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MULTIPLE PERSPECTIVES FOR MOBILE HEALTH APPLICATIONS: DESIGN, DEVELOPMENT AND EVALUATION OF DIFFERENT PROTOTYPES

PhD Thesis by

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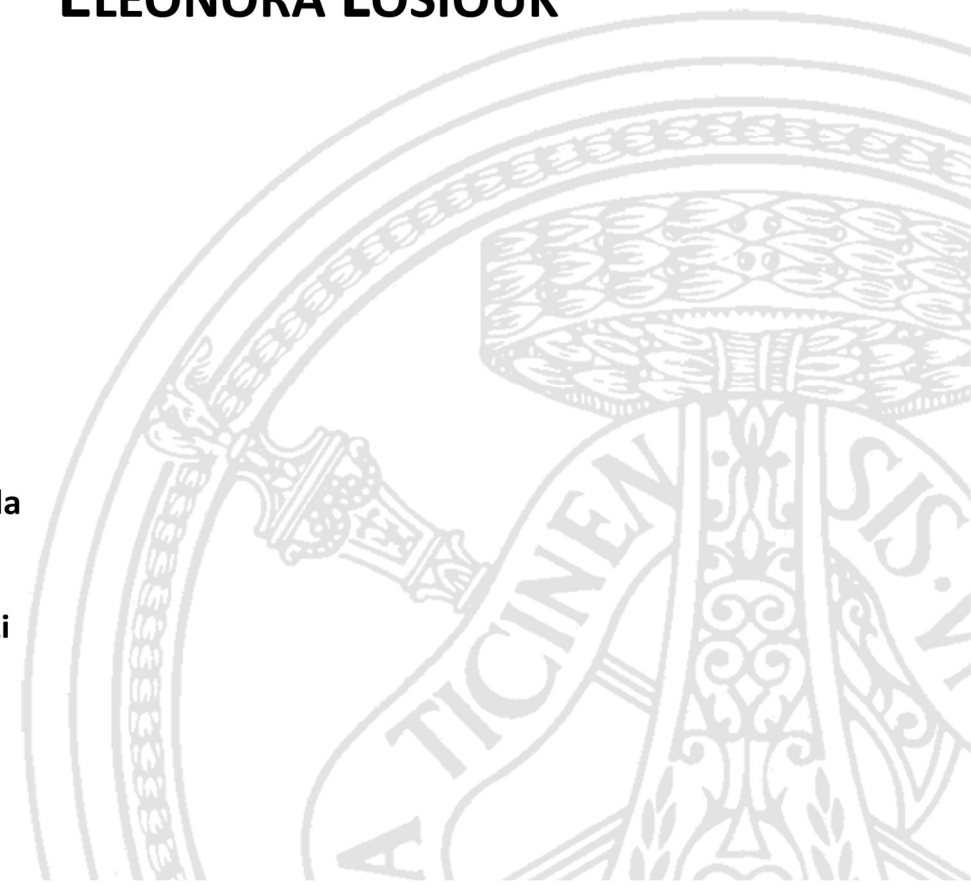

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A man is like a fraction whose numerator is what he is and
whose denominator is what he thinks of himself.
The larger the denominator, the smaller the fraction.

Lev Tolstoj

Abstract (English)

Today mobile devices such as smartphones and tablets reached a massive diffusion in industrialized as well as in developing countries. The variety of features provided by those devices makes them essential implements for their owners, who became accustomed to keep them always within an arm reach. Besides a personal use based on the individual skills and interests of their owners, mobile devices are being increasingly adopted also as a solution for distributing commercial services. Among the providers of those services, health-care institutions recently started adopting *mobile health* applications for supporting and complementing their medical interventions. Today *mobile health* can be exploited not only for improving the communication between patients and physicians, but also for supporting the delivery of health-care services and for enhancing the patient involvement in the management of his/her disease. However, even though *mobile health* has recently seen a diffusion, there are still some open problems that need to be addressed: quantification of the quality of an app, measurement of app liking, compatibility among different mobile devices, preparation of the users for adopting *mobile health* solutions, data protection and security. The main purpose of this PhD thesis has been investigating the last two open problems among the abovementioned ones: evaluating the effectiveness and reliability of *mobile health* solutions by considering first their suitability for the final intended users, instead of the new technological features provided. As a matter of fact, when a new technology or a new solution is introduced, it always draws most of the attention on the service provider side as it is perceived as a way to implement its business, and the focus is rarely directed at its potential users and the actual benefits, that may be achieved by them. To achieve my purpose, several prototypes of *mobile health* solutions were designed, developed and, finally, evaluated during my PhD thesis. The

results were used to provide an answer to the following scientific question: *Are we ready for the introduction of mobile health in support of health care?*.

During the first project, I investigated solutions for representing, administering and deploying medical checklists. Those are usually described in the literature as short and concise guidelines, containing specific and pragmatic information aimed at giving step-by-step instructions for completing a task. They are commonly used in stressful or timeless situations, such as those occurring in an emergency context. After an analysis of the already available commercial tools, the solution involved the adaptation of an Android mobile application, called *Gquest*, developed at the Laboratory of Biomedical Informatics of the University of Pavia for representing and administering questionnaires. More specifically, the adaptation involved: design and development of a web application as an editor to support the rendering of medical checklists into a computer interpretable format; development of a scripting engine for offline automatic calculations inside *Gquest*; integration into *Gquest* of a full vocal interaction system for helping paramedics that are busy with their hands while managing a patient. Once the adaptation of *Gquest* was complete, it was evaluated in a trial performed in Morgex (Aosta, Italy), where I administered two different questionnaires for evaluating the improvements introduced by *Gquest* in comparison to the usage of the paper-based protocols.

Both the second and the third projects regard a different context of *mobile health*, that is fostered by the growing expansion of sensors and wearable devices: the data transmission for supporting remote monitoring applications.

The second activity concerned the refactoring of a web application, previously developed for supporting remote monitoring in the clinical trials performed during the AP@Home European Project. The system was used for overseeing children affected by Type 1 Diabetes Mellitus that were undergoing an Artificial Pancreas therapy during a summer camp. Part of the activities of this second project involved also the evaluation, in terms of user perception and usability, of the remote monitoring service that was provided to the parents of children involved in the clinical trial. This was accomplished through the administration of two different questionnaires, before and after the use of the service respectively.

The same remote monitoring service, improved with new functionalities, was also used in the third project, that dealt with collecting glycaemia values in preterm newborns during their first seven days of life in a Neonatal Intensive Care Unit at the University Hospital of Padova. This activity required the development of a new mobile application for the transmission of glycaemia val-

ues acquired from a glycemia sensor through *Bluetooth Low Energy*. Moreover, the remote monitoring service was improved with a formula for the automatic calculation of the most appropriate glucose infusion rates.

Finally, during the last year of my PhD I started evaluating *mobile health* applications from a privacy and security point of view thanks to a collaboration with the Laboratory for Communications and Applications of the Ecole Polytechnique Federale de Lausanne (Lausanne, Switzerland). As part of the project, I worked on the evaluation of several techniques to be exploited for implementing a virtualized environment on a smartphone running the Android operating system. The main purpose of this evaluation was to analyze the feasibility of a solution based on the virtualization approach to address problems concerning the communication between Android applications and external medical devices through *Bluetooth* or *Near Field Communication* channels. As a matter of fact, once an application is granted the required permissions, it also gains full control of the associated resource, which means that it can communicate with any device available on that channel indiscriminately. This gives malicious applications the chance to steal sensitive data from external medical devices by simply declaring the associated permissions. Moreover, since those ones are not classified as dangerous permissions, the Android operating system automatically grants them to any application at the installation time.

The overall organization of my PhD thesis is the following one:

- Chapter 1 provides an overview of the mobile technology evolution and its increasing exploitation into the health-care scenarios. It introduces eight dimensions, that have been used to classify each project carried out during this thesis, and provides an overview of open problems affecting *mobile health*, as well as a summary of the research activities accomplished;

- Chapter 2 focuses on the *mobile health* context concerning clinical decision support systems. In particular, it describes the project involving *Gquest* starting from the requirements identification, moving to its adaptation and, finally, describing the evaluation accomplished by nurses and paramedic staff of the emergency Department of Aosta;

- Chapter 3 concerns real-time remote monitoring systems that provide decision support for the patients. It illustrates the different architectures after which a remote monitoring application was designed and upgraded throughout the AP@Home project. It then describes the optimization, in

terms of source code and database queries, accomplished to the system during this thesis and, finally, its evaluation made by the parents of children affected by diabetes involved in a clinical trial;

- Chapter 4 still refers to the remote monitoring *mobile health* context, but this time the project addresses the development of a remote monitoring system with a decision support component for the physician;
- Chapter 5 addresses the security problems arising when *mobile health* applications communicate with external medical devices through *Bluetooth* or *Near Field Communication* channels and illustrates the feasibility assessment of a solution based on the virtualization technique;
- Chapter 6 describes the lessons learned through the participation to the above mentioned projects and summarizes the work providing an answer to the scientific question that motivated my activities during the PhD.

Abstract (Italian)

Al giorno d'oggi la diffusione dei dispositivi mobili, quali smartphone e tablet, ha raggiunto una dimensione particolarmente pervasiva sia nei paesi industrializzati che in quelli in via di sviluppo. La molteplicita' delle funzioni offerte da tali dispositivi li rende ormai un elemento irrinunciabile per i propri possessori, che si sono abituati a portarli ovunque. Tuttavia, oltre ad essere considerati degli strumenti destinati ad un uso strettamente dipendente dalle abilita' e dalle preference del properietario, gli smartphone vengono sempre piu' adottati anche come strumento per la distribuzione di servizi. Nel panorama dei vari fornitori si stanno aggiungendo ultimamente anche gli enti che erogano servizi sanitari, che sempre piu' spesso ricorrono al canale mobile per supportare e integrare le prestazioni da essi offerte. Oggi il *mobile health* puo' essere sfruttato non solo per migliorare la comunicazione tra pazienti e medici, ma anche per supportare l'erogazione di servizi sanitari e per migliorare il coinvolgimento del paziente nella gestione della sua malattia. Tuttavia, anche se il *mobile health* ha visto di recente una piu' ampia diffusione, ci sono ancora alcuni problemi aperti che devono essere affrontati: come quantificare la qualita' di un'app, come misurare il livello di gradimento di un'app, la compatibilita' tra diversi dispositivi mobili, il livello di preparazione degli utenti ad adottare soluzioni *mobile health*, la protezione e la sicurezza dei dati. Lo scopo principale di questa tesi di dottorato e' stato quello di esaminare gli ultimi due aspetti fra quelli sopra elencati: valutare l'efficacia e l'affidabilita' delle soluzioni *mobile health* considerando prima la loro idoneita' per gli utenti finali, invece delle nuove caratteristiche tecnologiche fornite. Come spesso accade, ogni nuova tecnologia introdotta suscita sempre molta piu' attenzione e interesse da un punto di vista commerciale, in quanto viene vista come una nuova opportunita' produttiva, mentre viene destinato troppo poco peso a un'analisi

dei reali benefici che possono essere ottenuti dai suoi potenziali utenti finali. Per raggiungere il mio scopo, sono stati progettati, sviluppati e, infine, valutati alcuni prototipi di applicazioni mobile, che sono serviti per rispondere al seguente quesito scientifico: *Siamo pronti all'introduzione di soluzioni mobile come elemento di supporto all'assistenza sanitaria?*.

Nell'ambito del primo progetto, ho analizzato soluzioni per la rappresentazione, gestione e distribuzione di checklist mediche. Queste sono solitamente descritte in letteratura come linee guida brevi e concise, contenenti informazioni specifiche e pragmatiche, volte a fornire istruzioni dettagliate per completare un'attivita'. Sono comunemente utilizzate in situazioni stressanti o caratterizzate dalla mancanza di tempo, come nel caso di un contesto di emergenza. Dopo un'analisi iniziale dei prodotti commerciali gia' disponibili, si e' deciso di adattare *Gquest*, un'applicazione Android precedentemente realizzata presso il laboratorio di Informatica Biomedica dell'Universita' di Pavia allo scopo di rappresentare e disseminare questionari. In particolare, l'adattamento ha riguardato: la progettazione e lo sviluppo di un'applicazione web per supportare la realizzazione di checklist mediche in formato elettronico; lo sviluppo di un motore di script per effettuare calcoli automatici offline all'interno di *Gquest*; l'inserimento in *Gquest* di un sistema di interazione vocale completa rivolto ai paramedici che sono impossibilitati a utilizzare le mani nel momento in cui soccorrono una persona. Una volta completato l'adattamento di *Gquest*, l'applicazione e' stata valutata nell'ambito di un trial condotto a Morgex (Aosta, Italia), dove e' stata proposta come strumento per gli operatori sanitari di emergenza operanti sul territorio. In tale occasione, ho somministrato anche due questionari per valutare i benefici introdotti da *Gquest* rispetto all'utilizzo dei protocolli cartacei.

Sia il secondo che il terzo progetto hanno affrontato un differente contesto del *mobile health*, che e' stato favorito dalla crescente disponibilita' di sensori e dispositivi indossabili: la trasmissione di dati a supporto delle applicazioni di monitoraggio remoto. La seconda attivita', infatti, e' consistita nel refactoring di un'applicazione web, precedentemente sviluppata per supportare il monitoraggio remoto nell'ambito di studi clinici condotti durante il progetto europeo AP@Home. Il sistema e' stato poi utilizzato per supervisionare bambini affetti da diabete mellito di tipo 1, che si sono sottoposti a una terapia basata sull'uso di un Pancreas Artificiale nell'ambito di un trial clinico. Parte delle attivita' di questo secondo progetto ha riguardato anche la valutazione, in termini di usabilita' percepita dall'utente, del servizio di monitoraggio remoto fornito ai genitori dei bambini coinvolti nel trial clinico. La valutazione e' stata effet-

tuata attraverso la somministrazione di due questionari, uno precedente e uno successivo all'utilizzo del servizio.

Lo stesso servizio di monitoraggio remoto, arricchito di alcune nuove funzionalita', e' stato anche utilizzato nel terzo progetto per la raccolta dei valori di glicemia nei neonati prematuri nel corso dei loro primi sette giorni di vita presso il reparto di Patologia Neonatale dell'Ospedale Universitario di Padova. Questa attivita' ha richiesto lo sviluppo di una nuova applicazione per la trasmissione di valori di glicemia acquisiti da un sensore tramite il protocollo *Bluetooth Low Energy* recentemente apparso. Inoltre, il servizio di monitoraggio remoto e' stato migliorato mediante l'inserimento di una formula per il calcolo automatico dei valori di infusione di glucosio piu' appropriati.

Infine, nel corso dell'ultimo anno del mio dottorato ho iniziato ad analizzare le implicazioni che hanno le applicazioni mobili utilizzate in ambito sanitario anche dal punto di vista della privacy e della security nell'ambito di una collaborazione con il Laboratory for Communications and Applications dell'Ecole Polytechnique Federale de Lausanne (Lausanne, Switzerland). Come parte del progetto, ho lavorato all'analisi e valutazione di diverse tecniche, che potessero essere sfruttate per progettare un ambiente virtualizzato all'interno di uno smartphone dotato di sistema operativo Android. Lo scopo principale di questa valutazione e' stato analizzare la fattibilita' di una soluzione basata sulla virtualizzazione, che potesse risolvere un problema relativo alla comunicazione tra applicazioni Android e dispositivi medici esterni attraverso i canali *Bluetooth* o *Near Field Communication*. Infatti, dopo aver ricevuto i permessi necessari, un'applicazione Android ottiene il pieno controllo della risorsa richiesta. Cio' comporta che l'applicazione possa comunicare con qualsiasi dispositivo disponibile su quel canale, senza ulteriori controlli. In questo modo, eventuali applicazioni maligne possono acquisire dati sensibili da dispositivi medici esterni semplicemente facendo richiesta di specifici permessi. Inoltre, poiche' quelli relativi al *Bluetooth* e al *Near Field Communication* non sono considerati permessi pericolosi, Android li concede automaticamente a qualsiasi applicazione durante la sua l'installazione.

L'organizzazione generale della mia tesi di dottorato e' la seguente:

- Il Capitolo 1 fornisce una panoramica sull'evoluzione della tecnologia mobile e sul suo crescente utilizzo in ambito sanitario e illustra le otto dimensioni utilizzate per la classificazione di ciascun progetto, nonche' un'analisi dei problemi riguardanti il *mobile health* e un riepilogo delle attivita' di ricerca svolte;

- Il Capitolo 2 si concentra sul contesto del *mobile health* relativo ai sistemi di supporto alle decisioni cliniche. In particolare, descrive il progetto incentrato su *Gquest*, partendo dall'analisi dei requisiti e arrivando fino al suo adattamento e alla sua valutazione, effettuata da parte di infermieri e personale paramedico del Pronto Soccorso di Aosta;

- Il Capitolo 3 riguarda i sistemi di monitoraggio remoto in tempo reale che forniscono un supporto alla decisione per i pazienti. Vengono illustrate le diverse architetture con cui e' stata progettata un'applicazione di monitoraggio remoto nell'ambito del progetto AP@Home, la sua successiva ottimizzazione, in termini di codice sorgente e di query al database, condotta nel corso di questa tesi e, infine, la valutazione effettuata dai genitori di bambini affetti da diabete coinvolti in uno studio clinico;

- Il Capitolo 4 si riferisce nuovamente al contesto del monitoraggio remoto, descrivendo questa volta lo sviluppo di un sistema con la componente di supporto decisionale rivolta al medico, anziche' al paziente;

- Il Capitolo 5 affronta i problemi di sicurezza che si presentano quando applicazioni mobile comunicano con dispositivi medici esterni mediante *Bluetooth* o *Near Field Communication* e illustra un'analisi di fattibilita' per una soluzione basata sulla tecnica di virtualizzazione;

- Il Capitolo 6, infine, traccia un sommario degli insegnamenti acquisiti attraverso la partecipazione ai progetti sopra descritti e fornisce una risposta al quesito scientifico che ha motivato le mie attivita' nell'ambito del dottorato.

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List of abbreviations

AMA: Android Mobile Application
AP: Artificial Pancreas
API: Application Programming Interface
APK: Android Package Kit
app: application
APS: Artificial Pancreas System
ART: Android RunTime
BGL: Blood Glucose Level
BLE: Bluetooth Low Energy
CGM: Continuous Glucose Monitoring
CPG: Clinical Practice Guidelines
CSII: Continuous Subcutaneous Insulin Infusion
DEXG4: Dexcom G4 PLATINUM with Share
DR: Dexcom Receiver
DiAs: Diabetes Assistant
EMD: External Medical Device
EP: Emergency Protocol
FDA: Food & Drug Administration
GATT: Generic ATTribute profile
GIR: Glucose Infusion Rate
HTTP: HyperText Transfer Protocol
IA: Instance App
MC: Medical Checklist
mHealth: mobile Health
NFC: Near Field Communication
NICU: Neonatal Intensive Care Unit
OS: Operating System
PDA: Personal Digital Assistants
PQL: Perceived Quality of Life

RM: Remote Monitoring
SA: Supervisor App
SAP: Sensor Augmented Pump
SELinux: Security-Enhanced Linux
SMS: Short Message Service
SUS: System Usability Scale
T1DM: Type 1 Diabetes Mellitus
TTS: Text-To-Speech
UID: User IDentifier
VLBWI: Very Low Birth Weight Infant
WAP: Wireless Access Protocol

Chapter 1

Introduction

1.1 Mobile Health: an Overview

The mobile device market has been continuously growing during the past few years, counting today 2.32 billions of smartphone users worldwide that are expected to reach 2.87 billions by the end of 2020 [1]. The introduction of mobile devices as a mass-marked product deeply affected people habits and behaviours, and reshaped many work and collaboration paradigms, also including the delivery of public services. National Health Systems are among those expected to revolutionize their business models, switching from the classical hospital oriented model adopted thus far towards a patient centric one.

The use of mobile devices in a medical context supporting and enhancing the delivery of health services is commonly addressed as mobile Health (*mHealth*), despite no standard definition for this new emerging application field has been adopted yet. In an attempt to better characterize this field, the Foundation for the National Institutes of Health defined *mHealth* as "the delivery of healthcare services via mobile communication devices" [2]; the National Institutes of Health states that "Mobile health, or mHealth, uses mobile technologies as tools and platforms for health research and healthcare delivery" [3]; the World Health Organization states that *mHealth* is the "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [4]. Even though all those definitions are different from each other, the unifying element among all of them is the use of mobile technology, which includes Personal Digital Assistants (PDAs), mobile phones and smartphones. Those

different device categories appeared in sequence over the years, creating a parallelism between the technology evolution and its various medical exploitations in health care. In order to cast some light on the evolution of *mHealth*, Ali et al. [5] reviewed the scientific works addressing this subject published after 1990 and identified three different eras: from 1990 to 2007; from 2007 to 2012; from 2012 until today.

The first period (1990-2007) was characterized by the use of PDAs, which were small, handheld devices, with limited computational capabilities mostly designed to support storage/retrieval of information. Their main limitation was the lack of networking features, that always required to connect a PDA to a PC for the accomplishment of any networked operation. *mHealth* interventions accomplished until 2007 exploiting PDA devices were mainly focused on providing decision support, reminders and alerts [6, 7, 8]. For example, among the regular attending physicians and those involved in training, that were interviewed in a study assessing the frequency of use of PDAs in a clinical setting, 85%, out of the 87% that declared to frequently use PDAs, also admitted the influence that PDAs had in undertaking their overall clinical decisions [9]. Moreover, PDAs were also used to reduce human errors as they could provide immediate information about a patient and his therapy. As an example, they were used at various steps during the clinical decision process for preventing medication errors such as negative interactions among drugs [10].

Between 2007 and 2012 mobile phones evolved and, besides plain networking features such as Voice and Short Messages System (SMS), they also began to offer the possibility of integrating small custom-designed software applications (apps) able to exchange data through network protocols. They initially relied on the Wireless Access Protocol (WAP), but the most advanced models were also able to open straight TCP/IP connections exploiting HyperText Transfer Protocol (HTTP). This second wave of mobile phones, that included devices such as the popular N73 by Nokia (Espoo, Finland), was still very limited in their software and graphical capabilities. Nevertheless, attempts were made to introduce them into the health-care context, leveraging their newly emerging networking capabilities missing from their PDAs predecessors. In particular, those allowed to support prototypical interventions paving the way for the implementation of Remote Monitoring (RM) systems. As an example, Holtz et al. [11] provided a mobile phone app through which users could send an SMS containing information about their daily peak flow reading, in order to improve the asthma action plans and reduce the occurrence of adverse events. In the same way, Agarwal et al. [12] developed an app to send patients' blood

pressure readings remotely and make them available to physicians through a web interface.

After 2012 Ali et al. [5] mark the beginning of the smartphone era. In this period, the enhanced functionalities of the contemporary devices in terms of computational power, bandwidth and graphical capabilities, suggested their adoption in a new set of *mHealth* application contexts relying on the better user experiences affordable. Those applications include: disease prevention for healthy individuals, promotion of physical activity and balanced diet, disease diagnosis, patient awareness and prevention of disease complications [13, 14].

Today smartphone users can find a wide range of *mHealth* apps available directly on the official stores. Those apps vary from those helping users with the management of physical activities and weight loss to other ones addressing specific disease problems. Building up a comprehensive classification characterizing all the *mHealth* apps available today is not an easy task. On the app stores of the two leading mobile Operating Systems (OSs), the Google Play Store for Android (by Google) and the App Store for iOS (by Apple), *mHealth* apps can be found either under the "Medical" or under the "Health & Fitness" categories. However, the criteria adopted for choosing and adhering to a similar classification are not well documented. In fact, the unwary user may be led to believe that the "Medical" category contains apps that are classified as medical by the Food & Drug Administration (FDA), despite no such requirement is actually enforced on the app stores. According to the FDA, medical apps "are mobile apps, meet the definition of a medical device and are an accessory to a regulated medical device or transform a mobile platform into a regulated medical device" [15]. Nevertheless, even under the "Health & Fitness" category it is possible to find apps such as "iCare Health Monitor (BP & HR)" or "Instant Heart Rate" for analyzing the cardiac frequency and the blood pressure, that seem very similar in scope to apps considered as medical devices by the FDA [16].

Other classification systems have been considered for medical apps based on: the intervention strategy [17], the addressed health condition [18], or the context of application [19]. Fig. 1.1 shows all the contexts of application for the *mHealth* identified by the "Research 2 Guidance" group, which are namely: *Fitness Tracking*, *Medical Condition Management*, *Patient Health Record*, *Reminders and Alerts*, *Remote Consultation*, *Medical Compliance*, *Nutrition and Weight Loss*, *Diagnosis* and *Remote Monitoring*.

All the above mentioned classification systems are not exhaustive, especially from a developer point of view. For that reason, eight different dimen-

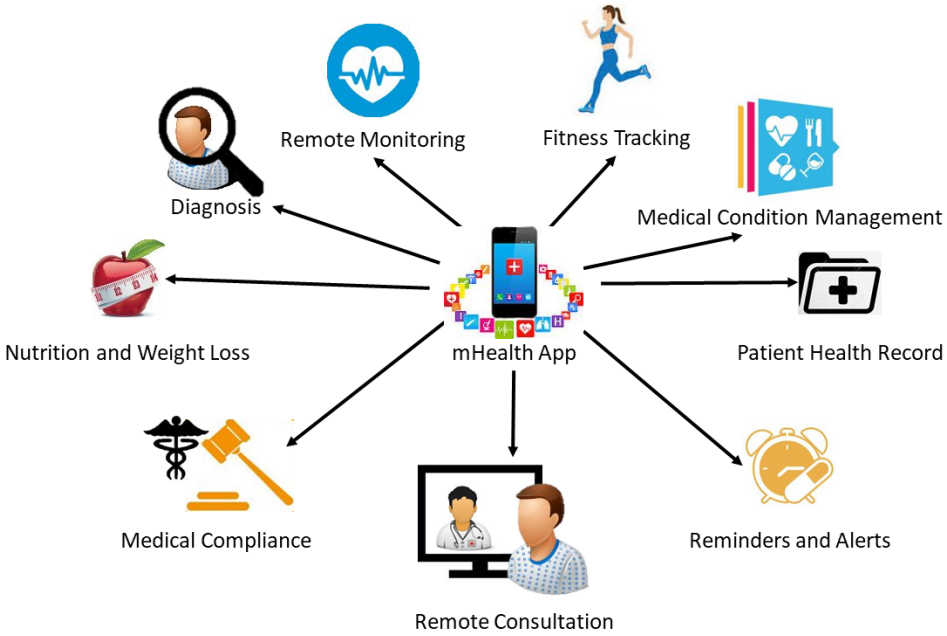


Figure 1.1: **Mobile health applications contexts.**

sions, that affect both design and functionalities of *mHealth* apps, have been identified as part of the work carried out in this thesis, and will be used to describe the prototypes developed and evaluated. Those dimensions, along with their possible values, are shown in Table 1.1 and will be introduced in the rest of this paragraph.

The *App Distribution* dimension refers to the strategy adopted by the developers to distribute their apps to the final users. Those strategies, as it is explained in the following, may be selectively constrained by the commercial policies enforced by the specific development platform adopted. Possible alternatives are: the App Store (e.g. the Google Play Store for Android or the App Store for iOS), Internet media sharing services (e.g. Gmail, Dropbox, Google Drive, public or proprietary web sites) or manual installation. All of the alternatives require full access to the app binaries including the compiled code, the resources and any ancillary file with configuration or deployment directives. Once the app has been compiled, the binary files are usually uploaded on the store. This step is often accomplished as the last part of the compilation process when the development and test phases have been completed. For those platforms, that are most restrictive in their deployment policies, such as

Dimension	Possible Values
App Distribution	App Store, Internet Services, Manual Installation
Target Users	Patients, Physicians, Nurses, Caregivers
Data Acquisition	Automated, Human Assisted, Hybrid
Data Analysis	Local, Remote (Synchronous or Asynchronous)
Data Storage	Temporary DB, Permanent DB, Others
Data Synchronization	Low Frequency, High Frequency
App Working Mode	Foreground, Background, Hybrid
App Update Policy	App Store, Internet Services, Manual Installation

Table 1.1: **The eight dimensions affecting design and functionalities of mobile health applications.**

iOS, this step is also locked-in, meaning that the developer never has direct access to the binary distribution of his app. As a result, the App Store for iOS apps is also the only way to distribute them at large. Other platforms, such as Android by Google, adopt a more lenient approach, producing a binary image that is available for installation on target devices independently of its publication on the official Store. In this case, the app may be shared through a third party Internet service or installed on a smartphone locally connected to the developer workstation. For each one of the above mentioned options the developers need to address specific issues:

- Stores: Every app may be published on the platform store, but in order to do so the developer should comply with a set of requirements, failing which his app is promptly removed. Those requirements are imposed to enforce a set of quality features to be fulfilled by the app. They mainly concern the visual design and user interaction, the app functionality (it should be the expected one with the minimum number of permissions granted to avoid malfunction or misuses), the software performance and stability, the safe and secure handling of user data and personal information and the appropriateness of the contents (the app should not use the intellectual property or brand of others);

- Internet service: if the development platform supports the release of the binary code of the app, the latter may be distributed through alternative channels such as Google Drive or Dropbox. It may even be sent as an attachment of an email. In all those cases, the user needs to enable the

installation of apps from "Unknown Resources", which might expose the smartphone to some threats, such as the installation of malicious apps;

- Manual installation: besides requiring to enable the installation of apps from "Unknown Resources", this solution also implies the physical availability of the device, which should be connected to a PC to allow the installation. This approach is usually adopted very early in the production cycle, when the app should be distributed to a small number of testers. Alternatively, it may be used to deploy apps specifically designed to support clinical studies, which means no use for the public at large, provided that the number of enrolled patients allows it.

Comparing all the solutions, the first one, in particular, has a big impact on developers: if the authors decide to publish their app on the Store, they need to carefully check the restrictions of the Policy Center, to prevent the app from being removed soon after the publication. Usually, apps on the store are provided by companies or passionate developers and rarely by research institutions. This might be due either to intellectual property issues making the app not suitable for public disclosure or to the app addressing the specific population enrolled in a clinical study. Another cause is represented by the legal issues related to the delivery of a medical intervention or the management of patient sensitive data that prevent the distribution of a service outside a study. In this last case, both an approval from the Ethics Committee and the signing of an informed consent agreement by the patients are required.

The *Target Users* dimension highlights the relevance of the final users during the app design process. Possible users of an *mHealth* app can be patients, physicians, nurses and caregivers. Their health conditions, level of autonomy and experience with technology definitely affect the level of usability and suitability that the app should have [20]. Moreover, the access to the mobile technology for patients may depend on whether they live in an independent home, in an assisted living or in a nursing home.

Most of the *mHealth* apps need to acquire some data from the user, either for processing them and consequently providing a feedback or for sending them remotely. The solution adopted for data acquisition differs according to the level of user involvement in the process. The possible values for the *Data Acquisition* dimension are: fully automated, fully human assisted or hybrid. The first case concerns apps linked to a medical data acquisition device, that regularly and transparently supplies data. Alternatively, the user may be asked to provide any information manually, thereby increasing errors. Hybrid

approaches concern the collection of multiple values using both strategies. The most appropriate solution depends on the data to be acquired by the app and on the availability of external devices performing data acquisition. If those are available, an automated solution is to be preferred since it is more comfortable for the user, it may be suitable for elderly or impaired patients, and may also prevent the occurrence of errors.

After being acquired, data need to be processed. Expressed by the *Data Analysis* dimension, this task can be accomplished either locally, by the app on the smartphone, or remotely, by a server. While a local processing is to be preferred, since it provides an immediate feedback to the user and a more fluid experience, the complexity of the computation and the need to access historical data or to exploit external data sources may impose a remote processing. In the latter case, the server may return a feedback to the app in a synchronous or asynchronous way according to the responsiveness required by the context.

During an app design process, it is important to immediately define whether the app is going to store locally any data and what kind of data. This is addressed by the *Data Storage* dimension. If the app is going to save just some basic information regarding its configuration (e.g. login, password, settings configuration, etc.) then the most appropriate solution is to use data structures such as the *Local Preferences*, which save persistent key-value pairs of primitive data types. On the other hand, if the information managed by the app come from an external data source or the user, thus representing a huge amount of data collected over time, they should be saved in a local database, optimized for their storage and retrieval. This might be a temporary one, if it is periodically flushed, or a permanent one, if data are saved permanently.

