UNIVERSITA' DEGLI STUDI DI PAVIA

FACOLTA' DI INGEGNERIA
DIPARTIMENTO DI INGEGNERIA INDUSTRIALE E DELL'INFORMAZIONE

DOTTORATO DI RICERCA IN BIOINGEGNERIA E BIOINFORMATICA
XXXI CICLO - 2018

EXPLOITATION OF PATIENT-REPORTED OUTCOMES IN THE MANAGEMENT OF CANCER OUTPATIENTS: INTEGRATION OF MOBILE TECHNOLOGY AND DIGITAL GUIDELINES

PhD Thesis by
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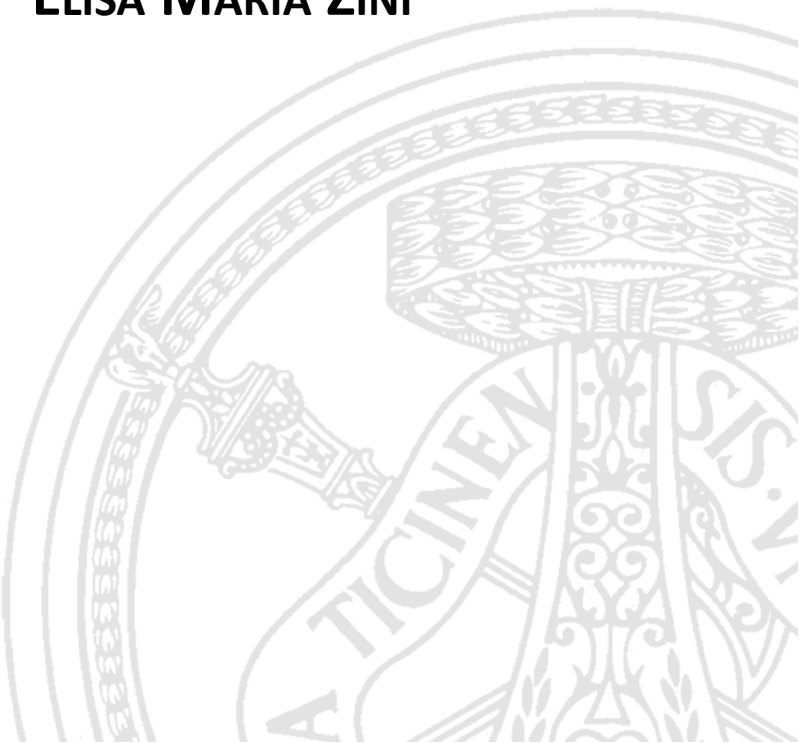

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The advance of technology is based on making it fit in
so that you don't really even notice it,
so it's part of everyday life.

Bill Gates

Abstract (English)

Today cancer is among the leading causes of death worldwide and its incidence is progressively increasing. However, at the same time, the survival trends have generally been improving. Thus, a better understanding of the short- and long-term impact of cancer and its treatments on patients' everyday lives is required, especially considering quality of life. In fact, many cancer survivors might face long-term disabilities requiring ongoing care and support, thus indicating that cancer can be considered a full-fledged chronic condition. Moreover, the increase in life expectancy has led to a consequent increase in the number of people affected by chronic diseases. Since hospitals have an ever-diminishing amount of beds and other resources, healthcare policymakers have been shifting the focus from acute hospital care to home care. As a result, most of the times, patients are treated at home, limiting the access to the hospital setting only to one-day assessments and follow-up visits.

Unfortunately, home care is still critical for heavy treatment regimens, such as cancer treatments, whose benefits often have as a counterpart toxicities severely impairing the patients' quality of life. However, usually, the sooner these toxicities are detected, the sooner

they can be treated, hence avoiding compromising the ongoing treatments. A suitable interaction with outpatients for acquiring frequent information about their symptoms during the treatment could help in early detecting or, possibly, preventing, adverse events. Historically, symptoms are monitored during office visits, generally scheduled at least every two or three weeks. Thus, patients might be concentrated on the visit itself and forget to discuss significant symptoms occurred days before, or they might also have difficulties contacting their clinicians between those encounters. For these reasons, the interest towards patients' self-management has been growing fast. In particular, the trend is to acquire data directly reported by patients, without interpretation by a clinician or anyone else, collecting the so-called Patient-Reported Outcomes (PROs).

Given today's wide availability of smartphones and tablets, patients generally prefer to use their personal devices for reporting their clinical data, as shown by several studies in the literature. However, despite this need, not many apps are available on the market allowing patients to report their outcomes. Moreover, these apps are usually generic, not customizable, and they cannot change their configuration over time according to a specific patient's clinical status. Some attempts to personalize reporting systems according to patients' clinical conditions have been reported in the literature; few of those examples exploit also a decision support system that suggests the doctor how to personalize the initial configuration of a monitoring system, adapting it to the patient's data. However, there seem to be no examples of a dynamic configuration of these systems based on clinical guidelines and changing based on the evolution of the patient's clinical status in time.

An important aspect of decision support systems is that they might need to timely access large amounts of data from varied sources, including PROs, data from monitoring sensors, either wearable or not, electronic health records (EHRs) and other hospital records. Therefore, the integration of data from all of these sources becomes crucial to the

delivery of accurate recommendations.

This dissertation proposes an architecture destined to integrate PROs, reported by cancer outpatients through applications for mobile devices, with other sources of data about those patients, in order to feed computer-interpretable guidelines. Those guidelines provide recommendations about the management of possible adverse events to the treatments undergone by patients, but also about the correct configuration of the app for collecting PROs, and the potential change of configuration in time, according to changes in the patient's clinical conditions.

This research activity has started with a requirements analysis for a system allowing outpatients to report PROs, considering functionalities required by both patients and doctors, and presenting some generic use cases. Then, the architecture has been designed and developed. The foreseen workflow implemented by this architecture starts with the formalization of paper guidelines through a dedicated tool, Alium, based on the PROforma language. The resulting computer-interpretable guidelines (CIGs) are then saved into a library accessible from the Alium execution engine, which retrieves patients' data from a middleware database, containing the integration of data from the EHR with data from a smartphone application for collecting PROs. Through a dedicated graphical interface, the doctor can see the patient's data and launch the execution of the desired CIG, choosing among the CIG for managing adverse events and the one for the correct configuration of the app (in terms of which clinical data and which questionnaires to collect and with which frequency), based on the specific patient's data. Recommendations are shown to the doctor as selectable items, so that the doctor can choose the ones to accept and the ones to discard. When accepted recommendations concern the app configuration, the system writes the new configuration into the database, and the app is updated at the next synchronization.

This dissertation describes in detail the materials and methods used

for each component of the architecture, starting with the integration database, whose structure is based on the HL7 virtual Medical Record (vMR) standard. The link between the database and the Alium execution engine, hosted on a remote server but accessible through APIs, is provided by a component expressly developed within this research activity. This component starts the execution of a guideline, queries the execution engine for the data necessary to the process continuation, retrieves those data from the database, and sends them to the execution engine, so that it can generate the proper recommendations; these recommendations are then retrieved and shown into the doctor's user interface.

Finally, two real-case applications are described, in which at least part of the architecture has been implemented in a hospital context. Both studies saw the collaboration of the National Cancer Institute in Milan. The first experience involved a system allowing patients affected by head and neck cancer and undergoing concurrent chemo-radiotherapy to report the symptoms of adverse events, clinical measures, and quality of life. This system was evaluated in a pilot study that will be extensively described in this dissertation. The second experience involved a system with similar purposes, directed to patients with different types of cancer and undergoing immunotherapy. In this case, no medical guidelines about the management of side effects existed, so the implementation was limited to the patient's app. Moreover, a terminology of patient-friendly symptoms was inserted into the app, in order to collect structured and reusable data.

Future directions of this research activity include an analysis of the doctors' compliance to the guidelines, storing the recommendations that they accept and refuse, and an assessment of the impact of the proposed architecture on the process of care of cancer outpatients. Moreover, it would be interesting to investigate new emerging standards for data integration, such as OHDSI on FHIR.

Abstract (Italian)

Al giorno d'oggi il cancro è tra le principali cause di morte in tutto il mondo e la sua incidenza sta aumentando progressivamente. Tuttavia, allo stesso tempo, le possibilità di sopravvivenza stanno generalmente aumentando. Di conseguenza, è necessaria una migliore comprensione dell'impatto a breve e lungo termine del cancro e dei suoi trattamenti sulla vita quotidiana dei pazienti, in particolare per quanto riguarda la qualità della vita. Infatti, molti pazienti che sopravvivono al cancro si trovano ad affrontare disabilità permanenti o a lungo termine, che richiedono cura e supporto continui, a indicazione del fatto che il cancro può essere considerato una malattia cronica a tutti gli effetti. Inoltre, l'aumento dell'aspettativa di vita ha portato ad un conseguente aumento del numero di persone colpite da malattie croniche. Poiché gli ospedali hanno un numero di letti e di altre risorse che diminuisce costantemente, i responsabili delle politiche sanitarie stanno spostando sempre di più l'attenzione dalle cure ospedaliere alle cure domiciliari. Pertanto, nella maggior parte dei casi i pazienti seguono la terapia a casa, limitandosi ad andare in ospedale solo per accertamenti in giornata e visite di follow-up.

Purtroppo, la cura domiciliare è ancora critica per quanto riguarda

i regimi terapeutici gravosi, come quelli per il cancro, i cui benefici sono spesso limitati da tossicità che compromettono gravemente la qualità della vita del paziente. Tuttavia, di solito, prima tali tossicità vengono rilevate e identificate, prima possono essere trattate, evitando dunque di danneggiare il trattamento in corso. Un'adeguata interazione con i pazienti domiciliari per l'acquisizione frequente di informazioni riguardo ai sintomi manifestati durante il trattamento potrebbe aiutare a identificare precocemente o, addirittura, prevenire eventuali eventi avversi. Tradizionalmente, i sintomi vengono monitorati durante le visite ambulatoriali, generalmente programmate almeno ogni due o tre settimane. I pazienti potrebbero dunque essere concentrati sulla visita in sé e dimenticare di ripotare sintomi significativi manifestati giorni prima, oppure potrebbero anche avere difficoltà a contattare il proprio medico tra un incontro e il successivo. Per questa ragione, sta velocemente crescendo l'interesse nei confronti dell'autogestione dei pazienti. In particolare, si tende sempre più ad acquisire dati che siamo riportati direttamente dai pazienti, senza alcuna interpretazione da parte dei medici o terze persone, raccogliendo i cosiddetti Patient-Reported Outcomes (PROs).

Data la odierna larga diffusione di smartphone e tablet, i pazienti preferiscono generalmente utilizzare i propri dispositivi per riportare dati clinici, come mostrano diversi studi in letteratura. Nonostante tale necessità, non ci sono però molte app sul mercato che permettano ai pazienti di riportare i propri outcome. Inoltre, queste app di solito sono abbastanza generiche e non è possibile cambiare la loro configurazione nel tempo sulla base dello stato clinico di uno specifico paziente. In letteratura sono stati riportati alcuni tentativi di personalizzare sistemi di monitoraggio secondo la condizione clinica di un paziente; in pochi di questi esempi viene sfruttato anche un sistema di supporto alle decisioni che consiglia al medico come personalizzare la configurazione iniziale di un sistema di monitoraggio, adattandola ai dati di un determinato paziente. Tuttavia, non sembrano essere presenti esempi di

una configurazione dinamica basata su linee guida mediche, che cambi in base all'evoluzione dello stato clinico del paziente nel tempo.

Un importante aspetto dei sistemi di supporto alle decisioni è che hanno bisogno di un accesso tempestivo a grandi quantità di dati provenienti da svariate fonti, che possono includere i PROs, sensori per il monitoraggio, indossabili o meno, cartelle cliniche elettroniche (EHRs) e altri registri ospedalieri. Perciò, l'integrazione di tutti questi dati diventa di fondamentale importanza per la distribuzione di raccomandazioni accurate.

Questa tesi propone una architettura destinata a integrare PROs, riportati dai pazienti domiciliari tramite applicazioni su dispositivi mobili, con altre fonti di dati riguardanti tali pazienti, allo scopo di alimentare linee guida informatizzate. Tali linee guida forniscono raccomandazioni sulla gestione di eventuali eventi avversi ai trattamenti seguiti dai pazienti, ma anche sulla corretta configurazione delle app per la raccolta dei PROs, e sull'eventuale modifica della configurazione nel tempo, in seguito al cambiamento delle condizioni cliniche del paziente.

