of the patients, to ease the combination of these data with the Electronic Health Record (EHR) and to facilitate interaction with the neurologist (or medical service), the patient and/or the caregiver.

The present chapter introduces a deeper view of the presented approach, describing the details of the implemented and used system for the works carried out during the evolution of REMPARK project.

3.2 REMPARK System Overview

The developed REMPARK system has been worked-on and designed as a Personal Help System (PHS) that provides a closed-loop detection and treatment capabilities for an improved management of Parkinson's Disease (PD) patients.

From the beginning, the REMPARK architecture was conceived and organized in two different levels:

- **The immediate level (BAN – Body Area Network)**. A minimum set of wearable monitoring sensors should be able to identify in real time the motor status of the patient. The identification of the status is made autonomously using embedded algorithms in the sensor. The sensitivity and specificity of these sensors are better than 80%. A gait guidance system, based on an auditory cueing system ACS, was envisioned as part of this level to help the patients in real time during their daily activities. The immediate level is also including actuation capabilities that will be triggered by certain conditions detected by the sensors:
  - activation of the ACS;
  - automatic administration of a questionnaire;
  - possible remote control of a delivering medication pump.

  A possible inclusion of a remotely-controlled pump was done in REMPARK project as a laboratory exercise with no real tests in the trials with patients. This is a challenging work aiming to give a response to the need of a more accurate and adapted dose control for infusion pump systems. It must be considered as a step forward in the improvement of the QoL of patients with advanced PD.
  All the information from and to the immediate level are carried out by a smartphone which is used as a gateway.
- **The mid-term level** (based on a server). This is where the data provided by the sensors are partially analyzed, along with disease management done automatically or/and by neurologists. This part of the REMPARK system provides interconnection between analysis performed in the sensor and data provided by the neurologist, caregivers or the patient. An important tool at this stage is the Disease Management System (described in Chapter 8) that opens the possibility to a high level management of PD and to the establishment of interaction between concerned people.

These two levels and their relationship are represented in Figure 3.1. Below, Figure 3.2 shows a more detailed content of the described levels, together with the associated functionality. In these levels, two different groups of algorithms are running. The first group is located in the Immediate level (BAN), mainly in the sensor and smartphone, and it is responsible for the ON/OFF detection, the different symptoms identification and the implementation of the gait guidance system. A second group of algorithms is responsible of the implementation of the Rule Engine at the second level.

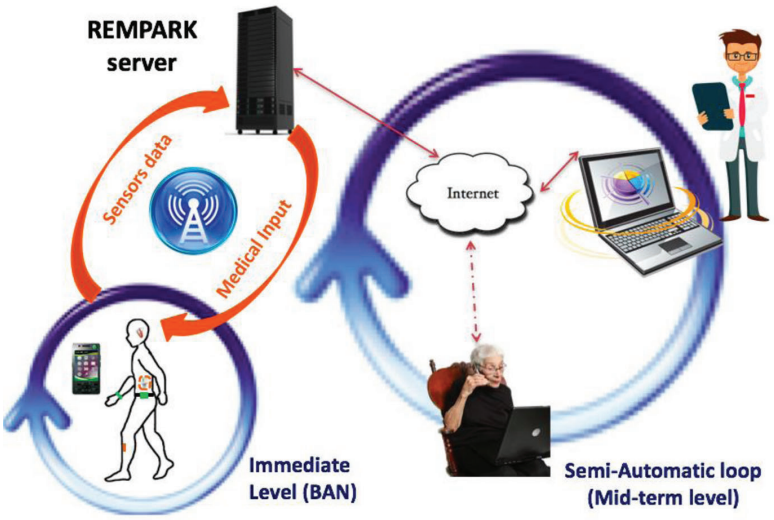

Figure 3.1 Hierarchical organization of REMPARK system.

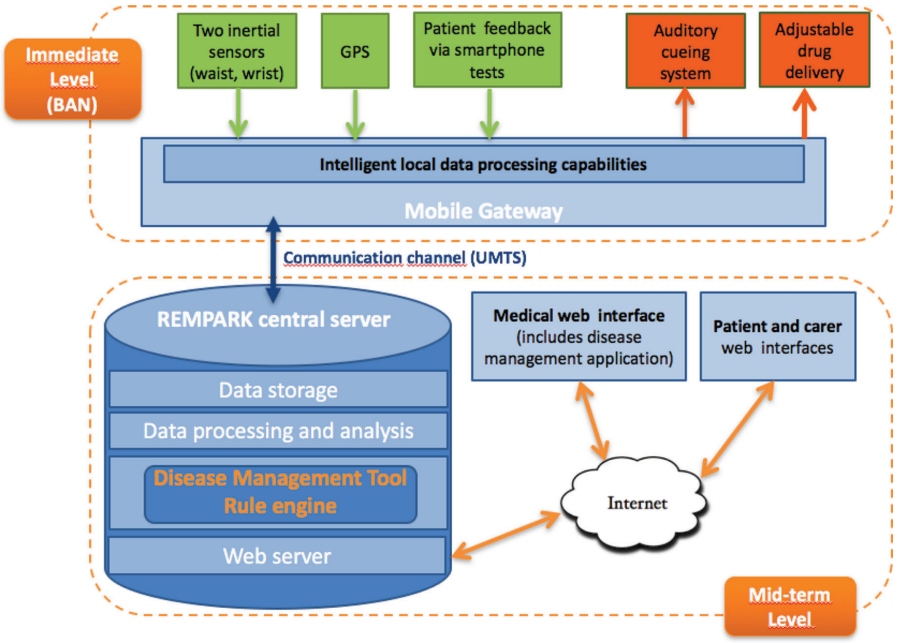

Figure 3.2 System architecture overview.

3.2.1 The Immediate Level

The Immediate Level corresponds to the Body Area Network (BAN) and acts in the short-term. It is composed of the sensors, the actuators and the 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 is done through Bluetooth V2.1, allowing enough autonomy for the patient. This level operates autonomously and it is a real operative closed loop. It is auto-adaptive by means of a constant evaluation of the actuator's effect, correcting its behavior in the short-term. The configuration of this level can be changed according to different patients' needs.