When the app needs to send its data remotely, the *Data Synchronization* dimension should be properly considered to define the best synchronization architecture. The app might be configured so that data are sent just after being produced or by regularly attempting transmission at predefined time intervals. The frequency of those intervals depends on the purpose of the *mHealth* app: if it is supposed to provide real-time monitoring in presence of a critical situation, the frequency should be as high as every 2-5 minutes; in any other case, such as for sending patient reported outcomes to the clinic, it might be low (e.g. once per day or week). In either case, a key issue concerns the policy for data transmission. In fact, data synchronization on mobile devices turns out to be a true distributed transaction involving at least two nodes: the smartphone and the remote data server. Thus, a suitable policy should consider the adoption of a *two-phase commit* protocol, to ensure that all data

will be eventually transmitted with no data loss nor duplicates on either sides, even when experiencing a high transmission failure rate. This may be due to network coverage problems resulting from the inherent mobile connectivity of the smartphone, or to its discontinued operation because of its limited power capabilities.

Despite the enhanced features and capabilities offered by smartphones, those are still devices with seriously limited resources, in particular concerning power consumption. Thus, despite smartphones are multitasking devices able to run several apps at once, the full processor power is mostly dedicated to the foreground app, which is the one with which the user is currently interacting. Unlike what happens with PCs or even laptops, background apps on smartphones are very limited in accessing the processor. App developers should therefore carefully design an app considering the possible values of the *App Working Mode* dimension: foreground, background and hybrid. To better clarify the meaning of those alternatives, some examples are provided. An *mHealth* app acting as a consultation support for the user might run only in foreground, since the user is supposed to be looking at the screen. An *mHealth* app dedicated to the automatic data acquisition may be run only in background, and work even while the user is performing different activities or when the device screen is turned off. Finally, an *mHealth* app that keeps sending notifications to the user, although it is not running in foreground, needs a hybrid approach.

Once deployed, apps might need to be updated, either in terms of the contents offered to the user or in terms of their specific functionalities. To this aim, the *App Update Policy* dimension, which is partially related to the *App Distribution* one, was envisioned. As a matter of fact, the contents update can be easily managed providing the app with a link to a remote server, from which new contents may be downloaded as soon as they are published. The second type of update, instead, which implicitly requires the change of the whole app code, strictly depends on the *App Distribution* dimension previously chosen:

- Store: the update process is fully managed by the store. Developers just need to upload the updated version of their app, that will be automatically advertised and installed on all the devices that downloaded the previous version;

- Internet service: users may be asked to install the new binary distribution shared through the Internet services;

- Manual installation: developers need to recall all the physical devices in order to manually perform the update of the app on those ones.

1.2 Open Problems of Mobile Health

As already mentioned, the different applications and uses of *mHealth* highly depend on the evolution of the technology, more specifically of the mobile one. Today *mHealth* can be exploited not only for improving the communication between patients and physicians, but also for supporting the delivery of healthcare services and for enhancing the patient involvement in the management of his/her disease. However, even though *mHealth* has recently seen a diffusion, there are still some open problems that need to be addressed: quantification of the quality of an app, measurement of app liking, compatibility among different mobile devices, preparation of the users for adopting *mHealth* solutions, data protection and security.

Measuring the quality of an app is a real problem, which is also further supported by the statistical analyses provided by AppBrain [21], according to which the 12.5% of all the apps available on the Google Play Store have been classified as poor ones and, if considering the specific categories, the percentages grow up to 14% for the "Medical" one and to 15% for the "Health & Fitness" one. Given the presence of so many poor quality apps, having a standard quality measurement system for mobile users would help them with making better choices. Even though no standard has been identified yet, some attempts have been proposed by the scientific community. First of all, when speaking about quality, it is important to define the point of view. If the quality of an *mHealth* app is evaluated from a medical professional one, then it will mostly address the contents (i.e., how these are consistent with evidence-based medicine and clinical guidelines) and with the outcomes provided, which should be equivalent to the ones obtained through the clinical experience. If, on the other hand, the quality is considered from the user point of view, it will regard the app usability. Considering this second type of classification, some solutions, such as App-Synopsis [22], rely on the auto-certification of the app manufacturers, while others, such as the one of Bonacina et al. [23], propose a one-shot pictorial schema through which users can easily identify the features of an app and evaluate its quality.

The second open problem of *mHealth* regards the evaluation of app liking, which highly depends on simultaneously considering both the main purpose

and the targeted users. For example, patients represent the first user category of *mHealth* apps, and their enrollment is connected with sending information or receiving information to/from interested parties. This may occur either when patients become actively engaged using the app for improving their knowledge about the disease or because they passively receive and obey any reminder or notification issued. Caregivers are another important user category, as they are the people spending the greatest amount of time with outpatients. Their commitment is mainly devoted to overseeing the conditions of the attended patient, and therefore their actions as users of *mHealth* apps involve receiving information from the patient. Physicians, in most countries, represent the link to healthcare services for patients, and are interested in receiving information from patients/caregivers. They may also provide return feedback summoning patients for visits upon the occurrence of specific conditions or suggesting slight changes to the therapeutic protocol adopted. Their connection to the network usually occurs through fixed appliances such as PCs, which means that an underlying infrastructure for storing data sent by patients should be available. Nevertheless, sometimes physicians also use dedicated *mHealth* apps, which are used as a handbook for drugs and dosages, or as a procedural reminder for the tasks they have to accomplish. This is also particularly true for paramedic staff of the emergency departments, which has to rely on mobile devices given their presence on the ambulance vehicles.

The compatibility of *mHealth* solutions with the huge overview of mobile OSs and mobile devices avaiable is another important issue. As a matter of fact, not only each OS requires its own programming language and development environment, but, even when adopting a single OS, developers have to face the multiplicity of smartphones models. Considering that they belong to different manufacturers and that each one can have different hardware properties, developers should test their app on each device to guarantee the compatibility. Some attempts that try to achieve apps compatibility over different OSs and devices are frameworks such as PhoneGap [24] and Cordova [25]. The main idea of these frameworks is developing apps in Javascript, HTML and CSS languagages, which are then compiled for a specific mobile OS. This means that developers can use few programming languages and then obtain apps runnable on any OS and mobile device. Unfortunately, introducing this level of abstraction involves also a loss in terms of features, given that those apps have a restricted access to device hardware.

The fourth open problem of *mHealth* is whether the users are ready to have it introduced in support of health-care services. As a matter of fact,

the attention is always addressed to *mHealth* apps, to their functionalities and features, to their performance and usability, to their optimal adaptation to a specific context of use. It is much more uncommon, instead, the evaluation of the preparation of future users of the system. Those ones should be carefully considered if we take into account tha they are the main evaluators of an *mHealth* app.

Finally, the last open issue regards the protection and security of patient sensitive data on the smartphones. Today there are a lot of *mHealth* apps that either automatically or manually receive data concerning glycemia value, blood pressure, heart rate or other physiological parameters. All those ones are sensitive data, that need to be carefully managed to prevent malicious apps from accessing and exploiting them. Even though mobile OSs are always under development and new versions are periodically released, security is always a big concern, especially when it addresseses sensitive data. This is also confirmed by the recent increased interest of the privacy and security research community in addressing specific issues that affect *mHealth* apps [26, 27, 28, 29].

1.3 Aim and Organization of The Thesis

The work accomplished within this PhD thesis mainly addresses one of the abovementioned problems, looking for a possible answer to the following scientific question:

Are we ready for the introduction of mHealth in support of health care?

To provide an answer, several prototypes of mobile apps have been developed in various contexts, targeting different classes of users. A preliminary decision to be undertaken concerned the selection of the development platform among all the different ones available today (i.e. Android, iOS, Windows Phone or BlackBerry) for implementing the prototypes. This has been an imposed decision, since there were not enough resources to afford a multi-platform development effort. Android and iOS are presently the most widespread mobile development platforms, thus the selection was initially restricted to those ones.

Since the release of their first devices, Android and iOS have been always competing against each other. The first Android company, founded in 2003 by Andy Rubin, Rich Miner, Nick Sears, and Chris White, aimed at developing an advanced OS for digital cameras and later switched to an OS for handset devices. In 2005 Android Inc. was acquired by Google, which contributed

to the disclosure of its source code in 2007, after the foundation of the Open Handset Alliance, a consortium of technology companies promoting the open source license. The very first Android mobile device, the Sooner, was supposed to be released in 2007, equipped with a non-touch screen, navigation keys and a physical QWERTY keyboard. However, the release of the first iOS device in 2007, equipped with a touch screen, prevented the launch of the Sooner. As a matter of fact, the iOS device pushed Andy Rubin to completely redesign the Sooner device and to release it only in 2008, this time equipped with a touch screen and a sliding, physical keyboard.

Apart from this initial glitch, Android has been the leading OS since 2011 and today accounts for 86.1% of mobile devices sold worldwide, while iOS only has 13.7% of the market share [30]. Besides its greatest availability, Android also adopted an open source policy with respect to iOS, and thus it is the preferred development device in research contexts. For that reason, all the prototypes were developed in Android. The development efforts started with simpler apps and proceeded with more complex ones, integrating additional components over time.

The simplest *mHealth* architecture, shown in Fig. 1.2, includes a user and a smartphone. The two-way arrow indicates that, after inserting some data, the user receives a feedback from the app.

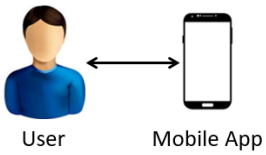


Figure 1.2: **The simplest architecture involving a mobile health application.**

The first prototype implemented in this thesis is an Android app, called *Gquest*, that was initially developed for representing and distributing questionnaires and later adapted for rendering Medical Checklists (MCs), more specifically the ones used by the nurses of an Emergency Department. As shown in Fig. 1.3, the new component introduced in the architecture is a remote server, with which *Gquest* interacts to download the new CLs and to send data collected during the CLs consultation. The two-way arrow between the smartphone and the remote server refers to the contents downloading and to the data uploading functionalities provided by *Gquest*.

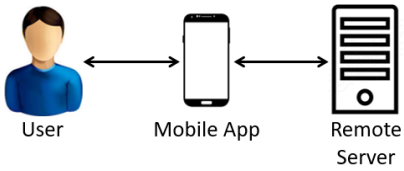


Figure 1.3: **The architecture configuration involving the *Gquest* mobile application.**

Fig. 1.4 illustrates a different architecture containing a web app as a new component that pertains to the second research activity. This regards the development of a RM system supporting the real-time remote collection and visualization of glycemia values, automatically acquired from patients affected by Type 1 Diabetes Mellitus (T1DM). In this case, the *mHealth* app is the Diabetes Assistant (DiAs). This is a prototype of an Artificial Pancreas (AP), developed as a modification of the Android OS and aimed at automating the glycemia control process that diabetic patients have to cope with every day [31]. For safety reasons, a RM system was required to oversee in real-time all the patients undergoing the AP treatment and immediately notify the staff upon the occurrence of a hyper- or hypo-glycemia episode. Those are very dangerous conditions and, more specifically, a prolonged hyperglycemia has been associated with both macro- (stroke, coronaropathy) and micro-vascular (nephropathy, neuropathy or retinopathy) complications on the long term.

The two-way arrow, in this case, refers to the standard client-server paradigm, according to which for every incoming request sent by the client, the server returns an appropriate reply.

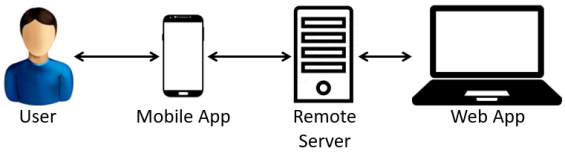


Figure 1.4: **The architecture configuration involving the remote monitoring web application.**

The fourth configuration, illustrated in Fig. 1.5, still belongs to the remote monitoring context, but the focus of this project was the communication between an External Medical Device (EMD) and a smartphone. For this reason,

a new component, namely a sensor, has been added. This acquires physiological data from the patient and sends them to an *mHealth* app, called *Neokid*. More specifically, the sensor is dedicated to the collection of glycemia values and it was applied on preterm newborns during their first seven days of life to improve their overall glycemia control.

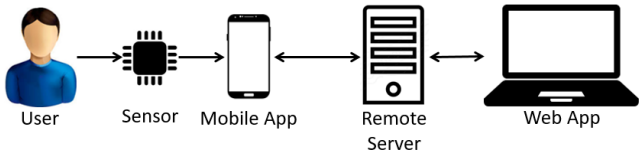


Figure 1.5: **The architecture configuration involving the *Neokid* mobile application.**

Finally, the very last part of this thesis has been focused on the feasibility evaluation of a solution for a specific issue belonging to the data protection and security open problem. Privacy and security issues concerning the Android OS have been widely studied by the research community and, recently, the same community has extended its interests to the *mHealth* context. In this field, the app reliability is of outmost importance, both because of the dangerous effects that app misuse could have on the final users and because of the sensitive data they manage. In particular, the problem addressed regards the protection of *Bluetooth* and Near Field Communication (*NFC*) channels involved in the data transmission between an EMD and an *mHealth* app. To prevent malicious apps from stealing the patient data transmitted, a solution based on the virtualization technique was proposed.

Chapter 2

Mobile Health Applications Supporting Decisions

The first *mHealth* context analyzed in this PhD thesis concerns the development and use of mobile apps to be exploited as decision support systems for clinical problems. More specifically, those systems encompass an editing environment through which medical knowledge is first acquired and then encapsulated into a target app, that is subsequently deployed on a wide set of mobile devices. Those systems represent an effective means for formalizing and disseminating clinical documents, such as MCs, to the patients or the healthcare staff. They are meant to support the whole implementation pipeline that starts with MC formalization, proceeds through their subsequent representation according to a suitable formalism and ends with their dissemination at large, by enabling their execution on users mobile devices.

As part of this thesis, an experimental solution for developing decision support systems running on mobile devices was implemented. The system allowed first to render in an electronic format the knowledge addressing the Emergency Protocols (EPs) used during rescue missions by the paramedic staff on board of emergency vehicles. The effectiveness of using mobile devices as a means of supporting medical decisions was then experimentally tested by a team of nurses and paramedic staff working on the ambulances of an Emergency Department located in the autonomous region of Aosta (Italy). To assess their perception about the system, two questionnaires were administered: one at the start (pre-study) and another one at the end of the study (post-study). Both the definition of the questions and the methodology followed for the

administration and analysis of the questionnaires were inspired by previous scientific works. It is then important to highlight that the activity described in this chapter has been focused on the development of an *mHealth* solution for the emergency context and not on the evaluation of its users' perception.

The dimensions defining the core component of the system, which is an Android mobile app called *Gquest*, are the following ones:

- *App Distribution* = manual installation: the trial involved only one ambulance equipped with the device on which *Gquest* was manually installed. No large scale deployment was implied in this experimental setting;
- *Target Users* = nurses and paramedic staff from the Emergency Department;
- *Data Acquisition* = manual/vocal: the MCs consultation could be performed either through a manual or through a vocal interaction with the mobile device. The last interaction mode exploited a navigation model requiring the user to pronounce specific keywords after listening a portion of the requested MC and its corresponding prompt;
- *Data Analysis* = local: every input provided by the user was immediately processed by *Gquest* on the smartphone;
- *Data Storage* = permanent DB: data collected by *Gquest* only concerned the navigation accomplished by the user during the consultation of MCs for documental purposes. Due to the limited amount of data produced, the DB did not need to be flushed frequently and was meant to preserve its data permanently;
- *Data Synchronization* = low frequency: data saved during MCs consultations were not meant to support the remote overseeing of the activities in real-time, but were collected for legal and documental purposes only, as well as for identifying usage patterns in the experimental setting. For that reason, data transfer occurred with a low frequency (e.g. once per day);
- *App Working Mode* = foreground: since MCs consultation implied the user attention both in visual and in vocal mode, *Gquest* was set up to work in foreground only and needed to be manually launched by the user;

- *App Update Policy* = link to the remote server: *Gquest* showed the full directory listing of the MCs available on a remote server. At any time, the user could download or update the version of a MC stored on *Gquest* by downloading it on the smartphone.

2.1 Introduction

Everyday people working in health care have to undertake decisions concerning the assessment of a diagnosis or a therapeutic action to be accomplished on a patient. While completing this task, those people have to cope with the large amount of scientific knowledge, the limited capacity of human memory [32], the complexity of the emerging medical practices and the stressful conditions that distinguish the emergency situations [33, 34]. All those elements make the decision process very error-prone [35] and inevitably affect the patient health status. An article published in 2016 [36] claimed that medical errors are the third leading cause of death in the US. Medical errors are defined as "an unintended act (either of omission or commission) or one that does not achieve its intended outcome, the failure of a planned action to be completed as intended (an error of execution), the use of a wrong plan to achieve an aim (an error of planning), or a deviation from the process of care that may or may not cause harm to the patient".

The amount of medical knowledge today is growing so fast that, according to Densen et al. [37], it is impossible to keep up with it for education, patient care and research. As a matter of fact, the time required for doubling the whole amount of medical knowledge has been continuously decreasing over the years: it was initially estimated to be around 50 years in 1950, it decreased to 7 years in 1980, it was 3.5 years in 2010 and it is even expected to be as small as 73 days in 2020. Due to this exponential growth and the time required for disseminating new knowledge to medic and paramedic staff, the administered quality of care is worsening, the variability among clinical practices is increasing and the costs for the health-care system are raising.

Besides the intrinsic large amount of medical information, the health-care staff also has to cope with the limited capacity of human memory [38]. Every human being can exploit three different types of memory: the sensory memory, the short term memory and the long term memory. The sensory memory is responsible for the acquisition of all the incoming stimuli generated through the senses. If not moved into the short term memory through the process of

attention, those are temporarily stored until the next overwriting acquisition. The short term memory keeps data for a longer time in comparison to the sensory one, but it has a big limitation: humans are able to memorize only between five and nine chunks per time, where a chunk refers to the minimum amount of information that a person can memorize. A chunk can be composed of a single element as well as of multiple ones. For example, when we have to memorize a mobile phone number made of ten digits, we usually group the first ones into the area code so that the total amount of chunks is reduced. As it happens for the data stored in the sensory memory, even those saved in the short term one have a limited lifetime. The only unlimited storage, in terms of both capacity and lifetime, is represented by the long term memory. Data can be transferred there through the memorization process, which involves either a repeated exposure to a stimulus or a multiple repetition of the information. For the above mentioned limitations, it is hard for health-care staff to permanently assimilate new information when it is affected by a very high rate of change.

As a promising solution to overcome those barriers, medical advisory boards were formed to identify suitable courses of actions to be adopted as standards in the most common situations. At first, this led to the formulation of Clinical Practice Guidelines (CPGs) as an attempt to combine knowledge described in the literature with clinical experience. CPGs depict the human resources that are required each time, their roles, and the actions to be accomplished according to the best practices [39]. Unfortunately, CPGs turned out to be often unsuitable for the daily practice because of their bulk size, which makes them difficult to skim quickly, and the expertise required to properly interpret and apply them. For this reason, in some medical areas, the current trend is to turn CPGs into MCs, which look like summarized CPGs, streamlined for rapid consultations or emergency situations.

MCs were originally meant as tools supporting decisions in order to minimize errors in time-tight complex activities, such as those faced by airline pilots, or as quick references in the manufacturing and repair industry. Their introduction in the medical area is rather recent, but examples are already documented in the literature. The models for representing MCs are various and differ according to their goal. For example, a MC designed to help with the preparation of a medical device or operating room is usually composed of a list of items, each one associated to a box that has to be checked after completing the corresponding task. However, if a MC is meant to support the health-care staff during the decision-making process, its preferred model looks like a typical flowchart. Their adoption is mainly oriented to support the cor-

rect use of technology, as in addressing the proper control of the laparoscopy equipment to prevent surgical errors and mortality [40], in improving surgical safety in resource-limited countries [41], or in preparing for the separation from cardio-pulmonary bypass [42]. Nevertheless, checklists are also entering the core of the clinical practice, as it happens in discriminating people with normal cognitive capabilities against ones with cognitive complaints [43], in screening individuals for post-traumatic stress disorder [44], or in preventing missing information during transitions of care, occurring when a patient is moved from a clinical setting to another one [45].

Even for those MCs that have been validated and are used in daily care, their adoption is not as widespread as it should be, mainly because of the inherent limitations by which the paper-based format, customarily adopted for their representation, is affected. Those include impediments for disseminating and updating them; the inability to collect feedback about their use or about the outcomes of their adoption; logical and formal errors introduced during their editing; the lack of formal validations over their consistency. The availability of a generalized approach for editing and distributing MCs could greatly simplify their adoption and use, thus improving the quality of care.

2.2 Related Work

Considering the aim of the project, which is providing a tool for the rapid consultation of EPs, the mobile technology was deemed to be the most suitable one.

Several Android mobile apps available on the Google Play Store were evaluated in order to possibly identify the one addressing all the needs of the project. Among those there were: *Atrial Fibrillation Scoring* [46], *First Aid by British Red Cross* [47], *First Aid Emergency & Home* [48], *First Aid* [49] and *St John Ambulance First Aid* [50]. However, the results coming through the analysis of those apps led to the conclusion that none of them was suitable enough mainly due to the following two reasons: the absence of an editor for entering and updating the contents (*Atrial Fibrillation Scoring*, *First Aid by British Red Cross*, *First Aid Emergency & Home*, *First Aid*, *St John Ambulance First Aid*) and the low usability level for consultation in emergency contexts (*First Aid Emergency & Home*, *First Aid*,*St John Ambulance First Aid*).

After excluding the existing commercial solutions specifically designed to address emergency contexts, apps able to render questionnaires were also con-

sidered. As a matter of fact, those rely on a model implementing conditional navigation among questions, so that any answer entered by the user is exploited to drive the subsequent questioning path. This feature can be exploited also for rendering MCs modeled in terms of flowcharts and for this reason platforms for questionnaires' modelling and administration were initially analyzed.

The evaluation involved commercial tools such as *SurveyGizmo* [51], *SurveyMonkey* [52], *FluidSurveys* [53] and *Google Forms* [54]. Although some of those run on mobile devices, their exploitation for rendering MCs inherently call for additional features that none of them is able to show. First of all, many of those tools require an active internet connection and are unable to properly operate in disconnected mode. Additional features include the possibility of performing some arithmetics, that is used for computing scores, or the possibility of interrupting the consultation of a MC and recovering it at a later time if needed. This applies when a MC references several steps to be accomplished over a considerable amount of time, so that the user should be allowed to resume the MC consultation at a later time from the very same point where he left. Managing the whole consultation process through alternative means (e.g. manual or vocal interaction) should be preferred for those environments in which the user is busy with his hands. In summary, apps for rendering questionnaires represent a valid starting point, but cannot be used for rendering MCs until they are properly adapted to this alternative context.

2.3 Adoption and Adaptation of *Gquest*

After excluding all the already available commercial solutions, the next option was to consider the *Gquest* mobile app, initially designed for administering questionnaires to home patients [55].

The main strength of *Gquest* resides in its capability to dynamically render any kind of questionnaire, regardless of its specific content. This level of abstraction is achieved through a model, which is rendered in an XML file format. Fig. 2.1 illustrates the six different components defining the whole *Gquest* data model, each one with its own XML attributes. According to this model, each *Questionnaire* component can contain multiple *Blocks*, that group *Questions* related to each other. Then, each *Question* can contain several possible *Answers*, which can include a simple *Label* or an *Input* element or both. Admissible *Input* elements are the following ones: *Checkbox*, *Selection*, *Text*, *Radio*.

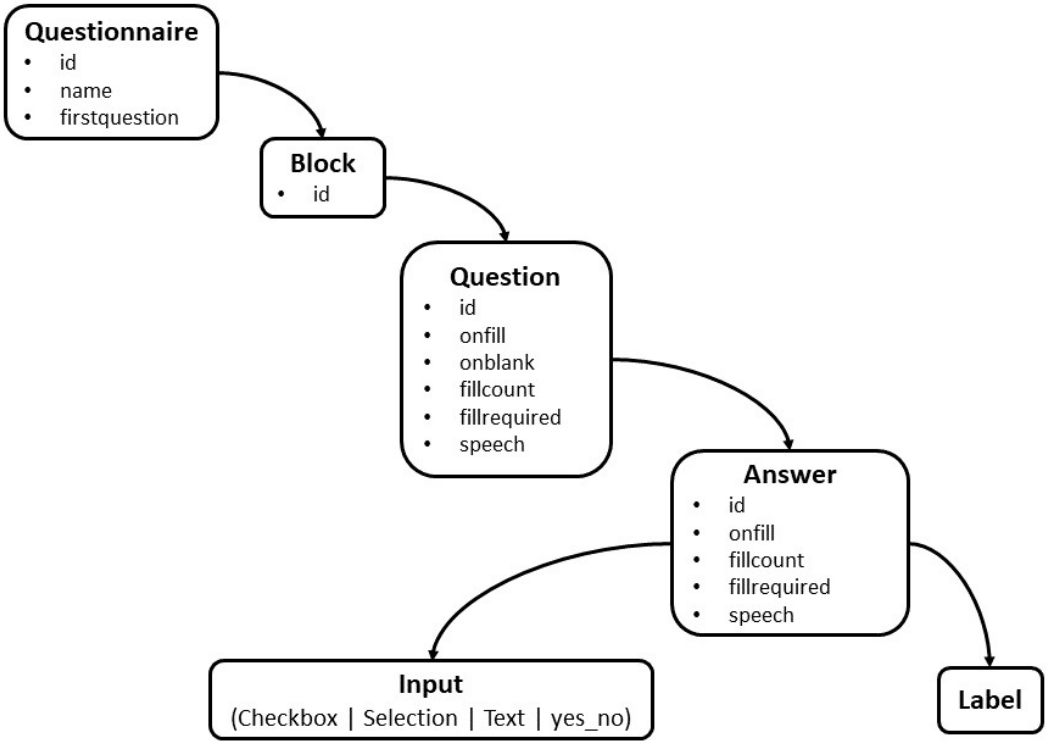


Figure 2.1: **The *Gquest* data model.**

The most particular attributes of the *Gquest* data model are the following ones:

- *fillrequired* specifies the number of elements which has to be answered for a specific component. Those elements could be: the *Answers* of a *Question*, the *Inputs* of an *Answer* or the items of a multiple selection element. Possible values for the *fillrequired* attribute are *no* (the user does not have to answer), *yes* (user has to answer to all elements), *atleast* (user has to answer to at least a specified number of elements) and *atmost* (user has to answer to at most a specified number of elements);

- *fillcount* provides the number of elements which the user has to answer to;

- *onfill* saves the id of the next *Block* which the navigation jumps to, if the user answers to the current *Question*;

- *onblank* saves the id of the next *Block* which the navigation jumps to, if the user does not answer to the current *Question*;

- *constraint* specifies the expected data type provided by the user. Possible values are *text*, *number* or *decimal*;

- *selectiontype* defines the rendering layout for multiple selection *Input* elements.

Given the features already provided, *Gquest* was subsequently adapted to the emergency context by adding some new features aimed to solve the main issues previously hindering the adoption and dissemination of EPs:

- Limitations in updating and disseminating newer versions: each time EPs contents change, accounting for new information or updates, the new versions have to be printed on paper and promptly distributed to all the staff members;

- Difficulty of consultation due to formal, logic or operational barriers: paper EPs do not undergo formal or logic validations, and errors or omissions are often discovered in them. In addition, the paramedic staff does not always take part in the process of formalizing the protocols and this lack of contribution affects the contents provided, that sometimes are unrelated from the real practice;

- Incapability of consultation due to time constraints: nurses and paramedic staff work under stressful conditions and their actions have to be accomplished quickly and on time. Those factors hinder the ability of doing simple calculations, such as those required to derive drug dosages based on the patient weight;

- Incapability of consultation due to physical barriers: when the staff people are busy with their hands in manipulating a patient, the consultation of an EP becomes very difficult and a full vocal interaction could be very useful;

- Impossibility of collecting feedback about EPs usage: due to clinical and legal reasons, the paramedic staff may need to prove that they have adhered to the standards, demonstrating that the applicable protocol has been properly consulted.

2.4 Designing the New Features of *Gquest*

The very first limitation by which all the mobile apps available on the Google Play Store were affected, that prevented their use for MC dissemination, was the absence of an editor for creating new contents or for updating old ones. To this aim, an editor (*GquestEditor*), customized for representing MCs according to the *Gquest* data model, was designed and developed as a web app. In Fig. 2.2 it is illustrated how the *GquestEditor* components match the primitives made available by *Gquest*.

When the editing process for a new MC is started, a new XML file is created and the user is shown a sequence of web pages, each one including a form for entering the attribute-value pairs of the specific *Gquest* model component. The user can create as many *Gquest* model components as needed to represent the MC, that may be saved in the *Working repository*. Here, MCs can be temporary saved even if they are incomplete or inconsistent with the *Gquest* model since no validation has been applied yet. When the editing process is finished and the MC is ready to be published, it eventually undergoes a formal and logic validation process, which ensures the correctness of the navigation path and the overall consistency of the MC. The validation process is performed according to the following rules:

- verifying the reachability of every node from the MC starting point;

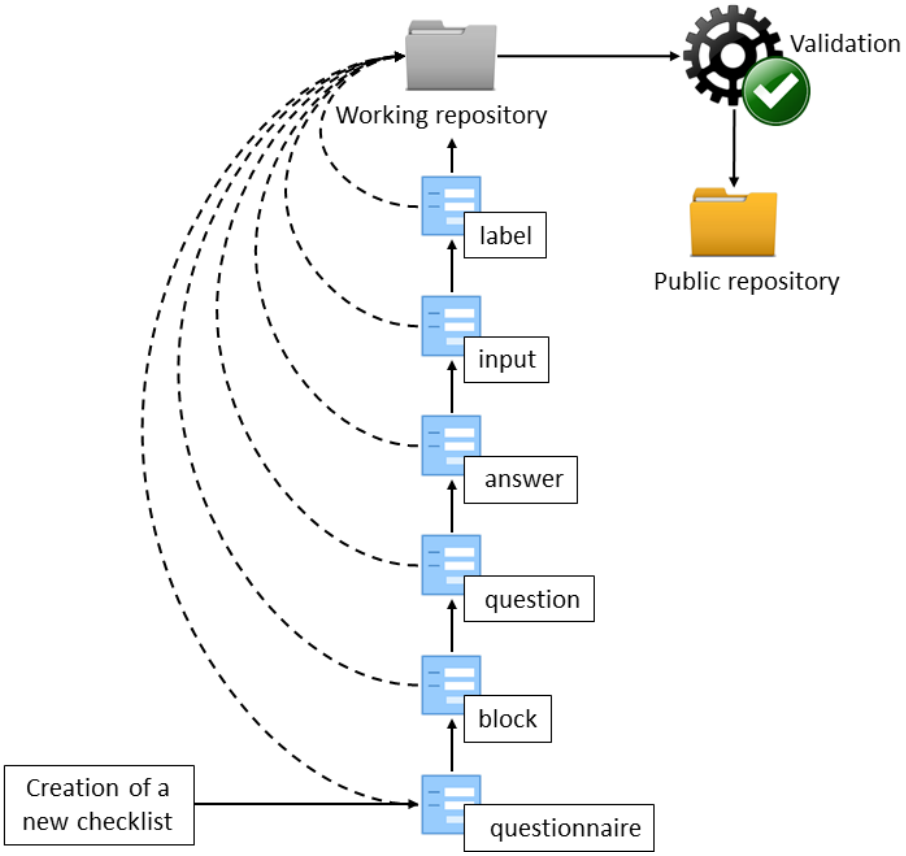


Figure 2.2: **Overview of the *GquestEditor* components.**

- notifying the presence of any cycle;
- ensuring that each node of the MC has a suitable path toward a termination node.

If the validation check does not return any error, the MC can be saved in the *Public repository* and then downloaded by the *Gquest* app.

Besides the development of the *GquestEditor*, also the *Gquest* mobile app needed to be adapted for the proper rendering of MCs in an emergency context. The first adaptation concerned the development of an engine for doing mathematical calculations. The overall design of the engine consists of three consecutive steps:

- Binding of variables: search and acquisition of variables values;
- Expression evaluation: formula calculation with the recently acquired values;
- Unbinding of variables: saving of the new values in different variables.

The integration of the engine inside *Gquest* required the definition of an additional XML component: the *Script*. Associated to the *Question* component, the *Script* retrieves all the values of the input fields provided by the user in the current screen, uses them to evaluate the expression and saves the result in a global variable. When the user switches screen, the *Script* retrieves the result from the global variable and shows it to the user.

An additional modification to the *Gquest* functionality, that was required by its exploitation in emergency situations, was concerned with enabling its use under any condition, even when the operator hands are busy. To this aim, a full vocal interaction system was designed, exploiting the Text-To-Speech (TTS) and the SpeechRecognizer modules, natively provided by the Android OS, and extending the *Gquest* data model. The vocal system requires that any text associated to the MC elements is uttered by the TTS, while the SpeechRecognizer is used to fill in input fields. Besides those two components, a grammar was defined to control the navigation among the screens and the interaction with their elements entirely based on voice commands. A simplified version of that grammar is shown in Fig. 2.3, where the main states and the transitions among them are introduced.