L'attività di ricerca è iniziata con una analisi dei requisiti per un sistema di raccolta di PROs da pazienti domiciliari, considerando sia le funzionalità richieste dai pazienti stessi, sia quelle richieste dai medici, e proponendo alcuni casi d'uso generici. L'architettura è stata poi progettata e sviluppata. Il workflow previsto e implementato da tale architettura parte dalla formalizzazione delle linee guida cartacee tramite un apposito tool, Alium, basato sul linguaggio PROforma. Le linee guida informatizzate vengono quindi salvate in una libreria accessibile dal motore di esecuzione di Alium, che recupera i dati dei pazienti da un database di middleware, contenente l'integrazione dei dati provenienti dalla cartella clinica elettronica con quelli di un'applicazione per smartphone per la raccolta di PROs. Attraverso un'apposita interfaccia grafica, il medico può vedere i dati del paziente e lanciare l'esecuzione della linea guida desiderata, scegliendo tra quella per la gestione degli eventi avversi e quella per la corretta configurazione

dell'app (quali dati e questionari raccogliere e con quale frequenza), sempre basandosi sui dati dello specifico paziente. Le raccomandazioni vengono mostrate al medico sotto forma di elementi selezionabili, in modo che il medico possa scegliere quali accettare e quali rifiutare. Quando le raccomandazioni accettate riguardano la configurazione dell'app, il sistema scrive la nuova configurazione nel database e l'app viene aggiornata alla sincronizzazione successiva.

La presente tesi descrive nel dettaglio gli strumenti e i metodi utilizzati per ogni componente dell'architettura, a partire dal database di integrazione, la cui struttura è basata sullo standard virtual Medical Record (vMR) di HL7. Il collegamento tra questo database e il motore di esecuzione di Alium, ospitato su un server remoto ma accessibile tramite API, avviene grazie ad una componente appositamente sviluppata nell'ambito di questa attività di ricerca. Questa componente ha il compito di inviare il comando di esecuzione di una linea guida, interrogare il motore di esecuzione circa i dati necessari alla prosecuzione del processo, recuperare tali dati dal database e inviarli al motore di esecuzione, in modo che quest'ultimo possa generare le dovute raccomandazioni, che vengono poi recuperate e inviate all'interfaccia utente del medico.

Infine, vengono presentati due casi reali di applicazione, in cui almeno una parte dell'architettura è stata implementata in un contesto ospedaliero. Entrambi gli studi sono stati svolti in collaborazione con l'Istituto Nazionale dei Tumori di Milano. La prima esperienza ha riguardato un sistema che permetta a pazienti affetti da tumore testa-collo sottoposti a chemio-radioterapia concomitante di riportare i sintomi di eventuali effetti collaterali, le misure cliniche e la qualità della vita. Il sistema è stato valutato in uno studio pilota, che sarà descritto approfonditamente in questa tesi. La seconda esperienza ha riguardato un sistema con scopi simili al precedente, indirizzato però a pazienti con diversi tipi di tumore e sottoposti a immunoterapia. In questo caso non esistevano linee guida mediche da formalizzare,

perciò l'implementazione ha riguardato principalmente l'app per il paziente. Inoltre, è stata inserita nell'app una terminologia di sintomi patient-friendly, in modo da raccogliere dati strutturati e riutilizzabili.

Possibili direzioni future di questa attività di ricerca includono un'analisi della compliance dei medici alle linee guida, registrando le raccomandazioni che vengono accettate o rifiutate, e una valutazione dell'impatto dell'intera architettura sul processo di cura dei pazienti domiciliari con il cancro. Inoltre, potrebbe essere interessante investigare nuovi standard emergenti per l'integrazione di dati, come OHDSI on FHIR.

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List of Abbreviations

AERS Adverse Events Reporting System

AMC Academic Medical Center

API Application Programming Interface

App application

BMI Body Mass Index

CDS Clinical Decision Support

CIG Computer-Interpretable Guideline

CPG Clinical Practice Guideline

CCRT Concurrent Chemo-Radiotherapy

CTCAE Common Terminology Criteria for Adverse Events

DSS Decision Support System

EHR Electronic Health Record

ePRO electronic Patient-Reported Outcome

ETL Extract, Transform, Load

FDA Food and Drug Administration

GSMA Global System for Mobile communications Association

GEM Guideline Element Model

HL7 Health Level 7

HNC Head and Neck Cancer

ICD the International Classification of Diseases

ICD9-CM ICD 9, Clinical Modification

ICF the International Classification of Functioning, Disability and Health

INT Istituto Nazionale dei Tumori

IoT Internet of Things

IRAE Immune-related Adverse Event

IVR Interactive Voice Response

LOINC the Logical Observation Identifiers Names and Codes

MedDRA Medical Dictionary for Regulatory Activities

OHDSI Observational Health Data Sciences and Informatics

ORN Osteoradionecrosis

PILs Patient / Package Information Leaflets

PRO Patient-Reported Outcome

qSOFA Quick SOFA

RMSE Root Mean Squared Error

SIRS Systemic Inflammatory Response Syndrome

SNOMED CT the Systematized Nomenclature of Medicine, Clinical Terms

SOFA Sequential [Sepsis-related] Organ Failure Assessment

SUS System Usability Scale

TNM Task Network Model

UML Unified Modeling Language

UMLS Unified Medical Language System

vMR virtual Medical Record

WHO World Health Organisation

Chapter 1

Introduction

Nowadays, cancer is among the leading causes of death worldwide. The incidence of cancer is progressively increasing: the International Agency for Research on Cancer [1] estimated that in 2012 there were 14.1 million new cases of cancer and 8.2 million deaths from cancer worldwide [2]. A more recent research estimates that there were 3.9 million new cases and 1.9 million deaths only in Europe in 2018 [3]. According to the same research, Europe alone contains 9% of the world population but has a 25% share of the global cancer burden. The third cycle of a global surveillance program that documents cancer survival trends (CONCORD [4]) includes the records of 37.5 million patients diagnosed with cancer from 2000 to 2014 [5]. The results of the study showed that survival trends are generally increasing, even for some of the most lethal cancers. Some countries showed a 5% increase in survival for liver, pancreatic, and lung cancers, and, for most cancers, more than 50% of patients are surviving. Therefore, it is important to understand more about the impact of cancer and its treatments on the patients' everyday lives, especially the short- and long-term impact on patients' quality of life and symptoms. Retzer et al. [6], in their review,

underline the key role played by Patient-Reported Outcomes (PROs) in this field: PROs may be used in addition to traditional clinical data to supplement clinical findings and achieve a holistic understanding of patients' status. The importance of PROs, however, extends beyond the clinical use in routine cancer care; their relevance is recognized also by the pharmaceutical industries, alongside with biomarkers of health improvement [7], and in cancer research. In the last case, they can guide future patients' choices and clinical decision making [6]. Their best use is complementary to the classical collection of patients' data, and they help in eliciting patients' perceptions of their health status. For this reason, the last trends in healthcare systems tend towards integrated models of service delivery. In these frameworks, decision support systems are usually distributed systems, with the purpose to guide both patients and their professional or informal caregivers. In order to provide accurate recommendations, these decision support systems usually need to access the data collected in the hospital setting and stored in electronic health records, complemented by PROs and data collected through monitoring sensors. Therefore a proper integration of all of these data becomes paramount.

Considering this context, the present work proposes an architecture destined to exploit patient-reported outcomes in the management of cancer outpatients by integrating mobile technology and computer-interpretable guidelines. This dissertation describes the architecture in detail and presents two case studies in which that architecture was implemented.

1.1 Dissertation Outline

Starting from the above-mentioned scenario, this dissertation will explore the topic of patient-reported outcomes in the management of cancer outpatients and how they can be integrated in the complex

infrastructure of health information systems in a standardized and structured form, to be reused within the process of care or in clinical decision support systems.

Chapter 2 explains the context of this work, introducing the recent trends of home care and remote patient monitoring. A definition of patient-reported outcomes follows, together with different forms of intervention aiming at supporting outpatients. Since the systems presented in this work involve a mobile component, an overview of the global mobile internet penetration and technologies is provided, together with a brief review of mobile applications for oncology on the market and in the literature. Finally, the chapter introduces Computer-Interpretable Guidelines (CIGs), mentioning several approaches developed for their formalization and execution and focusing in particular on those of interest for this work.

Chapter 3 focuses on the current trends in integrating electronically collected patient-reported outcomes and CIGs into the care workflow. It examines the available standards for the integration of data from different sources and for the representation of medical concepts.

Chapter 4 presents the functional requirements of the system. It presents an analysis of requirements for both patient's and doctor's sides of the system, including some use cases that better detail those requirements.

Chapter 5 describes the overall architecture of the system designed within this thesis work, detailing all of its components: the decision support tools, the data integrator, the applications for doctors and patients.

Chapter 6 presents two case studies in which the architecture under consideration was partly implemented, examining the specific contexts of use, the implementation, and the realized or foreseen evaluation.

Finally, **Chapter 7** gives some final considerations and concludes the dissertation, remarking on open issues and possible future directions of this research.

Chapter 2

Background

2.1 Home Care and the Need for Remote Patient Monitoring

During the last decades, due to the increase in life expectancy and consequently in the number of people affected by chronic diseases, and considering the often limited amount of hospital beds (e.g., in Italy this number halved from 1994 to 2012 [8]) and other resources, healthcare policymakers have shifted the focus from acute hospital care to home care. As a result, nowadays, most of the times a large number of patients are treated at home, and they go to the hospital only for one-day assessments and follow-up visits. Several care models have been proposed and experimented for that purpose.

Different Cochrane reviews [9, 10], report on the effects of early discharge with the "hospital at home" service, which provides active treatment by healthcare professionals at the patient's home, comparing it with in-patient hospital care. Generally, they report insufficient evidence that providing services to people at home after their early

discharge might increase the risk of death or readmission, or adversely affect patients' quality of life or the completion of daily activities (such as dressing or daily chores). Actually, patients who had a stroke or elderly patients seemed to have less risk of being admitted to residential care if they were discharged home early with "hospital at home" services. Moreover, patients seemed to be more satisfied with their care at home, and their caregivers, in most cases, did not report additional burden. On the other hand, those reviews could not prove with sufficient evidence that this kind of services allows a significant reduction of costs in the healthcare system. However, despite the non-reduction of costs, the improvement in patients' satisfaction and quality of life with comparable costs can also be considered a good result. An implementation of such a care model, involving a home-based nursing intervention for cancer patients, is reported in a pilot study by Font et al. [11]. Font demonstrates that such an intervention can potentially avoid or reduce the length of hospitalization in selected cancer patients with acute medical complications.

Other organizations focused, instead, on the continuity of care. For example, the PRISMA model (Program of Research to Integrate the Services for the Maintenance of Autonomy) has been adopted by the Quebec Ministry of Health and Social Services and has been shown to increase the quality of care for frail elderly with no additional costs [12].

In the past, home care was mostly oriented towards chronic conditions such as diabetes, cardiovascular diseases, or chronic respiratory diseases. However, more recently, due to the introduction of new therapies, the number of people living with cancer has increased. Many cancer survivors end up with long-term disabilities requiring ongoing care and support, thus indicating that cancer can be considered a full-fledged chronic and complex condition.

Nevertheless, home care is still particularly critical when patients undergo heavy treatment regimens. For example, the benefits of

chemotherapy or radiotherapy may be compromised by their associated toxicity, which may lead to a severe impairment of the patients' quality of life or even to death. The occurrence of toxicity may require reducing the treatment dose and intensity, thus increasing the treatment duration and negatively affecting its outcome. Another example is immunotherapy, one of the latest cancer treatments, which relies on the ability of the immune system to recognize tumor cells and contrast their growth. Despite its efficacy, unfortunately, this treatment might unbalance the immune system, favoring the development of a wide spectrum of autoimmune manifestations, also referred to as Immune-related Adverse Events (IRAEs) [13]. Usually, the later IRAEs are detected, the longer they need to be treated, sometimes even along with the suspension of the treatment, compromising its efficacy.

In order to avoid negative consequences to these treatment regimens, the prevention, the early detection, and the treatment of toxicities become essential tasks. Moreover, in order for clinical practice guidelines to be effective, they must rely on a suitable interaction with the patients for acquiring any information useful to early detect or, possibly, prevent, those events.