Considering the details indicated in the Figures 3.1 and 3.2, the main components or sub-systems having a direct interaction with the PD patient are the following:

- **Sensor module**: It is in charge, using appropriate technology, of the continuous monitoring of the patient's movement behaviour. It is able to detect and identify in real-time the different motor-related symptoms suffered by the patient.
- **Mobile gateway**: As it is inferred from Figure 3.1, it plays a central role in the system. It does not only interact with the remaining components, but also drives their behaviour by setting their functional parameters. In the REMPARK system the mobile gateway is implemented using a commercial smartphone and specifically developed software.
- **Drug pump**: It is intended to administer an appropriate drug dose depending on the patient's movement parameters (in REMPARK project, this part was only considered, for a feasibility demonstration and was treated from a theoretical point of view with a laboratory proof of concept).
- **Auditory cueing system (ACS)**: This component provides an auditory pattern intended to assist the patient in the case of abnormal movement patterns (such as FOG or shortened stride length).

3.2.2 The Mid-Term Level

The Mid-term Level (also called the Level 2), refers to the actuation in the medium-long term and constitutes a closed semi-automatic loop, as it will allow the intervention of medical professionals. The system is able to send

data to the server, allowing the patient's neurologist to regularly follow the evolution of the patient's disease in a more effective manner, as well as being able to take better informed decisions about the adjustment of the pharmacological treatment of the patient using the Disease Management System (DMS). The system is also able to generate alerts, according personalized thresholds, related to the status and evolution of the disease.

Data on the server can be automatically included in an Electronic Health Record (EHR). This way, the correct intelligent data treatment will help to evaluate and predict the evolution of the disease of a particular patient.

Below, the sub-systems responsible for the storage of the data generated at Immediate Level as well as for its high-level analysis are listed. The results of the high-level analysis are available to both the patient and the neurologist or clinician. The clinician can also interact with the system by changing/updating the medication profile of the patient.

- **Mobile gateway**: At this level, it is responsible for sending the data generated at the first level to the REMPARK server and to get the feedback test to be presented to the patient.
- **REMPARK server**: It is in charge of storing the data provided by the mobile gateway and of making this data available to the Rule Engine, described below.
- **Rule Engine**: This component filters the raw data stored in the server and makes it available to the patient and the caregiver using an appropriate interface. Through this interface, both the PD patient and the clinician/neurologist can be interconnected. The patient is able to access the personal record stored in the server. The neurologist can access the personal records of the supervised patients and eventually update their treatment plan based on this information.

3.3 Definition of the REMPARK System Main Characteristics

This section includes a description of the main characteristics of the system. Some characteristics were included according considerations already contained in the proposal of the project and after the analysis of the results obtained from the answers provided by potential users of the REMPARK system (patients, neurologists and carers) to specific questionnaires elaborated by the consortium [1, 2]. These will imply concrete requirements and constraints

for the system that were considered and included in the final version of the tested system.

The indicated references [1, 2] are publicly available reports on these activities which contain details of the administered questionnaires, the constraints of this administration, obtained answers and their analysis. As it is indicated in [1], there are three main conclusions derived from the answers provided by patients to the REMPARK questionnaire:

- The most prevalent motor disorders among patients are: ON/OFF phenomena, dyskinesia and FOG.
- The most prevalent gait problems among patients are: "reduced walking speed", "small steps" and "shuffling". These problems appear both at home and outdoors, and nearly half of the patients use a strategy to improve them.
- Over 80% of patients are familiar with the use of a mobile phone for making calls and sending SMS. However, they are not so familiar with smartphones based on a touch interface.

Regarding the answers provided by caregivers, as stated in [2], four main conclusions can be derived:

- "Reduced walking speed" and "small steps" are the most clinically relevant symptoms in the mild stages of PD. "Freezing of gait" and "difficulty in turning" are the most clinically relevant symptoms in the moderate stages of PD. In the advanced stages of PD, "falls" arises as a new main clinical occurrence.
- Patients use strategies to improve symptoms mainly in the moderate-advanced stages of PD. However, the strategies that PD patients adopt (mostly the use of a stick) are not considered as useful as verbal cueing (auditory).
- "Reduced walking speed" should be considered a symptom as relevant as "freezing of gait".
- The moderate stages of PD are the best target for the REMPARK system. This means that the system should pay special attention to the multifaceted clinical expression of PD during these stages.

Table 3.1 summarises the requirements for the REMPARK system derived from the feedback got from the final users through the proposed questionnaires.

It is worth noting that first and third requirements in Table 3.1 were already considered in the original goals and specifications of the REMPARK project, but second one was only detected after the evaluation of the questionnaires.

Table 3.1 Technical specifications derived from the user feedback

Requirement Heading	Requirement Description
Symptom detection	The system must be able to detect at least the following symptoms: "reduced walking speed", "small steps", "freezing of gait", "dyskinesia", "bradykinesia" and "falls".
Patient interface	The user interface in the mobile gateway must be operated by a PD patient in any stage of PD.
Symptom mitigation	The system must provide auditory cueing upon detection of "reduced walking speed", "small steps" and "freezing of gait" symptoms.

Concerning the symptom detection requirements of the system, the motor status of the patients will be evaluated based on the following parameters:

- Tremor
- Bradykinesia
- Freezing of gait (FOG)
- Stride length
- Gait speed
- Fall indicator
- Dyskinesia

The final conclusion on ON/OFF state is achieved by a real time execution of the included algorithms and an evaluation of their combination or presence during a given time period.

3.4 Subsystems Specification

In previous sections, main components of the REMPARK system and the processes that enable their interaction have been identified. Based on this, the present section elaborates the main technical specification for each individual component: the sensor module, the ACS Auditory cueing sub-system, the smartphone and the REMPARK platform.

As it will be discussed in Chapter 4, a very important part of REMPARK project was devoted to the gathering and construction of a Database, with the cooperation of a number of patients in order to extract the necessary knowledge for the development and implementation of the corresponding algorithms to be embedded in the processing part of the final sensor module. These embedded algorithms in the sensor module will be able to process and to determine in real time the presence of specific symptoms in a patient. It must be clarified here

that the presented and mentioned sensors hereafter (the wrist and the waist ones) have been used for data gathering and construction of the Database, but after discussion and final conclusions of REMPARK, the wrist sensor was finally not considered in the pilots, where only the sensor module located in the waist of the patient was finally used.

3.4.1 Sensor Module

The sensor module is the subsystem in charge of determining in real time if a specific indicator (of a concrete symptom) appears in the PD patient movement pattern. The detection of the indicators is obtained after a local process of the data acquired by the sensors included in the module. These indicators are sent at regular time intervals to the mobile gateway subsystem, that will thereafter decide the action to be performed based on their values.

The type and number of sensors to be used depend on the specific movement disorders to be detected. As it has been stated in the previous section, the movement disorders to be addressed by the REMPARK system are the following: Tremor, Stride length, Gait speed, Bradykinesia, Falls, Dyskinesia and FOG.