The transitions among states occur either as a consequence of uttering some text by the TTS (italic labels) or through the recognition of some speech

uttered by the user (capital labels). As an example, the top part of the diagram illustrates that soon after displaying a new screen (i.e. *Accessing Screen state*), its title is read by the TTS. The user may then control the navigation across different screens using the *GO BACKWARD*/*GO FORWARD* keywords of the grammar, or proceed through the different input fields available on that screen with the *NEXT*/*PREVIOUS* commands. When a new input field is accessed its associated text is read first, then the user is allowed to interact with it. This interaction depends on the type of the input field and is illustrated in the bottom part of the figure. Thus, for a *checkbox* or *radio* the user may utter the *SELECT*/*CANCEL* keywords of the grammar, while for a *multiple selection* he may say the keyword *CHOOSE* followed by the names of as many selections as required. Finally, a plain *textbox* may be filled in uttering the *WRITE* keyword followed by the actual words to be entered.

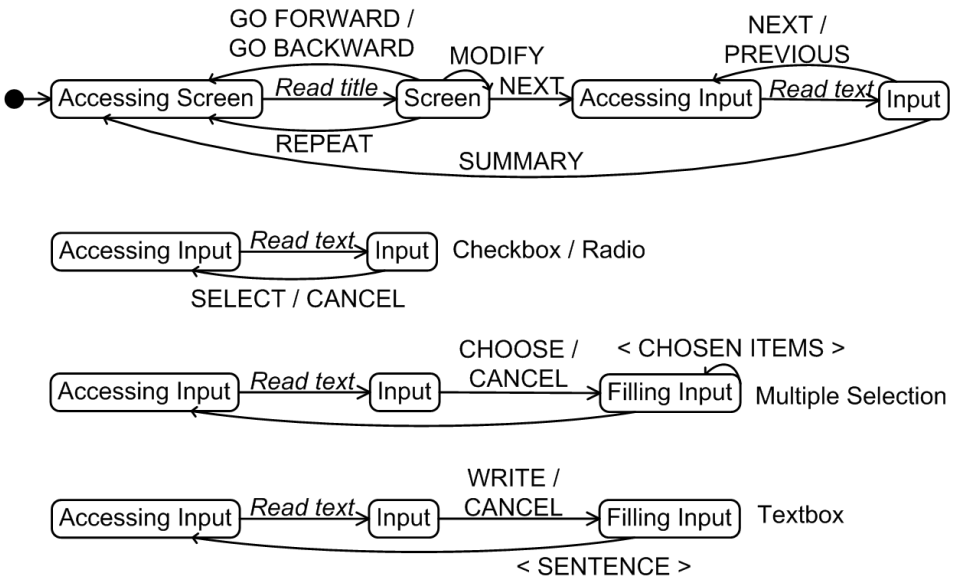


Figure 2.3: **The grammar used by the voice interaction system.**

Finally, to collect the data provided during MCs consultation, a synchronization system, that was developed and used in previous projects carried out at the Laboratory of Biomedical Informatics [56], was customized for the *Gquest* model and integrated into the mobile app.

2.5 Results

At the end of the adaptation process, the overall system, involving the *Gquest* mobile app and the *GquestEditor* web app, was exploited for rendering the MCs provided by an Emergency Department in Northern Italy. Those MCs concern the management of critical situations and are used for training volunteers and paramedic staff as well as for supporting them in managing complex cases. The following MCs were represented and made available: pediatric or adult *cardiac arrest*; *airways obstruction*; *ventilation and oxygenation management*; pediatric or adult *seizure*; *chest pain*; *generic pain*.

The whole lifecycle involving the definition and dissemination of MCs is illustrated in Fig. 2.4 and starts, as usual, with a consensus conference process. Once defined, MCs can be moved from the paper form to an electronic format through the *GquestEditor*, exploiting the customary building blocks (e.g. *start/stop*, *input/output*, *decision* and *recommendations*) augmented with the functionality required to define the emergency-specific features. Finally, once they have been encoded into a computer interpretable format, MCs can be downloaded by *Gquest*, that enables their rendering on the user devices.

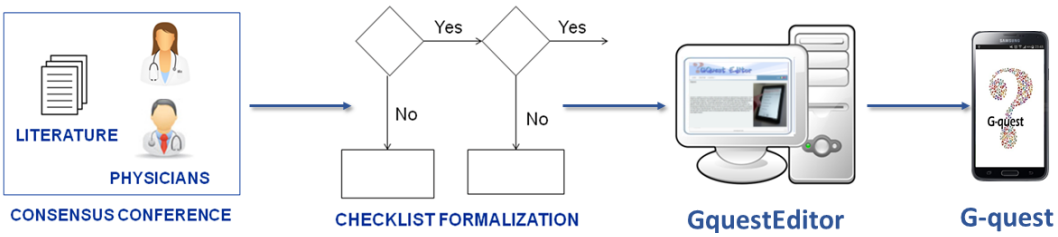


Figure 2.4: **The workflow involved in formalizing, distributing and rendering checklists.**

The resulting overall process encompasses two subsequent conversion steps. The first one is the transformation of the paper-based format of the MC into a computer-interpretable one, while the second one consists in the translation of that version into another one suitable for its rendering on *Gquest*.

Usually MCs are rendered in a paper format following the knowledge-based approach proposed by Latoszek [57]. Domain experts create a flowchart using the customary building blocks (e.g. *start/stop*, *input/output*, *decision* and *recommendations*) shaping the navigation across the whole MC and the order in which its recommendations should be provided. In Fig. 2.5 it is shown a

fragment of the *generic pain* MC rendered in paper format.

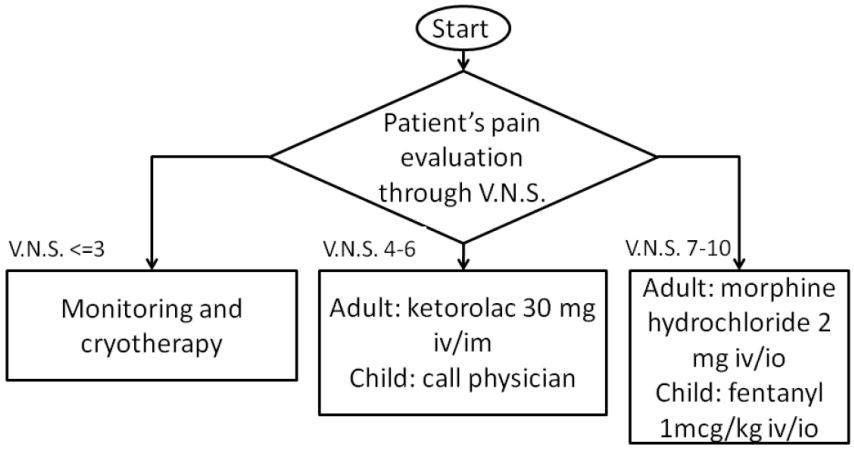


Figure 2.5: **A fragment illustrating the initial paper-based rendering of a medical checklist through a flowchart.**

The first conversion step makes use of the *GquestEditor* and requires a translation of the building blocks composing the MC into the primitives made available by it. Thus, decision blocks are translated into jump rules, inputs are rendered through data acquisition elements, while outputs and recommendations are rendered through textual display primitives, meant to provide structured instructions to the final user. Start and stop blocks are identified by the navigation path across the MC and rendered through special templates. Finally, it is possible to associate to each primitive the text that is pronounced by the TTS engine, once the MC is opened on the mobile device and the voice interaction system is enabled.

In Fig. 2.6 the main web page of *GquestEditor* during the editing process of a MC is shown: on the left a tree structure represents all the components already included in the electronic version of the current MC, while on the right a form for inputing the attributes values for the selected *Gquest* model component is available.

Once the electronic MC has been completed and validated, it becomes available for download on *Gquest*. The overall result is that each block, initially referenced on the paper, becomes a different screen on the mobile device, as illustrated in Fig. 2.7. The definition of the template, that is shared by all the *Gquest* screens, was driven by the purpose of making the interpretation of a MC

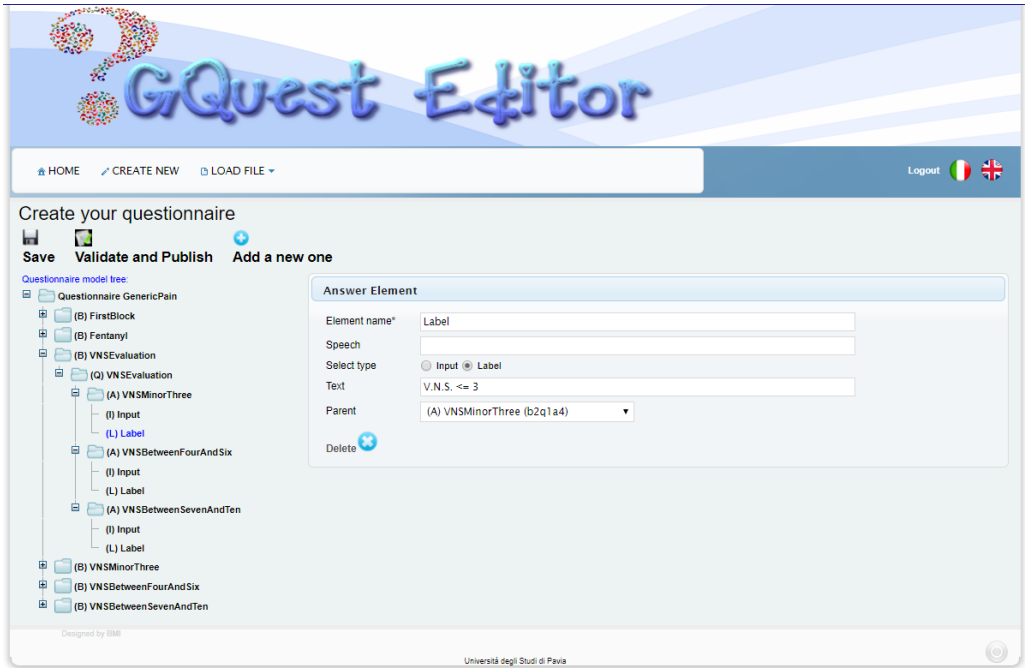


Figure 2.6: **Editing process of a medical checklist through *GquestEditor*.**

as simple and immediate as possible. For this reason, each screen displays only few sentences organized as follows. The upper part, which is well-rendered, contains a question or some leading information, while the main area may include input fields for capturing the user input, suggestions for completing the referenced task or additional details, depending on the specific situation. Besides the primary instructions of the MC, that are always shown on the screen, further information may be available on demand for the user whenever he presses the instruction buttons near some elements to which additional contents are linked.

Figure 2.7: **The result of rendering the blocks of a flowchart representing a medical checklist through different screens on *Gquest*.**

The arithmetic calculations are encapsulated as part of the MC definition, so that whenever the user fills in the input fields, the computation is automatically performed. This is illustrated in Fig. 2.8, where the specific drug dosage is computed for a patient according to his weight inserted by the user on the previous screen.

The layout of the app, while the voice command is working, is shown in Fig. 2.9. As it transpires, the text that is being uttered by the TTS (see the

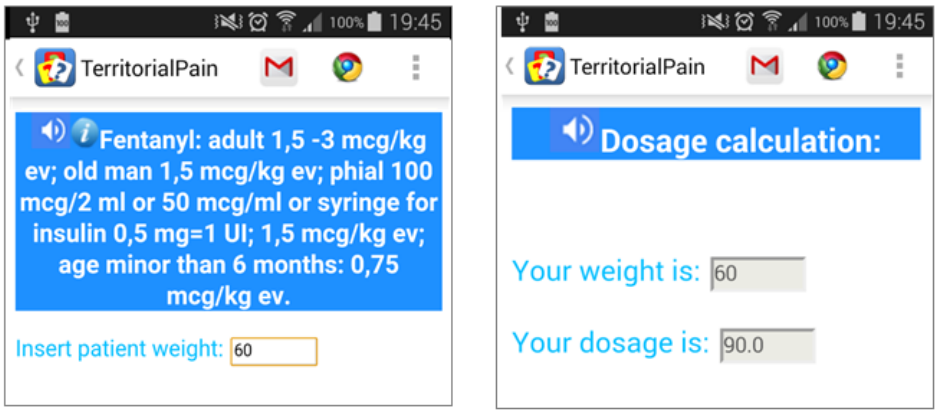


Figure 2.8: **Example of an automatic drug dosage calculation in *Gquest*.**

left screen) or the input field that is waiting for a vocal input from the user (see the right screen), are highlighted in red so that they may be easily identified.

Finally, an additional facility was considered to support users in reporting problems or suggesting enhancements concerning their own experience during the consultation of a MC. At the top of each screen an action bar is placed including shortcuts to some facilities, such as the email app or the internet browser. Clicking on the email icon, for example, the user may invoke the email app with the recipient instantiated with the response team email address, and the subject referring to the specific section of the MC that he is accessing at the moment.

2.6 Prototype Evaluation

To evaluate the efficacy of *Gquest* supporting MCs consultation under emergency situations, a study was planned involving nurses and paramedic staff from the Emergency Department of Aosta that provided the EPs. Because of the location and conformation of that region, many of its villages are very difficult to reach especially in winter. Thus, emergency or first aid care is often accomplished on a local basis by nurses, paramedic staff or even volunteers who do not undergo an extensive training and do not directly possess the skills to manage every possible situation they may face. The availability of a platform supporting them with the application of standard practices was therefore

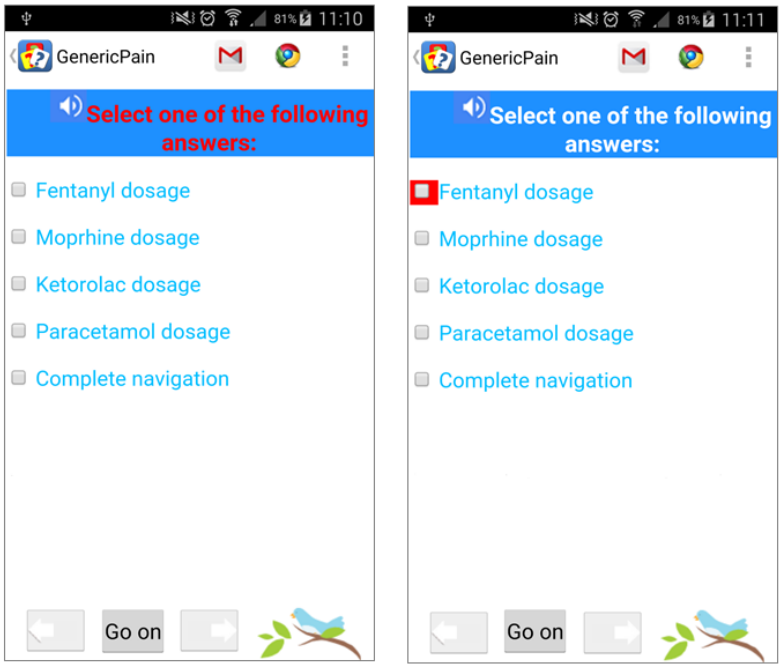


Figure 2.9: **Example of the full vocal interaction system in *Gquest*.**

considered very helpful.

For the deployment process, we took advantage of a project that was planning to upgrade some of the emergency vehicles with the *TomTom Bridge* as a device for receiving emergency calls and tracking vehicle operations. This is basically an Android smartphone enclosed in a rugged casing, meant to be used for business purposes. Besides hosting a special version of the *TomTom* software, being an Android device, it was able to host any standard app developed for that OS, so that it was possible to install *Gquest* on top of it. The pilot study was then scheduled in the detached location of Morgex, lasting for one month and involving eight nurses and paramedics, each having more than 8 years of experience.

2.6.1 Questionnaires Design

Before starting the study the nurses and paramedics were gathered for a training phase, during which the mobile platform was introduced, and the first questionnaire assessing the baseline situation was administered. Questions defining the pre-study questionnaire are shown in Fig. A.1 and Fig. A.2. Those were designed from scratch considering all the barriers that affect the daily activities of paramedics in an Emergency Department and that were expected to be improved by the adoption of *Gquest*.

At the end of the trial, the post-study questionnaire was administered to the nurses and paramedic staff involved. The questionnaire is illustrated in Fig. A.3, Fig. A.4 and Fig. A.5. This is composed of two different parts: the first one, aimed at evaluating the usability of the *Gquest* system, administers the same questions of the standard System Usability Scale (SUS) questionnaire [58]; the second part shows the answers provided by the users in the pre-study questionnaire and asks them to consider whether the *Gquest* system has improved, worsened or has been irrelevant for that specific aspect.

2.6.2 Questionnaires Analysis

After administering the two questionnaires all the answers provided by the eight nurses and paramedics involved in the pilot study were collected and analyzed.

Table 2.1 and Table 2.2 show the percentages of the selected answers for each question. Almost all the study participants (87.5%) declared to consult the EPs to recall the specific procedures described, while 62.5% do so only

PRE-STUDY QUESTIONNAIRE

1. Considering the paper emergency protocols (EPs):

	Never	Sometimes	Often	Always
a. Do you always find the EPs package on the vehicle?	☐	☐	☐	☐
b. Do you always find the needed EP in the package?	☐	☐	☐	☐
c. Do you have to search for an EP for long before finding it?	☐	☐	☐	☐
d. Do you have to wait for an EP until another member of the staff finishes his consultation?	☐	☐	☐	☐
e. Is the information provided in the EPs clear?	☐	☐	☐	☐
f. Is the information provided in the EPs complete?	☐	☐	☐	☐
g. Is the information provided in the EPs easy to be applied in practice?	☐	☐	☐	☐
h. Have you ever found any EP not up-to-date with recent scientific evidences?	☐	☐	☐	☐
i. Do you find calculating drug dosages difficult under stressful conditions?	☐	☐	☐	☐
l. Do you find searching for specific information inside an EP difficult?	☐	☐	☐	☐
m. How often do you consult EPs?	☐	☐	☐	☐
n. Are you unable to consult an EP while being busy with your hands?	☐	☐	☐	☐

1

Figure 2.10: **Pre-study questionnaire in English language administered before the trial in Morgex (Page 1).**

	Yes	No
o. If the EPs were in computer-interpretable format, would you like a full vocal interaction system for their consultation?	☐	☐
p. Do you think it is important proving the consultation of an EP under certain conditions (e.g. for medical and legal problems)?	☐	☐
q. Have you ever had this need?	☐	☐

2. Do you usually consult an EP in order to:

a. review the protocol?	☐
b. find specific information?	☐

Show below any other problem encountered during the protocols consultation

Please kindly check that you have answered all the questions.

THANK YOU FOR YOUR COLLABORATION

2

Figure 2.11: **Pre-study questionnaire in English language administered before the trial in Morgex (Page 2).**

POST-STUDY QUESTIONNAIRE

1. Please, fill in the questions below considering 1 as "Strongly Disagree" and 5 as "Strongly Agree":

	1	2	3	4	5
a. I think I would like to use this system frequently.	☐	☐	☐	☐	☐
b. I found the system unnecessarily complex.	☐	☐	☐	☐	☐
c. I thought the system was easy to use.	☐	☐	☐	☐	☐
d. I think that I would need the support of a technical person to be able to use this system.	☐	☐	☐	☐	☐
e. I found the various functions in this system were well integrated.	☐	☐	☐	☐	☐
f. I thought there was too much inconsistency in this system.	☐	☐	☐	☐	☐
g. I would imagine that most people would learn to use this system very quickly.	☐	☐	☐	☐	☐
h. I found the system very cumbersome to use.	☐	☐	☐	☐	☐
i. I felt very confident using the system.	☐	☐	☐	☐	☐
l. I needed to learn a lot of things before I could get going with this system.	☐	☐	☐	☐	☐

	Yes	No
Did you use Gquest, the component dedicated to the rendering of emergency protocols?	☐	☐

1

Figure 2.12: **Post-study questionnaire in English language administered after the trial in Morgex (Page 1).**

2. If your answer is yes, please, find below the answers you provided before starting the trial. Considering those ones, please, fill in the last column:

	Never	Sometimes	Often	Always	System Effect
a. Do you always find the EPs package on the vehicle?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
b. Do you always find the needed EP in the package?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
c. Do you have to search for an EP for long before finding it?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
d. Do you have to wait for an EP until another member of the staff finishes his consultation?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
e. Is the information provided in the EPs clear?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
f. Is the information provided in the EPs complete?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
g. Is the information provided in the EPs easy to be applied in practice?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
h. Have you ever found any EP not up-to-date with recent scientific evidences?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
i. Do you find calculating drug dosages difficult under stressful conditions?	☐	☐	☐	☐	☐ Improves ☐ Worsens

2

Figure 2.13: **Post-study questionnaire in English language administered after the trial in Morgex (Page 2).**

					☐ Irrelevant
l. Do you find searching for specific information inside an EP difficult?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
m. How often do you consult EPs?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
n. Are you unable to consult an EP while being busy with your hands?	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant

Do you usually consult an EP in order to:

		System Effect
a. review the protocol?	☐	☐ Improves ☐ Worsens ☐ Irrelevant
b. find specific information?	☐	☐ Improves ☐ Worsens ☐ Irrelevant

Please, write below any other problem encountered while using the system

Please kindly check that you have answered all the questions.

THANK YOU FOR YOUR COLLABORATION

3

Figure 2.14: **Post-study questionnaire in English language administered after the trial in Morgex (Page 3).**

when they need to acquire some specific information. All subjects said that sometimes they look for information in the EPs, but only a quarter of them attempted to always consult them.

Considering the influencing factors, what emerges is that working under stressful conditions, being busy with their hands, and the need to avoid wasting time, represent barriers towards consulting EPs for most members of the ambulance crew. In particular, 87.5% found hard to review an EP while keeping their hands on the patient and trying to intervene on him. More than half (62.5%) liked a full vocal interaction system so that EPs consultation could be supported in any case. Also the same percentage declared to have difficulties in doing mathematical calculations under stress. The opportunity of proving the adherence to an EP under particular conditions was considered an important issue by all of them (100%), even though none had ever felt this necessity till then.

Questions concerning the physical availability of the EPs, the formalization quality of their contents and the difficulties arising when updating them received answers that show a general positive feeling. Less than half (37.5%) complained that sometimes EPs are not available on the vehicle or that sometimes it takes time before finding the right one they are looking for. Only a quarter of them declared that they had to wait for an EP card until another member finished perusing it. EPs provided to the staff seemed to be well formalized since only few of them complained about the clarity (25%), the completeness (12.5%) or the easiness of consultation (25%). Finally, 12.5% asserted that sometimes they did not find the most updated EPs versions onboard.

As already done with the answers of the pre-study questionnaire, also the post-study ones were analyzed and results of the analysis are shown in Table 2.3 and Table 2.4.

The first ten questions are the ones provided in the SUS questionnaire, which is a standard used for measuring the usability of a system. Considering the answers provided, an overall SUS score of 51.25 over 100 was obtained calculating the average of all users SUS scores. The range of those scores varied between 35 and 77.5 and the detailed distribution of the answers provided to each question is shown in Table 2.3.

Even though none of the nurses and paramedics declared to have used the *Gquest* component during the trial, six out of eight answered also to the second part of the post-study questionnaire.

Table 2.4 shows, in terms of percentages, how users found *Gquest* either as

Question	Never	Sometimes	Often	Always
Do you always find the EPs package on the vehicle?	0%	37.5%	0%	62.5%
Do you always find the needed EP in the package?	0%	25%	12.5%	62.5%
Do you have to search for an EP for long before finding it?	62.5%	37.5%	0%	0%
Do you have to wait for an EP until another member of the staff finishes his consultation?	75%	25%	0%	0%
Is the information provided in the EPs clear?	0%	25%	12.5%	62.5%
Is the information provided in the EPs complete?	0%	12.5%	37.5%	50%
Is the information provided in the EPs easy to be applied in practice?	0%	25%	37.5%	37.5%
Have you ever found any EP not up-to-date with recent scientific evidences?	75%	12.5%	12.5%	0%
Do you find calculating drug dosages difficult under stressful conditions?	37.5%	50%	12.5%	0%
Do you find searching for specific information inside an EP difficult?	50%	50%	0%	0%
How often do you consult EPs?	0%	50%	25%	25%
Are you unable to consult an EP while being busy with your hands?	12.5%	50%	37.5%	0%

Table 2.1: **Percentages of answers provided by the paramedic staff to questions with four available choices in the pre-study questionnaire.**

Question	No	Yes
If the EPs were in computer-interpretable format, would you like a full vocal interaction system for their consultation?	37.5%	62.5%
Do you think it is important proving the consultation of an EP under certain conditions (e.g. for medical and legal problems)?	0%	100%
Have you ever had this need?	100%	0%
Do you usually consult an EP in order to review the protocol?	12.5%	87.5%
Do you usually consult an EP in order to find specific information?	37.5%	62.5%

Table 2.2: **Percentages of answers provided by the paramedic staff to questions with two available choices in the pre-study questionnaire.**

a helping, a worsening or an irrelevant tool for each barrier and limitation they experienced as workers in an emergency context. Finding the EPs package on the vehicle was considered the most improvable barrier (66.66%), but also using *Gquest* to automatically calculate drug dosages was considered important (50%). The 33.33% of paramedics thought that through *Gquest* it would have been easier to search for the required EP needed to handle an emergency situation, to find the required information inside that EP and possibly to update the EPs contents themselves whenever required by the management. Moreover, 16.66% declared that *Gquest* could help with the review of a complete EP, as well as with making EPs clearer and complete. On the other hand, *Gquest* was considered irrelevant for finding an EP more quickly, for preventing from waiting that another member of the staff finishes his consultation of the same EP, for applying the practical information of an EP more easily or for being able to consult an EP even when their hands are busy.

Given the small number of participants involved in the pilot study no comparison between answers provided in the two different questionnaires was performed.

Question	Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
I think I would like to use this system frequently.	0%	25%	37.5%	25%	12.5%
I found the system unnecessarily complex.	12.5%	25%	37.5%	12.5%	0%
I thought the system was easy to use.	25%	12.5%	37.5%	25%	0%
I think that I would need the support of a technical person to be able to use this system.	12.5%	50%	12.5%	25%	0%
I found the various functions in this system were well integrated.	12.5%	12.5%	37.5%	25%	0%
I thought there was too much inconsistency in this system.	12.5%	62.5%	25%	0%	0%
I would imagine that most people would learn to use this system very quickly.	12.5%	0%	25%	50%	12.5%
I found the system very cumbersome to use.	12.5%	75%	0%	12.5%	0%
I felt very confident using the system.	0%	37.5%	25%	25%	12.5%
I needed to learn a lot of things before I could get going with this system.	25%	62.5%	12.5%	0%	0%

Table 2.3: **Percentages of answers provided by the paramedic staff to questions with five possible choices in the post-study questionnaire.**

Question	Worsens	Irrelevant	Improves
Do you always find the EPs package on the vehicle?	0%	33.33%	66.66%
Do you always find the needed EP in the package?	0%	66.66%	33.33%
Do you have to search for an EP for long before finding it?	0%	100%	0%
Do you have to wait for an EP until another member of the staff finishes his consultation?	0%	100%	0%
Is the information provided in the EPs clear?	0%	83.33%	16.66%
Is the information provided in the EPs complete?	0%	83.33%	16.66%
Is the information provided in the EPs easy to be applied in practice?	0%	100%	0%
Have you ever found any EP not up-to-date with recent scientific evidences?	0%	50%	33.33%
Do you find calculating drug dosages difficult under stressful conditions?	0%	33.33%	50%
Do you find searching for specific information inside an EP difficult?	0%	66.66%	16.66%
How often do you consult EPs?	0%	83.33%	0%
Are you unable to consult an EP while being busy with your hands?	0%	83.33%	0%
Do you usually consult an EP in order to review the protocol?	0%	66.66%	16.66%
Do you usually consult an EP in order to find specific information?	0%	50%	33.33%

Table 2.4: **Percentages of answers provided by the paramedic staff to questions with three available choices in the post-study questionnaire.**

2.7 Discussion

The main goal of this study was to ensure the consultation of MCs anytime and anywhere and promote their representation and administration through alternative formats overcoming the limitations by which the paper format is affected. The choice of mobile devices as the actual tools for MCs consultation derives from their many advantages, including the possibility of saving in an electronic format a large number of MCs and making them available whenever needed. Mobile devices may also automatically send data concerning MCs usage to reference centers in order to track the adherence of their users to standards. This may help towards the implementation of workflow management systems combining medical and organizational knowledge [59]. Finally, the adoption of *Gquest* was motivated by the possibility of enhancing the consultation of MCs through the administration of educational material concerning the same context.

The administration of the pre-study questionnaire to the participants of the pilot study, and the consequent analysis of their answers, lead to two interesting considerations: physical barriers and necessity of proving adherence to EPs are really critical problems for the emergency staff, while the level of EPs formalization strictly differ from country to country. For example, for the autonomous region of Aosta, EPs seem to be quite well formalized and quite often available on the ambulances.

Comparing the answers provided to the pre-study questionnaire with the ones given to the post-study one, some conclusions on the overall trial can be done. For example, the 62.5% that complained about calculating drug dosages or that consult EPs just for retrieving a specific information found *Gquest* helpful. This was not the same for EPs clarity and completeness, that were not considered improvable by *Gquest* given that only the 12.5% complained about those aspects in the pre-study questionnaire. On the other hand, even though only the 12.5% declared that EPs sometimes are not up-to-date with the most recent scientific evidences, the 33% saw *Gquest* as a promising solution for improving the EPs contents updating process. Finally, none of the 87.5% that complained about consulting an EP with busy hands and none of the 62.5% that expressed their wish to use a full vocal interaction system considered *Gquest* as a solution to their complaints.

In conclusion, the study helped with better identifying the barriers limiting the activities of nurses and paramedic staff in an emergency context. Many features provided by *Gquest* were found useful and were considered as a pos-

sible solution to improve those barriers. However, the fact that none of the paramedics used *Gquest* during the trial highlights some limitations of the system. One of those might have been the distribution of the app installed on a *TomTom Bridge* and not on standard Android mobile devices. This choice could have affected some aspects, such as having only one device to be shared among many people or its alternate use between MCs consultation and road navigator. An interesting improvement of the study could be to install *Gquest* on the personal devices of each member of the paramedic staff.

2.8 Scientific Achievements

The contents described in this chapter were presented in the following peer-reviewed international conferences:

- **E. Losiouk**, S. Quaglini, M. Pesenti Campagnoni, G. Lanzola, A Mobile Platform for Emergency Care, *Stud Health Technol Inform. (Medical Informatics Europe Conference)*, 2015; 210: 818-822;
- **E. Losiouk**, G. Lanzola, E. Visetti, S. Quaglini, An Environment for Representing and using Medical Checklists on Mobile Devices, *Conference Proceedings IEEE Engineering in Medicine and Biology Society*, 2015;7328-7331;
- **E. Losiouk**, S. Quaglini, E. Visetti, F. Perfetti, G. Lanzola, Ambulance protocols: a mobile solution, *13th International Congress in Nursing Informatics*, 2016; 225:520-524.

Chapter 3

Mobile Health Applications for Real-Time Remote Monitoring Supporting Decisions on the Patient Side

This chapter concerns real-time RM systems that provide decision support for the patients. Those systems, that are also referred to sometimes as RMs in short, play a key role for outpatients that are affected by chronic diseases and are, therefore, required to self manage their treatment. For those patients, the compliance with the treatment is harder to achieve because the management of the disease has an impact on their daily activities and lasts for longer time periods, possibly spanning the whole life. Thus, the availability of a decision support system, triggering alarms and providing suggestions, may reduce the occurrence of dangerous situations and delay the disease progression with the associated onset of complications.

The system developed during this work addresses patients affected by T1DM and a novel treatment known as the AP, consisting in a control algorithm that automatically regulates the blood glucose concentration by dynamically adjusting the insulin delivery rate. The algorithm runs on a smartphone equipped with a customized version of the Android OS. It acquires data from a sensor placed on the patient and continuously calculates the best amount of insulin to be delivered. This information is used to drive the insulin pump, that is also attached to the patient. Given the complexity of the intervention, that

involves the use of a device accomplishing a non-mediated critical action, its first experiments required the support of a RM service for overseeing the patient status and the devices operation in real-time by both the clinic and the research staff.

The system was originally designed and developed during a previous project, targeting adult patients affected by T1DM, and encompassed two components: a remote web component and a mobile one. This last one hosted the control algorithm and was provided by University of Virginia (USA). The contribution of this thesis focused on tuning the RM component to make it more responsive and suitable for a new class of users. The updated system was deployed during a clinical trial involving children affected by T1DM and was provided to their parents so that they were allowed to oversee their children at any moment during the day. Even though the main purpose of this activity was the improvement of the RM component, two questionnaires were designed and administered to the parents involved in the trial in order to assess their perception about the system. Both the design and the administration of the questionnaires were inspired by previous research works.