Historically, the monitoring of symptoms is usually performed during scheduled office visits, which often have to respect strict time limits that must also include a physical examination and other tasks. Since the visits are generally scheduled at least every two or three weeks and patients might be concentrated on the visit itself, they might forget to discuss significant symptoms. Furthermore, patients might also have difficulties contacting their clinicians between those encounters.

For these reasons, the interest towards patients' self-management is growing fast, empowering patients, who acquire a central role in the management of their own illness [14, 15]. Studies in the literature show that patients enrolled in self-management programs experienced statistically significant improvements in health status, health behaviors, and self-efficacy, not to count the fewer accesses to emergency depart-

ments [16, 17, 18]. Therefore, considering also the previously mentioned shift towards home care, nowadays the trend is to acquire data directly reported by patients, collecting the so-called Patient-Reported Outcomes (PROs).

2.2 Patient-Reported Outcomes

The Food and Drug Administration of the United States defines Patient-Reported Outcomes as a *report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else* [19]. PROs have proved to be very useful to assess the patients' conditions, enhance the clinicians' awareness, improve symptom management [20, 21], identify psychosocial problems [22, 23], and ease patient-provider communication [24, 25]. They usually include physical parameters (e.g., pain, weight, blood pressure), psychosocial symptoms (e.g., fatigue, anxiety, depression), functional assessment scores [26, 27], or Quality of Life (QoL) scores [28].

Customarily, patients simply keep a paper diary in which they annotate on a daily basis the parameters required by the clinicians or the problems that occur. However, since patients with severe chronic conditions may be reluctant to discuss their symptoms with providers for several reasons, more focused interventions have been proposed in the literature.

The simplest form of intervention consists in regularly dispatching staff members at the patient's home. This intervention model has been proposed, for example, by Molassiotis et al. [29], within a Home Care Nursing program for patients with a diagnosis of colorectal or breast cancer who were receiving oral chemotherapy. The program introduced one standard home visit during the first week of chemotherapy, during which the therapy and its side effects were discussed, patients could

find answers to their doubts, and support was given. Subsequent home visits were offered when patients experienced multiple grade 3 toxicities or had difficulty coping with the chemotherapy. Moreover, patients received one monitoring phone call per week during all cycles, for minimum 18 calls during the whole intervention. More recently, Font et al. [11] have proposed a home-based intervention program named Bridge Project, which planned nursing interventions for each patient, including the administration of intravenous and/or subcutaneous medications, blood tests, symptom evaluation and control, supervision and promotion of adherence to oral medications, healthcare education, and scheduled telemonitoring phone calls according to specific patient and episode needs. This model of intervention is meant to reduce or avoid hospitalizations in outpatients, thus achieving a great clinical and economic value. These literature studies, describing pilot trials involving teams of five nurses, report indeed from moderate to significant improvements in the clinical management of outpatients. However, no information is provided about the possible costs of a large-scale intervention.

Other forms of intervention aiming at supporting outpatients while reducing healthcare-related costs use electronic systems for the collection of PROs. These systems, called electronic Patient-Reported Outcomes (ePROs) are becoming popular to collect data, analyze them, and summarize the results to both patients and doctors. Compared to the conventional paper-pencil approach, ePROs are more efficient and they also increase data quality [30, 31].

The collection of correct, complete, and timely data is a long-standing problem, which often comes along with the issue of data reusability. The recording of data once in a standardized and structured way at the point of care, so that they are reusable within the care process as well as for secondary purposes, is referred to as COUMT paradigm ('Collect Once, Use Many Times') [32]. Access to unambiguous data of good quality can avoid recollecting the same information in

different contexts, thus saving time that clinicians can dedicate to the acquisition of new information, preventing errors, and even increasing the research potential of clinical data [33]. Various technologies have been used as an effective means for acquiring ePROs with promising results: Interactive Voice Response (IVR) / phone calls, web-based forms/emails, videoconferencing, MMS, video or voice messages, SMS messaging, and applications for smartphones [34].

Telephonic IVR usually consists in predefined-frequency calls, often on a daily basis, which may become unbearable for patients in the long-term follow-up. Better results could be achieved if the patients were able to call the system only when they experience moderate or higher symptoms, as proposed for future developments of the SymptomCare@Home system [35, 36], which includes, together with the symptom monitoring functionality, automatic self-management coaching and a decision support-symptom management system for clinicians.

Web-based systems are more versatile. According to a review by Jensen et al. [37], more than half of the identified ePROs systems are web-based and accessible through computer or tablet. Examples of successful interventions include the web system for patients recovering from major gynecologic cancer surgery described by Cowan et al. [38] or the Comprehensive Health Enhancement Support System (CHESS) for people with HIV infection [39]. However, a major disadvantage of uniquely web-based interventions is the requirement for patients to be connected to the internet and to log in with username and password whenever they need to report symptoms, which could be unpractical and time-consuming. This problem is partially solved by those systems that provide a hub (usually a personal computer with specific software installed) at the patient's home with the task to aggregate data from sensors and PROs. These hubs are then connected through the internet to a remote server, to which they send encrypted data. An example is the CYCORE system for monitoring dehydration risk in head and neck cancer patients [40]. Nonetheless, the patients need to be at home

and have access to the hub in order to use these systems.

Conversely, native mobile applications may be more demanding in terms of effort, costs, and time to develop them, but they tend to be preferred by patients. In fact, with these apps patients can report symptoms as they occur, even outside the house and in the absence of an internet connection; the app saves data locally and synchronizes them to the hospital server when the connection is reestablished. Moreover, the login with username and password takes place once when the app is initialized, thus speeding up the reporting procedure. The feasibility study by Falchook et al. [41] enforces this concept: patients involved in the study expressed their preference for a reporting system delivered on smartphones rather than a website or paper surveys, and the use of the symptom reporting app was found to be substantially high even for the least compliant patients. Finally, the recent statistics about smartphone ownership and use highlight how mobile technology is acquiring increasing importance in everyday life [42].

2.3 Global Mobile Internet Penetration and Technologies

The Global System for Mobile communications Association (GSMA) (originally Groupe Spécial Mobile) [43] is an originally-European trade body that represents the interests of mobile network operators worldwide. Approximately 800 mobile operators are full GSMA members and a further 300 companies in the broader mobile ecosystem are associate members. GSMA Intelligence provides global mobile operator data, analyses and forecasts, and publishes every year authoritative industry reports and research, which cover every operator group, network and mobile virtual network operator in every country worldwide.

According to the GSMA Intelligence report "The Mobile Economy

2018" [44], more than 5 billion people were connected to mobile services in 2017, and the number of unique mobile subscribers will reach 5.9 billion by 2025, equivalent to 71% of the world's population. Figure 2.1 shows an infographic from that report, highlighting that also mobile internet adoption will increase significantly and that by 2025 4G will become the leading mobile network technology worldwide by number of connections, accounting for 53% of total mobile SIMs.

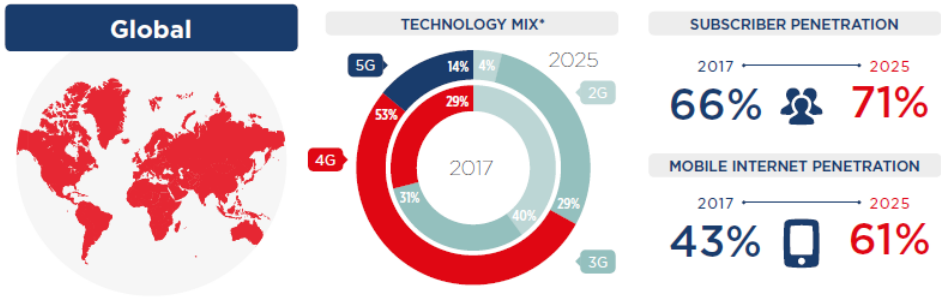


Figure 2.1: **Infographic about global mobile subscribers, mobile internet penetration, and technology mix.** [44]

According to the same report, smartphone adoption will grow by 20 percentage points globally between 2017 and 2025; by then, 75% of mobile connections will operate on smartphones, while the rest will operate on basic or feature phones and data-only devices, such as cellular tablets, dongles, routers or hotspots. Therefore, the smartphone will become the leading handset type by 2025. Figure 2.2 shows smartphone adoption as a percentage of total mobile connections, excluding cellular Internet of Things (IoT). With these figures in mind, it is easy to foresee that more and more people will use their phones on a regular basis to access not only messaging and social media, but also entertainment content, e-commerce, financial services, and even health services. These data suggest that ePROs may be successfully acquired through applications running on mobile devices.

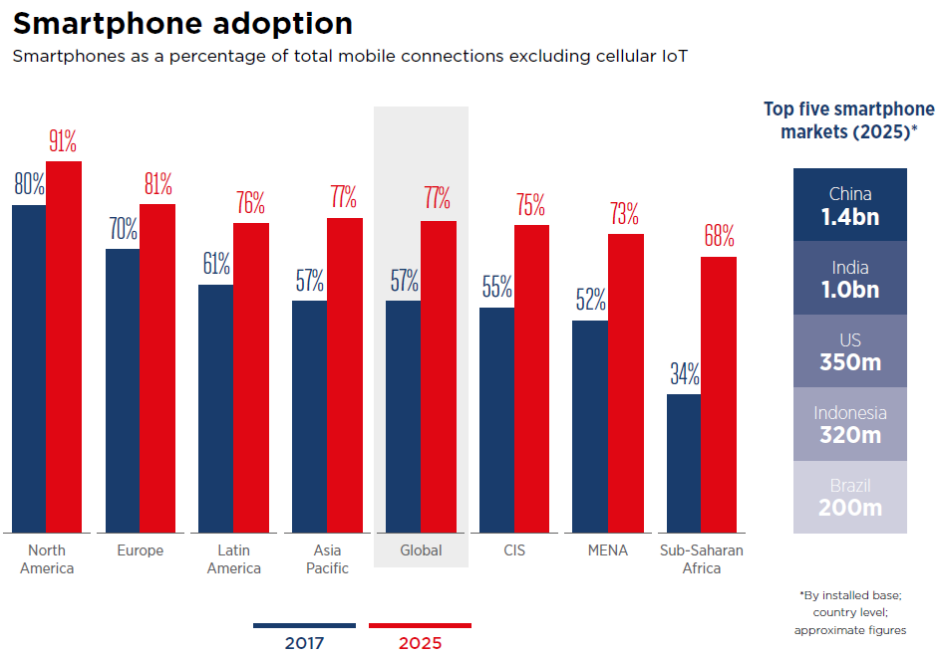


Figure 2.2: **Smartphone adoption as a percentage of total mobile connections excluding cellular IoT.** [44]

2.4 Mobile Apps in Oncology on the Market and in the Literature

In a recent study, Brouard et al. [45] reviewed mobile applications related to oncology with the purpose to evaluate their business model and scientific validation. The study was restricted to English applications from the Apple App Store and the Google Play Store (539 mobile applications were identified) and reported for each application the intended audience (general population, patients, or healthcare professionals), the purpose (e.g., information, prevention, support, help

for prescription), and the area of interest. In this study, an application could be characterized by up to three purposes, only one type of cancer (or the category "All cancer"), and only one origin. Figure 2.3 to 2.5 show an adaptation of these results.

Despite the fact that 39.3% of the apps dedicated to patients have monitoring purposes (Figure 2.3), a known issue of most of the apps found on the stores is that they are not customizable and cannot change their configuration over time according to the specific patient's clinical status. As a consequence, the information provided to the patients is often general and imprecise or, at least, not fitting their individual case. In fact, although several apps are developed in collaboration with prestigious institutions, such as the American Society of Clinical Oncology, none of them is actually meant to establish an active link with the physicians, which is the core feature of the approach presented within this thesis work.

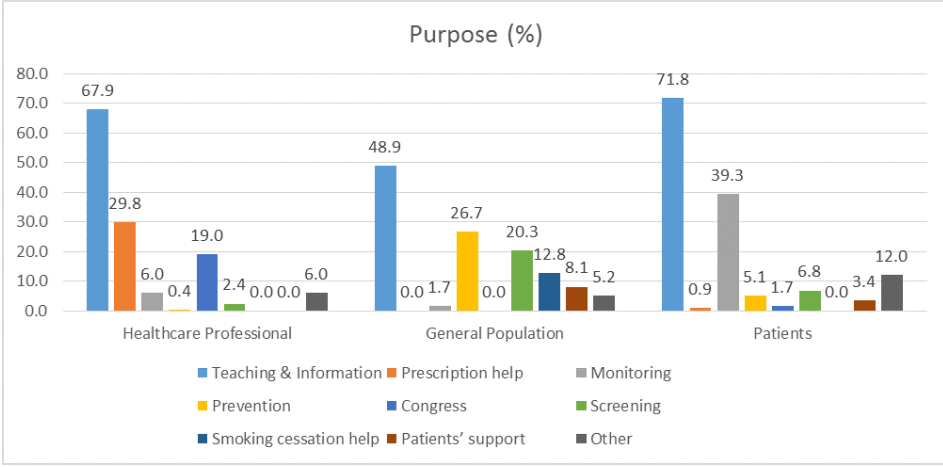


Figure 2.3: **Main purposes of the applications reviewed by Brouard et al.** An application could be characterized by up to three purposes. Adapted by [45].