- Tremor consists in an involuntary, rhythmical, forward and backwards movements of a body part, which are Caused by the rapid alternating contraction and relaxation of muscles. For three out of every four people who develop Parkinson's Disease (PD), the disease begins with a trembling or shaking in one of the hands. It can also appear in the feet, face or jaw. This rhythmic movement of the extremities in PD patients has a frequency typically between 4–7 Hz. Therefore, in order to detect this movement disorder, the REMPARK system should include a sensor unit to be placed in the wrist. This unit should contain a triaxial accelerometer and a data processing unit. In order to provide an indicator whose value is related to the presence of tremor in the hand the data processing unit should be able to carry out sensor readings with a frequency of at least 20 Hz.
- The determination of indicators related to stride length, gait speed and bradykinesia are interrelated, since the gait speed is given by the number of strides in a specified time window, and once stride length and gait speed are determined it is possible to derive an indicator for bradykinesia. Even if the stride length has been determined in the past using gyroscopes placed in the leg [3], it has been demonstrated [4] that a single triaxial

accelerometer placed on the patient's waist can be used to accurately measure stride length, gait speed, bradykinesia and falls.

- Dyskinesia is a medication side effect experienced by patients with Parkinson's Disease and shown in the form of involuntary movements. There are many papers in the literature that manage to successfully detect dyskinesia using inertial sensors. The most prominent research work in this area is performed by Manson et al. [5] which uses a triaxial accelerometer placed on the shoulder. The analysis is based on the comparison of a signal's characteristic with the severity of dyskinesia assessed by Abnormal Involuntary Movement Scale (AIMS) while the patient performs the following activities: sitting, talking, writing, drinking, preparing food, eating and walking. Characterizing the signal consists of obtaining the average value of the accelerations in the range of 1 to 3 Hz, obtained through a band-pass filter. This characteristic of the signal is demonstrated to be correlated with the value of the AIMS score. The study included 26 patients with Parkinson's Disease who were monitored for 20 minutes. Since a triaxial accelerometer placed on the waist will be used to measure stride length, gait speed and falls, the data provided by this sensor unit will also be used for detecting dyskinesia.
- Regarding the detection of FOG episodes, the first work that analysed the relationship between the frequency content of the signals generated by triaxial accelerometers and the presence of a FOG episode was presented in [6]. Two accelerometers were placed in the ankles of both healthy people and PD patients. It was observed that normal walking has a principal frequency around 2 Hz, while FOG episodes are characterized by a principal frequency in the range of 6–8 Hz. A second study was carried out in [7] with PD patients. In this study, a single triaxial accelerometer was placed on the patient's shin, and the signal was measured on the vertical axis (parallel to the leg). It was found that FOG episodes caused the appearance of frequency components in the range 3–8 Hz. This study was continued in [8, 9], where the analysis presented in [7] was extended to accelerometers placed in the patient's thigh and waist. Regarding the results obtained when the sensor was placed on the waist, it was found that they were similar and even better than those obtained when using other body locations. Therefore, the REMPARK system will use the waist accelerometer to derive an indicator related to the rising of a FOG episode. In order to cope with the different measurements that

this unit has to carry out the minimum sampling frequency should be 40 Hz.

From the previous explanation, a decision was initially taken and the sensor module to be used in the REMPARK system was constituted by two sensor units. One of these sensor units must be placed on the patient's wrist and the other on the patient's waist. These sensor units must contain, in principle, a triaxial accelerometer and a data processing unit. However, in order to provide additional contextual information to the acceleration data, it is considered convenient to include sensors too providing information related to the speed (gyroscope) and the orientation (compass). This information may improve the sensitivity and specificity of the measurements related to the movement disorder indicators to be generated by the REMPARK system.

As previously indicated, the sensor module has to communicate using a wireless link, such as Bluetooth, with the mobile gateway of the REMPARK system, in order to make the measurements accessible to both the patient and the caregiver. Therefore, in order to simplify the overall system and to make it more user-friendly it is envisioned that the sensor units placed in the waist and the wrist should establish a communication using the same wireless communication protocol.

It is important to bear in mind that during the construction of the already mentioned REMPARK database the raw data captured by the sensors will not be processed by the sensor units, since the goal of this project phase is to get enough representative data in order to develop efficient processing and detection algorithms. Thus, the sensor module should have some amount of local storage in order to save the sensor recordings. This local memory unit should be easily accessible in order to retrieve the data once the experiments with patients are finished.

Another important aspect to be considered is that the sensor module has to be operated by people with no technical knowledge. Hence, it has to offer a very simple procedure to start/stop its operation and to analyse its status at any time (preferably using visual information). Additionally, it has to be worn during extended periods of time (approximately eight hours during the experiments). This poses a constraint to the physical features (weight and size) of the sensor module, to the materials that have to be in contact with the patient's skin.

According to the above considerations, Table 3.2 summarizes some of the main requirements for the sensor module derived from operational features to be exhibited by this subsystem.

Table 3.2 Some important technical requirements for the sensor module

Requirement Heading	Requirement Description
Structure	The sensor module must contain a sensor unit placed in the patient's waist and a sensor unit placed in the patient's wrist.
Size – waist sensor unit	The dimensions of the waist sensor unit must be smaller than $150\times70\times30$ mm.
Size – wrist sensor unit	The dimensions of the wrist sensor unit must be smaller than $80\times70\times30$ mm.
Weight – waist and wrist sensor units	The weight of the sensor units must be low (around 200 g. for the waist unit and 150 g. for the wrist one)
Battery capacity	The battery on the sensor units must permit a normal continuous operation for at least 8 hours.
Operation – waist and wrist sensor units	The sensor units must be turned on/off using a single button.
User interface	The sensor unit must use a single led to display its state.
Communication	The sensor must be able to establish a wireless link with the mobile gateway. This requirement is only for the operative part and not used during the database construction phase.
Communication – additional specs	The waist and wrist sensors must be able to send to the mobile gateway its battery status. The waist sensor must be able to send to the mobile gateway data containing indicators for the following movement patterns: stride length, gait speed, bradykinesia, falls, dyskinesia and FOG.
Communication – security	The data sent by the waist and wrist sensor units to the mobile gateway must be encrypted.
Sensors – waist sensor unit	The waist sensor unit must contain a triaxial accelerometer, a triaxial gyroscope and a compass.
Sensors – wrist sensor	The wrist sensor unit must contain a triaxial accelerometer.
Data sampling rate	The waist sensor unit must be able to sample data from the sensors with a frequency of at least 40 Hz. The wrist sensor unit must be able to sample data from the sensors with a frequency of at least 20 Hz. It must be noted that during the Database construction, used frequency was higher (200 Hz for the waist sensor and 80 Hz for the wrist sensor).
Data processing	The waist sensor unit must contain a data processing unit able to calculate indicators for the following movement patterns: stride length, gait speed, bradykinesia, falls, dyskinesia and FOG. The wrist sensor unit must contain a data processing unit able to calculate indicators for the following movement patterns: tremor.
Comfort	The parts of the sensor unit in contact with the patient's skin must be constructed with a biocompatible material.