Considering the mobile component, the following dimensions give a general overview of its features:

- *App Distribution* = manual installation: since the AP is provided as a modification of the Android OS, it was manually installed on each device used in the clinical trials;
- *Target Users* = patient;
- *Data Acquisition* = automated and manual: information coming from the sensor located on the patient is automatically acquired by the AP leveraging the *Bluetooth* communication channel. Additional data (e.g. meals, physical activities, insulin boluses) need to be manually provided;
- *Data Analysis* = local: all the available data are immediately analyzed by the control algorithm running on the device to calculate the suitable amount of insulin to be delivered and possibly triggering alarms;
- *Data Storage* = temporary DB: due to the large amount of data generated by the sensors, the AP database needs to be periodically flushed;
- *Data Synchronization* = high frequency: to guarantee the real-time remote visualization of the data saved on the smartphone, those are synchronized to the remote server with a high frequency (i.e. 5 minutes);

- *App Working Mode* = foreground and background: the AP runs in foreground when it needs to interact with the user for accomplishing specific tasks (e.g. inserting configuration parameters, displaying alarms, manually acquiring traceable events). On the other side, the AP keeps working and analyzing data coming from the sensors in background;

- *App Update Policy* = manual reinstallation: as well as for the first installation, any subsequent update needs to be accomplished through a manual reinstallation of the AP on the device.

3.1 Introduction

Telemedicine is defined by the American Telemedicine Association as "the use of medical information exchanged from one site to another via electronic communications to improve a patient's clinical health status" [60]. As pointed out by this definition, the purpose of telemedicine systems is the exchange of clinical data. Those can then be exploited for increasing the level of support provided to citizens, tightening the relationships of the patients with the health-care specialists and improving their quality of life. However, the solutions adopted for data transmission have been changing over the years according to the available technology.

The introduction of mobile phones has deeply changed the architecture of telemedicine systems. The first ones strictly relied on PCs placed at patients home in order to allow them to enter their health-care data. However, this step was considered a big hindrance: preventing the patient to report any relevant event to the health-care providers whenever he wishes increases the chance of forgetting or wrongly recording data. On this basis, mobile phones immediately raised a substantial interest due to their promising features.

The first mobile phones were only capable of supporting text messaging in addition to plain calls. Thus, the first services for data collection had to rely on this functionality alone. Modern mobile devices host multi-core processors offering a great deal of computing power, they are controlled by a multitasking OS, possess enhanced graphic capabilities and allow full Internet connection. Thus, they are rather unique tools in that they combine the functionality of a regular phone with that of a computer, which makes them "smart" devices.

The evolving mobile technology has opened up new scenarios that seem instead particularly suitable for the management of chronic non-communicable diseases such as: Diabetes, Cardiovascular Diseases, Respiratory Diseases or

Chronic Kidney Diseases. The main advantage is that patients can stay in touch with the staff between visits, promptly detect any serious health condition requiring an intervention and improve their outcomes.

mHealth does not make available a new set of different health-care services, but it represents instead a new approach to deliver existing ones in a more suitable way for outpatients. Consequently, the majority of the studies available in the literature describe interventions aimed at changing patient behavior, possibly acquiring data patterns and providing useful suggestions, followed by interventions addressing self-monitoring and adherence to therapy or medication. Additional ones also focus on diagnosis, treatment or education.

For some of the above mentioned chronic non-communicable diseases, an immediate intervention is required as soon as an acute episode occurs. This is particularly true for the chronic obstructive pulmonary disease, which is caused by a prolonged exposure to tobacco smoke and can lead to dangerous exacerbations, that fast the disease progression. Patients affected by this disease feel the burden of performing even simple activities due to their short breath caused by airways obstruction and reduced lung capacity. A prompt intervention in case of exacerbations can improve the patient quality of life, prevent unscheduled doctor visits and reduce the number of hospitalisations. To this aim, Van der Heijden et al. [61] designed a probabilistic model able to predict the occurrence of exacerbations by analyzing lung function and blood-oxygen. The model is implemented on a smartphone device, which exploits the *Bluetooth* communication to acquire patient data from a a micro-spirometer and a pulse-oximeter.

Another interesting work, aimed at providing patients with a system for the immediate intervention in case of abnormal condition, is the one published by Aliev et al. [62]. Its purpose is to monitor changes of the heart activity by analyzing the sounds acquired through a smartphone microphone. During a training period, the patients are asked to place the smartphone microphone on their chest several times per day in order to record the traces that will be used as the reference model of their own heart activity. The future acquisitions will be then compared to those traces and, whenever there is a significant mismatch with them, a recommendation to consult a physician will be issued.

Among the chronic diseases, that benefit from immediate interventions on the patient side, T1DM is the one targeted by the activity described in this chapter. This is caused by the destruction of the beta-cells in the pancreatic islets of Langerhans where insulin is produced and secreted. As a consequence, individuals affected by T1DM suffer from an insulin deficiency preventing the

use of glucose as a fuel for the body and require a suitable insulin therapy to control Blood Glucose Level (BGL). Without the administration of exogenous insulin patients affected by T1DM develop a very high BGL, which causes serious complications on the mid-term including retinal, renal, neurological, and cardiovascular ones. Insulin enables the use of glucose by the body thus lowering BGL, but exceeding in the treatment may severely decrease BGL below the minimum values compatible with life. This problem is commonly referred to as hypoglycemia, that is a serious life threatening condition. In summary, people affected by T1DM face the problem of closely monitoring their blood glucose and should maintain a strict control over BGL to reduce hyperglycemia without increasing the risk for hypoglycemia.

Technology for diabetes treatment has largely improved over time and nowadays insulin can be administered by small external mechanical pumps injecting the drug in the subcutaneous tissues, according to the so-called Continuous Subcutaneous Insulin Infusion (CSII) paradigm [63]. Patients with T1DM are then supposed to monitor their BGL by measuring its concentration in blood drops obtained from finger pricks several times per day. Recently, minimally invasive subcutaneous sensors allowing Continuous Glucose Monitoring (CGM) have appeared on the market [64]. Although not substitutive for finger-prick measures, they provide a valuable support for diabetes treatment, especially when used in conjunction with CSII resulting in the so-called Sensor Augmented Pumps (SAPs). With SAPs the patients are still responsible for adapting their insulin infusion based on their current BGL and accounting for external events (e.g. meals, physical exercise, stress, etc.), facing every day a challenging control problem. Therefore, devices for automatic blood-glucose control via closed-loop insulin modulation, such as the AP, could represent a major improvement in diabetes therapy, as witnessed by the growing interest in literature [65, 66, 67].

3.2 Background

The RM service was originally developed within the AP@Home project. This was a project funded by the European Union in 2010 within the 7th Framework Programme with the aim of designing and implementing the AP as a treatment for patients affected by T1DM. The service was tuned during AP@home [56] to support patient safety and was used throughout all its experiments [68, 69], enabling also the collection of any data produced. In order

to fully understand the motivation that pushed towards the optimization of the RM service, a brief description of the different system architectures that were subsequently designed is required.

Since the core component of an AP is given by the algorithm calculating the most appropriate amount of insulin to be delivered, several ones were developed during the AP@home project and each of them required a strict validation. This was achieved by planning different clinical trials, every time enrolling patients over an increasing time span and involving an improved technological solution to improve their mobility and comfort. Thus, from an overall point of view, during the AP@Home project three different system architectures were evaluated.

The very first set of experiments of automated insulin delivery of the AP@home project, accomplished during 2011, started with a fully supervised trial of only one day, taking place at a clinic under highly controlled conditions. The control algorithm ran on a notebook and the link towards the glucometer and the insulin pump was accomplished by adopting the Artificial Pancreas System (APS) [70]. This was a software platform, developed at the University of California in Santa Barbara, consisting in an environment for running the controller that also took care of directly managing the external devices. The devices selected for the experiment were the *Dexcom Seven Plus* glucometer manufactured by *Dexcom Inc.* (San Diego, US-CA) and the insulin pump *Omnipod*^{TM} by *Insulet Corp.* (Bedford, US-MA). Fig. 3.1 shows the set of tools including the patch-pump and sensor in foreground and the control units just behind, linked through wires to the notebook. In addition, a special control unit, endowed with an infrared port, was purchased to remotely control insulin delivery from the notebook through an infrared-to-serial replicator.

During those first trials, the development of a RM infrastructure, with the aim of sending in real-time over the network every piece of information concerning the glucometer, the insulin pump and the AP itself [71], was already started. The purpose was to oversee the evolution of the patient status both as a safety measure preparing for longer unsupervised trials and for collecting all the data in sight of the subsequent post-experiment analyses.

After the successful completion of this preliminary trial, the AP@home team started upgrading the architecture to improve mobility and comfort for the patients in sight of longer trials. The notebooks had to be abandoned in favour of wearable devices, as well as the APS that was substituted by the *DiAs*, provided by the University of Virginia. This is a platform for AP prototyping and testing, distributed on Android devices and able to encapsulate

Figure 3.1: **The devices used with the first architecture adopted in the clinical trials of the AP@Home project.**

the controller algorithms and to interface with the external devices [72].

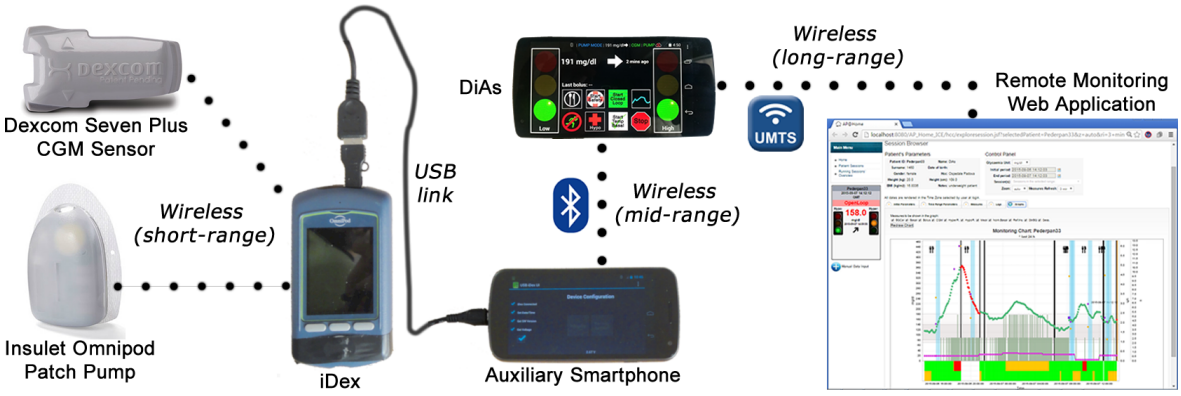


Figure 3.2: **The second architecture used in the clinical trials of the AP@Home project after switching to mobile devices.**

The first configuration adopted encompassed the same devices already used during the former experiments, substituting the notebook with the *DiAs* running on an Android smartphone, and adding the *iDex* as an extra component as shown in Fig. 3.2. The *iDex* was an experimental device (produced by *Insulet Corp.* through an agreement with *Dexcom, Inc.*), that combined into a single unit the functionalities of both the *Dexcom Seven Plus* and the *Omnipod*^{TM} controls units. Moreover, the *iDex* had a serial/USB interface that allowed to interact with both devices, thus becoming the only communication endpoint for the *DiAs*. Unfortunately, for technical reasons the *DiAs* could not make use of the USB port available on the smartphone, that needed to remain available also for recharging purposes. Thus, an additional component was needed to act as a USB/serial-to-bluetooth port replicator (i.e. an auxiliary smartphone) forwarding the signal from the *iDex* to the *DiAs* onto a *Bluetooth* connection. Meanwhile, the RM system was enhanced and ported to the Android environment resulting in a long-range wireless link [56]. This architecture was used for the intermediate trials occurred during the years 2012-2013 before "going home", where the experiments were accomplished at a hotel, lasted for 48 hours and also included a 2-night stay. Unfortunately, the brittleness of the short range link turned out to be a serious source of problems, in particular overnight, when the patient undressed the pouch and laid it on the bedside table [69].

To overcome those limitations a different glucometer, the *Dexcom G4 Plat-*

inum by *Dexcom, Inc.* (San Diego, US-CA), and a different pump, the *Roche Accu-Chek Spirit Combo* by *Roche Diagnostics Gmbh.* (Mannheim, DE), were adopted. The *iDex* was then removed and the control unit of the *Dexcom G4 Platinum* was linked directly to the auxiliary smartphone via USB. The *Roche Accu-Chek Spirit Combo* natively integrated *Bluetooth* and therefore communicated directly with the *DiAs*, since its developers were granted access to the communication protocols by *Roche*. This simplified architecture was used during the year 2013 and improved the overall reliability of the system because of the separation of the channels through which the glucometer and the insulin pump reached the *DiAs*. However, the auxiliary smartphone was still required, adding some unneeded complexity anyway.

A major change in the architecture occurred only when *Dexcom, Inc.* finally introduced the *Dexcom G4 Platinum with Share* that natively included *Bluetooth* connectivity. This eventually removed the need for the auxiliary smartphone altogether, streamlining the architecture and bringing it to the final shape that is reported in Fig. 3.3. This architecture was used to accomplish the final trial of the project lasting 2 months with overnight closed-loop at the beginning of the year 2015.

Figure 3.3: **The final architecture used in the clinical trials of the AP@Home project.**

3.3 Related Work

Since the beginning, developers of RM services for patients affected by Diabetes had to face with manufacturing companies that provided BGL measurement devices. The real revolution that paved the way for the first RM systems was the massive diffusion of the PCs. As a matter of fact, at first the downloading of data from those devices was allowed only using serial ports and offered logbook applications through which it was possible to display and analyze data on the PC screen using charts. Those applications were used either by specialists, that downloaded data from their patients' glucometers at regular visits, or by technology-savvy patients that annotated BGL readings with additional information for an improved control. *Roche* was the first company to sell *Acculink*, a complete RM system. This was essentially a proprietary modem that allowed patients to regularly send data from their *Accu-Chek* glucometers to their doctor's office even without owning a PC. *Roche* also provided the application to be installed at the clinic for receiving and storing patient data ensuring a better follow-up by doctors among scheduled visits [73].

Presently, almost any manufacturer supports downloading data from their glucometers. However, this happens through different proprietary protocols that prevent the actual integration of data into a single application. Moreover, few manufacturing companies are interested in running RM services by themselves. Among those there is *Medtronic* with its *Carelink Network*. This lack of interest was recognized and exploited by *DiaSend* (Askim, SE) that started its business in 2006 offering integration capabilities for all the major glucometers on the market, also including many pumps. The patient may use either his PC or his smartphone to download data from the devices and upload them onto a remote server managed by *DiaSend*, so that they become easily accessible to the clinical staff. The company claims that almost 2000 clinics worldwide have made arrangements with them and nearly 350,000 patients are regularly using it. However, *DiaSend* services are mainly meant to share patient data with the treating staff and therefore only provide off-line monitoring for trend analysis in retrospective studies, with no real-time reporting on the actual patient status.

A different case of RM service involves smartphones with powerful processors and high resolution displays, that have been increasingly exploited by manufactures to simplify the acquisition of BGL measurements and importing their values into the digital world. An interesting example is provided by the different RM model adopted by *Dexcom, Inc.* (San Diego, US-CA) with their

G5 Mobile Continuous Glucose Monitoring System. Besides the basic glucometer, the system encompasses two different smartphone applications: the *Mobile/Share App* and the *Follow App*. The former is installed on the patient smartphone and allows viewing real-time glucose data and trends directly on its display. Using that app the patient may designate up to five people as followers, thereby including caregivers, clinical staff, family members or significant others. Once those people install the *Follow App* on their smartphones, they will all receive in real-time the CGM readings and be notified about critical situations occurring to the patient to possibly undertake actions.

Finally, the need for a monitoring platform that overcomes the inherent limitations of proprietary protocols is best witnessed by the *Nightscout Project* [74], that was initially born as *CGM in the Cloud* and turned into *The Nightscout Foundation* [75] during year 2014. It is an open source project, started by parents of children affected by T1DM, that aims at implementing a platform for real-time access to the patients CGM data via websites, smartphones or smartwatches for the serenity of their parents. Presently, they are able to interface with sensors manufactured by *Dexcom* (*G4*, *G4 with Share*, *G5*) *Medtronic* (*640g*, *530g*, *Veo*) and *Abbott* (*FreeStyle Libre*).

3.4 Optimization of the Remote Monitoring Service

Thanks to the evolution of the system architecture supporting mobility and guaranteeing a high level of usability for the patient, the duration of the clinical trials increased, as well as the number of the patients involved. Under those conditions, the RM service became then more important and had to be rendered highly responsive to properly enable the supervision of the patient status by the physicians and the bioengineering staff. For those reasons, a strong optimization effort of the RM was undertaken, affecting both the source code and database access on the back-end. The results obtained through the optimization procedure will be illustrated by considering the two main pages of the web app.

The first one is the overview panel shown in Fig. 3.4. This page provides an overview of the health status of all the patients currently involved in a clinical trial. As a matter of fact, every small panel is associated with a specific patient and shows the following information: the last glycemia value received, the operating mode of the AP (*ClosedLoop*, *OpenLoop* or *SafetyMode*), the

glycemia trend, calculated over the most recent values, and the hypo- and hyper-glycemia risk. Moreover, in case of dangerous events the panels are surrounded with a red border and additional information is provided inside the panel itself.

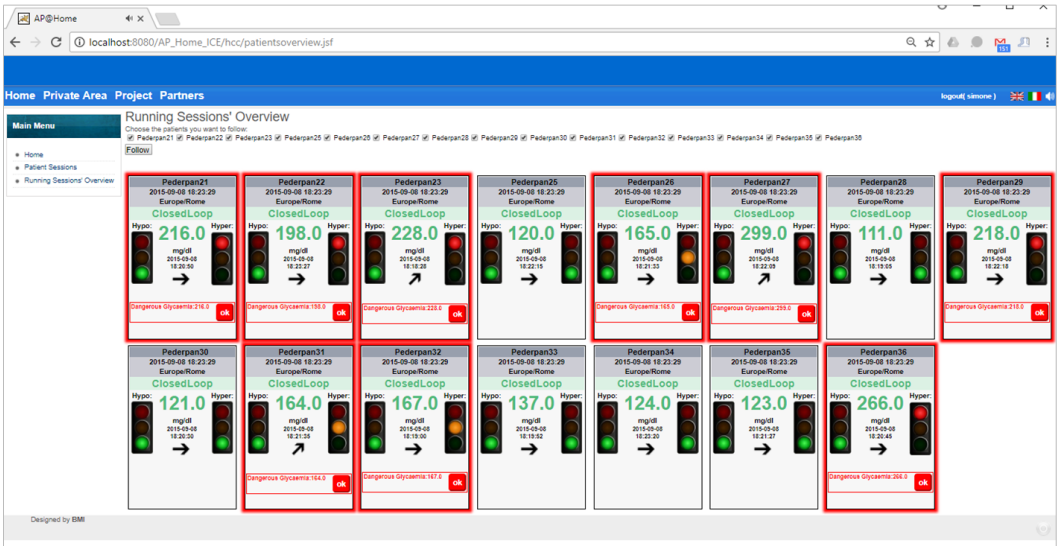


Figure 3.4: **Overview panel of the remote monitoring service showing the health status of all patients involved in the clinical trial.**

The second most important web page of the RM is shown in Fig. 3.5. In the upper left panel, this offers a summary of the patient conditions by reporting the following relevant information: the last glycemia reading, its trend and a hypo-/ hyper-risk assessment. In the central panel, instead, the page includes a chart with a number of physiological variables such as: glucose concentration measured every 5 minutes, insulin delivery rates, meal intake, and risk assessments throughout the period displayed. By using the checkboxes above the panel, it is possible to choose which variables to display in the chart.

The analysis of the database queries of the first RM implementation led to the identification of the following main problems:

- A large amount of queries retrieved the same information several times;
- The same queries were executed multiple times;
- The indexes defined in the database model were used inappropriately;

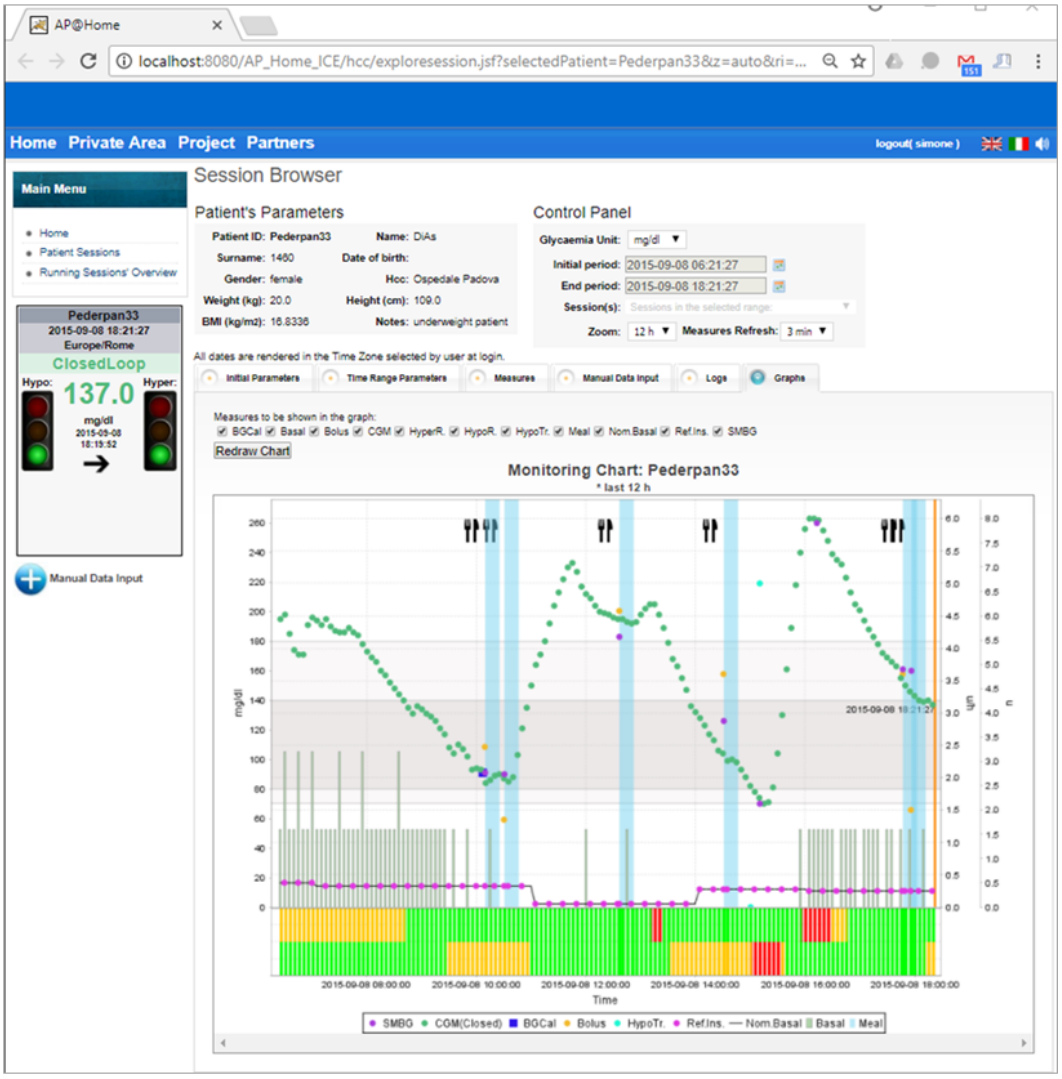


Figure 3.5: **Patient detailed panel of the remote monitoring service.**

- Filters in the WHERE rules of the queries were not enough constrained.

Table 3.1 illustrates the five different queries used to retrieve all the information displayed in the overview panel shown in Fig. 3.4. Besides *Query1*, that was executed only once to get all the patients associated to a specific hospital center undergoing the trial, the other queries were executed multiple times. More specifically, for each patient retrieved through *Query1* *Query2* identified all the sessions with a START event. Then, for each session *Query3* checked if it had a STOP event, *Query4* searched for the last registered event and *Query5* got the timezone of the patient.

Query Name	**Number of Returned Rows**	**Time of Execution (sec)**	**Number of Executions**
Query1	N1=109	0.031	1
Query2	N2=27	0	N1
Query3	1	0	N2
Query4	3	0	<=N2
Query5	1	0	<=N2

Table 3.1: **Statistics over the queries used in the first implementation of the remote monitoring service for retrieving the information displayed in the overview panel.**

This analysis highlights how information retrieved through *Query2*, *Query3*, *Query4* and *Query5* could, instead, be obtained through just a single query, without repeating the same ones multiple times. The execution of the same query multiple times always decreases the performance of app. As a matter of fact, it requires every time to open and close a connection towards the database and it is therefore a highly demanding operation, that should be done as few times as possible.

The results obtained after the optimization are shown in Table 3.2. *Query1* was preserved, but the others were merged into a single query (*Query2*), executed only once.

As it can be seen from Table 3.3, the database queries used in the second main page of the RM service, shown in Fig. 3.5, were even worse. Twenty-two queries were used and three of them (*Query7*, *Query8* and *Query9*) were executed multiple times. Moreover, most of them retrieved the same information from the database and were redundant.

Query Name	Number of Returned Rows	Time of Execution (sec)	Number of Executions
Query1	109	0.031	1
Query2	6099	0.14	1

Table 3.2: **Statistics over the queries used for retrieving the information displayed in the overview panel after the optimization procedure.**

Query Name	Number of Returned Rows	Time of Execution (sec)	Number of Executions
Query1	1	0.016	1
Query2	2	0.016	1
Query3	2	0.016	1
Query4	2	0.016	1
Query5	2	0	1
Query6	N3=3	0.047	1
Query7	1	0.016	N3
Query8	1	0	N3
Query9	1	0	N3
Query10	3	0.016	1
Query11	1	0	1
Query12	9	0	1
Query13	6	0	1
Query14	2777	0.078	1
Query15	3195	0.015	1
Query16	14	0.047	1
Query17	4	0.031	1
Query18	11	0.015	1
Query19	27	0.016	1
Query20	8	0	1
Query21	3	0.016	1
Query22	1	0	1

Table 3.3: **Statistics over the queries used in the first implementation of the remote monitoring service for retrieving the information shown in the patient detailed panel.**

Table 3.4 shows the results of the optimization procedure. The original twenty-two queries were substituted by three queries among which the first one (*Query1*) is responsible for retrieving almost all the information needed in the web page.

Query Name	Number of Returned Rows	Time of Execution (sec)	Number of Executions
Query1	6099	0.14	1
Query2	1	0.031	1
Query3	6	0.015	1

Table 3.4: **Statistics over the queries used for retrieving the information shown in the patient detailed panel after the optimization procedure.**

3.5 Prototype Evaluation

Once the optimization procedure was completed, the RM service was offered to the parents of T1DM children, enrolled in a clinical trial accomplished during a summer camp held in 2015 [76] and aimed at controlling BGL through the use of an AP system on children. During the camp, the RM service was used to oversee in real-time the physiological parameters of the children and was made available to each attending parent, allowing him to oversee his child. The goal was to assess the parents' attitude in the use of a RM system and their perception about its usefulness. To that purpose two questionnaires were administered, before and after the RM system use, and then the responses provided were analyzed.

3.5.1 Clinical Trial Description

The trial was performed at a summer camp in Bardonecchia, a small village located in the Northern part of Italy. It lasted for 8 days enrolling 31 patients aged 5 to 9 years selected by pediatric diabetologists practicing at 5 different major centers in Italy.

As soon as the patients were admitted at the camp, they were randomly assigned to one of the two groups: one group used the AP in the first part of the study and the manually controlled therapy in the second, while the other

group did the opposite. Both study parts lasted for 3 days (72 hours) and were separated by a 1-day wash-out period. The clinical results of the study can be found in [76]. The 31 children enrolled in the clinical trial were accompanied by 21 single parents and 10 parent couples. The RM service was available only during the AP segment of the study, i.e. only for 3 days.

3.5.2 Questionnaires Design

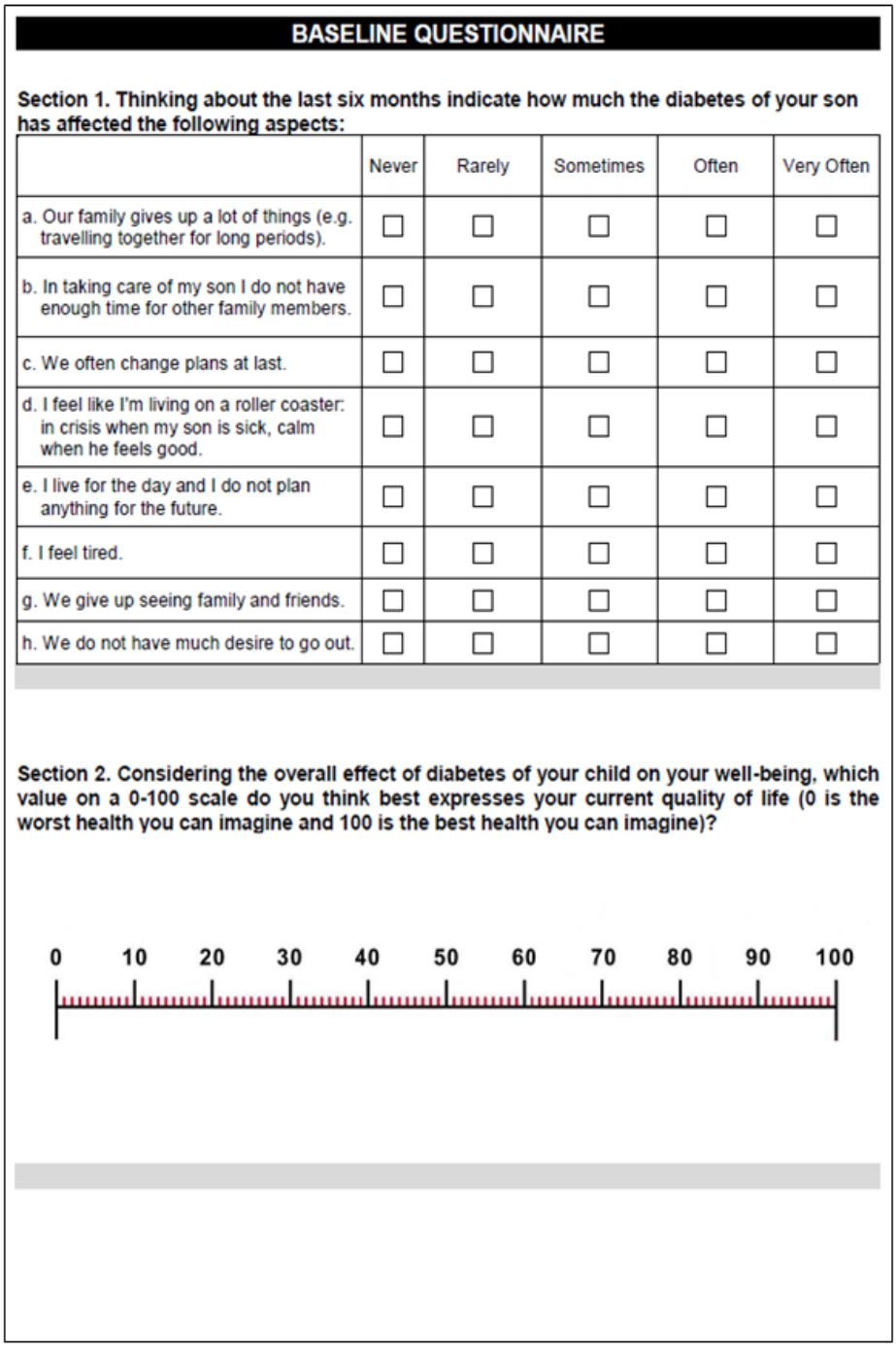
To assess the users' perception of the service, two questionnaires were proposed to the parents attending the camp: a first one just before starting to use the AP system with the associated RM service and a second one after having experimented its use.

The main purpose of the pre-study questionnaire, that is shown in Fig. B.1 and Fig. B.2 and has been partially inspired by a previous work [77], was the definition of a baseline for the feelings related to the daily management of diabetic children and for the impact of the disease on the Perceived Quality of Life (PQL).

The post-study questionnaire, that is shown in Fig. B.3, Fig. B.4 and Fig. B.5 and has been partially inspired by previous works [78, 79], aimed at capturing the parents' perception about the usefulness of the RM service. Besides questions concerning the parents experience and their willingness to use the RM service in the future, the post-study questionnaire also asked parents to consider the responses previously provided in the baseline questionnaire and to revise those affected by the use of the RM service. The *Likert* scaling method [80] was adopted for some of the questions.