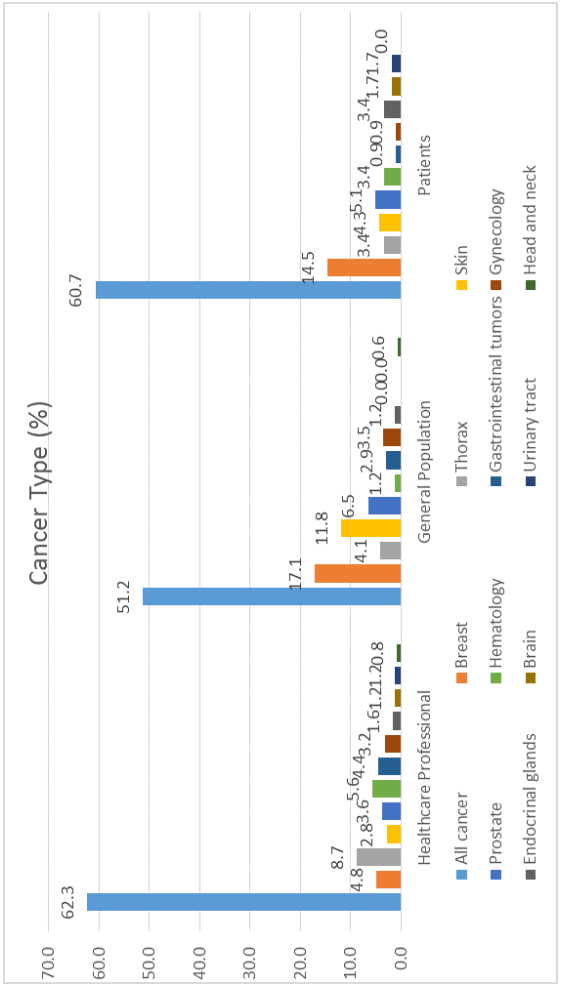


Figure 2.4: **Cancer types addressed by the applications reviewed by Brouard et al.** Adapted by [45].

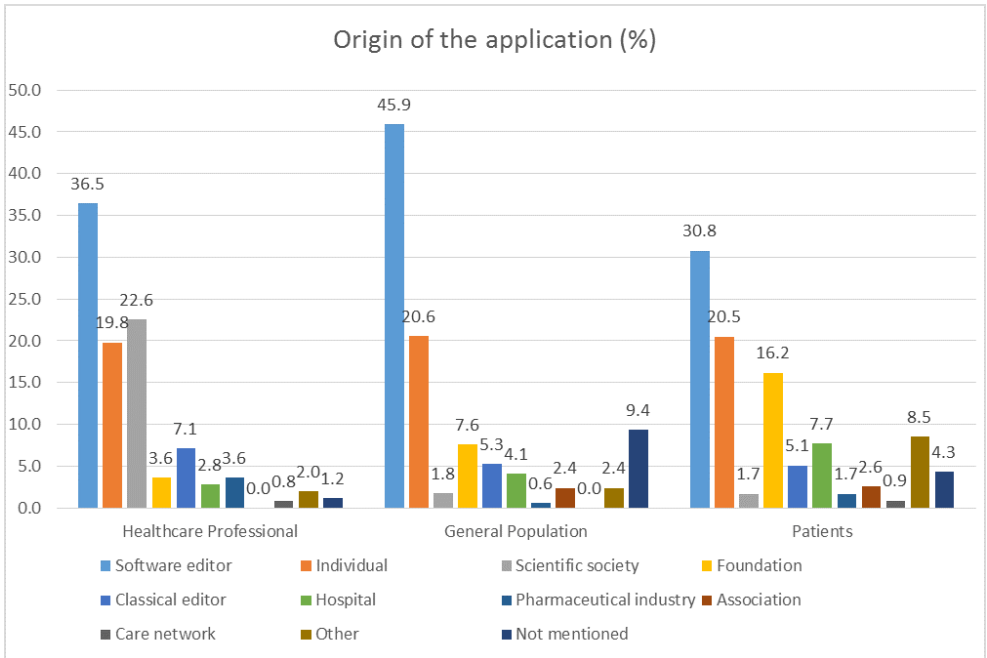


Figure 2.5: **Origin of the applications reviewed by Brouard et al.** Adapted by [45].

Nevertheless, in the literature, attempts to personalize applications do exist, even though they are addressed to diseases different from cancer. For example, the EU project MobiGuide [46, 47] developed an app for the monitoring of patients with atrial fibrillation (needing stroke prevention) or gestational diabetes. The app needs an initial configuration about the most frequent "contexts" a patient may live in, and the changes induced by those contexts in the patients' routine (e.g., "working days" versus "vacation", "regular physical activity" versus "increased physical activity"). Changes may affect, for example, the meal times and, in turn, the timing of the reminders for taking medications related to meals. Moreover, when the physician prescribes a new drug, the patient's app is automatically updated to issue reminders also for that drug. While representing a progress towards personalization, MobiGuide represents and runs guidelines only to generate recommendations related to the patient's treatment; no explicit recommendations about the app configuration are delivered.

Other systems use computer-interpretable guidelines to generate patient-tailored educational material, but they are web-based. For example, the system described by Jones et al. [48] generates relevant evidence-based material matching the guidelines with a patient profile, consisting in demographic and physical variables, and mails it to the patient via paper documents. Similarly, the Interactive Health Communication Application for patients with type 2 diabetes or chronic low back pain [49] provides information to patients about their disease, self-management education, and decision support.

However, to our knowledge, there are no examples of a dynamic configuration of apps based on guidelines. This is also witnessed by Ventola in his recent discussion about future trends of m-health [50], where he points out that mobile apps, in order to evolve into efficient clinical decision support systems, should incorporate artificial intelligence-oriented algorithms. He also adds that there is a need to develop standards for mobile apps so that they can seamlessly

contribute to advanced patient monitoring systems that are custom-designed for each patient. Accordingly, the effort presented in this dissertation goes exactly in that direction.

2.5 Computer Interpretable Guidelines

According to the definition given by the Institute of Medicine (US) Committee to Advise the Public Health Service on Clinical Practice Guidelines in 1990, Clinical Practice Guidelines (CPGs) are *systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances* [51]. CPGs provide more or less formal representations of medical knowledge necessary for the process of care. They aim to uniform the treatment of patients affected by similar pathologies in different health environments, improve the quality and efficacy of care and reduce healthcare costs as much as possible. In order to be effective, they need to be integrated with the care flow and provide recommendations at need [52].

There are several methodologies and technologies to present and disseminate CPGs. Most of them are still in a paper format (traditional volume, pocket leaflet, brochure), while others are in an electronic format. In this last case, we can underline the difference between a simple hypertext and Computer-Interpretable Guidelines (CIGs), which are systems able to provide recommendations to the doctor based on a specific patient's health status.

Numerous studies have shown the difficulties of disseminating (and therefore using) scientific evidence in the clinical practice through textual guidelines. The formalization of CPGs into CIGs allows the development of guideline-based Decision Support Systems (DSSs), which combine the knowledge contained in the CIGs with the patients' clinical data, in order to offer personalized advice. The use of these systems significantly improves the quality of care, especially if they are used

together with health information systems such as Electronic Health Records (EHRs) [53]. In order to create a CIG, the knowledge engineers collaborate with clinical experts to better interpret the guideline in narrative form, which often involves making some "implicit" medical knowledge explicit. This is of utmost importance to avoid interpretation and inference mistakes by the information systems. CIGs are defined using specific modeling languages, methodologies and tools for the acquisition and representation of knowledge. As described in a review by Peleg [52], different approaches have been developed to represent and execute clinical guidelines with data from a specific patient. These representations can be classified into three main categories: (i) document models, (ii) decision trees and probabilistic models, and (iii) task-network models.

Document models are idealized abstractions of a guideline document, masking certain details and highlighting others [54]. An example is the Guideline Element Model (GEM) [55], which is an XML-based knowledge model for guideline documents, and provides a hierarchy of more than 100 elements relating to a guideline's identity, developer, purpose, intended audience, method of development, target population, knowledge components, testing and review plan.

The second category of representation is decision trees and probabilistic models. A *decision tree* is a probabilistic model that can be evaluated by determining the expected utility or outcome and the optimal action strategy. Decision trees can also be used without probabilities, to specify a hierarchical decision algorithm that conceptually organizes the knowledge contained in the guideline, allowing the user to easily browse it [56, 57].

Finally, *Task Network Models (TNMs)* hierarchically decompose clinical guideline algorithms into networks of tasks that unfold over time, formally allowing the execution of the represented knowledge against patient data by an execution engine. Numerous task-network languages have been developed over the years to represent the know-

ledge contained in medical guidelines; among those, we can remember Arden Syntax [58], Asbru [59], EON [60], GLIF [61], GUIDE [62], GLARE [63] and PROforma [64]. The specific description of each of those languages is beyond the aim of this thesis, but a comprehensive illustration and comparison can be found in [65] and in the papers by their authors [58, 59, 60, 61, 62, 63, 64]. Most of these languages have common characteristics. For example, they can allow the graphical representation of tasks and networks, in order to simplify the guideline formalization process. Moreover, all of them support the specification and execution of actions, decisions, data enquiries, and hierarchical plans; they also support parallel tasks and their formalism facilitates the representation of if-then rules. On the other hand, each of those languages gives relevance to different features. For example, Asbru allows specifying process intentions and outcome intentions of the guideline and of its major subplans; GLARE emphasizes the management of temporal knowledge; GLIF gives priority to the sharing of CIGs among implementing institutions, etc.

In order to properly formalize CPGs into a computer-interpretable format using a TNM, an authoring tool is advisable, since it is a software explicitly designed to help users in speeding up and simplifying the formalization process, thanks to a dedicated graphical user interface.

2.5.1 PROforma and Alium

A number of authoring tools have been developed in the past [65] but only a few achieved the necessary stability for being used in the clinical practice. Among those, there is Alium, developed by Deontics Ltd (London, UK) [66] and recently renamed "Deontics Authoring Workbench", which is based on PROforma, a formal language combining logic programming and object-oriented modeling [64]. PROforma is also a knowledge representation language in that it is structured around a set of concepts and attributes conceived to be easily intelligible by

clinical professionals, thereby facilitating the encapsulation of medical knowledge and the customization of clinical procedures. Moreover, among the major formal languages for guideline representation available in the literature, PROforma was specifically designed by its authors to support guideline design and dissemination in the form of DSSs and workflow management systems [53]. Given that in the proposed architecture the modeling of clinical practice guidelines is instrumental for the implementation of a DSS, PROforma and Alium seemed to be a suitable choice for authoring and executing guidelines.

PROforma

PROforma represents processes as a set of components [67], the most frequently used being tasks and data items. PROforma defines four classes of tasks [64, 68]:

- *Action*: a procedure that needs to be executed in the external environment (e.g., a surgical procedure, a drug administration, or a database update);
- *Enquiry*: a point in the guideline where information must be acquired from an external person or system. Therefore, to define an Enquiry, the required information must be specified (data type, range of possible values, and other properties);
- *Decision*: a point in the guideline where a choice must be made, such as the choice of a therapy or a diagnosis. For each Decision, it is necessary to define the possible options, relevant information, and arguments in favor or against the different options;
- *Plan*: a collection of tasks grouped together for a specific reason, e.g., because they share a common clinical or therapeutical goal, use a common resource, or have to be executed in the same moment.

Actions, Decisions, Enquiries, and Plans all share common properties:

- *Name*: the task unique name;
- *Caption*: the name identifying the task in the user interface. It should be a brief comment allowing the user to easily identify the task functionality;
- *Description*: a longer comment providing the user with more details about the task;
- *Precondition*: a logical expression to be evaluated and that must be true in order for a task to be executed; otherwise, the task is discarded;
- *Constraints*: logical constraints that block a task execution before one or more other tasks have been executed.