(*Continued*)

Table 3.2 Continued

Requirement Heading	Requirement Description
Battery certification	The Li-ion batteries used in the sensor module must have test certificate according to standard UL 1642.
Battery charger certification	The battery chargers used for the sensor module must have a test certificate demonstrating compliance with IEC 60950.

3.4.2 Auditory Cueing Subsystem

This section describes the REMPARK Auditory Cueing System (ACS) system for gait-cueing and FOG intervention. This system intends to be a self-calibrating/adaptive gait guidance system for helping PD patients in real time, during their daily activities.

PD patients are usually affected by symptoms associated with a reduced motor performance and gait disturbances that affect their ability to walk independently and safely [10]. One of the key problems of PD patient's gait is the particular difficulty with the internal regulation of stride length, reflected as an inability to generate sufficient stride length, even though the control of cadence (or step rate) is intact and can be easily modulated under a variety of conditions [11, 12]. Some patients may increase the stepping frequency to compensate the reduced stride length [12–14]. With the disease's progression, other episodic gait disturbances can appear, e.g. start hesitation and FOG episodes [12]. Festination of gait, characterized by small and rapid steps, is also a common symptom of advanced PD [15]. By applying adequate external regulatory rhythmic stimulations, movements' speed and amplitude can be modified [16], so that gait performance is improved, even under complex environments [9, 12, 17, 18].

The ACS systems would therefore be able to adapt the rhythm of cueing to the specific needs of each patient and each situation, being activated and deactivated at the adequate times, taking into account the real time feedback sent by inertial sensors (i.e. relative to the gait's quality), as well as the feedback provided by the patient (i.e. a subjective feedback related with the quality of cueing that is being applied).

3.4.2.1 Gait guidance ACS functional description

The cueing system is intended to be used every day, during daily activities. The smartphone (seen at this point as a control unit) will be responsible for the control of the auditory cueing actuator, and will be able to program the cue parameters taking into consideration the specific needs of the patient in each situation, in a self-adaptive way (Figure 3.3).

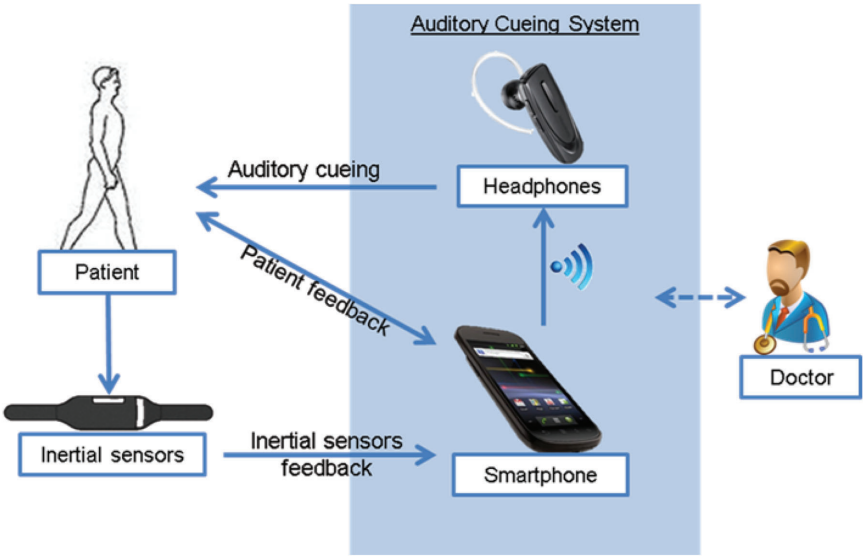

Figure 3.3 Simplified representation of the ACS functionalities.

The system must be mainly controlled in a self-adaptive way and should not require user intervention to trigger or adapt a cueing response. Thus, it is required that the system operates in real time, together with the feedback provided by inertial sensors.

Since continuous auditory cueing might not be acceptable for PD patients [9] the system will provide the cueing automatically only when required, i.e. when the patient is walking and a context of impaired performance or an inefficient walking pattern is perceived (based on the available REMPARK sensor subsystem measures).

In concrete, the final parameters and symptoms considered for triggering of the ACS system are the presence of a bradykinetic walk and FOG episodes, suffered by the patient (see Table 3.3).

The detection of gait impairments is performed through a real-time comparison with the baseline data characterizing the normal range of walking parameters values for a specific individual patient.

It must be clear that, according to the previous explanation, there exists a very close relationship between stride length, speed of walking, cadence and bradykinetic walk. Hence, changes in these parameters, characterizing a bradykinetic walk, must be referred to baseline measurements of a patient [19].

Table 3.3 Parameters/Measures considered by the ACS

Parameter/Measure	Description
Bradykinesia	Slow movements, slow walk
FOG episodes	Transient period in which gait is halted.

This means that even if a low stride length is detected, this parameter can be considered normal if the baseline walking speed is also low.

The determination of "normal values" needs to be done carefully, so that meaningful values are considered for impairments detection. To get this information, some initial tests (called here the calibration sessions) can be performed with each patient before starting to use the REMPARK system. The therapist/doctor must be the responsible for conducting these tests, in order to accurately control the protocols and the results. The REMPARK system will also be able to detect the FOG episodes, which are also considered as an input for the ACS subsystem.

Based on the detection of the triggering symptoms and their comparison with the baseline values, the ACS automatically activates or deactivates the cueing. Also given these measures, the cueing rates must be automatically adjusted to the specific needs of the patient in each situation. This autonomy requires a constant evaluation of the effects of cueing on the patient, and the automatic adjustment of cueing rates according to the patient's response. The requirements related to the specific situations are detailed on Table 3.4.

The ACS will provide the cueing in the form of sounds. Once the patient hears these sounds, he/she will try to synchronize the rhythm of steps with the rate of the sounds provided. Sound beats can be single (i.e. pace one step per stride) or double (i.e. pace both steps per stride). According to [20], gait is more effectively modulated when both footfalls are paced, which means that a double beat must be used. Specific voice recordings of alerts and information must be produced when the patient is not able to synchronize with the rhythm of cues. These alerts must help the patient to synchronize with cueing rate and ask for some patient's feedback.