3.5.3 Questionnaires Analysis

Questionnaire responses were analyzed using the *R* statistical tool [81]. Center, parents' gender, children's gender and children's age were investigated as explanatory variables of the questionnaires' scores. Kruskal-Wallis and Wilcoxon tests were used to check differences among the groups identified according to the four variables above. In case of a statistically significant analysis of variance, Wilcoxon test was executed on each pair of groups. The analyses were conducted both on the responses provided to each question and on the sum of the responses to questions belonging to the same section. All the possible responses for multiple-choice questions followed the same ordinal scale weighted with a numerical score ranging from 1 (very negative feeling) to



BASELINE QUESTIONNAIRE

Section 1. Thinking about the last six months indicate how much the diabetes of your son has affected the following aspects:

	Never	Rarely	Sometimes	Often	Very Often
a. Our family gives up a lot of things (e.g. travelling together for long periods).	☐	☐	☐	☐	☐
b. In taking care of my son I do not have enough time for other family members.	☐	☐	☐	☐	☐
c. We often change plans at last.	☐	☐	☐	☐	☐
d. I feel like I'm living on a roller coaster: in crisis when my son is sick, calm when he feels good.	☐	☐	☐	☐	☐
e. I live for the day and I do not plan anything for the future.	☐	☐	☐	☐	☐
f. I feel tired.	☐	☐	☐	☐	☐
g. We give up seeing family and friends.	☐	☐	☐	☐	☐
h. We do not have much desire to go out.	☐	☐	☐	☐	☐

Section 2. Considering the overall effect of diabetes of your child on your well-being, which value on a 0-100 scale do you think best expresses your current quality of life (0 is the worst health you can imagine and 100 is the best health you can imagine)?

0 10 20 30 40 50 60 70 80 90 100

Figure 3.6: **Baseline questionnaire in English language administered before using the remote monitoring service (Part 1).**

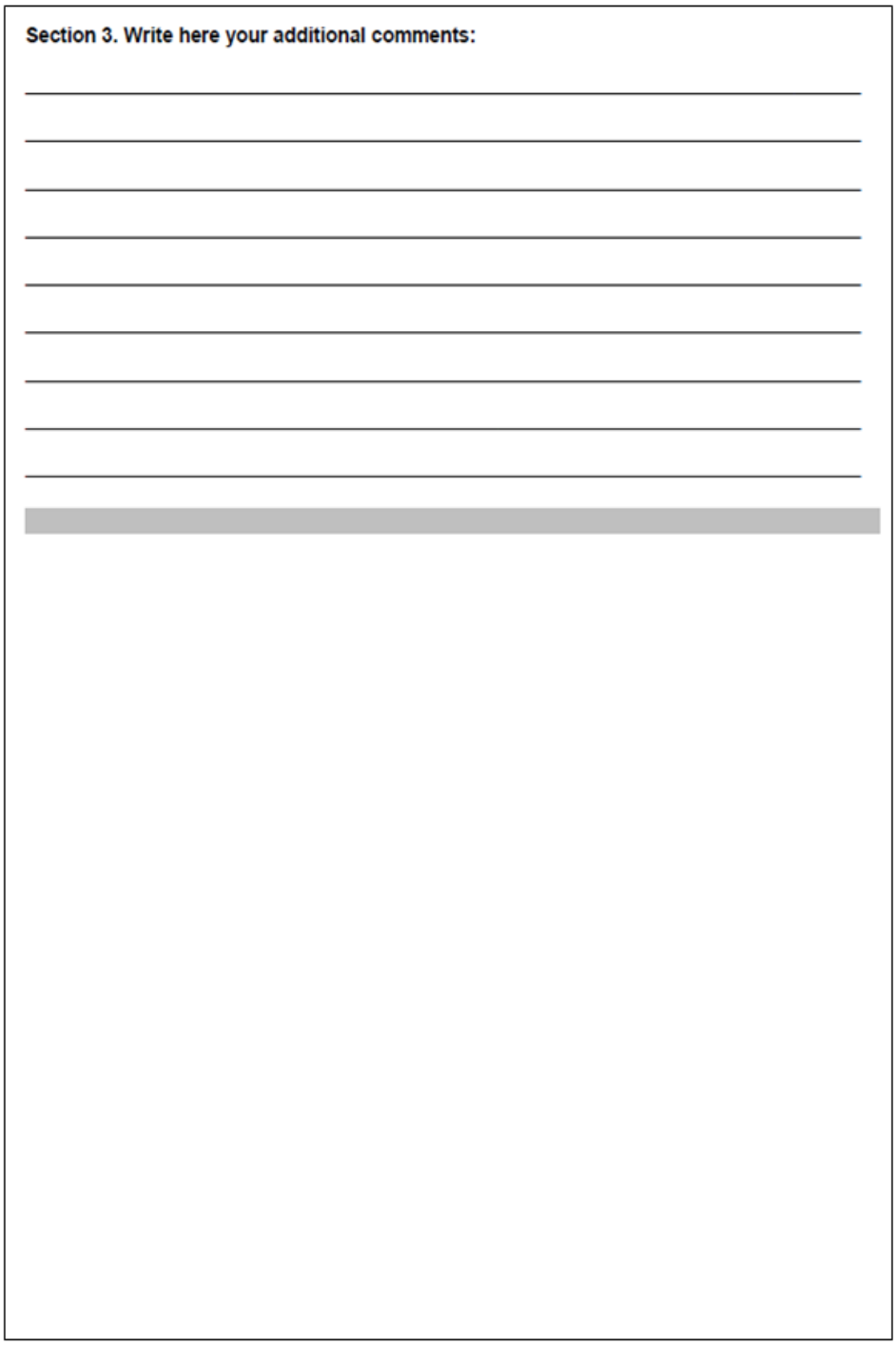
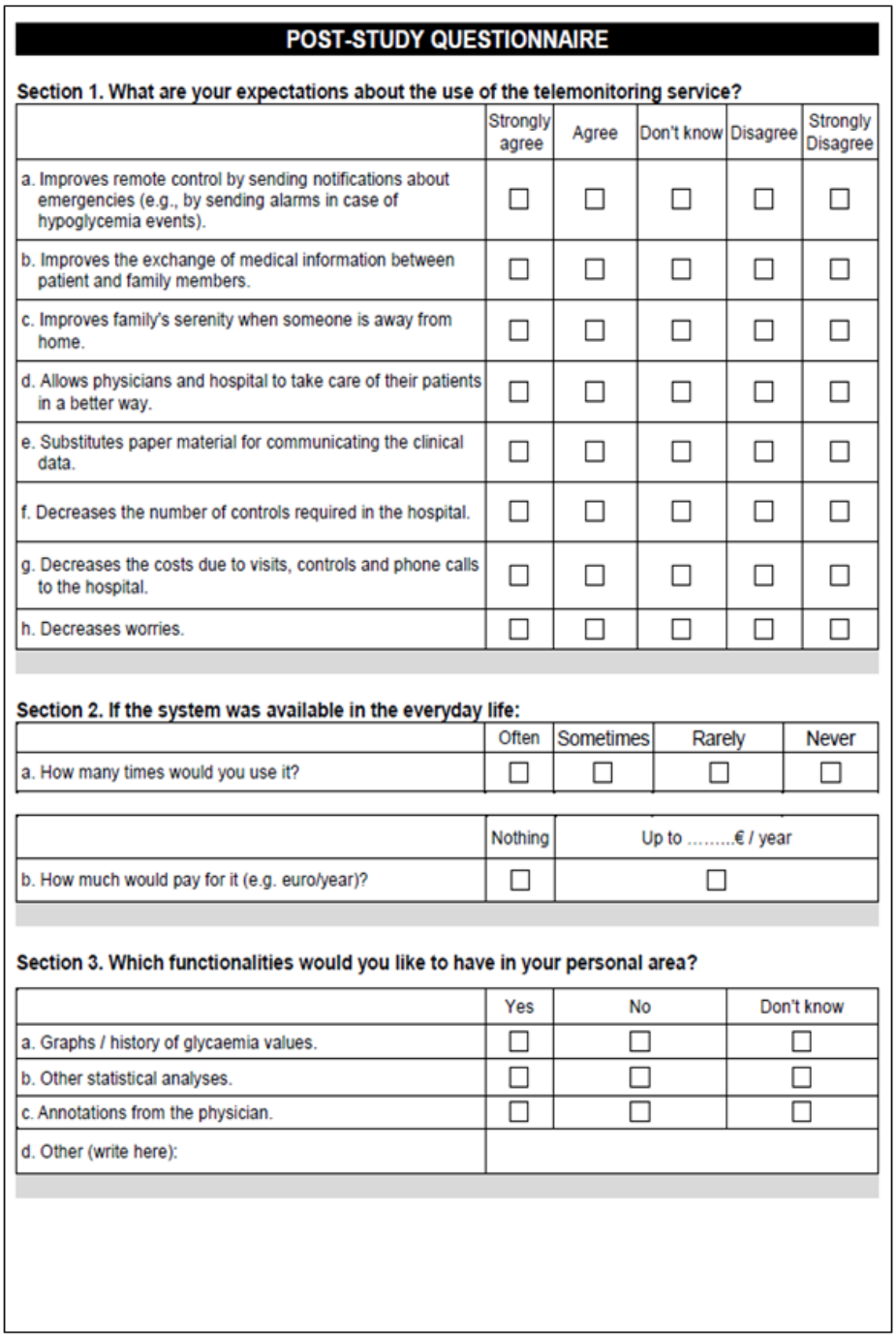


Figure 3.7: **Baseline questionnaire in English language administered before using the remote monitoring service (Part 2).**



POST-STUDY QUESTIONNAIRE

Section 1. What are your expectations about the use of the telemonitoring service?

	Strongly agree	Agree	Don't know	Disagree	Strongly Disagree
a. Improves remote control by sending notifications about emergencies (e.g., by sending alarms in case of hypoglycemia events).	☐	☐	☐	☐	☐
b. Improves the exchange of medical information between patient and family members.	☐	☐	☐	☐	☐
c. Improves family's serenity when someone is away from home.	☐	☐	☐	☐	☐
d. Allows physicians and hospital to take care of their patients in a better way.	☐	☐	☐	☐	☐
e. Substitutes paper material for communicating the clinical data.	☐	☐	☐	☐	☐
f. Decreases the number of controls required in the hospital.	☐	☐	☐	☐	☐
g. Decreases the costs due to visits, controls and phone calls to the hospital.	☐	☐	☐	☐	☐
h. Decreases worries.	☐	☐	☐	☐	☐

Section 2. If the system was available in the everyday life:

	Often	Sometimes	Rarely	Never
a. How many times would you use it?	☐	☐	☐	☐

	Nothing	Up to .....€ / year
b. How much would pay for it (e.g. euro/year)?	☐	☐

Section 3. Which functionalities would you like to have in your personal area?

	Yes	No	Don't know
a. Graphs / history of glycaemia values.	☐	☐	☐
b. Other statistical analyses.	☐	☐	☐
c. Annotations from the physician.	☐	☐	☐
d. Other (write here):			

Figure 3.8: **Post-study questionnaire in English language administered after using the remote monitoring service (Part 1).**

Section 4. Consider the responses provided in the first section of the baseline questionnaire and express whether the telememonitoring service can affect them in a positive, negative or irrelevant way.

	Never	Rarely	Sometimes	Often	Very often	Effect of the system
a. Our family gives up a lot of things (e.g. travelling together for long periods).	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
b. In taking care of my son I do not have enough time for other family members.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
c. We often change plans at last.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
d. I feel like I'm living on a roller coaster: in crisis when my son is sick, calm when he feels good.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
e. I live for the day and I do not plan anything for the future.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
f. I feel tired.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
g. We give up seeing family and friends.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant
h. We do not have much desire to go out.	☐	☐	☐	☐	☐	☐ Improves ☐ Worsens ☐ Irrelevant

Figure 3.9: **Post-study questionnaire in English language administered after using the remote monitoring service (Part 2).**

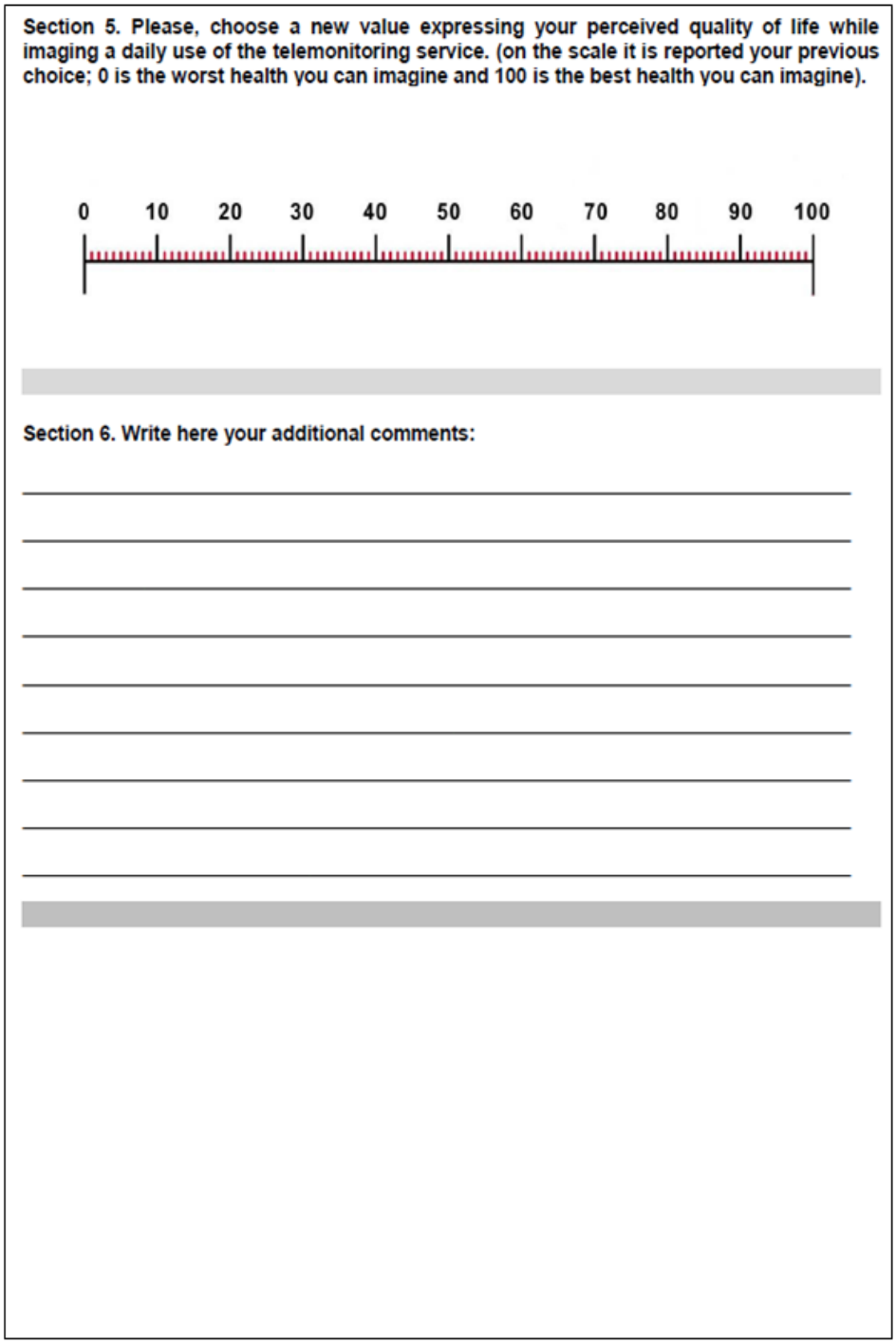


Figure 3.10: **Post-study questionnaire in English language administered after using the remote monitoring service (Part 3).**

5 (very positive feeling). Spearman's correlation analysis was used for identifying the relationship between two numerical variables. Baseline vs. post-study comparisons of numerical values were performed using the Wilcoxon test for paired data. A stepwise multiple regression analysis was used to identify possible independent predictors of PQL.

Finally, the SentiStrength tool [82] was used to analyze free text comments reported in the questionnaires through Sentiment Analysis. This is a branch of text mining dealing with the computational processing of opinion, sentiment, and subjectivity expressed in natural language.

Overall 41 baseline and 38 post-study questionnaires were collected. That difference is due to one child dropping out and some parents of children in the second arm leaving the camp soon after the closed-loop session and before questionnaires administration. Parents were both fathers (n=16) and mothers (n=25) of female (n=11) and male (n=20) diabetic children from five to nine years old (5yrs=3; 6yrs= 4; 7yrs=10; 8yrs=10; 9yrs=4; median=7.5yrs; 1st-3rd quartile=6.98-8.24yrs). Families came from five different locations in Italy: Milano (n=8), Napoli (n=4), Roma (n=3), Torino (n=10) and Verona (n=6).

3.5.4 Baseline Questionnaire Analysis

Section 1 was first analyzed to understand how the parents' life is affected by the disease of their child. Classification of the responses into positive ("Never" or "Rarely") or negative ("Sometimes", "Often", "Very Often") tendencies revealed nearly equal distributions (49% positive tendency; 51% negative tendency). Fig. 3.11 provides a general overview of the positive responses, stratified according to four explanatory variables.

Families coming from different locations seemed to feel different levels of burden, as illustrated in Fig. 3.12. The median score of all questions in Section 1 (encompassing 8 questions totaling [0-40]) varies from 21 in Verona to 32 in Milano and the analysis of variance on the total score showed a p-value of 0.009. Responses provided by fathers and mothers did not show any statistically significant difference. Children's gender also did not affect parents' responses, while children's age turned out to be positively and significantly correlated with the total score of the responses, as shown in Fig. 3.13. Finally, parents pointed out fatigue as one of the most severe consequences of managing diabetes every day, together with the continuous rapid change of their children's health status (questions *1d* and *1f*).

In the second section, parents were asked to rate their PQL on a 0-100

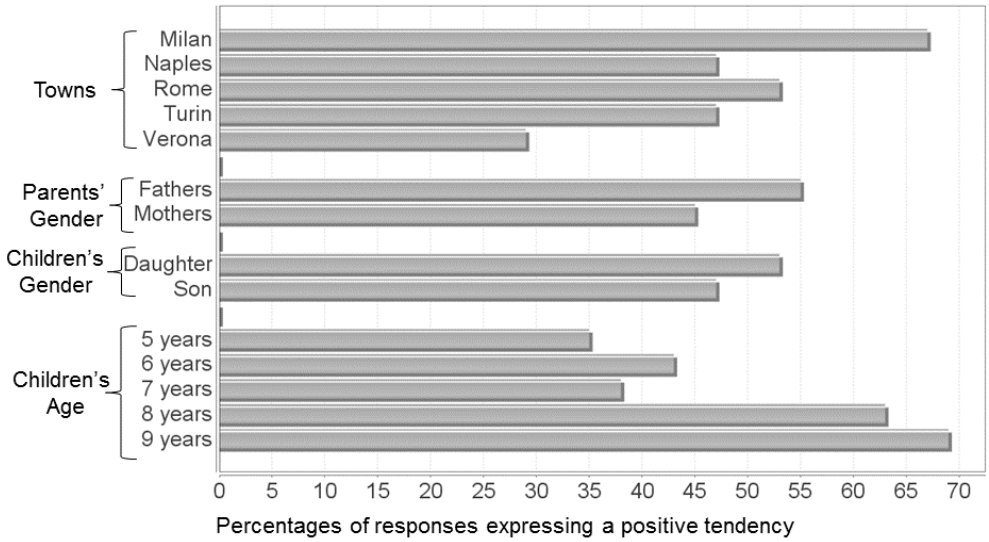


Figure 3.11: Baseline questionnaire, Section 1: percentages of responses expressing a positive tendency (i.e. "Never" or "Rarely") stratified according to explanatory variables.

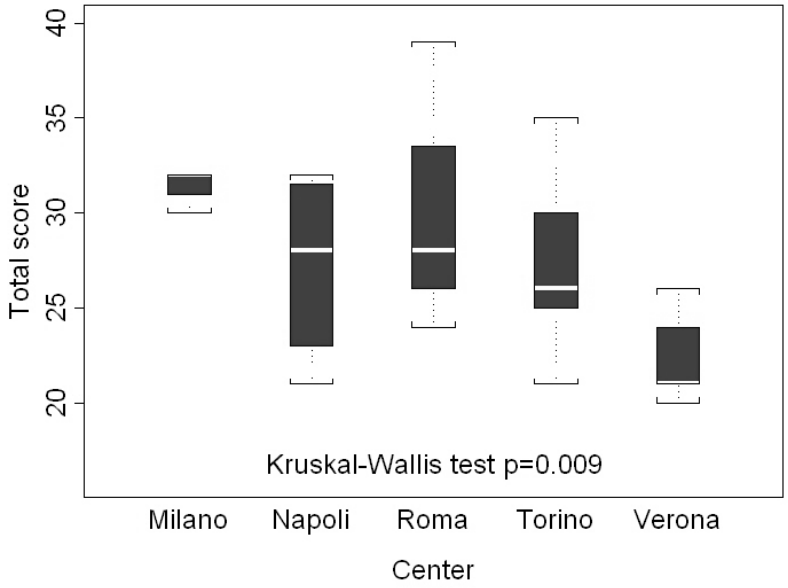


Figure 3.12: Baseline questionnaire, Section 1: total scores according to the five centers.

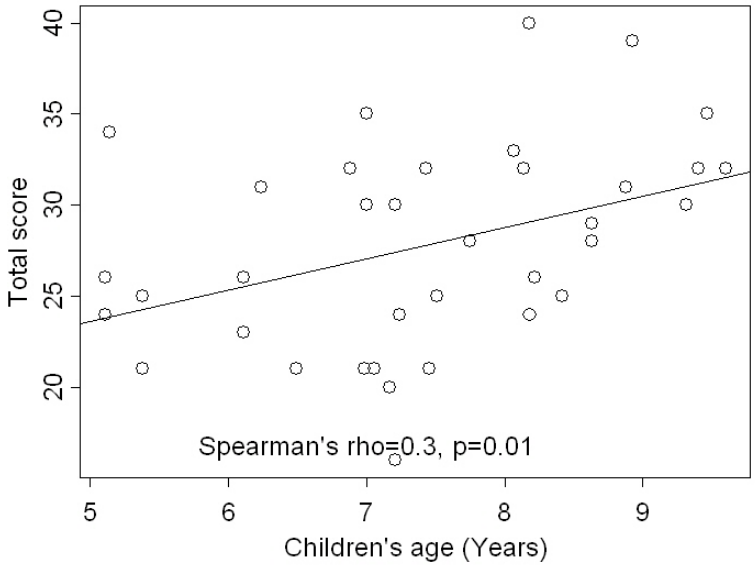


Figure 3.13: Baseline questionnaire, Section 1: correlation between total score and children's age.

scale. The mean PQL value was 64.13 and no statistically significant differences were found among groups. With a borderline statistical significance (p=0.07), fathers showed a more positive attitude with respect to mothers.

At univariate regression analysis, the responses to the following questions were identified as significant predictors of PQL: "Our family gives up a lot of things (e.g. travelling together for long periods)" (*1a*; p-value=0.015), "In taking care of my son I do not have enough time for other family members" (*1b*; p-value=0.008), "I feel like I'm living on a roller coaster: in crisis when my son is sick, calm when he feels good" (*1d*; p-value=0.01), "I feel tired" (*1f*; p-value=0.006) and "We give up seeing family and friends" (*1g*; p-value=0.03). However, a stepwise multiple regression analysis including parents' and children's gender together with children's age, revealed that only "fatigue" and "having a male child" are retained in the model as significant independent aspects that affect PQL (multiple R squared=0.29).

3.5.5 Post-study Questionnaire Analysis

In the first section parents were asked to assess whether RM could improve the communication with the health-care staff. Overall in 85% of the responses they expressed their agreement, in 12% they expressed neutrality and only in 3% they expressed disbelief.

Considering the four explanatory variables, only the children's age seemed to affect parents' responses: the smoothing curve obtained with a locally-weighted polynomial regression in Fig. 3.14 shows higher scores when children enter the school-age.

According to the parents the possible advantages of using the RM are: "Improves remote control by sending notifications about emergencies (e.g., by sending alarms in case of hypoglycemia events)", "Improves the exchange of medical information between patient and family members", "Improves family's serenity when someone is away from home" and "Allows physicians and hospital to take care of their patients in a better way" (median=5, on the ordinal scale 1-5), followed by "Substitutes paper material for communicating the clinical data", "Decreases the costs due to visits, controls and phone calls to the hospital" and "Decreases worries" (median=4) and "Decreases the number of controls required in the hospital" (median=3).

Concerning the willingness to pay, the median value is 200 euro/year, ranging from 0 to 3000 euro/year. Considering the explanatory variables, no statistically significant differences were found, except for the towns (p-value=

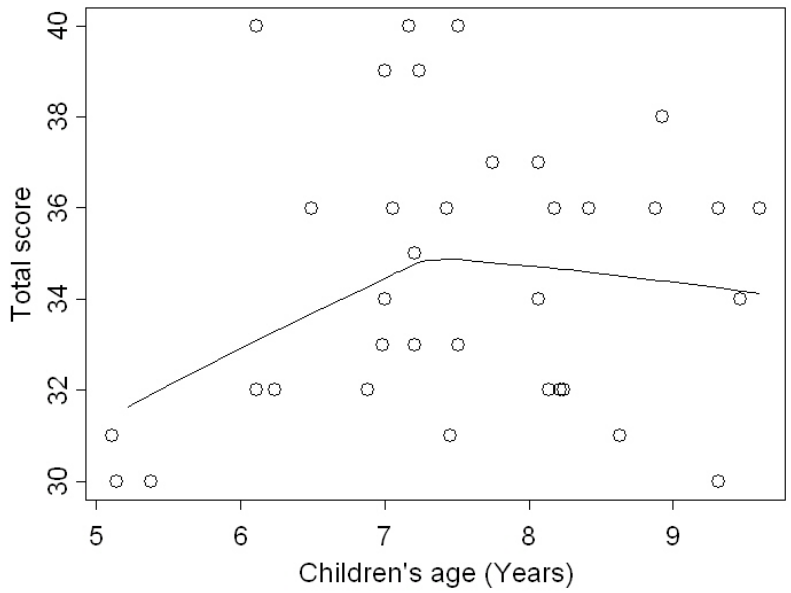


Figure 3.14: Post-study questionnaire, Section 1: total score according to children's age.

0.005), with Verona and Napoli being the locations with the lowest willingness to pay. Independently from the amount of money that parents were willing to pay, all of them expressed their desire to use RM.

The fourth section was focused on understanding which aspect of diabetes management could be improved by the RM. Parents were asked to repeat Section 1 of the baseline questionnaire after experiencing the RM service, indicating if its use could improve, worsen or was irrelevant for each of the 8 items previously answered. None of the parents said that using RM could worsen the management, 49.65% expressed a potential improvement, while 50.35% said that the RM was deemed to have no impact. However, parents' "fatigue", which emerged through the baseline questionnaire as the worst effect of diabetes management, was considered the most improvable item through a daily usage of the RM.

In the last section, the parents were asked again to provide an estimate of their PQL if the RM was regularly available in their daily life. The mean value was 78.39, which was significantly higher than in the baseline questionnaires

(p-value=0.0001).

PQL improvement was significantly correlated with responses to questions "Our family gives up a lot of things (e.g. travelling together for long periods)" (*4a*; p-value=0.01), "We give up seeing family and friends" (*4g*; p-value=0.01) and "We do not have much desire to go out" (*4h*; p-value=0.05). A stepwise multiple regression analysis identified improvements in *4a* and *4g* as the only independent factors positively affecting PQL (multiple R squared=0.32). This is explained by the highest correlation found between questions *4a* and *4h*.

Finally, comparing the sentiment analysis scores achieved by processing the comments in the free text sections in both questionnaires, a significant decrease of negative scores was found (median and quartiles of the difference between positive and negative scores: -1[-2;0] baseline; 1[0.75;2] post-study; p-value=0.028).

3.6 Discussion

Technology presently offers suitable solution to support RM and patient education for managing diseases [83, 84]. The aim of this study was to evaluate how a RM service could help parents of children affected by T1DM in managing the disease, reassuring them and improving their PQL.

Responses provided to the baseline questionnaire gave a general overview of the parents' feeling about diabetes. Studies focusing on the parents' feelings identified three different stressful conditions: (a) low self-efficacy in helping with the disease, (b) the occurrence of hypoglycemia events, and (c) their responsibility in the overall management of diabetes [85]. Moreover, the level of responsibility of family members, and the burden of their stress, is inversely related to the child's age, since the younger the patient is, the more attention he requires. This was confirmed by the results of the analysis, since parents of young children actually declared a more negative attitude in coping with diabetes. The borderline result about the more positive attitude of fathers with respect to mothers is in line with other studies [86], possibly suggesting that fathers are less emotionally involved since they are usually busier and spend more time outside.

Besides acquiring the baseline of parents' feelings before the intervention, an outcome for measuring the users' perception of the RM had to be selected. A previous review concerning RM systems identified the following possible outcomes: BGL monitoring, improvements in glycemic control, patient satis-

faction and improvements in self-management [87]. The parents' satisfaction was selected as the main outcome for evaluating the RM considering that those are responsible for enacting the children's treatment. BGL monitoring and glycemic control were discarded as they were the primary outcomes of the underlying clinical trial, the goal of which was to assess the efficacy of an AP running in closed-loop in comparison with the manually controlled therapy. Even self-management was unsuitable since the therapy was managed by the AP and closely supervised by the clinical and bioengineering staff. The parents' satisfaction was assessed through the administration of a post-study questionnaire as already done in previous studies [88, 89, 90].

Results showed that most of the parents believed in a possible improvement for what concerns the interaction with the healthcare staff, while half of them also believed on an enhancement in their personal serenity. Neutrality and disbelief also conveyed some skepticism about the possible reduction in control visits and their associated costs. This may be due to the increased serenity felt by parents if children are visited face-to-face. The parents of the oldest children appreciated RM more than others. The reason may be found in the greater wish of independence and self-management shown by grown-up children, and by the consequent need for parents to find an alternative way to stay updated with their children's status without being too obtrusive [87]. This is supported by responses indicating that parents were highly confident about the support provided by RM to the family own serenity when children are away. Moreover, a correlation between the appreciation of the RM shown by the parents and the school age was found. As a matter of fact, in Italy education starts when children are 6 years old, and as soon as children start going to school they also begin to use the technology (e.g. smartphone apps) as a means of staying in touch with the family. This in turn leads parents to better appreciate the RM potential for reporting on the disease status of their children, highlighting the advantages of the service.

To sum up, despite this study highlighted some skepticism about the usefulness of the RM service by some parents, it also showed their interest in using it as a means of improving the management of T1DM and the communication with the health-care staff. The interest in the service was also emphasized by the responses of 61% of the parents willing to pay a fee for it. Given that the Italian national healthcare service grants most services for free, this is an indirect proof of the perceived usefulness of the RM. The parents' positive attitude towards the RM matches their satisfaction and confidence in the AP technology, as emerged from a specific investigation performed through the

administration of questionnaires and structured interviews during the same camp [91].

Finally, the main limitation affecting the study is that parents were provided with the RM for a very short period of time in an unusual context of use, such as a clinical trial performed at a resort village. Due to this limitation, the perceived usefulness measured during this trial may not be directly correlated with the actual one. Thus a next step could envision extending the RM use over a longer time frame, as in a home trial, to test the system in a context closer to the real life exploiting electronic means for questionnaire administration [55].