Moreover, some classes of tasks have additional properties:

- **Decisions**
  - *Candidates*: the options to consider when taking a decision. Each Candidate might have one or more Arguments in favor or against;
  - *Arguments*: arguments in favor, against, or relevant for a particular Candidate. An Argument involves a logical expression that will be evaluated by the execution engine, a brief caption, and a textual user-friendly description.
- **Plans**
  - *Termination condition*: an expression defining the conditions on which the task can be *completed*;

– *Abort condition*: an expression defining the conditions on which the task is *discarded*.

In PROforma guidelines are stored as instances of the PROforma task ontology and using a language derived from the time-oriented control-flow language called Red Representation Language (R^2L) [53]. Therefore, a guideline consists of a series of declarations of tasks and relationships between them, and it can be organized in a hierarchy of Plans. Before the execution, guidelines are translated into another language, called L_{R2L} (Logic of R^2L), a language based on predicate logic. This language is used as input for the execution module.

Figure 2.6 shows an excerpt from a guideline written in R^2L. As it is evident, representing an entire guideline, which can involve defining hundreds of tasks, using R^2L can become very burdensome and it is not certainly a good communication means for clinicians and engineers. In order to encourage clinicians' to collaborate with knowledge engineers, a more intuitive language is needed. For this reason, PROforma also offers a graphical representation (Figure 2.7), on which several editors are based.

```
plan :: Protocol1 ;
        caption :: 'Management of weight loss (simplified)' ;
        precondition :: problem = weight_loss ;
        goal :: clinical_goal = manage : weight_loss ;
        component :: enquiryl ;
        Component :: decisionl ;
                schedule_constraint:: completed(enquiryl) ;
        Component :: decision2 ;
                schedule_constraint:: completed(decisionl) ;
        component :: plan1 ;
                schedule_constraint :: completed(decision2) ;
        Component :: plan2 ;
                schedule_constraint :: completed(decision2) ;
        component :: plan3 ;
                schedule_constraint :: completed(decisionl) ;
end plan .

decision :: decisionl ;
        caption :: 'Diagnosis?' ;
        goal :: goal = manage : cancer ;
        source ::
                age; mandatory :: yes ;
                smoker; mandatory:: yes ;
                biopsy; mandatory :: yes ;
                pain: site; mandatory :: yes ;
                pain: time; mandatory :: yes ;
        choice_mode :: single ;
        support_mode :: symbolic ;
        candidate :: cancer ;
                argument :: ( age = elderly) + ;
                argument :: ( smoker = yes) + ;
                argument :: ( biopsy = positive) + ;
                argument :: ( pain: time = immediate) + ;
                argument :: ( pain: site = epigastric) + ;
                recommendation ::
                        netsupport( decisionl, cancer) >= 1 ;
        candidate :: peptic_ulcer ;
                argument :: ( age = young or age = adult) + ;
                argument :: ( biopsy = negative) + ;
                argument :: ( pain: site = epigastric) + ;
                argument :: ( pain: time = delayed) + ;
                recommendation ::
                        netsupport( decisionl, peptic_ulcer) >= 1 ;
end decision .
```

Figure 2.6: **Excerpt of a guideline in R^2L.**

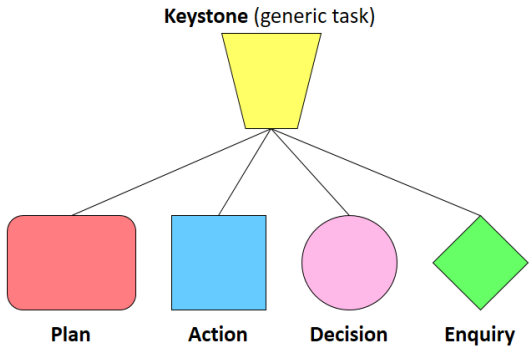


Figure 2.7: **The PROforma graphical representation.** Adapted by [64].

In this graphical representation, processes are represented as directed graphs, in which nodes are tasks to be executed and arcs, portrayed as arrows, represent constraints in the order of execution of the tasks. An arc indicates that the task at the head of the arc cannot start until the task at the tail of the arc (*antecedent* task) has been completed. A task can only be considered for activation when all its scheduling constraints have been met, i.e. when all its antecedent tasks have been completed or discarded. For example, in Figure 2.8, the Action "Post-Treatment Visit" cannot begin until the Enquiry "Treatment Phase?" has been completed. Scheduling constraints are not mandatory in PROforma: if they are not stated, tasks activate simultaneously, unless there are preconditions on them [69].

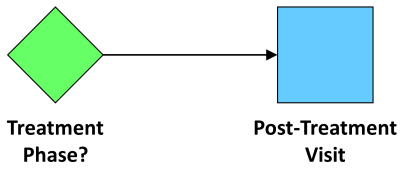


Figure 2.8: **Example of a scheduling constraint in PROforma.**

As anticipated, tasks have a *state* property, which can take four different values: *dormant*, *in progress*, *discarded*, and *completed*. Initially, All tasks are in the *dormant* state, and they can transition between states during the execution of the guideline. A task is *dormant* if it has not been started and it is not yet possible to say whether it will be started, *in progress* if it has been started, *discarded* if the logic of the guideline implies that it should not be started or completed, and *completed* if it has ended. Figure 2.9 illustrates the allowed transitions between task states.

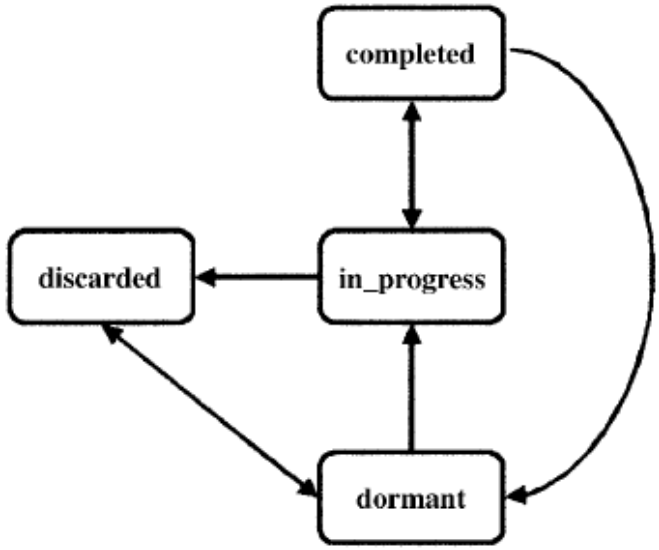


Figure 2.9: **Task state transitions in PROforma.** Figure by [67]. An arrow between two states indicates that a transition between those states is possible. The reason there are transitions out of the *completed* and *discarded* states is that tasks may be cyclic, that is, that they may be enacted many times during the enactment of a plan. The transition from *completed* to *in progress* occurs when the task itself cycles, and the transitions from *completed* and *discarded* to *dormant* occur when its parent plan cycles.

Alium

Alium integrates in a single application documents markup, process design, data and clinical logic definition, an execution engine, and a web interface allowing users to test the care pathways and clinical guidelines formalized with the editor. The care pathways modeled in Alium do not necessarily have to be based on a single paper document, but they can integrate several documents (called *Source Documents*), such as local and national guidelines, scientific papers, or protocols describing medical practices in a specific hospital. The Alium editor allows creating a clinical pathway using PROforma to define processes, data, clinical logic and decisions. All these elements can then be linked to specific sections of the source documents.

Once the process has been modeled in Alium, it can be executed by the Deontics execution engine, which keeps track of the activities that must be executed to continue in the care process and provides information to external agents (human users or other software components). The engine can be accessed through a specific set of Application Programming Interfaces (APIs), which may be invoked from an external environment to provide the data required as the guideline input, to activate the execution of the inferential processes encapsulated within the guideline itself and, finally, to collect the outputs.

Below, a list of key concepts in Alium:

- **Task**: the definition and properties of tasks are the same as in PROforma;

- **Data**: in Alium, a *data item* defines a piece of structured data that can be used in the application. For example, the patient's age, weight, or blood pressure. The value of each data item can be obtained from an external system (e.g., an EHR), directly or derived from other information, or manually inserted by a user. Data items can be of different types; the allowed data types are:

Text, Integer, Data/Time, Date, Time, Real, Set of Text, Set of Integer, Set of Real. It is also possible to define a range of values that a data item can accept. Moreover, a data item can be defined as *dynamic*, in which case the system computes its value according to a formula based on other data; for example, the Body Mass Index can be computed based on the patient's height and weight. Finally, data items can be defined as *mandatory*; in this case, the Enquiry that requires the data item cannot be completed until its value has been provided by the user or the system;

- **Evidence**: a statement, usually directly linked to a passage in a source document, that describes what claims are recommended (for or against) in a given clinical condition;
- **Claim**: a part of the evidence statement that describes one or more options that are recommended for or against when the given condition is true. They are usually linked to a passage in the source document(s);
- **Candidate**: a claim that has been formally connected to a decision task, allowing, however, the pathway author to reuse the candidate in other decisions;
- **Argument**: a formal logical rule that links data to decision-making: the rule is activated by specific values of some data items and produces recommendations (claims) accordingly. Each argument has also a weight determining if it is for or against the claim and how strongly. An example of argument, extracted from the guideline about the management of side effects of chemoradiotherapy described in Section 6.1.3, is shown in Figure 2.10, where it is possible to identify the elements of an Argument:
  - Condition: if gene repair disorders are diagnosed

- Data: gene repair disorder diagnosis
- Claim: consider avoiding radiotherapy (RT)
- Evidence: the part of guideline text provided in Figure 2.10.

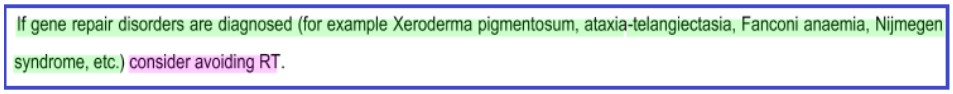


Figure 2.10: **Example of an Argument in Alium.**

Chapter 3

Current Trends: integration of ePROs and CIGs into the careflow

Recently, healthcare systems are asked to apply better integrated models of service delivery. In this framework, DSSs should be distributed systems, which should guide patients and caregivers (both professional and informal caregivers) wherever they are.

A crucial aspect for the success of a DSS is its integration with the patient's data. More data a DSS can access and timelier this access is, more accurate the recommendations delivered by the DSS will be.

Nowadays, the possibility of acquiring data is dramatically increased with respect to one decade ago. Thus, the integration of data from ePROs systems, monitoring sensors, either wearable or not, and EHRs is likely destined to improve the quality of care. In turn, patients' satisfaction with care and, consequently, compliance with treatments should increase.

However, there is still not enough clarity regarding the effects of

these new models of integration. The study by Baxter et al. [70] reports the effects of models of integrated care on actual and perceived service delivery in the United Kingdom, including the efficiency, effectiveness, and quality of care. After reviewing 161 studies, the authors conclude that models of integrated care are able to enhance patient satisfaction, increase perceived quality of care, and enable access to services, but the evidence for other outcomes, including service costs, remains unclear. It could be argued that the reduction of service costs per se, without considering the patients' perception of the provided service, could be of no use, if not even counterproductive in the long term. In fact, patients tend to be noncompliant with interventions that do not meet their needs. Conversely, the increase of patient satisfaction with a system could mean that patients will be compliant with the proposed treatments, leading in the long term to fewer accesses to the emergency departments.

From the technical point of view, the integration of data from multiple sources for clinical practice requires solutions that are stable and cross-platform, in order to handle complex and multivariate realities.

Several studies addressed this issue, starting with the Mobiguide project [46, 47] mentioned in Section 2.4. Mobiguide envisaged a data integrator component, based on the information model provided by the Health Level 7 (HL7) virtual Medical Record (vMR) standard [71]. The data integrator encapsulated the data storage, hiding its complexity from the rest of the components, while at the same time providing APIs suitable for inserting and reading data [72]. Another system exploiting the HL7 vMR for integrating the input clinical data in a DSS is described by Velicovski et al. [73], who offer a suite of services for the early detection and assessment of chronic obstructive pulmonary disease.

The following Sections will discuss how the integration of different data sources, among which a mobile app for collecting ePROs, was addressed within this thesis work.