The ACS implemented and used in REMPARK (see additional information in Chapter 7) is comprised of two physical components – headphones and the smartphone – that will interact (directly or indirectly) with other subsystems. The smartphone will be able to decide when and how to actuate in each specific situation; headphones are placed on the patient's ear and will produce the sounds acting as cueing. The above Figure 3.3 is presenting this architecture.

Table 3.4 General functional requirements of the ACS system

Requirement Heading	Requirement Description
Cueing type	ACS must provide cueing automatically, in a self-adaptive, non-continuous way, taking into account the specific needs of the patient in each situation.
Operation mode	Cueing must operate only when the patient is walking.
System interaction	ACS must be able to work in real time, together with the feedback provided by sensors.
Functional requirements	ACS must be able to detect a bradykinetic gait based on walking speed, stride length and the occurrence of FOG episodes, as measured by movement sensors.
Stimulus type	ACS must provide stimulus in the form of sounds.
Sound rhythm	Sounds must pace both left and right footfalls.
Alerts	ACS must be able to provide voice recordings with alerts and instructions, when required.
Configurability	ACS must be able to program the activation and deactivation of sound stimulus at the adequate times/situations.
Adaptation	ACS must be able to automatically adapt the rhythm of cues (sound stimulus) to the specific needs of each patient in each situation.
Evaluation and Rating	ACS must be able to constantly evaluate the effect of cueing on the patient and to enable the patient to rate the cueing session.

A headset (ear-set) was selected to be included in the auditory cueing system. Ear-sets are usually small and aesthetic and, as they are placed in a single ear, they enable the patient not only to hear the auditory cueing but also to perceive the auditory stimulus from the surrounding environment.

The auditory stimulus will be provided in the form of metronome sounds. Since different rhythms of stimulus are going to be produced, the easiest way to apply cueing is to use metronome sounds, because its rate is easier to be adapted than, e.g., the music.

Since the headset will produce the sounds streamed by the smartphone, it must therefore be compatible with Advanced Audio Distribution Profile (A2DP). This profile defines how audio can be streamed from one device to another over a Bluetooth connection. A2DP is designed to transfer a unidirectional 2-channel stereo audio stream.

Alternatively, audio can be produced by a non-A2DP device, by channelling the audio to the stream that carries phone call audio to the headset. This option was, also, considered as an option.

3.4.2.2 Need of an adaptive ACS

When an external rhythmic auditory pacing is applied, the patient tries to couple his/her footfalls with the beats, which helps to normalize the walking pace (cadence) [20, 21]. As stride length and stride frequency tend to change as a function of walking speed, this adaptation of cadence might offer a strategy to indirectly influence the stride length regulation in these patients, while controlling for walking speed [19].

The effects of auditory cueing may, however, differ for patients with or without FOG, referred as "freezers" and "non-freezers", respectively [18]. It is well known that cueing rates higher than baseline walking rate are contraindicated for freezers. Based on the study by [22], it is recommended the use of a lower rate setting for freezers and an increase of up to 10% for non-freezers. In both cases, the latest goal of training with the ACS is to maximize stride length while walking at as fast a cadence as possible. If these two variables are increased during training, then walking speed is also increased [16].

The cueing rate settings need, then, a careful consideration, i.e. the intended speed of walking and the quality of movements, and the different responses to the cues by different subgroups of patients suffering from PD. Given these conditions, a set of requirements related with the auditory cueing rate must be carefully considered:

- Preference
- Safety
- Walking rhythm
- Different modalities
- Adaptation to the user

As the person can dictate his/her own preferred walking rhythm, the perception of this baseline rhythm is crucial, so that REMPARK ACS can be the most fitted and comfortable as possible to each situation. The comfortable walking rate is used as a basis to establish the auditory cueing tempo being provided if it is necessary.

The baseline rhythm can be perceived when gait is considered normal (without evident motor symptoms). After the person has started to walk a few strides, it is possible to estimate this rhythm (at least 3 strides are required to reach a steady-state walking in healthy young subjects [23]). When this estimation is not possible, the normal cadence at the preferred speed, as calculated during the calibration session, can be used. When setting the cueing

rates, it is important to guarantee that the applied rates will never compromise the safety of the person, both during dual task and walk alone.

Therefore, gait cannot be stimulated beyond the person's limits and the stimulus cannot provide a negative effect on the walking pattern of the individual. A too high cueing rate, for example, may lead to small steps (low stride length) at a high cadence, which is an inefficient walking pattern.

As PD patients face different problems and intensities of problems considering the different stages of the disease and medication states (i.e. ON/OFF state and freezer/non-freezer classification) [24, 25], the ACS system must enable the introduction of different settings/configurations for different patients.

The self-adaptive cueing system will have the possibility to be adjusted/modified in several ways by the patient and by the doctor/therapist. The ACS system must offer the following characteristics regarding user's interaction: configurability to the specific needs of different patients, configuration of different parameters done by caregivers (rate, modality, baseline, rate change . . .), voluntary deactivation, adjustment of the volume and the tone.

3.4.3 Drug Delivery Pump Considerations

The development of a wireless communication module for subcutaneous infusion pumps of liquid medicines opens an opportunity for real-time control of the applied dose. A system of closed-loop control would be possible for the case of some diseases in which the result of treatment can be measured by a sensor, i.e. the drug infusion could be adjusted to the needs of the patient in real time.

This idea has been explored in the case of diabetes, in which the glucose level in plasma can be measured accurately and thus this information may be used to control the basal dose of insulin to be delivered via a subcutaneous pump infusion. From this hypothesis, various feedback systems that include automatic and semi-automatic (with a doctor in the decision loop) feedback have been successfully developed, in which insulin infusion is controlled according to the level of glucose in the blood. In contrast, drugs for Parkinson's treatment are often given using a pre-established scheduling and dosage. However, regardless of the route of administration, intermittent delivery of the programmed dosage produces fluctuations in the level of the drug in plasma (known as 'peaks and valleys') that produce variations in the effects of the drug in the central nervous system.

The amount of drug in each administration and the time between administrations is calculated so that the peaks of plasma do not exceed the upper therapy limit (which may produce unwanted side effects) and that the valleys do not fall below the lower therapy limit (which may cause the therapeutic effect to disappear). Unfortunately, it is not always possible to maintain drug levels in plasma within the therapeutic range. What is more, as the disease progresses, the goal of staying in the therapeutic range is increasingly difficult to achieve and therefore, the time intervals between administration of drug become shorter and the doses higher. Contradictory to this, such doses and time intervals seldom completely control symptoms and therefore, the OFF periods and dyskinesias occur eventually.