3.7 Scientific Achievements

The contents described in this chapter were published in the following peer-reviewed international and national journals, and presented in the following peer-reviewed international conferences:

- S. Del Favero, F. Boscari, M. Messori, I. Rabbone, R. Bonfanti, A. Sabbion, D. Iafusco, R. Schiaffini, R. Visentin, R. Calore, Y. Leal Moncada, S. Galasso, A. Galderisi, V. Vallone, F. Di Palma, **E. Losiouk**, G. Lanzola, D. Tinti, A. Rigamonti, M. Marigliano, A. Zanfardino, N. Rapini , A. Avogaro, D. Chernavvsky, L. Magni, C. Cobelli, D. Bruttomesso. Randomized summer camp crossover trial in 5- to 9-year-old children: outpatient wearable artificial pancreas is feasible and safe, *Diabetes Care*, 2016; 39(7):1180-1185;

- A. Troncone, R. Bonfanti, D. Iafusco, I. Rabbone, A. Sabbion, R. Schiaffini, A. Galderisi, M. Marigliano, N. Rapini, A. Rigamonti, D. Tinti, V. Vallone, A. Zanfardino, F. Boscari, S. Del Favero, S. Galasso, G. Lanzola, M. Messori, F. Di Palma, R. Visentin, R. Calore, Y. Leal, L. Magni, **E. Losiouk**, D. Chernavvsky, S. Quaglini, C. Cobelli, D. Bruttomesso, Evaluating the experience of children with type 1 diabetes and their parents taking part in an artificial pancreas clinical trial over multiple days in a diabetes camp setting, *Diabetes Care*, 2016, 39(12): 2158-2164;

- **E. Losiouk**, G. Lanzola, S. Del Favero, F. Boscari, M. Messori, I. Rabbone, R. Bonfanti, A. Sabbion, D. Iafusco, R. Schiaffini, R. Visentin, S. Galasso, F. Di Palma, D. Chernavvsky, L. Magni, C. Cobelli, D. Bruttomesso, S. Quaglini, Parental Evaluation of a Telemonitoring Service for

Children with Type 1 Diabetes, *Journal of Telemedicine and Telecare*, 2017, 1357633X17695172;

- G. Lanzola, **E. Losiouk**, S. Del Favero, A. Facchinetti, A. Galderisi, S. Quaglini, L. Magni, and C. Cobelli, Remote Blood Glucose Monitoring in mHealth Scenarios: A Review, *Special Issue for Sensors, Sensors*, 2016, 16(12), 1983;

- F. Boscari,S. Del Favero, M. Messori, I. Rabbone, R. Bonfanti, A. Sabbion, D. Iafusco, R. Schiaffini, R. Visentin, R. Calore, Y. Leal, S. Galasso, A. Galderisi, V. Vallone, F. Di Palma, **E. Losiouk**, G. Lanzola, D. Tinti, A. Rigamonti, M. Marigliano, A. Zanfardino, N. Rapini, A. Avogaro, D. Chernavvsky, L. Magni, C. Cobelli, D. Bruttomesso, Il Pancreas artificiale in eta' pediatrica: prima esperienza italiana, *Giornale Italiano di Diabetologia e Metabolismo (GIDM)*, 2016, 36(3): 125-133;

- **E. Losiouk**, G. Lanzola, R. Bonfanti, D. Iafusco, I. Rabbone, A. Sabbion, R. Schiaffini, A. Galderisi, M. Marigliano, N. Rapini, A. Rigamonti, D. Tinti, V. Vallone, A. Zanfardino, F. Boscari, S. Galasso, A., Troncone, S. Del Favero, R. Visentin, R. Calore, M.Y. Leal, F. Di Palma, M. Messori, D. Chernavvsky, L. Magni, D. Bruttomesso, S. Quaglini, C. Cobelli, Perceived utility of a remote monitoring system for pediatric subjects affected by type 1 diabetes in PEDarPAN (PEDiatrics artificial PANcreas) summer camp, *Proceedings of Advanced Technologies & Treatments for Diabetes 2016*;

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- S. Del Favero, F. Boscari, M. Messori, I. Rabbone, R. Bonfanti, A. Sabbion, D. Iafusco, R. Schiaffini, R. Visentin, R. Calore, Y. Leal, S. Galasso, A. Galderisi, V. Vallone, F. Di Palma, **E. Losiouk**, G. Lanzola, D. Tinti, A. Rigamonti, M. Marigliano, A. Zanfardino, N. Rapini, A. Avogaro, D.

Chernavvsky, L. Magni, C. Cobelli, D. Bruttomesso, Multi-center randomized cross-over italian pediatric summer camp: AP vs SAP in 5-9 year old children, *Proceedings of Advanced Technologies & Treatments for Diabetes 2016*.

Chapter 4

Mobile Health Applications for Real-Time Remote Monitoring Supporting Decisions on the Physician Side

The project described in this chapter still refers to the *Remote Monitoring mHealth* context, but this time addresses the development of a RM system with the decision support component on the physician side, instead of the patient one, as it has been described in the previous chapter.

The project started thanks to a close collaboration with a medical research group working at the University Hospital of Padova that proved the clinical benefits of introducing a CGM system for preterm newborns hospitalized in the Neonatal Intensive Care Unit (NICU). As a matter of fact, glucose concentration in blood, better known as glycemia, is a very underestimated physiological parameter in NICUs. Its value is currently monitored by performing few measurements per day, acquired through heel pricks or arterial samplings. Unfortunately, the frequency of those samplings is quite low in preterm newborns, who are Very Low Birth Weight Infants (VLBWIs), due to their fragility. As a result, hyper- or hypo-glycemia events occurring between two separate measurements remain often unnoticed. Even with the adoption of a CGM system glucose, data are still sampled through individual devices that are not integrated into a central monitoring system. Thus, the healthcare staff had to regularly visit the cradles, watch the glycemia trends and pay

attention to alarms. The aim of the project deals with the implementation of a system, based on mobile technologies, that sends the data acquired through commercial glucometers to a central database, so that they become available in real-time for the staff in the ward room. Moreover, in the RM system an algorithm, described in the literature for recommending the most appropriate glucose infusion rates based on the last readings of the patient, was introduced supporting the staff in deciding the dose and reducing errors.

The dimensions describing the mobile app developed, called *Neokid*, are the following ones:

- *App Distribution*= manual installation: given the specificity of the communication between the *Neokid* app and the external device and also considering the legal issues introduced by storing the patients data in a server located at the University of Pavia, the app was manually installed only on the devices used in the clinical trials;

- *Target Users*= physician;

- *Data Acquisition*= automated: *Neokid* automatically collects data from the sensor exploiting the *Bluetooth Low Energy* (BLE) communication channel;

- *Data Analysis*= remote: the main purpose of *Neokid* is data collection and consequently data transmission towards a remote server. For this reason, no data evaluation or analysis was developed on the mobile component;

- *Data Storage*= temporary DB: since data are acquired every 5 minutes and the database fills very fast, it needs to be frequently flushed, just after the data have been sent to the remote server;

- *Data Synchronization*= high frequency: to support the real-time remote visualization feature data need to be sent with a high frequency (e.g. every 5 minutes);

- *App Working Mode*= background: besides few screens for the app configuration, *Neokid* always works in background, collecting data from the sensor;

- *App Update Policy*= manual reinstallation: the choice towards the manual installation also affects further updates of the same app, that require therefore the manual reinstallation on all the devices equipped with *Neokid*.

4.1 Introduction

The *Remote Monitoring* context in *mHealth* is very huge and systems belonging to it can assume different configurations, that vary according to the target disease and to the purpose addressed. In the previous chapter, the systems that have been considered aim at supporting both the real-time RM and the decision support on the patient side to increase the level of patient empowerment in managing his chronic disease. However, another interesting application of RM systems regards the improvement of the daily workload which members of the health-care staff have to cope with. More specifically, those systems can allow to oversee the patient health status from a remote location, securely collect all his/her data, identify the overall patient trend and, in some cases, even include some kind of decision support to simplify and standardize the action of the staff.

Examples of systems that mainly address the disease management from the physician side instead of the patient side are available in the scientific literature. Among those Leu et al. [92] developed a smart shirt containing several body sensors that acquire physiological data from the patient while he is wearing it. The data collected are continuously sent to a smartphone, which is responsible for their transferring towards a remote server. Then, they are analyzed and stored so that physicians can access to the same data and see the warning messages concerning the dangerous conditions that need to be promptly solved.

Another different project is Lifephone [93], which was partially supported by the *Vodafone Foundation Italy* in the years 2006-2007. The aim of the project was to help the self management of uremic patients that were cared for renal failure at a regional hospital in Northern Italy, undergoing peritoneal dialysis as a treatment. Renal failure is a complication of diabetes that irreversibly prevents the accomplishment of essential kidney functions such as filtering waste products from blood and balancing the body fluids. Peritoneal dialysis foresees filling the abdominal cavity of the patient at least 3 times per day with a suitable solution as a way of purifying blood through osmosis. The

treatment requires a continued and strict monitoring of blood pressure and weight to prevent over- or under-hydration that may eventually lead to stroke or cardiac failure. Since the treatment is managed by the patient, the clinical staff should regularly oversee it, to undertake corrective actions whenever they are needed. A RM app was designed running on a smartphone that acquired readings from a scale and a sphygmomanometer through the *Bluetooth* communication channel. The smarpthone relayed those data to a server where they became available for the physician's perusal through a web app. The service included compliance monitoring aids for the patient, in terms of notifications on the smartphone, reminding him to take measurements at scheduled times. Alerts were provided, instead, for the physician, notifying the onset of hazardous situations that needed to be acknowledged.

4.2 Motivation of the Study

The usual setting of a monitoring room in a NICU includes multiple cradles where VLBWIs are lying, connected to different sensors and to a glucose infusion pump. VLBWI parameters and signals are displayed on a single monitor located next to the cradle. The sampled signals usually include: cardiac frequency, oxygen saturation and blood pressure. The same monitor may also trigger alarms whenever dangerous conditions occur, in order to draw the attention of the staff.

Another physiological parameter monitored in a NICU is the glucose concentration in blood, which is assessed performing multiple arterial samplings or heel pricks during the day. However, the fragility of VLBWIs greatly reduces the number of samples that are acquired per day with respect to adult patients. The administration of blood glucose is accomplished according to the therapeutic schema, and relies on the feedback provided by those readings. However, due to the reduced number of samples, it runs in open-loop for most of the time, possibly giving rise to dangerous situations. As a matter of fact, hyper- or hypo-glycemia events may occur between two measured samples without being detected. Those are two significantly risky conditions that have been proved to be particularly dangerous in VLBWIs. Hyperglycemia has been associated to an increased mortality and morbidity [94, 95], while hypoglycemia is considered to be connected with future neurological impairments [96] that are observed only later during the child growth.

The adoption of a CGM system would definitely solve the problem of un-

detected events and also reduce the pain suffered by VBLWIs because of the acquisition of the glucose samples. As a matter of fact, a CGM sensor lasts for several days during which it remains positioned on the skin safely fastened by band-aids. Thus, the pain is only experienced when the sensor is applied or removed. Moreover, a CGM sensor is able to automatically acquire samples nearly every 5 minutes therefore providing a continuous stream of data that enable a more accurate delivery of the therapy. Despite some skepticism about the use of CGM in intensive care [97, 98], Beardsall et al. [99] pointed out that the real benefit of adopting a CGM system also in intensive care is providing "continuous information regarding trends in glucose levels".

A recent study conducted at the NICU of the University Hospital of Padova, in Italy, proved the effectiveness of adopting a CGM system in the intensive care [100]. The authors compared the standard therapy, based on multiple heel pricks distributed over time and a continuous glucose infusion, with a new therapy based on a CGM system coupled with a computer-based algorithm for glucose infusion rate (GIR) adjustments [101]. The results of that comparison show that the new approach increases the time spent by VLBWIs in tight glycemic range during their first week of life, avoiding both hypo- and hyperglycemia and reducing glucose variability.

Despite the clinical achievement, the health-care staff of the NICU in Padova was overburdened by the additional tasks introduced by this change. The chosen CGM system was the *Dexcom G4 PLATINUM with Share* (DEXG4), by *Dexcom Inc.*(San Diego, CA), encompassing two components: the Dexcom sensor applied on the VLBWI's thigh and the Dexcom Receiver (DR). This is a small portable handheld unit, with a size comparable to that of a smartphone, displaying the data acquired by the sensor and triggering alarms in case of dangerous values.

The DEXG4 has been clearly designed for adult patients, or at most for young ones, that always keep the DR with them and use it for regularly checking their glycemia values and trends. In the case of VLBWIs, the task of monitoring glycemia values was accomplished, instead, by the health-care staff, that needed to look at each VLBWI's DR. Unfortunately, the low transmission range of the network component used by the sensor for sending data to its matching DR requires that the two components remain close to each other. This restriction prevented the health-care staff from bringing all the DRs into the NICU monitoring room for visualizing the data of all the patients at a glance or hearing the alarms.

The second additional task was connected with running the algorithm for

GIR calculation. This was provided in an Excel file where the physicians had to manually enter each time the last glycemia values observed on the DR in order to obtain the proper GIR suggestion. Since there was no computer close to the cradles where VLBWIs were treated, the physicians had to manually record the values for each one of them on a paper form, bring it to the monitoring room, and eventually enter those values into the Excel file to finally get the GIR. Besides the inherently associated burden, this workflow was also subject to possible mistakes in a highly event driven location such as a NICU.

Finally, the data were available only locally on each separate DR. Thus, for the accomplishment of any research requiring the availability of any data, or even for documental purposes, the health-care staff had to remove the DR from the cradle, bring it into a separate room where a computer was available, and manually download the data using the Dexcom dedicated program.

The contribution of this work concerns the development of a RM service through which the health-care staff was able to oversee the glycemia values of multiple VLBWIs in real-time and automatically receive regular GIR suggestions as well. Compared to previous RM services adopted at NICU settings, this system is the first one able to support both real-time visualization of data from a remote location and suggest the proper GIR treatment, personalized for each patient, based on those data.

4.3 Related Work

The comparison with previous RMs used in a NICU setting was performed looking for scientific works published after 2010. The reason for setting this limitation to the search in the past is due to the lack of biomedical sensors able to operate in CGM mode before that time, as well as to the lack of ICT solutions supporting our use case [102]. In fact, the small size of a VLBWI's thigh inherently requires a miniaturized sensor separated from the DR that, besides displaying the actual data, should also allow forwarding those data to an external equipment through wired (e.g. *USB*) or wireless (e.g. BLE) connections.

During the past years many RMs have been adopted in NICU settings, but their technology was mainly intended to provide remote consultations with the experts. Quite surprisingly, no works either involving the direct transmission of data coming from a patient's sensor or addressing the specific issue of glycemia monitoring were found. This is in line with the remarks of the clinicians

participating to this study, complaining that so far there is no commercial solution able to centralize the monitoring of glycemia in a clinical setting. A selection of the most common uses of RMs in a NICU setting referenced in the literature is provided below:

- Retinopathy of prematurity: it is considered one of the leading cause of blindness in the world. Thus, the reduction of the time required for its diagnosis and starting the associated treatment is highly important. RMs have been used in this context to provide the remote consultation with medical experts [103, 104];
- Reduction of the number of visits after discharge: in addition to the standard follow-up appointments, families have been offered RMs to have video calls with the health-care staff from their homes [105];
- Neonatal resuscitation: in order to increase the effectiveness of low-risk birth centers, RMs have been introduced to provide remote consultations with medical experts [106];
- Emotional support for families: RMs have been introduced to provide real-time video images of VLBWIs to their families at home [107].

4.4 Methods

The main challenge was to develop a system able to support both the real-time data monitoring from a remote location and the automatic calculation of GIR suggestions. As an additional challenge, when the clinical team was joined, both the clinical context and the biomedical technologies had already been chosen, and the trial was just about to start. More specifically, the clinical study was scheduled at the NICU of Padova Hospital, the formula for the GIR calculation was the one developed by Steil et al. [101] and the CGM system was the DEXG4.

The identified requirements for the RM service were the following ones:

- Automatic data collection: VLBWIs' values were automatically read from a DR and visualized on the remote component;
- Real-time data visualization: the health-care staff was able to see patients' values on the remote component in real-time, with a reasonable delay caused by the DR time cycle for sending out data;

- Calculation of GIR suggestions: the remote component showed the automatically calculated GIR suggestions;
- Alarms triggered in case of dangerous events;
- Manual insertion of additional events, not traced by the DR: VLBWIs might experience some clinical episodes that were not detected by the DR, but that could be correlated with the glycemia trend. The healthcare staff could keep track of those events by manually inserting them into the remote component.

After analysing the requirements and the setting of the NICU in Padova, the need for a new component, in addition to the remote one, was identified: an Android Mobile Application (AMA) dedicated to data acquisition from the DR and to data transmission towards a remote server. Reasons behind this decision can be found in the need of having a device equipped with both BLE, for communicating with the DR, and network connectivity, for sending data towards the server. Mobile devices running at least the 5.0 version of the Android OS support both those functionalities at a very competitive price if compared with the purchase of a dedicated hardware that needed to be assembled and customized by ourselves.

The AMA was designed with these three main features: connection to the DR in order to acquire data using the BLE channel; data synchronization towards a remote server; data temporarily saved in a local buffer to prevent data loss in case of network connectivity problems.

The data transmission based on the BLE channel involves at least two components: a peripheral device and a central device. Before starting the communication with a specific device, the peripheral one works in advertising mode and broadcasts an advertising message to all the nearby devices supporting BLE. If one of those wants to communicate, it sends a request and, after the authentication phase, a new connection is established. The peripheral device then stops being in advertising mode and prevents other devices from seeing it. At this point, the peripheral device works as a *GATT server*, while the central one as a *GATT client*, that always starts a transaction towards the server sending requests and waiting for responses. GATT, which means Generic ATTribute profile, is a data protocol used by BLE devices for exchanging messages. In each GATT transaction data are organized in services and characteristics so that each service contains multiple characteristics and each characteristic contains real data.

Fig. 4.1 shows all the components of the AMA, plus the *GATT server* exposed by the DR. Those components are connected with arrows that describe the direction of the data flow or of the communication between them. As a peripheral device, the DR exposes a *GATT Server* interacting with a customized *BluetoothGattCallback*, that contains the names of services and characteristics specific for the DR. When the *GATT server* answers to a previous query, the packaged data are sent to the *Dexcom Processor*, that is responsible for unpacking the data and forwards them to the *Data Observer*. This adjusts the data according to the model and, finally, saves them into the *Local Database* of the AMA. In the same time, an *Android Service* is running and periodically verifies whether the connection with the DR is still alive and forces the *Telemedicine Processor* to transmit the local data towards the *Remote Server* through the *Synchro Service* component.

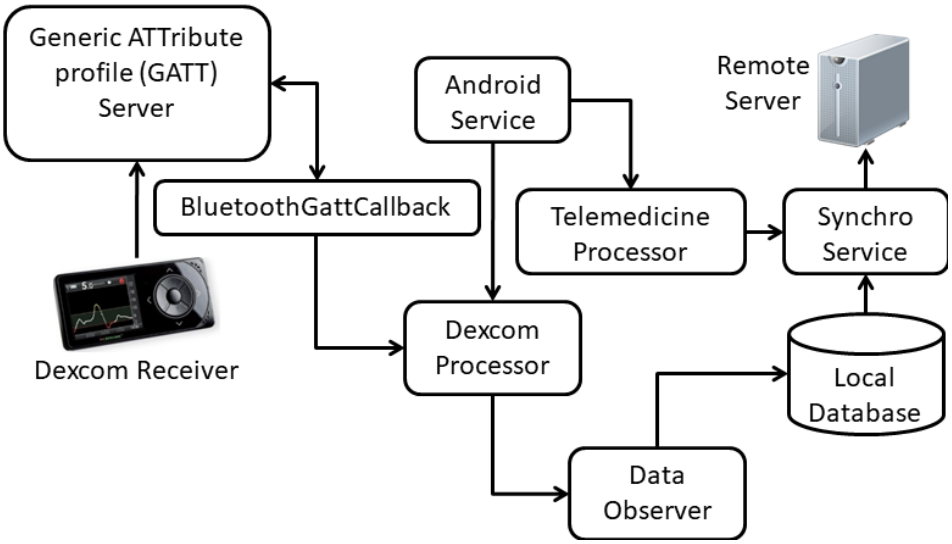


Figure 4.1: **The software modules composing the Android mobile application.**

Concerning the second component, the one dedicated to the real-time and remote data visualization, a web app was considered more appropriate to guarantee a full accessibility regardless of the device or the OS of the device used to access it. As a matter of fact, every computer and mobile device, such as a smartphone or a tablet, can support a browser able to render web contents. More specifically, the same RM service described in the previous chapter was

chosen to be used also in this study because it already supported some useful features, such as the real-time visualization or the overview of all patients' health status. However, some updates were still needed in order to fully satisfy each requirement: the configuration of an account for the hospital of Padova, the implementation of the algorithm for GIR suggestions and the support for the manual insertion of specific events.

The first task concerns modeling the database of the RM service, which considers both patients and physicians as final users of the service and associates each one of them to a hospital center. Regardless of the hospital, patients can always see only their own data, while physicians can have a general overview of all patients' health status. However, patients and physicians belonging to different hospital centers can see different views. Supporting the clinical trial in the NICU of Padova required setting up a new hospital center, associating to it all its physicians and patients, and defining the views to be provided.

Considering the algorithm for GIR suggestions, the implementation provided in the Excel file to the health-care staff of the NICU was first analyzed and then developed in Java code in order to make it compatible with the framework used to realize the RM service.

Finally, since the RM service already supported the insertion of manual events into the database, its model was extended to support the new defined events. The tables defined in the database model responsible for the representation of patient's data are the following ones:

- *DataPoint*: for measurements concerning the patient (blood glucose, blood glucose calibration, CGM value, etc) or contextual parameters (age, patient id, sex, weight, height, etc.);
- *DataRange*: for measurements (physical activity, meal, etc) or parameters (basal, correction factor, etc) having both a starting and stopping time;
- *Event*: for remarkable events concerning the patient's conditions (hypo- or hyper-glycemia risks), remote equipment operations (starting session, stopping session, etc), notifications or logs.

For the NICU setting the *Event* table was extended to support the following events: intraventricular hemorrhage, acidosis, pneumothorax and painful procedures.

The final architecture is shown in Fig. 4.2. The data flow starts from the *Dexcom Sensor* that acquires glycemia values from the *Preterm Newborn*

and sends those to its paired *Dexcom Receiver*. Then the *Android Mobile Application* works as a bridge between the *Dexcom Receiver*, located next to the cradle, and the *Remote Server*. Finally, the synchronized data are provided to the *Health-Care Staff* through a *Web Application* visible on any portable device or PC. The chosen configuration requires to have a single device, running the AMA, for each patient enrolled in the clinical trial.

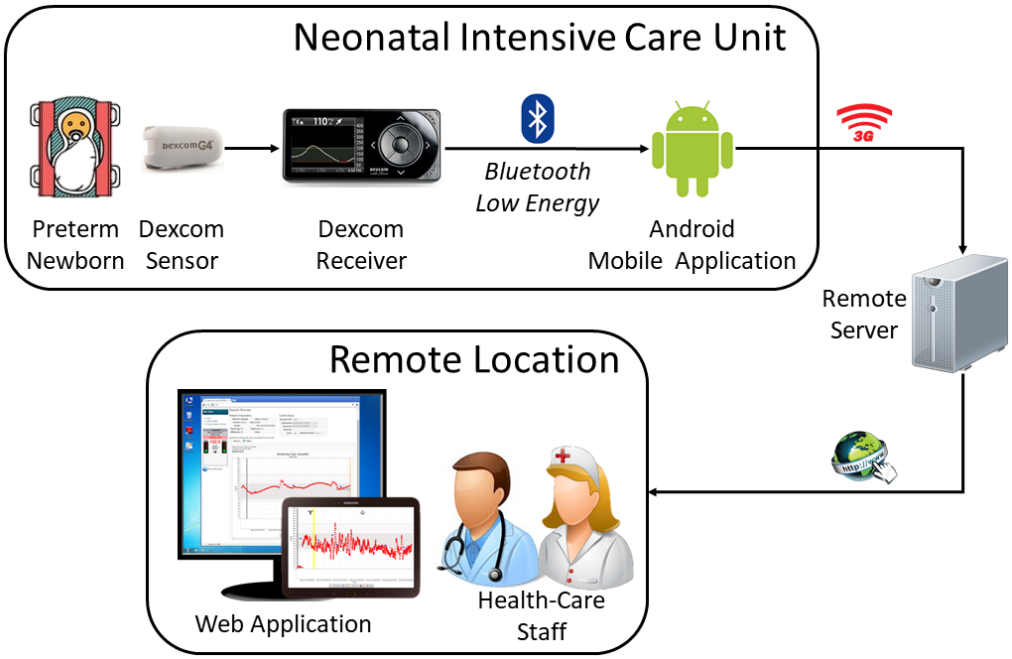


Figure 4.2: **The remote monitoring service architecture.**

4.5 Results

The screens of the AMA, which is called *NeoKid*, are shown in Fig. 4.3: the main one is provided in Fig. 4.3(a), while those used for the configuration are shown in Fig. 4.3(b). The configuration process is performed during the patient's enrollment and involves three different interfaces: the link towards a DR, the link towards the remote server and the patient's profile. The establishment of a connection with an external device is accomplished after scanning all the nearby devices supporting BLE, sending a pairing request to the chosen

DR and, finally, completing the authentication attempt through the validation of the DR's serial number. The configuration of a connection to the remote server requires the complete URL of the repository and the credentials of the synchronization account. Finally, the patient's configuration involves a numerical identifier and, optionally, the patient's name and surname. For privacy reasons those data were not provided during the clinical trial and patients were identified only with numbers.

Once the configuration phase is completed, *NeoKid* can keep running, providing information about the data acquisition and data transmission status. As shown in Fig. 4.3(a), its main screen displays the time and value of both the last glycemia and calibration measurements acquired from the DR. Moreover, in the upper part of the screen, on the *ActionBar*, two icons provide a visual feedback on the connection towards the DR and the remote server.

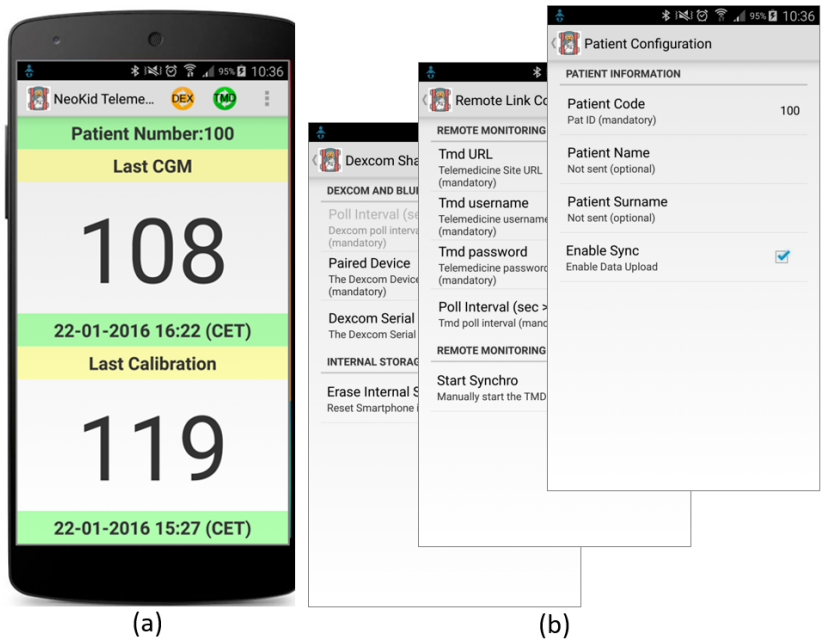


Figure 4.3: Screens of the *NeoKid* mobile application.

The most important views of the RM service are shown in the following figures: the overview panel in Fig. 4.4, the detailed panel in Fig. 4.5 and, finally, the panel containing GIR suggestions in Fig. 4.6.

The first one is the overview panel already described in the previous chapter, which provides a general overview of the health status of all the patients

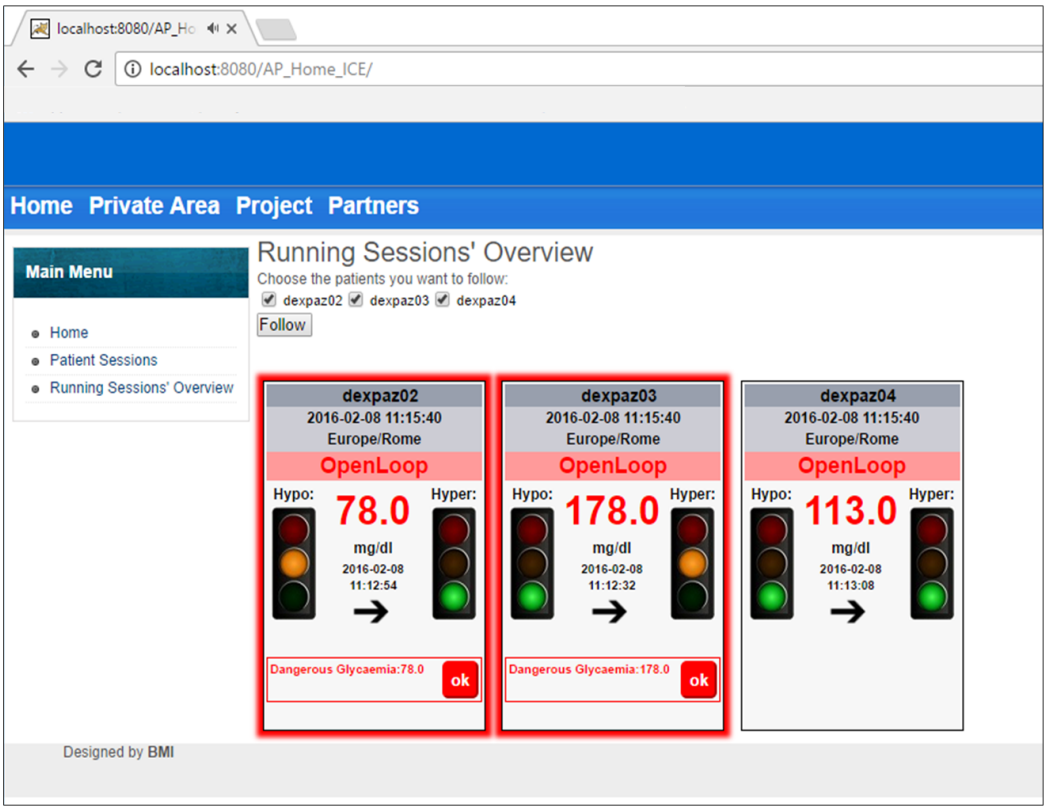
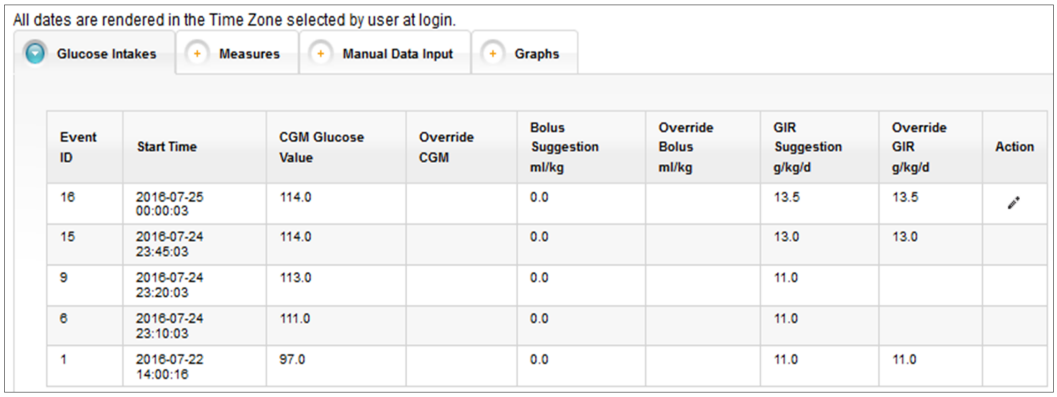


Figure 4.4: The overview panel of the remote monitoring service.

Figure 4.5: The detailed panel of the remote monitoring service.



Event ID	Start Time	CGM Glucose Value	Override CGM	Bolus Suggestion ml/kg	Override Bolus ml/kg	GIR Suggestion g/kg/d	Override GIR g/kg/d	Action
16	2016-07-25 00:00:03	114.0		0.0		13.5	13.5	
15	2016-07-24 23:45:03	114.0		0.0		13.0	13.0	
9	2016-07-24 23:20:03	113.0		0.0		11.0		
6	2016-07-24 23:10:03	111.0		0.0		11.0		
1	2016-07-22 14:00:16	97.0		0.0		11.0	11.0	

Figure 4.6: The panel containing glucose infusion rates suggestions of the remote monitoring service.

currently involved in the clinical trial. For each one of those, a small panel shows the last glycemia value received with its associated hypo- or hyper-glycemia risk, displayed as coloured traffic lights, and the glycemia trend calculated considering the most recent values. When a dangerous condition is detected, an alarm is turned on and the panel is surrounded by a red border. The conditions that trigger an alarm are customizable and for each one of them a message is displayed inside the panel. For the clinical study described in this work, an alarm was triggered whenever a hypo- or hyper-glycemia risk was detected or there were no incoming data for more than 15 minutes.

Selecting one of the patient panel the physician can see the detailed panel, which provides, in addition to some generic patient's information, a series of alternate views selectable through different tabs. Those are customized for each hospital center registered in the web app database and for the NICU of Padova the following ones were defined: a view for GIR suggestions, a view for a textual representation of CGM and calibration values, one for manually inserted data and, finally, one for a graphical representation of the collected data. Fig. 4.5 shows the chart visible in the last tab under the patient detailed view: here, glycemia values are represented through red circles, interspersed with calibration values shown as blue squares. The same chart provides the current time value, expressed as a vertical, orange bar, and additional events that have been manually inserted. For each one of those a dedicated icon has been selected, such as the one in Fig. 4.5 that represents an episode of intraventricular hemorrhage. Next to the tabbed panel, the same small panel of the overview page is provided and under this a button opens a new view dedicated to the manual insertion of events. Finally, when the real-time mode is enabled, the whole page automatically refreshes and shows new incoming data.

Fig. 4.6 shows the view with the algorithm suggestions. Each row of the table contains: time and value of the evaluated CGM (second and third columns), the glucose bolus value (fifth column) and the GIR value (seventh column), both calculated by the algorithm. For each one of those, an additional column (fourth, sixth and eighth columns) is provided to let the health-care staff overwrite the value automatically shown by the RM service. Finally, the last column contains a button through which GIR and bolus suggestions can be confirmed or deleted. This feature regards only the first row of the table and is available only when the RM service is running in real-time mode. All the other rows provide suggestions already confirmed by the health-care staff and definitely saved in the web app database.