3.1 Standards for the Integration of Data from Different Sources

DSSs, in order to be effectively used, need to be complemented with the information available in patients' EHRs [74, 75]. However, in the phase of DSS design the access to the EHR data model is usually not available, because it strictly depends on the choices of the different organizations and institutions. Moreover, there could be different sources of data, adopting different models, which have to be integrated. For example, the data collected through a monitoring app for outpatients are usually not enough to generate useful recommendations, since they lack the information concerning the patient's background and the results of laboratory tests that are available in the EHR. Thus, the data coming from the app need to be complemented with those available in the EHR, in order to obtain personalized recommendations for the specific patient. For this reason, a middleware layer is required with the purpose of collecting all the integrated data sources available at each setting. This allows to completely decouple the system implementation from the specific standards that may have been adopted at an installation setting.

In order to conform to current standards, and based on a recent comparison between different schemas [76], in this work the HL7 vMR for Clinical Decision Support (CDS) Logical Model, Release 2 [71], which originates from academic research [77], was adopted. A vMR for CDS is a model for representing clinical data, such as clinical knowledge and patient-related information, in the form of a simplified version of the clinical record that only includes data relevant to CDS. In order to ensure clinical quality, avoiding errors due to complexity, the vMR uses a simplified version of the HL7 Version 3 Release 2 data types and a simplified representation of clinical data. The model consists of a set of classes and it is built upon two axes. The first axis represents the type

of clinical information involved (e.g., *Procedure*, *Observation*, *Problem*, *SubstanceAdministration*, *AdverseEvent*, *Goal*, *Encounter*, *Supply*); the second one represents the clinical workflow moment (e.g., *Procedure-Proposal* represents a procedure that has to take place, generated by the CDS or by a consulting clinician, *ProcedureOrder* represents an order for a procedure to be done, while *ProcedureEvent* represents the actual event of performing a procedure) [72].

3.2 Terminological Standards

Many CPGs tend to include generic concepts and terms in their recommendations. For example, there could be a recommendation with a precondition referring to immunosuppression, which can be caused by immunosuppressive drugs or autoimmune diseases. However, in the EHR doctors usually prescribe drug therapies specifying the administered active substance or product, or they indicate the specific disease, not its generic category. Thus, in order to properly match the active substance name with the term "*immunosuppressive drug*" or the specific disease with "*autoimmune disease*", an additional inferential process, external to the guideline, is required. Moreover, the lack of uniformity between the terminologies used by the different sources is a typical problem of data integration processes and can lead to redundancies.

Several standards have been developed through the years by different organizations, with the purpose of uniforming and standardizing concepts. Cornet and Chute [78] thoroughly analyze the evolution of health terminologies, classifications, and ontologies over the past twenty-five years. They provide a clear distinction, based also on Cimino's work [79, 80], between terminologies, ontologies, and classifications:

- A *terminology* is a system of concepts with assigned identifiers and human language terms, typically involving some kind of

semantic hierarchy;

- An *ontology* is a terminology invoking formal semantic relationships between and among concepts;
- A *classification* is a terminology system intended to exhaustively describe a domain or topic;
- A *statistical classification* is a classification where all concepts are mutually exclusive, to avoid counting things twice.

According to Cimino's Desiderata [79], the criteria for a good terminology included poly-hierarchy and "no residual categories". However, these criteria are not met by statistical classifications. In their review, Cornet and Chute underline how this does not mean that statistical classifications are bad terminologies, but they are use-case specific.

The most visible statistical classification is the multiple versions of the International Classification of Diseases (ICD), whose 11th revision was recently published (June 2018), and whose 10th revision (ICD-10) was published in 1990 but was not adopted until 2015, to the point that today the previous version, ICD 9, Clinical Modification (ICD9-CM), is still widely adopted. Several studies highlight that ICDs, being statistical classifications, group terms in chapters organized by similarity of theme, but there is no formal relationship between the various chapters. Hence, these are more suitable as outputs for general reporting purposes, such as, for example, public health surveillance [80, 81]. They are not, however, much suitable as a standard data infrastructure for clinical applications that require a higher degree of specificity, such as DSSs.

Conversely, a terminology such as the Systematized Nomenclature of Medicine, Clinical Terms (SNOMED CT) better depicts the complexity of reality, with a view to integrate all data sources and provide decision support to clinicians. In fact, as explained in Section 3.1, the use

of a data integrator allows an abstraction from the data models and coding systems used by the specific institutions, entrusting the mapping between the hospital databases and the data integrator to specific Extract, Transform, Load (ETL) mapping routines[1].

Therefore, within this thesis work, in order to simplify the ETL processes responsible of joining data from different sources and in order to feed these data to the DSS, the same standard terminology was adopted both in the data integrator and in the formalized guideline. This was possible also because Alium natively interfaces with the BioPortal web service provided by the National Center for Biomedical Ontology [82], supporting three different terminology standards: the Logical Observation Identifiers Names and Codes (LOINC), SNOMED CT and ICD9-CM. For the reasons stated above, the adopted standard was SNOMED CT. The system is, however, open to the future use of other standards, considering the ongoing efforts to harmonize SNOMED CT and the International Classification of Functioning, Disability and Health (ICF) [83], together with studies to reach a semantic alignment between ICD classifications and SNOMED CT [84].

As an example of how Alium and SNOMED CT would deal with the immunosuppression problem presented at the beginning of this Section, Figure 3.1 shows the general concepts "*Immunosuppressant (substance)*" and "*Autoimmune disease (disorder)*" in SNOMED CT and a partial view of their children, that may recursively have their own children.

[1] As a matter of fact, in this context the data integrator acts similarly to a data warehouse, since data are collected from multiple sources (hospitalizations, control visits, and home monitoring) and integrated for analytic purposes.

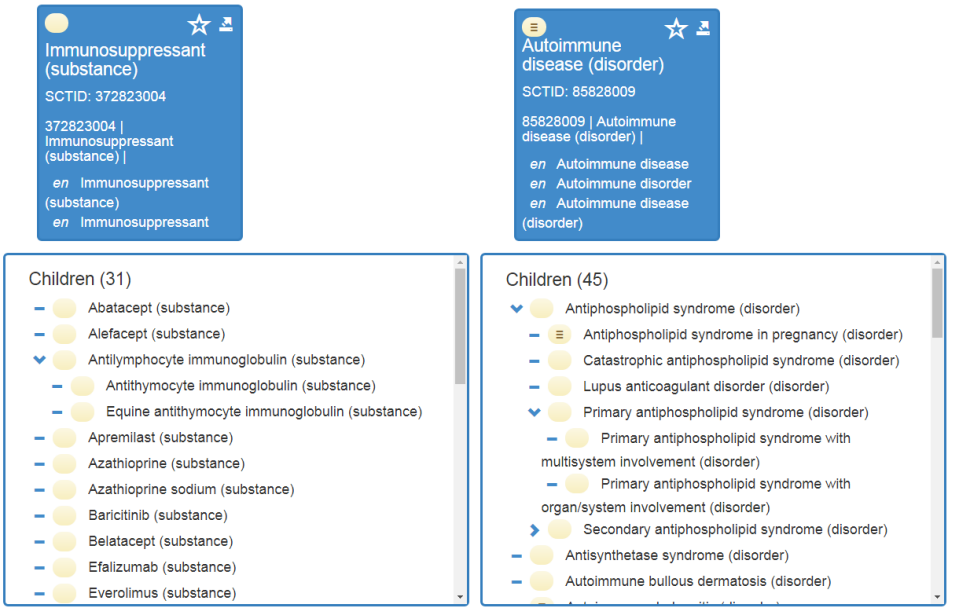


Figure 3.1: **General terms "Immunosuppressant (substance)" and "Autoimmune disease (disorder)" and their children in SNOMED CT terminology.**

Since it is not known a priori which of the children terms will be entered by the doctor in the patient's record, knowledge has to be explicitly added to handle this situation. The Alium editor facilitates this task by supporting the integration of terminologies and ontologies into the PROforma model [85]. In particular, it provides an Expression Editor to build workflow-processing rules for the engine (e.g., tasks preconditions), through expressions and conditions. Concerning the example of immunosuppression, the rule shown in Figure 3.2 could be used to detect if the patient is actually immunosuppressed.

```
if (comorbidities_relevant_list term_includes "SCT:85828009
[Autoimmune disease]"
   or drugs term_includes "SCT:69431002 [Immunosuppressant (product)]"
   or drugs term_includes "SCT:372823004 [Immunosuppressant
   (substance)]", "yes", "no")
```

Figure 3.2: **Example of a rule in the *Alium Expression Editor* for navigating the SNOMED CT terminology.**

In that rule, *comorbidities_relevant_list* and *drugs* are two data items required as input for the guideline, while *term_includes* is a function provided by Alium and available in its *Expression Editor*. In particular, this function can only be used in presence of an ontology, because it navigates the terms hierarchy. For example, if *comorbidities_relevant_list* included "*SCT:200936003 [Lupus erythematosus]*", the rule *comorbidities_relevant_list term_includes "SCT:85828009 [Autoimmune disease]"* would return *true*. In fact, the function *term_includes* returns *true* if the input concept is the *same-as* or a *child-of* any member of a Set data item, *false* otherwise. Through this rule, the taxonomy can easily be navigated to detect if the patient is immunosuppressed. In the same way, rules can be created using terms as generic as possible in the ontology hierarchy, to develop a lexicon related to the clinical problem considered.

Chapter 4

Functional Requirements

After the observations made in Chapter 2, the first step of this work consisted in a requirement analysis aimed at identifying the different levels of support that smartphones and tablets provide in the healthcare context and the functionality of the backend. This involves an analysis from the viewpoints of both patients and physicians.

Klasnja and Pratt [86] provide a useful classification of the different intervention strategies used in mobile-phones health applications. More recently, Cooley et al. [15] have analyzed the perspectives of patients and caregivers on decision support for the management of symptoms and quality of life. In that study, regarding eHealth-based systems, patients and caregivers identified several needs: (i) the ability to track their symptoms over time, (ii) access to web-based information, including imaging and charts, (iii) decision support recommendations about contacting the clinician, (iv) peer support, and (v) access to medical records. Moreover, they identified interventions of personalized advice and tailored supportive care as desirable.

4.1 Patient Side

Based on those works and taking into account previous experiences in collecting patient information [87, 88] and supporting therapy compliance [89] using mobile devices (and patients' comments following those experiences), a set of desirable requirements for the mobile component of the architecture presented in this work can be pointed out. That set of requirements has been classified into the following taxonomy:

- **Education**
  - General
    - Educational material from authoritative sources, in order to help patients in better understanding their disease and the treatment they are receiving (e.g., the motivation for diagnostic tests, treatments, side effects, etc.). The educational material should be concise and it should also include day-by-day practical information, such as first remedies to possible side effects that can occur[1], and how to prepare for invasive tests or interventions;
    - Links to web pages containing more details and verified information.
  - Personalized
    - Suggestions for the prevention of complications and side effects, contextualized to the specific PRO being entered or the whole patient history;
    - Advice on healthy diet and habits, contextualized to patient-specific conditions, providing also examples of

[1]Please note that it is not possible to "prescribe" any treatment, because that is an exclusive task of physicians. However, it is possible to show educational material, as it already happens with paper leaflets that are provided to patients, usually when they are discharged from the hospital or during visits.

recipes. For example, this is particularly useful for patients with swallowing deficits, who are fed through a nasogastric tube.

- **Data Acquisition**
  Measurement scales may include *subjective* and *objective* measures. In subjective measures, human judgment (by the clinician, or the patient, or both) is involved in the assessment, while objective measures involve no judgment in the collection of information (although judgment may be required in its interpretation). At the same time, measures can be *direct* or *indirect*; in the second case, the outcome of interest cannot be measured directly, but it can only be measured through indicators, which capture only part of that concept [90, 91]. Therefore, PROs to be acquired can be classified into four different categories: (i) objective direct (such as clinical measures), (ii) subjective direct (such as symptoms), (iii) objective indirect (e.g., cardiovascular risk can be derived with a certain level of probability from smoking habits, blood pressure, cholesterol levels, etc.), and (iv) subjective indirect (such as questionnaires). Moreover, nowadays, the evaluation of costs that patients had to meet due to the therapy is acquiring growing importance within studies that evaluate different types of intervention in the healthcare system, such as the introduction of new technology, information systems, or mobile apps. While the acquisition of direct costs for the National Health System is rather common and follows established criteria [92, 93, 94], the identification of out-of-pocket costs for outpatients is much more complicated and rare [95, 96]. Based on these considerations, the data acquisition can be classified as:

  - *Manual*: It involves the acquisition of objective direct / subjective direct / subjective indirect measures, and costs.