Recently, it has been hypothesized that if the drug levels are maintained within the therapeutic range, control of symptoms associated with Parkinson's Disease will be improved substantially [26].

To this end, therapeutic solutions are being developed, aimed at eliminating the programming/intermittent administration of medication and replacing it by a continuous, controlled administration. It is precisely for this reason that subcutaneous administration of dopaminergic drugs was made possible by the development of infusion pumps that maintain drug levels in plasma in the desired range for as long as possible.

The purpose of using these pumps is to maintain the level of drug in plasma within the desired range, and, at least, change the dose on a schedule based on time (different doses depending on the time of day, assuming the needs of the patient). The development of "automatic" infusion pumps, able to adjust the drug dose based on the patient's symptoms will be welcomed both by patients and by doctors as a breakthrough in controlling the symptoms of Parkinson's Disease.

Apomorphine is an agonist dopaminergic with a very short average life, which is administered subcutaneously. There is extensive experience in the use of apomorphine for the treatment of Parkinson's Disease, including its administration in the form of bolus or flow for the release of "lock states" and the corresponding basal treatment.

In order to address the symptoms in real time with apomorphine, a subcutaneous infusion pump that can adapt to them is required, that is, it should receive orders from a device capable of monitoring symptoms.

Even if drug infusion pumps were not tested with patients within the framework of the REMPARK project, one of the project goals was to test if the REMPARK system may be useful to create an automatic or semi-automatic feedback loop that will improve the treatment of PD patients. For this purpose,

a commercial apomorphine infusion pump was used in the REMPARK system. The pump was modified with the necessary electronic components so that it was able to communicate with the mobile gateway so as to receive commands related to the drug dose to be administered. The pump should be able to operate both in bolus and in infusion mode. Additionally, the electronic system added to the pump should permit a manual user interaction.

In REMPARK project, the organization of a specific pilot action, with real patients, using a drug delivery system control was discarded because it was out of the real possibilities of the project activity. Alternatively, it was decided to consider this effective possibility, preparing all the requirements and conditions from a technical and functional point of view. This activity was based on an already developed experience by some of the participants [27].

3.4.4 The smartphone Technical Requirements

The smartphone is at the core of the REMPARK BAN, receiving data from sensors and sending instructions to actuators. Furthermore, it serves as a gateway between the BAN and the server, by receiving settings and preferences from the server and sending the data gathered in the BAN. In consequence, the smartphone is a critical device in the BAN, as without it the system would be unusable. Figure 3.4 shows the connections of the smartphone on the REMPARK system, as well as the directions of the information exchanged.

We split the requirements of the smartphone into hardware and software. The hardware requirements are mainly related to the characteristics of the smartphone including connectivity. It must provide battery life, as well as other usability requirements.

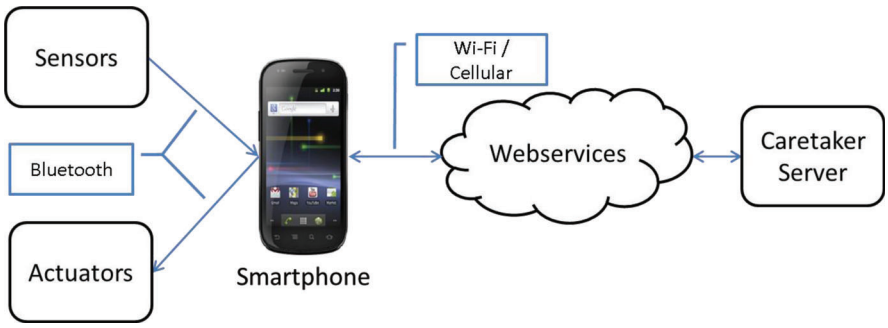

Figure 3.4 Smartphone connectivity and information flows.

Connectivity-wise, the smartphone should be able to form the BAN itself, connecting to all sensors and actuators using Bluetooth protocol. To connect to the caretaker server, it will need an Internet access enabled. Here, cellular connectivity is mandatory (GMS or UMTS) and Wi-Fi will be used whenever possible. Although most smartphones in the market today already come with all these radio interfaces, we need to ensure that they are present and available; for instance, we need to ensure that the smartphone has a SIM card with a data plan enabled, so that cellular data is available. As this is a critical component of the system, we need to ensure that it is always on, or at least minimize its downtime. To this end, it is critical to have a suitable battery that will last for the whole day while the patient is away from a power source. We expect the system to last at least 8 hours working on battery power alone, as this is the maximum expected time a person will be away from a power source.

With regards to the usability of the smartphone, we expect it to be big enough and have enough resolution so that older adults with some visual difficulties can use it. Furthermore, the device needs a touch screen interface to provide direct interaction and a more reduced learning curve.

As a result of a review of relevant literature, and interviews with doctors and relatives, we identified major changes on PD affected people's fine motor skills, changes that makes it very hard for them to do precise movements both on ON and OFF stages. Hence, we need a screen large enough to accommodate buttons as big as necessary in order to offer them good interaction experience.

- On/OFF state, they have their fine motor movements mostly conditioned by Bradykinesia and rigidity. Causing slower movements and loss of agility thus precise movements become very difficult. Possibly they can do some precise selections but with great effort. Whereas tremor although being generally a rest tremor, sometimes can still be active while on movement, and thus makes a precise movement even harder.
- While on ON state even when most PD symptoms are gone, on later stages of the disease, PD affected people have dyskinesia which can be impairing as the other symptoms, since it make them do involuntary movements and thus making it very difficult to do precise selections as well.

Moreover, with the aim of interacting with a touch screen, a user does not need to apply much pressure to activate it, which is also beneficial to PD affected people since they also have lack of strength and are much more comfortable with smooth gestures.

In order to ensure these preconditions and to guarantee that we can extend the smartphone functionality in any way we require it to have an open-source

operating system and main drivers, so that we can access, change and compile them to any software version we need.

Concerning the smartphone related software aspects, they will consist of distinct components:

- **Server Communication:** The smartphone will need to exchange information with the REMPARK Server.
- **End-user Applications:** The smartphone will provide a number of applications related to the management of the disease or the REMPARK system.
- **Data Processing and Event Detector:** The smartphone will analyse the data received from the sensors and will raise specific events.
- **Sensor Communication:** The smartphone will gather information from waist sensor.
- **Actuator Communication:** The smartphone will control the actuators upon receiving orders from the Server, an input from the user or after processing the data gathered by the sensors.