Finally, among the four selectable views shown in the detailed panel, the ones that regard GIR suggestions, automatically collected data and manual inserted data support the download of an Excel file containing the same information displayed on the web page.

4.6 Discussion

At the end of the development phase, the service was used in two different trials, involving twelve and five VLBWIs respectively. In the first one, the real-time monitoring feature of the overall system was tested, without the algorithm for GIR suggestions being integrated yet. No technical issues were encountered and data were properly collected by the RM service, that triggered alarms in case of dangerous conditions. In the second clinical trial, instead, the integration of the algorithm was provided and helped the health-care staff in managing the patients' treatment care. Some load tests were performed in order to evaluate the system stability with a large number of connected devices. A plausible scenario for this setting could be the use of the system as a regional service.

On the whole, physicians expressed a positive feedback about the service, pointing out all the improvements they achieved in their daily workload:

- Having an immediate overview of each patient's health status;
- Intercepting multiple simultaneous dangerous events, even when they occur on VLBWIs located in different rooms;
- Trusting on a secure data collection system;
- Relying on additional support from other members of the health-care staff that can monitor patients from different locations.

4.7 Scientific Achievements

The contents described in this chapter were published in the following peer-reviewed international journals and presented in the following peer-reviewed international and national conferences:

- G. Lanzola, **E. Losiouk**, S. Del Favero, A. Facchinetti, A. Galderisi, S. Quaglini, L. Magni, and C. Cobelli, Remote Blood Glucose Monitoring in

mHealth Scenarios: A Review, *Special Issue for Sensors, Sensors*, 2016, 16(12), 1983;

- **E. Losiouk**, G. Lanzola, A. Galderisi, D. Trevisanuto, G. M. Steil, A. Facchinetti, and C. Cobelli, A Telemonitoring Service Supporting Preterm Newborns Care in a Neonatal Intensive Care Unit, *3rd IEEE International Forum on Research and Technologies for Society and Industry*, 2017;

- **E. Losiouk**, G. Lanzola, A. Galderisi, D. Trevisanuto, G. Steil, A. Facchinetti, and C. Cobelli, Continuous glucose monitoring improves euglycemic range in preterm infants vs. conventional sparse sampling: necessity of a glucose telemonitoring service in neonatal intensive care units, *Proceedings of the 5th GNB Conference*, 2016;

- L. Martini, A. Galderisi, **E. Losiouk**, A. Facchinetti, L. Brombin, F. Cava, B. Galeazzo, C. Daicampi, E. Baraldi, G. Steil, G. Lanzola, C. Cobelli, D. Trevisanuto, Iperglicemia e care neonatale: il monitoraggio glicemico continuo dimostra un'associazione nel neonato pretermine, *Congresso Nazione Societa' Italiana di Neonatologia (SIN)*, 2016.

Chapter 5

Privacy and Security Issues concerning Mobile Health Applications

The activity described in this chapter addresses some security problems that arise when *mHealth* apps communicate with EMDs through *Bluetooth* or *NFC* channels. More specifically, the threat model considered includes a malicious app that, after being granted *Bluetooth* and *NFC* permissions [108], connects to an EMD and steals its sensitive data transmitted through one of those communication channels. This security problem has been already analyzed by other research groups that proposed solutions either based on a modification of the Android OS or requiring root privileges enabled on the smartphone. In comparison with those previous works, the novelty of the approach proposed in this thesis consists in devising a solution that can be run in any Android device, without asking the user to modify the OS or grant root permissions. This goal can be achieved using the virtualization technique, which allows to create a new environment, in addition to the standard one provided by the Android platform, where any app can be run and its behaviour can be potentially modified at runtime. Even though previous works have already developed solutions based on the virtualization technique, the lack of official Android documentation and the limited number of supported open source projects made this activity really challenging.

Techniques and results illustrated in this chapter were partially identified and analyzed during my period abroad, which was carried out at the Labora-

tory for Communications and Applications of the Ecole Polytechnique Federale de Lausanne (Lausanne, Switzerland) under the supervision of Professor Jean-Pierre Hubaux.

5.1 Introduction

Android is a multi-process, Linux-based OS where each app is executed as an isolated process within its own address space. The security policies adopted by the Android OS affect each app both at the Linux system level and at the Android framework level. As a matter of fact, at installation time each app is assigned a unique Linux User IDentifier (UID) and is given access to a private directory. Under this path, the app can save its own private data, such as files and databases. The UID, that distinguishes every app, is used by the Android OS to apply restriction policies on the file system: each app can access only its own private directory and not the ones owned by other apps. Besides writing their own data, apps might also need to acquire other information, that is made available on the mobile device through local resources (e.g. location service, SD card, camera, etc.) or external resources (*Bluetooth*, *NFC*, audio, SMS, Internet). Since the access to those resources is protected, Android defines a set of permissions that an app has to request by declaring them in its *AndroidManifest.xml* file. Once granted, the app is assigned the Linux group associated to that resource and receives full access to it. The process is repeated for evey app requesting a permission for a resouce and, at the end, different apps with the same permissions granted will share the same privileges and information. This security policy has been found to be really dangerous, especially for permissions related to communication channels: since Android can control only the access to a communication channel, any app with granted permissions can communicate with any device available on that channel indiscriminately.

Moreover, another significant limitation of Android permissions is the process through which they are granted to apps, which depends on the protection level assigned among the following possible values:

- *normal*: automatically granted;
- *dangerous*: requires user confirmation;
- *signature*: the app that asks for this type of permission must be signed with the same key as the app declaring it;

- *signature or system*: granted to apps signed with the system key or saved in the system image.

Before the appearance on the market of the Android version 7.0, the complete list of permissions requested by an app was shown to the user at installation time. Starting with Android 7.0 *normal* permissions were removed from the list, so that the user has to navigate in the phone settings in order to see them. Moreover, checking permissions requested by an app can be done only after its installation.

The combination of the above mentioned limitations paved the way for the accomplishment of very dangerous attacks from a security and privacy point of view. As a matter of fact, malicious apps wishing to steal sensitive data saved in an EMD and transmitted through either the *Bluetooth* or the *NFC* channels, just need to declare the associated permissions, almost without notification for the user.

5.2 Threat Model

The threat model considered in this project addresses apps trying to steal sensitive data provided by EMDs through *Bluetooth* and *NFC* channels. For this purpose, it is assumed that those apps have been installed on a mobile device, where the official app also resides, and have been granted *Bluetooth* and *NFC* related permissions (BLUETOOTH, BLUETOOTH_ADMIN and NFC).

As described by Naveed et al. [109], those apps face two main challenges: the detection of the EMD availability and the identification of the most appropriate moment to start communicating with it. The first challenge is solved assuming that the official app and the malicious one are both installed on the same device. The regular activation of the official app by the user is considered by the malicious app as a strong proof of the EMD physical availability. The second challenge arises from the *Bluetooth* protocol specification, according to which a peripheral device, in this case the EMD, can be connected with one device per time. To cope with this restriction, the malicious app needs to exploit a very short time window to connect to the EMD. To achieve this aim, three possible situations were identified: the pre-connection, the post-connection and the disruption. The pre-connection refers to the time that exists between the official app launch and the exact moment in which the connection is established. The post-connection indicates the time immediately after the interruption of the connection between the official app and the EMD.

Finally, the disruption implies first disabling and then re-enabling the *Bluetooth* connectivity on the whole smartphone. This way, the malicious app can break the communication channel between the official app and the EMD and start soon after its own one.

Considering the *NFC* channel, during the communication between an app and an EMD, the latter plays the role of a passive *NFC* tag that, after being scanned, sends its information and data to the smartphone. Then, the Android OS becomes responsible for intercepting those data and finding an app that is able to handle them. Once that app is found, the Android OS creates an *Intent* object where the incoming data from the EMD are saved and sends it to the app. The identification of an app able to manage EMD data depends, first of all, on the information declared in the *AndroidManifest.xml* file of the installed apps. As a matter of fact, to receive data coming from an external *NFC* tag an app has to register the associated *Intent Filter*, specifying also a priority level with which it would like to receive the data. When the Android OS catches data from an *NFC* tag, it searches for all the apps declaring the associated *Intent Filter* and, according to their priority level, it chooses the one to which data are eventually sent. If multiple apps declare the same priority level, the user is shown a list of those apps and is asked to select the one that will receive the data. Thus, for a malicious app wishing to receive data coming from an *NFC* tag, there are two possible options: registering the associated *Intent Filter* with a higher priority than the official app, or running in foreground with the foreground dispatch system enabled. The last approach allows the malicious app to gain the highest priority among all the apps declaring the same *Intent Filter* and definitely entitles it to receive the data [110].

5.3 Solution Requirements

Given the widespread diffusion of *mHealth* apps connecting to EMDs and the easiness with which malicious apps that steal sensitive data are developed and diffused, the following solution requirements were defined with the aim to address the widest number of people:

- No modification of the Android OS: installing a modified version of the Android OS is not a trivial task and can be achieved only by a limited number of users;

- No root access: as well as for modifying the Android OS, requiring root

privileges on the device to run the solution would decrease the number of final potential users;

- No repackaging technique: this process requires app decompilation, modification and a subsequent re-compilation of the original app with a different signature than the original one. Even though this approach does not require specific skills from the user, it prevents an app from being automatically updated after the installation. As a matter of fact, the update process implies an equivalence between the signature of the installed app and the one of the app published on Google Play Store. Using the repackaging technique, the signature is automatically broken and the update process is prevented.

To address all the above mentioned requirements, the virtualization technique was chosen. Without root permissions or modification of the OS, this technique allows to create a new environment, in addition to the Android standard one, in which any app can run without modifying its behaviour. Moreover, since the virtualized environment can control the calls made by the app running inside it, it is also possible to intercept the ones concerning any connection attempt towards an EMD and, potentially, block it in case of malicious app.

5.4 Related Work

Considering the limitations of the *Bluetooth* and *NFC* channels, previous works already proposed possible solutions [109, 110]. However, those require either a modification of the Android OS or root permissions on the device.

As far as the virtualization technique is concerned, contributions from both the scientific literature and the commercial market were found. Backes et al. [111], as well as Bianchi et al. [112], used the virtualization technique for the following purpose: defining an isolated environment to run apps and have a finer control over their behaviour. As a matter of fact, according to the authors of both papers, once an app is installed and launched, it is quite difficult to know which data it is accessing to or which procedures it is doing. A virtualized environment has a complete supervision and can dynamically notify the user anytime a leakage of sensitive data occurres.

The aim addressed by the third paper on the same topic [113] concerns the malicious apps that run benign ones in their own virtualized environment to gain a complete control over them (i.e. user interactions with the app, private

data saved by the app, etc.). The authors emulated the attack providing sufficient proof to claim that it can be performed without being noticed by the user.

Finally, the fourth paper concerning the virtualization [114] is pretty close to the third one for the chosen attack. However, instead of simulating the attack, the authors provided a set of techniques that let an app notice whether it is running in a virtualized environment or not.

Interesting commercial solutions were found in *Android for Work*, *Samsung Knox* and *Parallel Space* products. Each one of them provides a virtualized environment where apps can run, but with two different purposes: either preventing apps, that belong to different environments, from seeing each other or running multiple instances of the same app with different accounts (e.g. WhatsApp, Skype).

It is important to highlight that no research work or commercial tool based on the virtualization approach has been already developed nor can be used to protect *Bluetooth* and *NFC* communication channels yet.

5.5 System Design

The solution devised was partially inspired by a previous work [112] and involves two different apps: the Supervisor App (SA) and the Instance App (IA). Starting with the SA installed first, the overall worklflow of the solution consists of the following steps:

- SA runs and listens for the event triggered by the Android OS every time a new app is installed. When this happens, SA inspects the *AndroidManifest.xml* file of the app, looking for *Bluetooth* and *NFC* related permissions. If the app declares any of those, the user is asked to stop the app process and run it in the virtualized environment. If the user agrees, SA triggers the download of a new IA (Fig. 5.1);

- SA stops the process of the first app and launches the IA, which defines the virtualized environment for running the compiled code of the first app (Fig. 5.2);

- Every attempt to connect to an EMD made by the code of the original app is intercepted by the IA and notified to the SA. This last one then asks the user to approve the attempt of connection. Only after the user

approval, the communication between the IA and the EMD is enabled (Fig. 5.3).

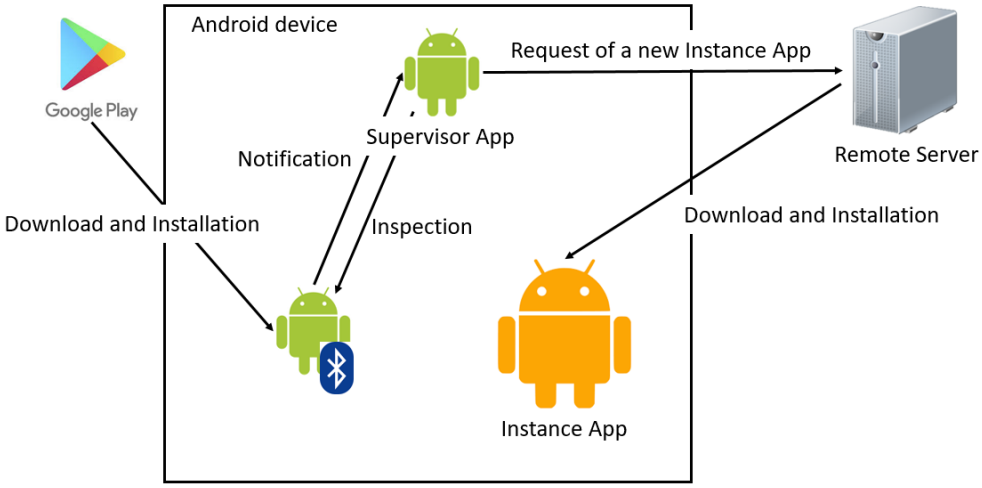


Figure 5.1: **First step of the devised solution.**

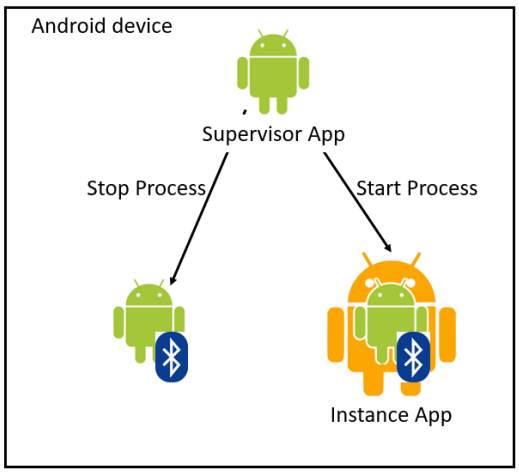


Figure 5.2: **Second step of the devised solution.**

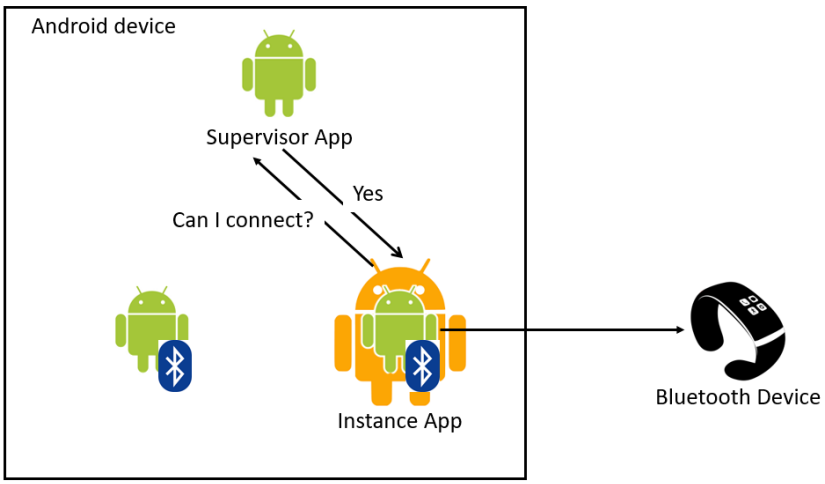


Figure 5.3: **Third step of the devised solution.**

Given the above workflow, three milestones can be identified: system initialization, definition of a virtualized environment, *Bluetooth* and *NFC* channels protection.

5.6 System Initialization

The system initialization part involves the development of the following SA's features: detection of any new app installation; inspection of the new app *AndroidManifest.xml* file to identify any *Bluetooth* and *NFC* related permissions; interruption of the new app process.

Every time a new app is installed, the Android OS triggers the PACKAGE_ADDED event. This can be caught by any app that has previously registered a *BroadcastReceiver* for the specific event.

At installation time, the Android OS creates a *PackageInfo* object containing all the information declared in the app *AndroidManifest.xml* file. Through the *PackageManager* service any app can obtain the *PackageInfo* object associated to another app (method *getPackageInfo(String packageName, int flags)*) and inspect its permissions.

Finally, to stop an app process the method *killBackgroundProcesses(String packageName)* is provided as an Android Application Programming Interface (API) and can be called by any app declaring the associated permission.

5.7 Definition of a Virtualized Environment

The development of the IA prototype was the main part of the project, as well as the most demanding one: the IA defines the virtualized environment where potentially any app can run and the Android APIs invoked by it are dynamically intercepted. In order to achieve this goal, a deep analysis of the scientific literature, open source projects and Android source code was done.

The creation of a virtualized environment involves three challenges: the dynamic loading of external compiled code, the definition of an appropriate *Context* in which the external compiled code is run and the dynamic interception of the calls made by the compiled code running.

Considering the first issue, Poeplau et al. [115] gave a complete overview of the different approaches available in Android for loading external compiled code:

- Android class loaders: standard class loaders are Java objects aimed at loading the compiled code of the Java classes they are associated to. The Android ones support also the dynamic loading of Android Package Kit (APK), jar and dex files formats;
- Package *Context*: Android APIs provide the method *createPackageContext (String packageName, int flags)* through which an app can retrieve the *Context* object of a different one and use it to launch its main activity;
- Native code: using the Java Native Interface, Android developers can write native code (C and C++) and interact with it from the Java source code. In native code it is possible to run executable files;
- Java class *Runtime* to execute binaries: by exploiting the *Runtime* Java class, it is possible to execute binary files;
- APK installation: the *PackageManager* service exposes some APIs through which it is possible to trigger the installation of an app.

Before addressing the problem concerning the creation of an appropriate *Context* for the external compiled code, a brief description of the *Context* object itself is required. An Android *Context* is distinctively associated to a single app and contains essential information enabling its correct execution at runtime. More specifically, the most important data saved in a *Context* object

are: app permissions, app components (i.e. *Activity*, *Service*, *BroadcastReceiver* and *ContentProvider*), app resources (images, strings, etc.) and app class loaders. For this reason, when the compiled code of an app is run inside a *Context* different from its own one, the above mentioned elements need, in some way, to be provided. Two possible approaches can be followed to define the appropriate *Context* for the compiled code of an app. The first one consists in the definition of a customized IA for each app that is going to be run inside it. More specifically, this strategy implies that the *AndroidManifest.xml* of the IA contains the same permissions and components of the app. This means that, once the user has agreed to run an app inside the virtualized environment, SA triggers the installation of the specific IA. The second approach is much more challenging from a development point of view, but it reaches a higher abstraction level. As a matter of fact, it aims at defining a single version of the IA which can support the execution of any compiled code. To achieve this goal, the *AndroidManifest.xml* file should be properly defined in terms of declared permissions and components. Since the compiled code the IA is going to run is not known a priori, the IA should declare all the existing Android permissions so that at runtime any compiled code will already have the access to any resource. Considering the components, the IA should declare a random number of dummy components in its *AndroidManifest.xml* file and, during runtime, map each real component used by the compiled code into a fake one. As a matter of fact, an Android app has to declare all the required components in its *AndroidManifest.xml* file so that the Android OS can collect them all during app installation. Then, the execution of each component is directly managed by the Android OS, after receiving a request from the app. For example, when an app needs to open a new *Activity* (i.e. a new screen), it sends a request to the Android OS, which replies providing the new *Activity* to be launched. In the case of the IA, the mapping of real components with fake ones needs to be done at runtime by intercepting each request sent by the compiled code and dynamically changing the component required to be launched. More specifically, if the compiled code requires to open a new *Activity* called *SecondActivity*, but the IA has registered only dummy activities, it has to intercept the request for the *SecondActivity* and change it with a request for a dummy one.

To achieve the purpose of defining a virtualized environment, a deep search and analysis of existing open source projects and previous works was done and, finally, the *DroidPlugin* tool was found [114]. This is an Android project that can be merged with the source code of a generic app and allows to load and

execute the compiled code contained in an APK file. Once the configuration for importing *DroidPlugin* is done, it just needs the path towards the APK file location. The design of *DroidPlugin* follows exactly the second approach among the two ones described for preparing the appropriate *Context* object. In its *AndroidManifest.xml* file *DroidPlugin* declares all the available Android permissions and a set of dummy components, with which the official ones are dynamically replaced. For those reasons, *DroidPlugin* does not require any modification when launching compiled code coming from different APK files.

DroidPlugin was succesfully tested with some commercial apps communicating with external devices (*Glimp* and *Dexcom G5 Mobile*), as well as with the *Neokid* app developed during this thesis.

5.8 Bluetooth and Near Field Communication Channels Protection

Even though a solution for creating a virtualized environment was found, further search was required to identify a suitable technique to intercept the connection attempts made by the compiled code of an app that communicates with EMDs.

Analyzing both processes for starting a connection through *Bluetooth* and *NFC*, two Android methods were found suitable to potentially allow/block a connection attempt. Concerning the *Bluetooth* communication, the method *connectGatt(Context context, boolean autoConnect, BluetoothGattCallback callback)* called on a *BluetoothDevice* object is the one responsible for establishing a connection with an EMD. Considering *NFC*, the method *onNewIntent(Intent intent)* of the *Activity* class is called by the Android OS to transmit the data received from an *NFC* tag towards the specific app.

To dynamically intercept the calls made by an app three approaches were identified: ptrace() Linux command, hooking the *libc* standard C library and hooking Android methods in Android RunTime (ART).

The first technique is based on the ptrace() Linux command and it relies on the fact that each Android method called is translated into a sequence of system calls sent to the kernel. As illustrated in Fig. 5.4, to exploit the features of ptrace() two processes are always required: the monitoring process and the monitored one (i.e. the IA process in this case). The monitoring process attaches to the IA one and receives a notification every time there is a request to execute a system call. More specifically, every time the IA enters and exists

a system call, its process is stopped and a notification is sent to the monitoring process. This can then inspect which system call has been requested and with which arguments, that can be eventually modified at runtime.

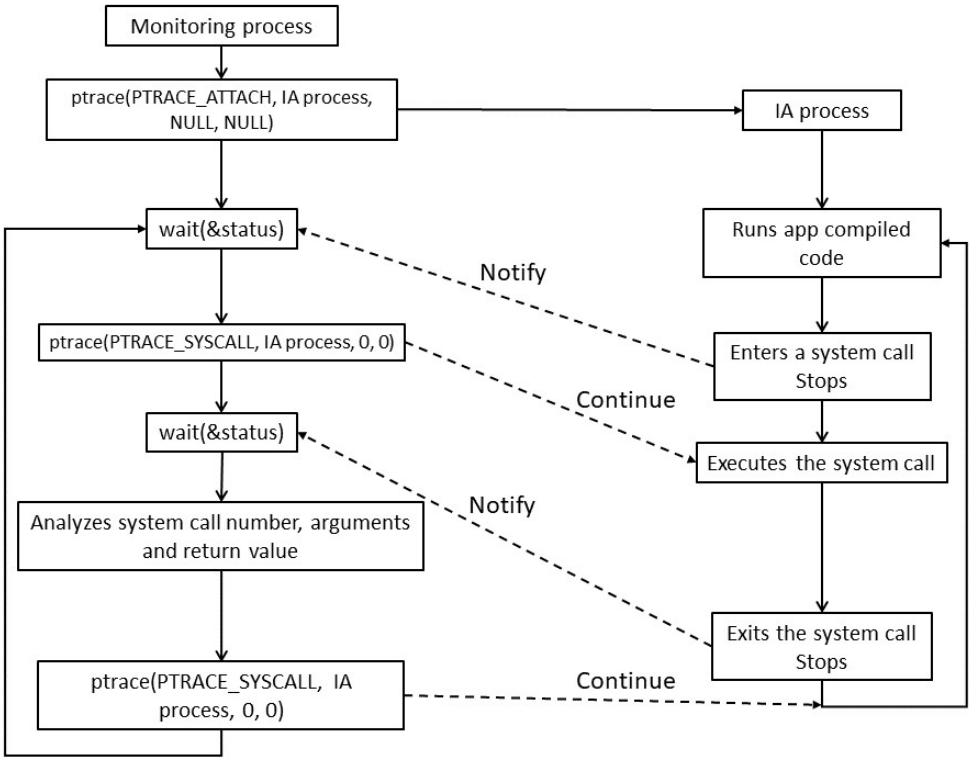


Figure 5.4: **Workflow designed to intercept the system calls of a process through ptrace().**

For the purpose of this project, the goal was to find the appropriate system call involved in the attempts to connect to EMDs and manage its arguments to allow/block the connection.

The second technique is illustrated in Fig. 5.4 and, in some way, is related to the first one. As already stated, an app needs the Android APIs to interact with the surrounding environment and other installed apps. Each Android API method is mapped to a sequence of system calls, which are C functions provided by the C standard library or *libc*. When the hooking is not applied (left part of the Fig. 5.4), the calls made by an Android app are directed to the specific C functions. In the other case (right part of the Fig. 5.4), a

new shared library (*my.so*) is provided in addition to *libc* and the pointers originally addressing *libc* are dynamically redirected towards *my.so*. Finally, when receiving the call, *my.so* can potentially inspect it and then forward it to the original function located in *libc*.

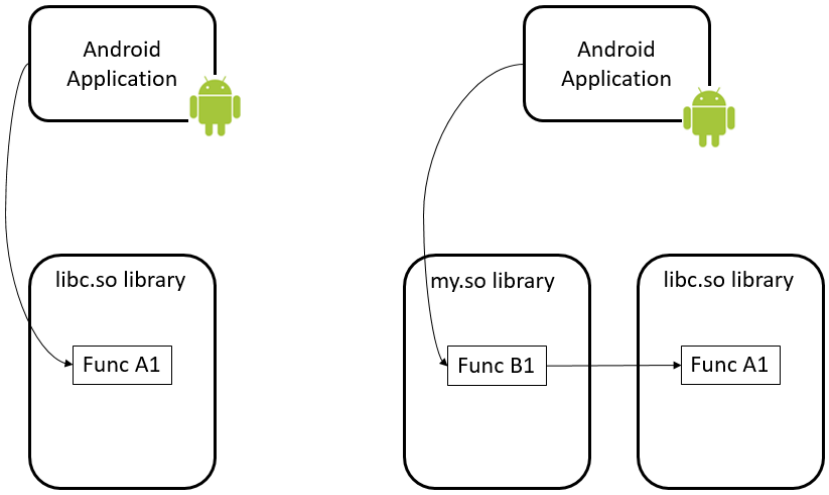


Figure 5.5: **Overview of the libc hooking technique.**

Finally, the third technique, described in Fig. 5.6, uses the data structures located in ART, which is the new environment responsible for the execution of apps from Android 4.4.

ART involves three components:

- *libart.so*: a shared library file containing the overall logic of ART;
- *boot.art*: an image file that contains C++ structures (*Class* and *ArtMethod*) mirroring classes and methods of the Android APIs. Every structure has a pointer to its binary code;
- *boot.oat*: an image file containing the binary code.

At runtime, the binary code of a generic app contains links to classes and methods belonging to the Android APIs. Those links are resolved by *libart.so*, that accesses to the internal data structures saved in *boot.art* for retrieving the pointers to the binary code. The principle of hooking Android methods in ART is similar to the one defined for *libc* hooking: each *ArtMethod* saves a pointer to

its binary code, which can be redirected to a different binary code responsible for its inspection and consequent forward to the original destination.

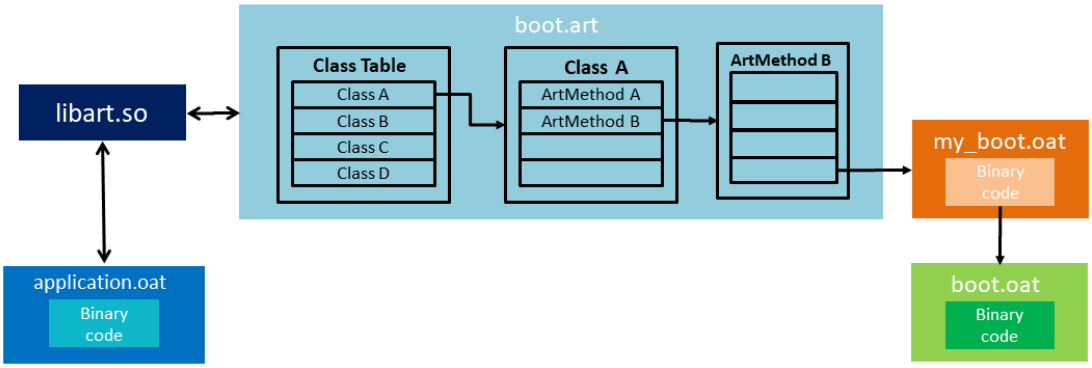


Figure 5.6: **Overview of the technique for hooking Android methods in Android RunTime.**

After collecting enough documentation for each one of the above mentioned techniques, a comparison was done.

Unfortunately, ptrace() was found unsuitable for additional restrictions, recently included in the Android OS by Google. As a matter of fact, starting with Android version 4.3 the security level of the OS has been enhanced by the introduction of Security-Enhanced Linux (SELinux). This applies a set of predefined rules that either allow or block specific operations in the Android OS. Among those, ptrace() is classified as a dangerous one and, therefore, its use is prevented. As a confirmation, when trying to use ptrace() in Android, the kernel logs contain the following message:

type=1400 audit(0.0:25): avc: denied ptrace for scontext=u:r:init:s0
tcontext=u:r:untrusted_app:s0 tclass=process

By default SELinux runs in ”Enforcing” mode in Android, but it can be switched to ”Permissive” mode so that its rules are no more applied. However, since this update needs root permissions, it does not meet the solution requirements of this project.

Between the *libc* hooking and the ART hooking approaches, the second one was chosen. Even though hooking Android methods gives a worse result in terms of performance, it is much more usable since the hook is directly

applied on the method and no identification of the associated C functions is required.

Therefore, considering the ART hooking approach, some open source projects were analyzed: *ARTDroid* [116], *ProbeDroid* [117], *ArtHook* [118], *Legend* [119] and *AndFix* [120]. Among those, only *Legend* was found suitable for the purposes of this project. *Legend* is a library that can be imported in the source code of another app and provides an easy notation for hooking Android methods.

After the identification of a proper tool for intercepting the calls made by an Android app, the final solution consisted in the union of both *DroidPlugin*, for creating the virtualized environment, and *Legend*, for calls interception. The union of both tools gave promising results since the prototype was able to launch the compiled codes of different APK files and intercept some methods (e.g. the *Activity* class or the *TelephonyManager* class), but some problems were encountered for methods related to *Bluetooth* connection. Therefore, on the basis of the above mentioned findings, accomplishing hooking with *Legend* requires a modification of its source code for the proper invocation of *Bluetooth* APIs.

5.9 Discussion and Conclusions

Over the past few years the evolving empowerment of smartphones features paved the way for an increasing use of mobile technology in daily activities related to health care and fitness. A very interesting functionality is the connection with external devices: *mHealth* apps requiring this capability vary from non medical ones used by generic users (e.g. aimed at tracking cardiac frequency, training or sleeping activities, etc.) to different others expolited for medical purposes (e.g. aimed at measuring glycemia values, cardiac arrythmias, blood pressure). However, even if the combined use of smartphones and other devices is increasing, Android OS still misses an efficient security policy for managing the communication channels (*Bluetooth*, *NFC*, audio, etc.).

The limitations of Android OS described in this chapter have been already addressed in the literature, but the novelty of the investigation accomplished in this work resides in the constraints defined for the final solution, which is the first one requiring neither root privileges nor any modification of the Android OS.

Among the several ones, the most critical challenge was the identification

of a suitable technique for intercepting the calls made by an Android app with the predefined constraints. The analysis that was carried out led to some interesting considerations concerning the current state of the art on this topic.

The first one regards the availability of documentation. The three identified techniques require a deep knowledge of the Android OS, that goes beyond the standard development of a mobile app. As a matter of fact, if for standard Android mobile development a lot of documentation and examples are provided, there is a lack of description of the OS internals. Deeper details can be found only in the Android source code or in scientific publications of research groups that already analyzed it and chose to share the acquired knowledge with the rest of the community.