It can require reporting structured information, but it can also offer the possibility to enter free text;

- *Automatic*: It involves wireless or USB connections with sensors or wearable devices for automatically collecting objective direct measures.

- **Reminders**
  Timely reminders should be raised and logged as soon as they are generated. In this way, time-stamped information could be used for checking their promptness and the patients' compliance. Useful reminders are:

  - reminders for entering data according to the plan configured by the doctor;
  - reminders for taking the prescribed medications.

- **Visualization**

  - Graphical trends of reported symptoms, clinical parameters charts, and questionnaire scores.

- **Communication**

  - Interaction with the medical staff (e.g., via e-mail), attaching the report of symptoms, clinical parameters, and questionnaires;
  - Synchronization of PROs to a hospital server so that they are added to the patient's EHR and become immediately available for perusal.

Asking a patient to provide PROs in terms of symptoms [97] and questionnaires [26] represents a powerful means not only to ascertain the severity of a disease, but also to accomplish a functional assessment

on the patient. A functional assessment may have a strong prognostic influence on the disease evolution, in particular for cancer patients, and it may be used either to adjust the treatment, or to prepare and support a shared decision-making process during the next scheduled visits [98].

To provide the above-mentioned functionalities at best, it can be argued that doctors should be supported by a suitable tool in providing an initial configuration for the mobile device of individual patients, according to their health status. Moreover, the same tool should be able to update that configuration over time according to the evolution of the treatment effects, as they emerge also through PROs. Based on the above discussion, such a configuration translates into deciding which parameters and questionnaires should be collected, as well as their collection frequency.

4.2 Doctor Side

The support for the doctor is usually provided by a service at the clinic backend that is best implemented as a web application integrated into the hospital information system [99]. Also in this case, based on the literature [100, 101] and on previous research experience in developing reporting systems for physicians [102, 103], it was possible to define the following set of requirements, with the aim of making the most of the PROs that are regularly reported by patients between scheduled visits:

- Configuration of the app, by setting:
  - Which clinical parameters and questionnaires the patient has to report and the reporting frequency;
  - The patient's type of cancer and the therapy drugs he/she is being administered, in order to personalize other sections

of the app.

- Overview of the patients' disease evolution through temporal plots and aggregation charts (e.g., bar and pie charts);

- Real-time automated alerts (possibly with the addition of alerts via e-mail) when patients report symptoms severity above predefined thresholds. The alerts should also be logged as soon as they are generated, in order to check their promptness and the doctors' compliance.

- DSS for the following purposes:

  - Notify to the treating staff (through alarms) the onset of critical situations, so that any required action may be promptly undertaken;

  - Help in preparing the next scheduled visit shortly beforehand, summarizing the patient evolution since the last face-to-face encounter and possibly suggesting some adaptation of the treatment;

  - Help with the task of configuring (and possibly reconfiguring) the mobile device, to continue the provision of suitable advice and reminders when the patient is at home, in sight of the next scheduled visit.

  The DSS should be easily configurable according to the specific medical knowledge of the domain, customized by the treating staff. Thus, a CIG embedded into the DSS could be exploited for generating standard recommendations for doctors, based on both the data collected at the hospital and PROs.

4.3 Use Cases

This section reports a summary of the use cases for the generic scenarios derived from the previous requirements. Depending on the specific context, these use cases will be instantiated with some specific information concerning the application domain. Below, use cases are reported according to the Unified Modeling Language (UML) standard.

Use Case 1: Education

Level: Summary
Main Success Scenario:

1. The Doctor thinks it is necessary to inform, educate and train the Patient
2. The Doctor assembles the personalized material for the Patient and sends it to the App
3. The Patient opens the App on the smartphone
4. The Patient enters the section regarding the educational material
5. The App shows the general and the personalized educational material
6. The Patient peruses the material
7. The App keeps track of the time spent reading the material

Note: Educational material can be supplied in several ways, in the form of textual material, video lessons, slides and diagrams, etc. The choice on how to provide it to patients depends on the specific application domain, but also on the particular purpose that we aim to achieve. For example, in the case of an application for patients' rehabilitation,

the material could describe a series of exercises to be followed step by step. In this case, the better choice is to provide video lessons as an interactive guide for patients. On the other hand, if the educational material were aimed at suggesting behaviors to adopt as a new life style, then a textual format could be more appropriate.

Use Case 2: System-initiated Data Acquisition and Visualization

Level: Summary
Precondition: The Doctor decides which data (e.g., clinical parameters, questionnaires) the Patient has to report and the reporting frequency and personalizes the App accordingly.
Main Success Scenario:

1. The App generates notification reminders for the data to be reported at proper times
2. The Patient acknowledges the notifications
3. The App prompts the information to be acquired
4. The Patient enters the required data
5. The Patient sees a summary or chart of inserted data
6. The App synchronizes the data to the hospital server
7. The Doctor sees the data

Extensions:
6a. The App fails synchronization due to the lack of internet connection:
6a.1. The App retries until the connection is re-established

Note: In order to evaluate the patient's health status, the doctors are interested in the main parameters that help interpreting the clinical state evolution and/or identifying the onset of complications. According to the specific dynamics, it is possible to set the frequencies of a periodic collection.

Use Case 3: Patient-initiated Data Reporting and Visualization (e.g., Symptoms, Costs, Events)

Level: Summary
Main Success Scenario:

1. The Patient experiences an event
2. The Patient opens the App on the smartphone
3. The Patient enters the event and its details
4. The Patient sees a summary or chart of inserted data
5. The App synchronizes the data to the hospital server
6. The Doctor sees the data

Extensions:

5a. The App fails synchronization due to lack of internet connection:
5a.1. The App retries until the connection is re-established

Chapter 5

Overall Architecture

This chapter describes the prototypical architecture for integrating ePROs and CIGs providing decision support about the management of cancer outpatients. The architecture has been defined according to the requirements identified in Chapter 4 and exploiting some of the tools for data integration introduced in Chapter 3. An outline of the overall system architecture is shown in Figure 5.1.

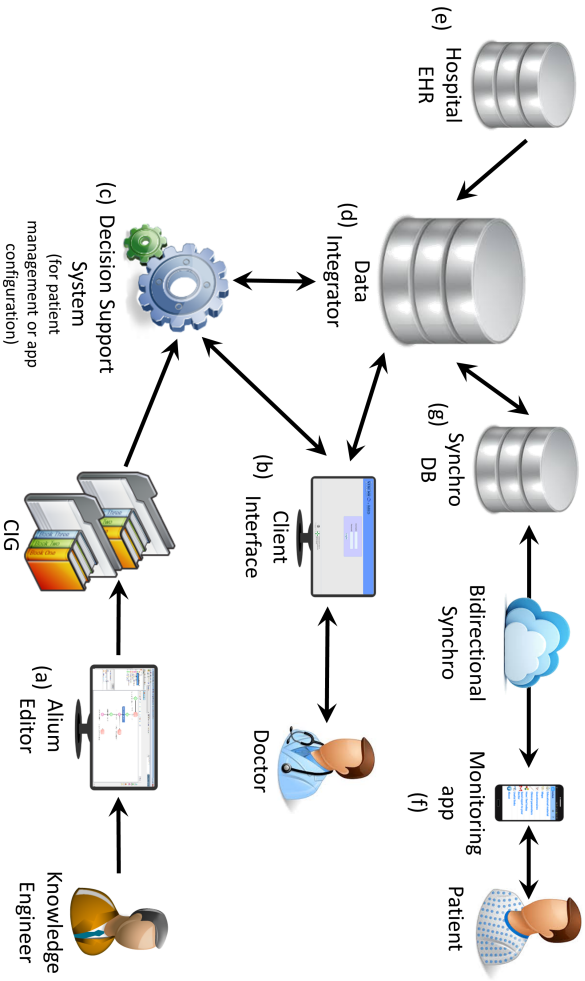


Figure 5.1: **The overall architecture.**

The knowledge engineer authors a care pathway through the Alium editor (a) and makes the resulting CIG available in a digital library stored on the same remote server where the Alium engine runs. Through the dedicated client interface (b), the doctor can see the patients' data and choose among the available CIGs the one to execute (c), according to his wish of receiving decision support about the configuration of the mobile app (f) or, alternatively, the patient's management. As a result, the possible decision options and/or recommendations are prompted in the client interface. The Alium engine executing the CIG is fed with data from the middleware database (d), which integrates information from different sources, among which the EHR (e) and the database that collects the data synchronized by the mobile app (g). The resulting recommendations appear in the client interface as a list of selectable items, so that clinicians can choose the ones they decide to follow and discard the others. It is important to highlight that the DSS can produce a different set of recommendations according to the CIG selected at the beginning of the process. In fact two different CIGs can be derived from the same CPG: (i) a clinical CIG about the patients' management (e.g., diagnosis and treatment of side effects) and (ii) a CIG providing recommendations about the configuration of the monitoring app (parameters, questionnaires, other content dedicated to the patient). This separation allows the doctors to distinguish the recommendations directed to themselves from the ones that patients should follow when they are at home. Moreover, when the recommendations regard the app configuration, the system writes the new configuration back into the database and the app is reconfigured at the next synchronization. The different components aggregated into the architecture will be described in detail in the following sections.

5.1 The Alium Client Engine

As mentioned in Section 2.5.1, in addition to the editor, Alium also provides a reliable execution engine that can be accessed through a specific set of APIs. These APIs may be invoked from an external environment to provide the data required as the guideline input, to activate the execution of the inferential processes encapsulated within the guideline itself and, finally, to collect the outputs. To properly exploit the APIs, during this thesis work a client engine was developed with the purpose to connect to the remote Alium server and handle the communication with it. The client was designed to be independent of the specific use case and it includes a general model of clinical information. A draft diagram of the main classes of the *Alium Client Engine* supporting the integration of Alium within this project is shown in Figure 5.2. The whole class diagram was too complex to be portrayed in a single figure.

The *AliumClientEngine* class is the main element of the client. Its main tasks are:

- establishing the connection to the remote server;
- starting the execution of the guideline;
- identifying the data items or decision candidates requested by the guideline to continue the execution. Note that some of those items are abstractions obtained by elaborating raw data through purposely developed routines, because Alium does not perform temporal abstractions on data (e.g., decrease of weight greater than 10% in 6 months);
- activating the extraction of relevant observations from the database and their manipulation, in order to render them in a form suitable to the Alium engine;

- feeding the retrieved values to the guideline;
- collecting the guideline recommendations.

To establish the connection, *AliumClientEngine* relies on the *AliumConnection* class, which contains the implementation of all the calls to the remote server. *AliumClientEngine* depends also on the classes of the package *it.unipv.aliumdss.databasexml* to connect to the XML database and retrieve the necessary data; the retrieved information is then rearranged to fit in one of the data model categories, represented by the classes of the package *it.unipv.aliumdss.model*.

Figure 5.2: **A partial class diagram for the *Alium Client Engine*.**

5.2 The Data Integrator

In this work, a mapping was performed between the most common types of data required in the medical context under consideration and the suitable HL7 vMR classes for their representation. Table 5.1 shows the correspondences arising from this analysis.

Table 5.1: **Association between data types required by the medical context and the HL7 vMR classes.**

Type of Data	**HL7 vMR Class**
Clinical Findings	
Visit	EncounterEvent
Procedure (physical examination, surgery or other procedures different from substance administration)	ProcedureEvent
Observations of point values or abstractions on data (including laboratory results, imaging study findings, diagnostic test results, vital signs, other physical examination findings)	ObservationResult
Patient Problems	
Allergy	AllergyOrIntolerance
Clinical Diagnosis	Problem
Adverse Event or Adverse Reaction	AdverseEvent

Patient History	
Chief Complaint (including PROs, among which the clinical parameters and summary scores of the questionnaires)	ObservationResult
Past Surgical History	ProcedureEvent
Past Medical History	Problem
Medical Administration Record and Home Medications	SubstanceAdministrationEvent
Social History (e.g., smoking status, alcohol intake, etc.)	ObservationResult
Signs and Symptoms	ObservationResult

Since HL7 provides a set of XML Schemas as examples of a potential platform-specific implementation of the vMR, with a similar approach patients' data are stored in a middleware XML database, namely BaseX (http://basex.org), where each XML file contains all the data about a single patient, including diagnoses, therapies, and observations, modeled according to the HL7 vMR classes. Concerning questionnaires, only the summary scores were stored, extending the class *ObservationResult*. Thus, according to this design, data from different sources are integrated through a layer of conversion and adaptation, including ETL processes, to adjust them to the format required by the DSS.