In regards of the Server Communication, the smartphone must guarantee the communication with the REMPARK server, establishing a communication channel with the caretaker server whenever needed, and use encryption methods that must ensure:

- **Data integrity:** both the smartphone and the server must guarantee that the information they receive was correctly transmitted and unaltered.
- **Data security:** the mechanism must ensure that no one else can have access to the information being transmitted, as well as ensure that no one can alter the information while it is being transmitted.
- **Authentication:** both the smartphone and the server will be able to authenticate themselves to each other, thus guaranteeing that information is being transmitted to the right party.
- **Non-repudiation:** tightly coupled to the authentication mechanism, non-repudiation aims at guaranteeing that: (1) every message is signed, so that the sender cannot deny that it had sent the message; (2) no one else can impersonate the sender. This will guarantee that every message is accounted for.

The final set of the smartphone requirements is related to provide a set of applications, both giving users and medical caretaker's tools to better manage this disease. To the users, it provides assistive applications to help them with their daily lives and to the medical caretakers it provides valuable medical information of the state of the disease. These applications range from actuators controllers (e.g. for auditory cueing), assistive applications to help the users

with their daily living (e.g. medication reminders) questionnaires to input medical or routine information and prompts to validate specific situations detected when acute events are detected.

The smartphone is also the interface to the caretaker server, so it must provide a way for patients to use the services provided by the server, e.g., check health status, contact the doctor, see appointments. Table 3.5 provides an overview of these requirements.

The REMPARK smartphone must receive and process the data from the sensors. The processing will be achieved through a set of algorithms to assess the status of the patient and control the BAN actuators. These algorithms will be adapted to the particular needs of each user. As such, the smartphone will fine-tune the algorithms by updating its information with the caretaker server. Furthermore, after analysing the data, the smartphone should decide on the action, or event, to trigger. These actions can be:

- to enable an actuator for the interaction with the patient
- to raise an alarm so that medical staff can respond
- to ask some input, or confirmation, to the patient.

The smartphone will also provide an Actuator Communication component to interact with the actuators. The actuator actions must be triggered either by the smartphone in the cases described above, or directly by the server if, for instance the medical staff decides that the patient should receive some input in real time (e.g., a medical questionnaire). Furthermore, when communicating with the actuators, the smartphone must ensure that: (1) messages sent to the actuator are not replicated, so that the actuator does not trigger the same action twice; (2) no messages for the actuator are lost, to guarantee that the actuator really acts; (3) actions of the actuator are personalized for each patient, for instance, the auditory cueing system uses the frequencies that better suit the patient.

Table 3.5 Requirements of the smartphone end-user applications

Requirement Heading	Requirement Description
Questionnaires	The smartphone must enable the user to answer medical questionnaires sent by the doctor.
User answers	The smartphone must enable the user to answer specific prompts to validate alerting detected situations.
User input	The smartphone should enable the user to input routine information such as the time of intake of the medications, quantity and quality of the sleep or other information.
Actuators	The smartphone should enable the user to adjust the behaviour of the auditory cueing.

3.4.5 The REMPARK Platform Architecture and Functionality

The REMPARK platform is composed of all the services that will store and process information, namely, the server and the Rule Engine blocks. While the so-called server will have the role of keeping the database and hosting all the services, the Rule Engine will use these data to make further analysis and store new processed-data. All this information will be used by the medical application to show relevant information to clinical professionals that is why it is got an interaction with the server. Likewise, the Mobile Gateway will also interface the server to store measures and alerts. Figure 3.5 shows an overall architecture view of the main blocks that make up the REMPARK's platform and its main interactions.

An important element of the REMPARK platform is the server, enabling the potential service. There are two main functionalities. The first one deals with measures and the second one with alerts. Both functions are deployed as REMPARK's services in the server and they will provide also methods to insert and extract both measures and alerts of any type. These services will be exposed so that the blocks that interface the Server (i.e. Rule Engine, Medical Application and Mobile Gateway) can use them.

Other identified service is the Patient Service. The Server must provide a way to register new patients and associate them with their information (i.e. measures, alerts) as well as providing some basic information report about them and their associated hospital, if necessary. Finally, it might be useful to have questionnaires' information available and that is why a specific service dealing with this functionality should be implemented. Figure 3.6 shows the services that the server will expose to their interfaces.

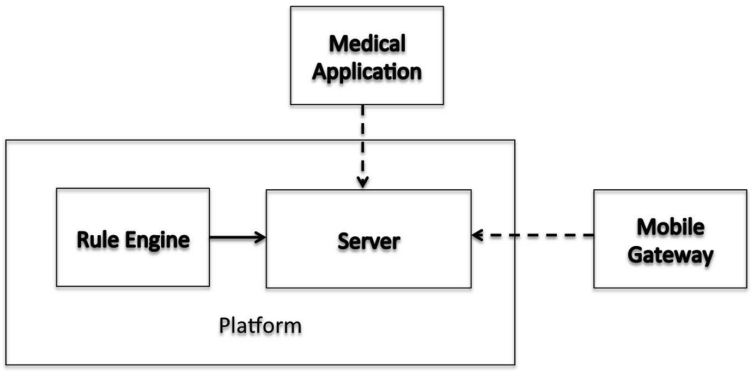

Figure 3.5 Platform functional architecture.

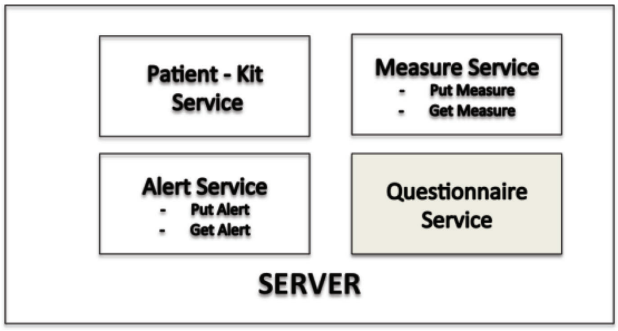

Figure 3.6 Server services.

Table 3.6 summarizes the main technical requirements of the REMPARK server

Table 3.6 Technical requirements for the REMPARK server

Requirement Heading	Requirement Description
Service	Server must expose some public services so that the Mobile Gateway, the Rule Engine and the Professional Application can access the generated data.
Service	Server must provide services that are able to store and extract for each specific patient.
Measures	Server must provide a service to store measures which will be used by the Mobile Gateway, Rule Engine and the Professional's application.
Measures	New measures must be able to be added in a simple fashion.
Getting Measures	Server must provide a service that allows receiving measures and is accessible by the Mobile Gateway, Rule Engine and Professional Application.
Alerts	Server must provide a service to notify about alerts which will be used by the Mobile Gateway, Rule Engine and the Professional's application.
Alerts	New alerts must be able to be added in a simple fashion
Storing Alerts – Mobile Gateway	• Patient has fallen. • No connection with motion sensor. • Emergency button. • Sensor is running out of battery. • Mobile phone is running out of battery.
Storing Alerts – Rule Engine	• Mobile Gateway has lost connection with the platform. • Mobile Gateway has resumed connection with the platform.