The second consideration concerns the availability of open source projects for intercepting the calls made by an Android app. For each one of the identified techniques, different challenges were faced:

- ptrace(): no open source solutions are available, besides few snippets of code about the general use of ptrace();
- *libc* hooking: existing solutions are based on older Android versions [121], are not publicly available [111] or are no more updated [122] ;
- Android methods hooking: existing solutions either work on older Android versions [113] or are based on the new ART environment, which is very little documented;

Thus the purpose of this investigation was to evaluate the feasibility of a solution based on the virtualization technique and designed for protecting the communication channels in the Android OS. The analysis accomplished has confirmed that virtualization is the most suitable approach to be pursued for protecting communication channels such as *Bluetooth* and *NFC*, even though this requires some adaptation of the libraries available in the public domain. Moreover, the protection of communication channels through the virtualization approach can prevent a malicious app from both obtaining sensitive data contained in an EMD and gaininig control of it. When the EMD is an active medical device, such as an insulin pump, the threat is particularly dangerous since the malicious app can make it administer an amount of insulin that could even lead to patient death. However, the solution described in this chapter covers also this type of attacks since, besides the purpose, the communication with EMDs is always performed through the same Android APIs. Thus, besides the several challenges, the aim of the project was successfully achieved.

Chapter 6

Discussion and Conclusions

The overwhelming evolution of mobile technology over the past few years has deeply affected our daily lives. Today smartphones provide a lot of features in addition to the standard ones associated to the old mobile devices (e.g. placing phone calls or sending messages). Presently, apps exist for using smartphones to navigate the web, exploit the localization/mapping features, interact with social media or even leverage the sensors available on board. Every day people make use of those features in order to: work out of office, keep track of their fitness exercises and improve their achievements, make bank transactions or keep in touch with their family and friends. However, even though the smartphones usage patterns among people are well known, their exploitation in the delivery of useful services for the citizens has not been completely analyzed yet. Among those, the health-care system could undergo a big revolution with the introduction of *mHealth* apps: patients could manage their diseases more easily through mobile apps reminding them when it is time to take a pill, or tracking their physiological values and allowing them to keep more frequently in touch with their treating physicians. However, for every intervention introduced through an *mHealth* app, the level of user involvement is a very important issue. As a matter of fact, several specific user features (e.g. age, health status, purpose of using the app, conditions under which it is used, etc.) influence the design and functionalities that an *mHealth* app should have to be most effective in accomplishing its task. Moreover, independently from the efforts spent by the developers in the design and implementation of an app, it is important to ascertain whether the final users are really ready to use that app.

Given the above mentioned considerations, the purpose of this PhD thesis has been to evaluate whether people are up-to-date with the current technology for *mHealth* and whether they are willing to keep up with its evolution. On this basis, the scientific question addressed by the thesis is the following one:

Are we ready for the introduction of mHealth in support of health care ?

To find a possible answer to that question several prototypes of *mHealth* apps have been designed, developed and evaluated considering the different perspectives identified by the following eight dimensions: *App Distribution*, *Target Users*, *Data Acquisition*, *Data Analysis*, *Data Storage*, *Data Synchronization*, *App Working Mode* and *App Update Policy*. Finally, another issue that has been analyzed in this thesis is the level of reliability of *mHealth* apps, more specifically of those communicating with EMDs through *Bluetooth* or *NFC* channels.

6.1 Main Achievements

The main achievements given by this PhD thesis regard the lessons learned through the involvement in each one of the illustrated projects, which have been also found to have some similarities with previous research works [123] . More specifically, the lessons are the following ones: the integration of methods used by health-care staff and technologists to verify the efficacy and stability of a solution; the proper way to translate the existing clinical interventions into mobile solutions through the exploitation of smartphones features; dealing with a continuously evolving technology; the choice of the most appropriate device to be used in a trial; the importance of user characteristics.

The first issue concerns the different approaches used by clinicians and developers to evaluate the effectiveness of a solution. The former usually adopt the randomized clinical trial technique to compare if the newly introduced intervention is better than the previous one; the latter adopt iterative strategies that allow them to gradually modify and improve the quality of their product. A successful approach might be to merge the two strategies so that the technological product is deeply tested and fixed before its actual use in a clinical trial. If that approach had been adopted in all the projects described in this thesis, it would have definitely improved the users perception towards each *mHealth* solution developed. For what concerns the RM set up for the trial involving children affected by T1DM, its design was defined during the AP@Home

project. Its functionalities and the information to be provided to the users were refined trial after trial through several meetings between the developers implementing the solution and the physicians and bioengineers running the service. Thus, when the RM was provided to the children parents during the trial located in Bardonecchia, its usability level had been already validated and, consequently, it was also well appreciated by the parents. On other hand, the project with the health-care staff of the NICU in Padova made use of the same RM core functionality already used in Bardonecchia, with very few additional features including the *Neokid* mobile app. The new functionalities of the RM were designed together with physicians while *Neokid*, acting as a relay for the data generated by the glucometer, did not require a lot of planning on the health-care side. As a matter of fact, after configuring the *Neokid* mobile app, the smartphone just needed to be left near the cradle in order to acquire and retransmit glycemia values. In fact, in that case the aim was to achieve the easiest configuration procedure as possible.

The second issue regards the proper way to use a mobile app for accomplishing a clinical task, an activity or an intervention. According to Ben-Zeev et al. [123], this process is not just a translation of a manual activity into an electronic one, but it requires to consider how smartphone features can be exploited to improve the execution of a specific task. This is particularly true for *Gquest*, the aim of which was to render in electronic format MCs that were previously distributed only in paper format. A very limited solution to achieve this purpose would have been to provide MCs as PDF files, downloading them on the smartphone so that they were available for consultation. However, this approach would not have exploited all the features offered by a smartphone. *Gquest*, instead, added the following functionalities: guided navigation through each block of the MC, interrupting and resuming MC consultation from the same point where the user left, arithmetic calculations and a full vocal interaction system.

The third issue addresses the problem of keeping up with a continuously evolving technology. More specifically, the problem is raised by the different times required for the design and development of new IT solutions (Android OS version, frameworks, programming language, etc.) with respect to the one required for designing, implementing testing and certifying new medical devices. For the latter, the process is inherently very long, mainly because of the several regulatory steps required to ensure the device safe use on patients. Since, on the contrary, the evolution of ICT technologies occurs at a much faster rate, a possible solution for being successful, when developing an *mHealth*

app that interacts with a medical device, is to take into account some sort of backward compatibility. This should be accomplished with the twofold purpose of interfacing with old devices and standards and quickly move to more recent ones as soon as the devices are updated. This issue affects all the *mHealth* solutions described in this thesis: *Gquest* for the Android OS updates, *DiAs* for both the Android OS updates and the release of new insulin pumps or glycemia sensors, *Neokid* for both the Android OS updates and the release of new glycemia sensors.

The fourth issue concerns the choice of the smartphones to be used in a trial and more specifically whether to rely on the personal devices of the patients or buy new ones. According to Ben-Zeev et al. [123], each decision involves additional issues. Choosing to go with a patient's personal smartphone guarantees a high level of involvement of the final user that feels already confident with the technology, can better appreciate the new intervention and can use the same smartphone for both personal purposes and the trial. On the other hand, it is likely that smartphones differ from each other (in terms of Android OS version, screen size, capacity, carriers and data plans) and that they might be damaged or customized for the specific user. Moreover, testing an *mHealth* solution on every smartphone model is a quite demanding process. For what concerns the second choice (i.e. buying new smartphones), the authors highlighted that the patients might use the second device less frequently, unless all their contacts, apps and data are moved on it. However, not all the participants might be interested in that solution, but they could be more motivated if the new device is left to them at the end of the trial. Analyzing the remote monitoring projects no uncertainty was found. Since the *DiAs* was distributed as a modified version of the Android OS, it could be only installed on new devices, that were totally dedicated at running the control algorithm and had other features (e.g. making phone calls, sending messages, taking photo) disabled. Similarly, *Neokid* worked as a bridge between the receiver located in the NICU room and a remote server. Therefore, no personal smartphone could have been used for that purpose.

The last issue is about the importance of taking care of the final users of a system. Once a prototype is completed and safety issues have been addressed and verified, developers should deeply consider suggestions coming from the actual users in order to make their system more targeted to the final context of use [124]. This becomes even more important when different actors are involved, including fragile or older patients [125].

6.2 Limitations and Margins of Improvement

Some of the projects illustrated in this thesis have been affected by few limitations. Among those, in particular, *Gquest* could have given different results if members of the paramedic staff were continuously involved in the design process and if a different choice for the devices to be used in the trial was done. As a matter of fact, no meetings with nurses and paramedics of the Emergency Department of Aosta had been scheduled before the trial, but only few ones were organized with the Head of the Department who was not a final user of the system. This led to the identification of all the requirements and needs for the emergency context mainly from previous published works. As a consequence, even if the final solution had been properly designed for the specific trial, it could have been rendered more suitable for that purpose if the final users had been also involved in the design phase and not just in the trial. Moreover, instead of installing *Gquest* on the *TomTom Bridge*, with which the ambulance was equipped, it could have been provided directly on the smartphone belonging to each member of the paramedic staff.

6.3 Further Developments

The experiences collected through the evaluation of the different prototypes developed gave promising feedback about the adoption of *mHealth* solutions in health care. Both parents of children affected by T1DM and health-care staff of the NICU in Padova were satisfied about the *mHealth* system with which they were provided. On the other hand, nurses of paramedic staff expressed the need for a technological solution that could support them with the consultation of MCs, but they did not find *Gquest* as an optimal solution. Overall, those experiences lead to conclude that the health-care staff, as well as the caregivers and the patients themselves, are ready for the introduction of *mHealth* solutions. However, each solution needs to be specifically designed for its expected users so that its interventions can be the most effective as possible. Finally, the last activity regarding privacy and security issues of Android smartphones always reminds us that we should be careful with technological solutions, especially with those ones that manage our sensitive data.

The projects concerning *Gquest*, *DiAs* and *Neokid* ended with the trials set up to evaluate their usability and effectiveness. Among all the projects described in this thesis, only the one regarding security and data protection might be carried on as a future development. As a matter of fact, after the

successful identification of the techniques that can be used for the virtualization approach, a complete solution to protect Android communication channels could be now developed.

Appendix A

Pre-study and Post-study Questionnaires in Italian Language for Assessing the Users' Perception of *Gquest*

QUESTIONARIO DI INIZIO STUDIO

1. Considerati i protocolli cartacei per la gestione delle emergenze:

	Mai	Talvolta	Spesso	Sempre
a. Trova sempre sull'ambulanza il pacchetto con i protocolli?	☐	☐	☐	☐
b. Riesce sempre a trovare lo specifico protocollo necessario al caso fra quelli presenti nel pacchetto dell'ambulanza?	☐	☐	☐	☐
c. Le capita di dover cercare a lungo un protocollo prima di trovarlo?	☐	☐	☐	☐
d. Le capita di aver bisogno di consultare un protocollo quando già un altro operatore lo sta consultando?	☐	☐	☐	☐
e. Le informazioni presenti nei protocolli cartacei sono ***chiare***?	☐	☐	☐	☐
f. Le informazioni presenti nei protocolli cartacei sono ***complete***?	☐	☐	☐	☐
g. I protocolli cartacei sono ***facili da seguire passo passo***?	☐	☐	☐	☐
h. Le capita di trovare sull'ambulanza una versione di un protocollo non aggiornato alle ultime evidenze scientifiche?	☐	☐	☐	☐
i. Le capita di avere qualche difficoltà nello stabilire il dosaggio corretto dei farmaci?	☐	☐	☐	☐
l. Ha difficoltà nel reperire un'informazione puntuale all'interno del protocollo stesso?	☐	☐	☐	☐
m. Con che frequenza consulta i protocolli?	☐	☐	☐	☐
n. Le capita di non poter consultare un protocollo perché ha le mani occupate?	☐	☐	☐	☐

Figure A.1: **Pre-study questionnaire in Italian language administered before the trial in Morgex (Page 1).**

	Sì	No
o. Se il protocollo fosse informatizzato, gradirebbe un'interazione vocale con esso?	☐	☐
p. Ritiene che sia importante poter dimostrare di aver seguito un protocollo in certe occasioni (e.g. per problemi medico-legali)?	☐	☐
q. Le è capitato di doverlo fare?	☐	☐

2. In genere consulta un protocollo:

a. al fine di ripassare la procedura	☐
b. solo per recuperare un'informazione puntuale	☐

Indichi qui sotto qualunque altro problema rilevato nella consultazione dei protocolli

Controlli cortesemente di avere risposto a tutte le domande.

LA RINGRAZIAMO PER LA SUA COLLABORAZIONE

Figure A.2: **Pre-study questionnaire in Italian language administered before the trial in Morgex (Page 2).**

QUESTIONARIO DI FINE STUDIO

1. La preghiamo di compilare le risposte sottostanti considerando 1 come "Fortemente in disaccordo" e 5 come "Fortemente in accordo":

	1	2	3	4	5
a. Penso che mi piacerebbe usare questo sistema frequentemente.	☐	☐	☐	☐	☐
b. Ho trovato il sistema complesso senza che ce ne fosse bisogno.	☐	☐	☐	☐	☐
c. Ho trovato il sistema molto semplice da usare.	☐	☐	☐	☐	☐
d. Penso che avrei bisogno del supporto di una persona già in grado di utilizzare il sistema.	☐	☐	☐	☐	☐
e. Ho trovato le varie funzionalità del sistema bene integrate.	☐	☐	☐	☐	☐
f. Ho trovato incoerenze tra le varie funzionalità del sistema.	☐	☐	☐	☐	☐
g. Penso che la maggior parte delle persone potrebbe imparare ad utilizzare il sistema facilmente.	☐	☐	☐	☐	☐
h. Ho trovato il sistema molto macchinoso da utilizzare.	☐	☐	☐	☐	☐
i. Ho avuto molta confidenza con il sistema durante l'uso.	☐	☐	☐	☐	☐
l. Ho avuto bisogno di imparare molto prima di riuscire ad utilizzare al meglio il sistema.	☐	☐	☐	☐	☐

	Si	No
Ha avuto modo di utilizzare Gquest, ovvero la parte del sistema relativa ai protocolli?	☐	☐

Figure A.3: **Post-study questionnaire in Italian language administered after the trial in Morgex (Page 1).**

2. Se sì, qui sotto trova le risposte che aveva fornito all'inizio del trial. La preghiamo di compilare, alla luce di quelle, l'ultima colonna:

	Mai	Talvolta	Spesso	Sempre	Effetto del sistema
a. Trova sempre sull'ambulanza il pacchetto con i protocolli?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
b. Riesce sempre a trovare lo specifico protocollo necessario al caso fra quelli presenti nel pacchetto dell'ambulanza?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
c. Le capita di dover cercare a lungo un protocollo prima di trovarlo?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
d. Le capita di aver bisogno di consultare un protocollo quando già un altro operatore lo sta consultando?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
e. Le informazioni presenti nei protocolli cartacei sono *chiare*?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
f. Le informazioni presenti nei protocolli cartacei sono *complete*?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
g. Le informazioni presenti nei protocolli cartacei sono *facili da seguire passo passo*?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
h. Le capita di trovare sull'ambulanza una versione di un protocollo non aggiornato alle ultime evidenze scientifiche?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza

Figure A.4: **Post-study questionnaire in Italian language administered after the trial in Morgex (Page 2).**

i. Le capita di avere qualche difficoltà nello stabilire il dosaggio corretto dei farmaci?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
l. Ha difficoltà nel reperire un'informazione puntuale all'interno del protocollo stesso?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
m. Con che frequenza consulta i protocolli?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
n. Le capita di non poter consultare un protocollo perché ha le mani occupate?	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza

In genere consulta un protocollo:

		Effetto del sistema
a. al fine di ripassare la procedura	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
b. solo per recuperare un'informazione puntuale	☐	☐ Migliora ☐ Peggiora ☐ Non influenza

Indichi qui sotto qualunque altro problema rilevato nell'utilizzo del sistema

_____

_____

_____

Controlli cortesemente di avere risposto a tutte le domande.

LA RINGRAZIAMO PER LA SUA COLLABORAZIONE.

Figure A.5: **Post-study questionnaire in Italian language administered after the trial in Morgex (Page 3).**

Appendix B

Pre-study and Post-study Questionnaires in Italian Language for Assessing the Users' Perception of the Remote Monitoring Service

QUESTIONARIO DI INIZIO STUDIO

Sezione 1. Ripensando agli ultimi sei mesi indichi quanto il diabete di suo figlio abbia influito sui seguenti aspetti:

	Mai	Raramente	A volte	Spesso	Molto spesso
a. La nostra famiglia rinuncia a molte cose (e.g. viaggi insieme per tempi prolungati).	☐	☐	☐	☐	☐
b . Nel prendermi cura di mio figlio non mi rimane molto tempo per gli altri membri della famiglia.	☐	☐	☐	☐	☐
c. Cambiamo spesso i piani all'ultimo minuto.	☐	☐	☐	☐	☐
d. Mi sembra di vivere sulle montagne russe: sono in crisi quando mio figlio sta male, sono sereno/a quando sta bene.	☐	☐	☐	☐	☐
e. Vivo alla giornata e non pianifico nulla per il futuro.	☐	☐	☐	☐	☐
f. Mi sento stanco/a.	☐	☐	☐	☐	☐
g. Rinunciamo a vedere parenti e amici	☐	☐	☐	☐	☐
h. Non abbiamo molto desiderio di uscire.	☐	☐	☐	☐	☐

Sezione 2. Considerando nel complesso l'influenza del diabete di suo figlio sul suo benessere, come quantificherebbe su una scala 0-100 la sua attuale qualità di vita (0 come peggior stato di salute che può immaginare e 100 come miglior stato di salute che può immaginare)?

Figure B.1: **Baseline questionnaire in Italian language administered before using the remote monitoring service (Part 1).**

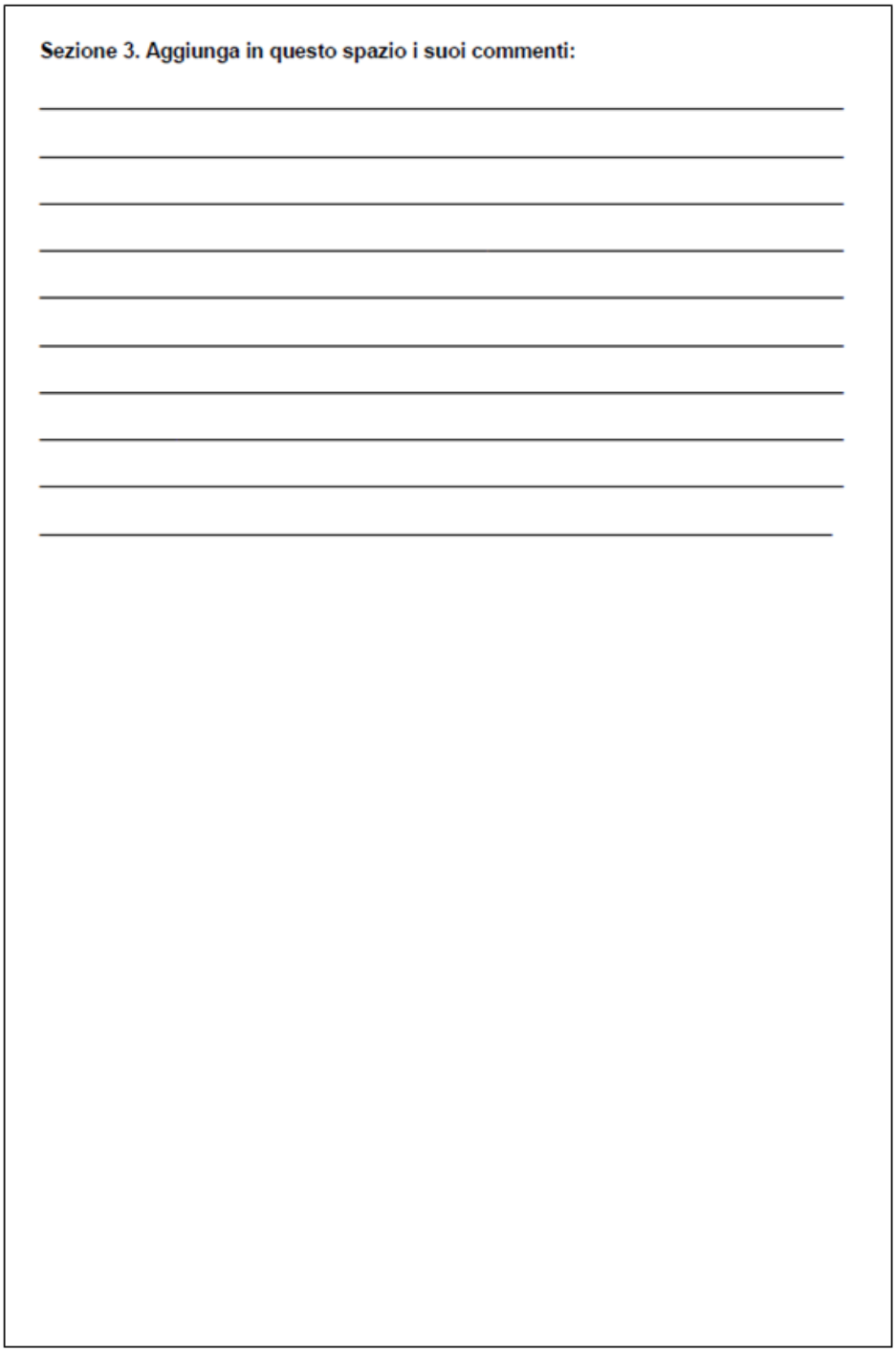
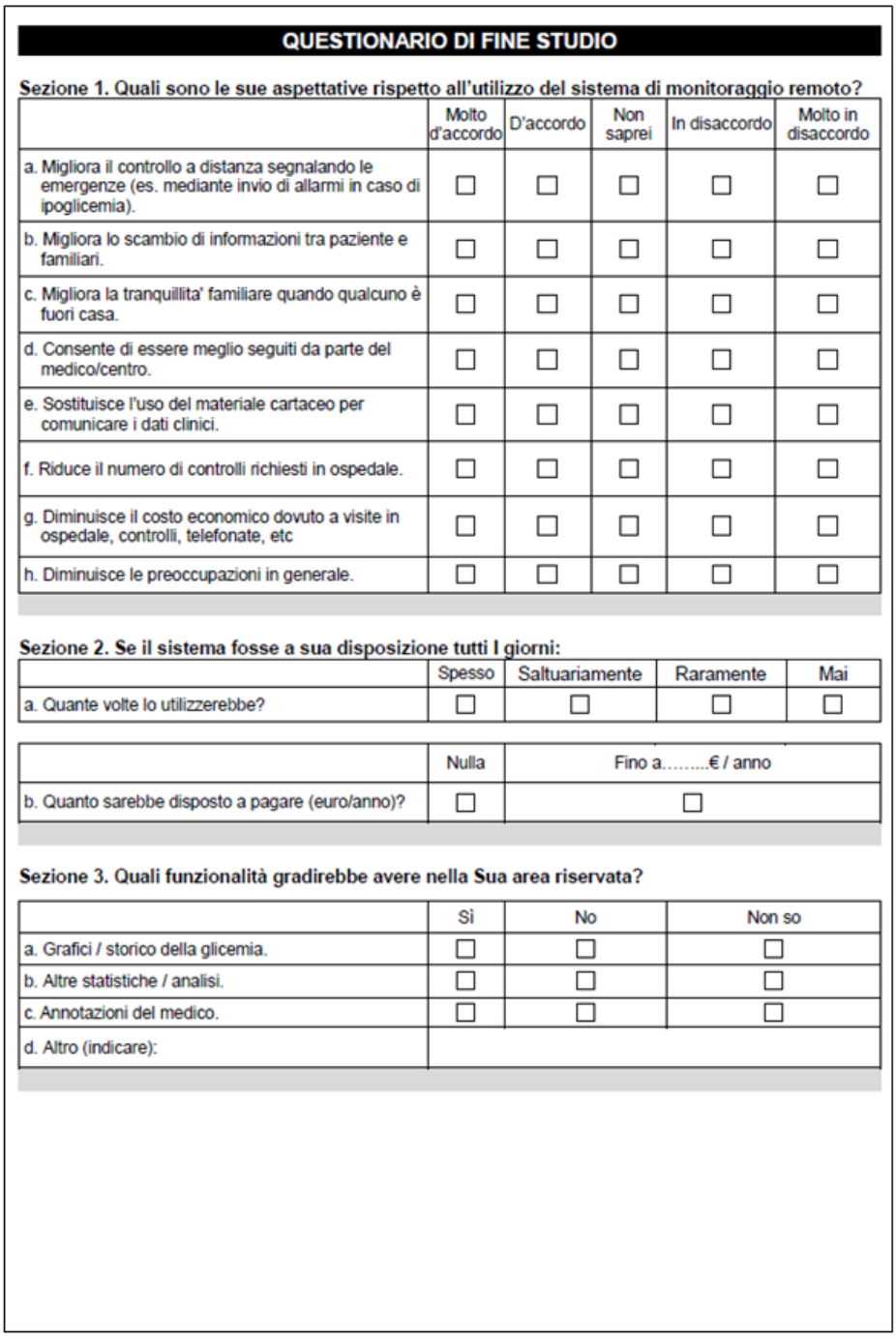


Figure B.2: **Baseline questionnaire in Italian language administered before using the remote monitoring service (Part 2).**



QUESTIONARIO DI FINE STUDIO

Sezione 1. Quali sono le sue aspettative rispetto all'utilizzo del sistema di monitoraggio remoto?

	Molto d'accordo	D'accordo	Non saprei	In disaccordo	Molto in disaccordo
a. Migliora il controllo a distanza segnalando le emergenze (es. mediante invio di allarmi in caso di ipoglicemia).	☐	☐	☐	☐	☐
b. Migliora lo scambio di informazioni tra paziente e familiari.	☐	☐	☐	☐	☐
c. Migliora la tranquillita' familiare quando qualcuno è fuori casa.	☐	☐	☐	☐	☐
d. Consente di essere meglio seguiti da parte del medico/centro.	☐	☐	☐	☐	☐
e. Sostituisce l'uso del materiale cartaceo per comunicare i dati clinici.	☐	☐	☐	☐	☐
f. Riduce il numero di controlli richiesti in ospedale.	☐	☐	☐	☐	☐
g. Diminuisce il costo economico dovuto a visite in ospedale, controlli, telefonate, etc	☐	☐	☐	☐	☐
h. Diminuisce le preoccupazioni in generale.	☐	☐	☐	☐	☐

Sezione 2. Se il sistema fosse a sua disposizione tutti I giorni:

	Spesso	Saltuariamente	Raramente	Mai
a. Quante volte lo utilizzerebbe?	☐	☐	☐	☐

	Nulla	Fino a.....€ / anno
b. Quanto sarebbe disposto a pagare (euro/anno)?	☐	☐

Sezione 3. Quali funzionalità gradirebbe avere nella Sua area riservata?

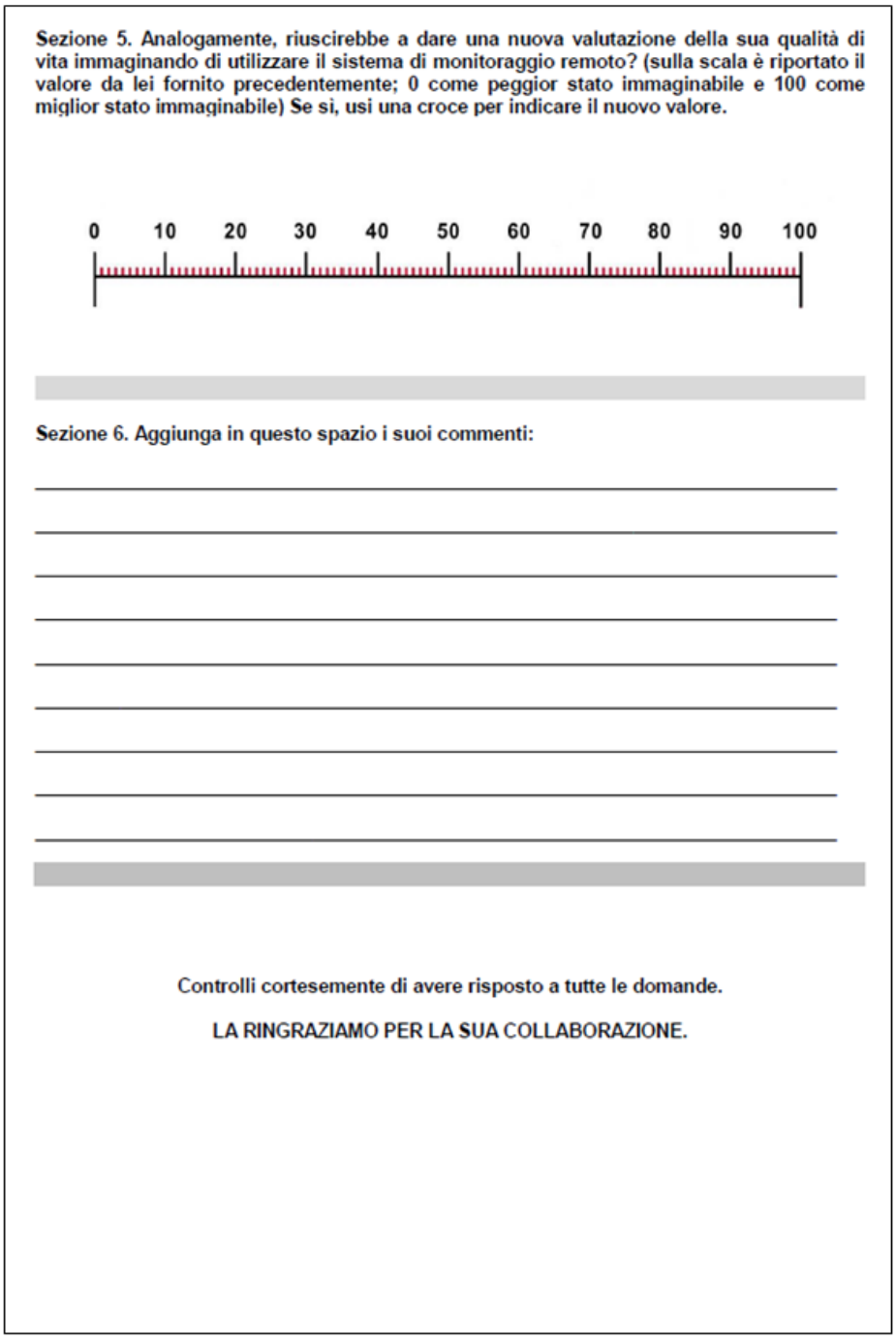
	Sì	No	Non so
a. Grafici / storico della glicemia.	☐	☐	☐
b. Altre statistiche / analisi.	☐	☐	☐
c. Annotazioni del medico.	☐	☐	☐
d. Altro (indicare):			

Figure B.3: **Post-study questionnaire in Italian language administered after using the remote monitoring service (Part 1).**

Sezione 4. Riveda le risposte che aveva dato precedentemente alla luce del sistema di monitoraggio remoto che le è stato illustrato: secondo lei tale sistema potrebbe influenzare qualcuno dei seguenti aspetti? Indichi con una croce sull'ultima colonna.

	Mai	Raramente	A volte	Spesso	Molto spesso	Effetto del sistema
a. La nostra famiglia rinuncia a molte cose (e.g. viaggi insieme per tempi prolungati).	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
b . Nel prendermi cura di mio figlio non mi rimane molto tempo per gli altri membri della famiglia.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
c. Cambiamo spesso i piani all'ultimo minuto.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
d. Mi sembra di vivere sulle montagne russe: sono in crisi quando mio figlio sta male, sono sereno/a quando sta bene.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
e. Vivo alla giornata e non pianifico nulla per il futuro.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
f. Mi sento stanco/a.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
g. Rinunciamo a vedere parenti e amici	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza
h. Non abbiamo molto desiderio di uscire.	☐	☐	☐	☐	☐	☐ Migliora ☐ Peggiora ☐ Non influenza

Figure B.4: **Post-study questionnaire in Italian language administered after using the remote monitoring service (Part 2).**



Sezione 5. Analogamente, riuscirebbe a dare una nuova valutazione della sua qualità di vita immaginando di utilizzare il sistema di monitoraggio remoto? (sulla scala è riportato il valore da lei fornito precedentemente; 0 come peggior stato immaginabile e 100 come miglior stato immaginabile) Se sì, usi una croce per indicare il nuovo valore.

0 10 20 30 40 50 60 70 80 90 100

Sezione 6. Aggiunga in questo spazio i suoi commenti:

Controlli cortesemente di avere risposto a tutte le domande.

LA RINGRAZIAMO PER LA SUA COLLABORAZIONE.

Figure B.5: **Post-study questionnaire in Italian language administered after using the remote monitoring service (Part 3).**

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