3.4.5.1 Important functional parts

As it was indicated in Figure 3.2, there is a set of important functional pieces embedded in the REMPARK server that are crucial for the implementation of its final functionality. They are the Rule Engine sub-system (RE), the Disease Management System (DMS) and the user-Web interface.

3.4.5.1.1 *Rule Engine*

The Rule Engine (RE) is a subsystem which is intended to analyze and process data from sensors at regular time intervals. The main idea is to perform tasks, such as post processing (e.g. filtering and transformation) or data analysis (e.g. verify that the most recent pulse and/or blood pressure measurement was within an acceptable range), at regular time intervals. The tasks and their timing were defined by medical and technical partners along the project.

Four components make up the RE: (1) a timer, (2) a processing service, (3) a task manager and (4) a data manager. The data manager encapsulates the access to the main REMPARK database. It is the main interface to REMPARK system and provides the means to read and write data (i.e. measures and alerts). The task manager will decide when a task needs to be executed at a certain point in time. The processing service is fed with a set of tasks which it executes. A timer is used to (re-)initialize the processing of tasks at regular time intervals.

In order to implement the tasks, it must be specified: (1) how often a particular task needs to be performed (e.g. every minute, every five minutes), (2) the data that the performance of this particular task requires (e.g. pulse data or data from the inertial sensor), (3) how recent the data needs to be (e.g. last fifteen minutes, at least two hours old or just the most recent value) and (4) the task itself (e.g. check whether pulse is within acceptable range).

3.4.5.1.2 *Disease Management System*

The Disease Management System (DMS) is an application for managing the patient's health by the medical staff. Data and medical information are integrated into the DMS to support medical decisions. These decisions have influence on changes in the treatment plan and raising alerts to the medical team who has to take care of it. The DMS for REMPARK was developed as a web application using the .NET platform with C# as the programming language.

The DMS is based on the REMPARK database as the resource for every data coming from the patient. The information is sent through the communication module and written to the database. The DMS will have access to the data as a raw data and to the processed data coming from the RE.

Every user of the DMS will be linked to a specific user profile. Every profile will be exposed to the relevant data according to pre-defined specifications. Four profiles have been defined:

- Supervisor – The main authority in the site (Doctor, nurse or other) that will have access to the management parts of the system. The supervisor can register new users and manage the profiles.
- Doctor – The Doctor is the highest medical authority in the call center/ point of care. Therefore, the doctor will have full access to the treatment plans of the patients related to the specific patients' doctor.
- Nurse – Every nurse will be assigned to several patients who will be monitored by another specific nurse. The supervisor will have the ability to allow one nurse to access another nurse's patient in case of absence of the nurses. This exceptional access will be time limited. A nurse can be assigned also to all patients at the call center.
- Patient – The patient will be related as a DMS user in order to allow the patient access a web interface/web site for watching the information related to him/her. A patient cannot be deleted from the database. Instead, the patient's status can be changed to "Not Active" and it will not be shown in the DMS lists (or report) but will remain in the database.

Important operative tools, included in the DMS are:

- Patient's Record. The patient's record must include the patient details, patient relative details (a contact person in case of emergency), a technical part with documentation of the equipment implemented in the patient's home (ID, IP, etc.) and a treatment plan.
- Treatment Plan. For each patient registered in the REMPARK program a treatment plan is created by the neurologist according to the patient's evaluation and clinical history. The treatment plan will include the necessary exercises, medications, normal ranges for every measurement the patient will have the sensors connected to the Mobile Gateway at the patient's home.
- All of the above will be documented in the DMS. The treatment plan can be viewed by any of the medical team assigned to the patient but only the doctor can change an existing medication treatment plan. In some cases, a nurse could also be able to change the treatment plan. These special cases, if any, will be defined in the Clinical Protocol. A change in the treatment plan can be a result of changes in the patient's health, patient's environment, etc.
- Alerts. The alerts will be raised in two ways.

1) Alerts that were sent by the Rule Engine after processing raw data.
2) Alerts that came directly from the Mobile Gateway without any pre-processing.

- Clinical protocols. The clinical protocols can be described as set of flow charts allowing the neurologists to make decisions according to the collected information. It is actually a set of medical instructions for every situation, change (or lack of change) in the patient status. These protocols can be updated or changed from time to time according to the medical considerations.

Table 3.7 compiles the requirements of the DMS according to the description.

3.4.5.2 Platform technical constraints

Before analysing the different services that must be supported by the server, it is important to estimate important parameters that can compromise the performance of the whole system, such as the maximum storage, the maximum number of simultaneous transactions and the bandwidth.

Just as an example, calculations were made considering the constraints imposed by the pilots organized in REMPARK project. Final technical decisions were:

- Maximum storage requirement of 100 Gbytes, permitting to operate with 60 patients during 1,5 years, considering that a probable transmission rate of 1 Kbyte per minute should be necessary, with the sensor connected during 12 hours a day.

Table 3.7 Compiled requirements for the DMS

Requirement Heading	Requirement Description
BAN data	DMS will store all data from the BAN.
Medical monitoring	DMS will monitor medical aspects of the patient.
Technical monitoring	DMS will monitor technical aspects of the patient regarding the REMPARK project.
Alerts	DMS will raise alerts when information about irregular behaviour or measurement will come from the gateway.
Questionnaires	DMS will allow managing questionnaires.
Treatment plan	The treatment plan will be created in the DMS.
Data integrity	No data could be deleted from the database.
Monitoring interface	The DMS will have a monitoring interface.
Data interface	The DMS will have an interface for showing patient's data.
Website	The DMS will have a patient personal website.
Reports	The DMS will be able to publish reports.

- Concerning the bandwidth, it was estimated that 1 Mbps channel is more than enough for the requirements of REMPARK.
- The maximum number of parallel transactions, considering the previous figures, overcome the necessary characteristics.

3.5 Conclusion

The present chapter has presented and described the architecture, functionality and technical requirements of the REMPARK system, organized along some different sub-systems specifically designed for fulfilling the functional objectives of the proposed project, finally implemented and tested in real piloting experiences.

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