Regarding the structure of the XML files stored in the middleware, in this work only the subsection of the tags and attributes provided by the HL7 vMR that suited our purposes was considered. Those tags are described in the following paragraphs and figures.

N.B. Every time a tag is described as "coded field", it means that, according to the HL7 vMR, it owns the following attributes:

- *codeSystem*: HL7 code for the terminology / ontology / coding system (e.g., HL7 code for SNOMED CT: 2.16.840.1.113883.6.96);
- *codeSystemName*: extended name of the terminology / ontology / coding system;
- *code*: the concept code according to the terminology / ontology / coding system used;
- *displayName*: the concept extended and human-readable name.

As mentioned earlier, each XML file is dedicated to a single patient. Therefore, after the tag *vmr* that indicates that the file is an EHR extract, the first tag is the *patient* tag.

Every *patient* tag, then, may contain the following tags:

- *id*: a unique identifier for the patient;
- *center*: the reference hospital or institution for the patient treatment;
- *hr_code*: the code of the patient's health record;
- *address*: the patient's address. It is composed of several parts, such as street, city, county, ZIP code, country, etc.;
- *name*: the patient's name. It is composed of parts, such as given name, family name, title, etc.;
- *telecom*: the telephone number. This tag has attributes "use", to define the type (home, office, etc.), and "value", that contains the telephone number;

- *birthTime*: the patient's birth date;
- *race*: coded field;
- *gender*: coded field.

These tags constitute the patient's demographics. Figure 5.3 shows a diagram of this structure, including the cardinalities of each inner tag: the minimum cardinality is set to 1 when the tag is mandatory for the DSS, while the maximum cardinality indicates the maximum number of tags of that kind that are allowed.

The rest of the XML (a diagram is shown in Figure 5.4) reports the contents of the EHR that are relevant to the DSS (visits, prescriptions, diagnoses, procedures, etc.). All clinical events in the HL7 vMR descend from the class *ClinicalStatement*. For this reason, all the patient's clinical events are contained in the tag *clinicalStatements*, which, in turn, contains a tag *encounterEvents* that is a collection of tags of type *encounterEvent*, representing the visits and containing the following children tags:

- *id*: a unique identifier for the visit;
- *encounterType*: the type of visit (routine, screening, professional, etc.);
- *transactionTime*: date and time of the insert transaction into the database;
- *encounterEventTime*: date, start time (low) and end time (high) of the event;
- one or more *relatedClinicalStatement* tags: any clinical event (observation, procedure, diagnosis, etc.) that happened during the visit under consideration.

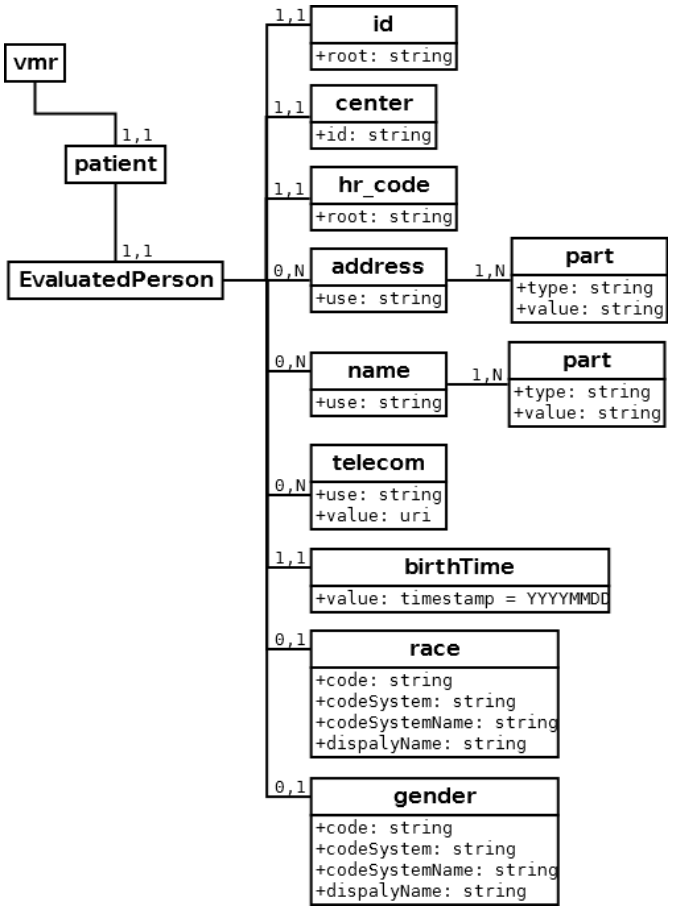


Figure 5.3: **Diagram of the XML tags for the patient's demographics.**

Figure 5.4: Diagram of the XML tags for the clinical statements related to a patient.

Events of interest can be of different types, as it can be seen from Table 5.1. Their children tags and attributes are detailed in the following paragraphs and figures.

ObservationResult

Children tags:

- *transactionTime*: date and time of the insert transaction into the database;
- *observationEventTime*: date and time of the observation;
- *observationFocus*: coded field representing the observed concept;
- *observationValue*: it can contain one of these mutually exclusive tags:
  - *text* (with the only attribute *value*), for a textual value of the observation;
  - *physicalQuantity* (with attributes *value* and *unit*), for a numeric value;
  - *concept* (coded field) if the observation value itself can be expressed using a terminology code;
- *extension*: optional tag used to add information that cannot be directly represented through the HL7 vMR classes. For example, if the observation is an abstraction, this tag will include the concept considered by that abstraction as a *referenceConcept*.

The whole structure is represented in Figure 5.5.

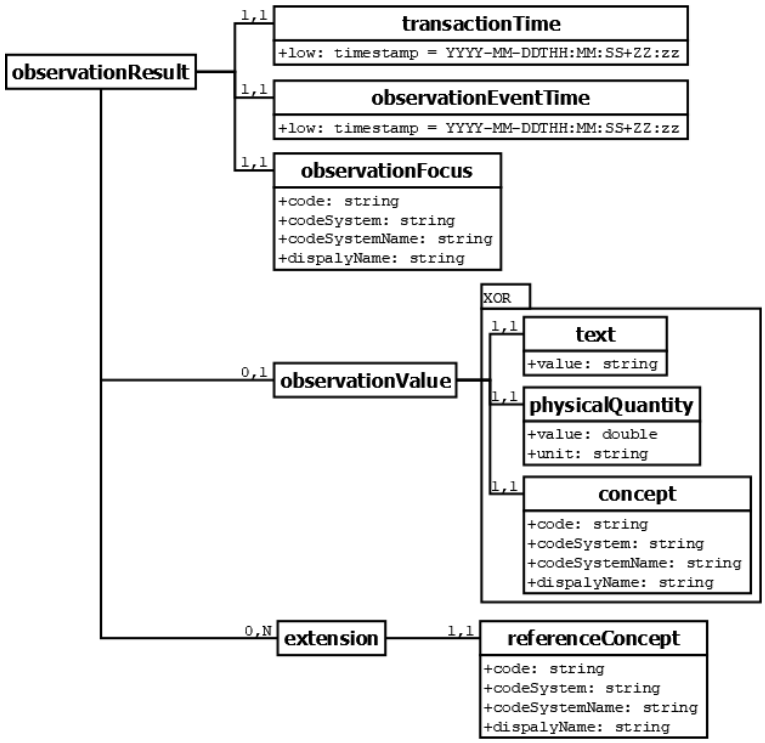


Figure 5.5: **Diagram of the XML *observationResult* tag.**

AdverseEvent

Children tags:

- *transactionTime*: date and time of the insert transaction into the database;
- *adverseEventTime*: date and time of occurrence of the adverse event;
- *adverseEventCode*: coded field representing the adverse event;

- *adverseEventAgent*: coded field representing the agent that could have caused the adverse event (if existing);
- *severity*: coded field representing the severity of the adverse event manifestation.

The whole structure is represented in Figure 5.6.

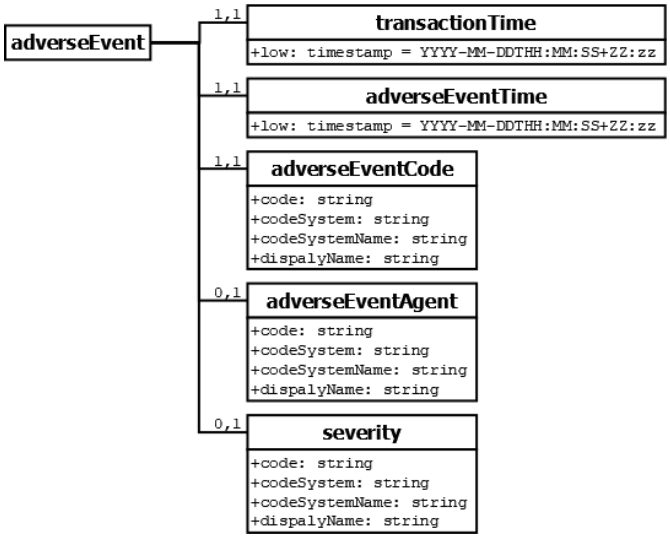


Figure 5.6: **Diagram of the XML *adverseEvent* tag.**

Problem

Children tags:

- *transactionTime*: date and time of the insert transaction into the database;
- *diagnosticEventTime*: date and time of the diagnostic event;

- *conditionEffectiveTime*: date and time of the condition onset (usually it precedes the diagnosis);
- *conditionCode*: coded field representing the diagnosed condition.

The whole structure is represented in Figure 5.7.

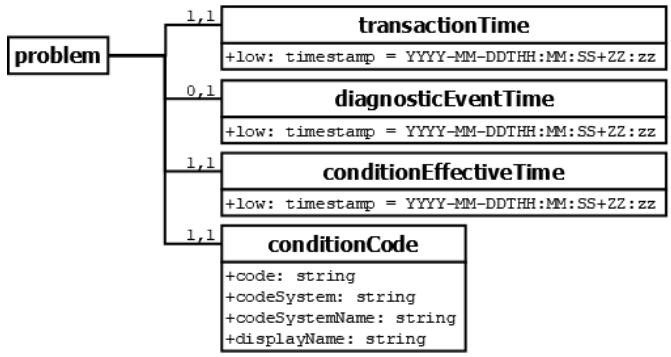


Figure 5.7: **Diagram of the XML *problem* tag.**

AllergyOrIntolerance

Children tags:

- *transactionTime*: date and time of the insert transaction into the database;
- *diagnosticEventTime*: date and time of the diagnosis;
- *conditionEffectiveTime*: date and time of the allergy or intolerance onset (usually it precedes the diagnosis);
- *conditionCode*: coded field representing the diagnosed allergy or intolerance;

- *agent*: coded field representing the agent that caused the allergy or the intolerance;
- *severity*: coded field representing the allergy/intolerance severity.

The whole structure is represented in Figure 5.8.

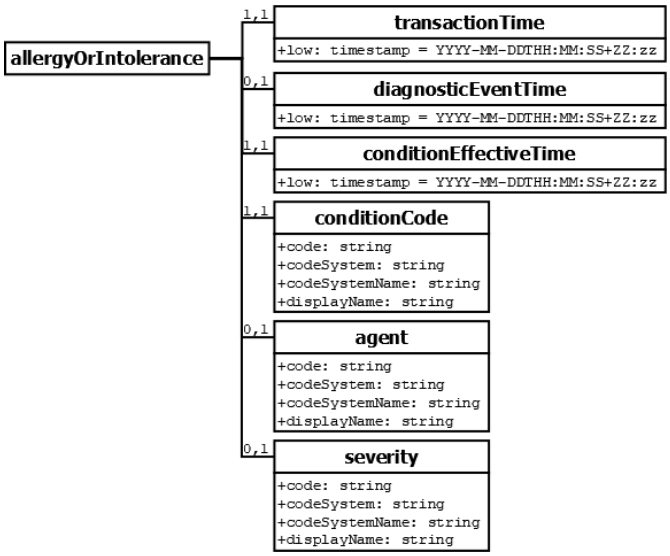


Figure 5.8: **Diagram of the XML *allergyOrIntolerance* tag.**

ProcedureEvent

Children tags:

- *procedureCode*: coded field representing the procedure;
- *transactionTime*: date and time of the insert transaction into the database;

- *procedureTime*: date and time of the procedure;
- *relatedClinicalStatement*: every procedure can contain related events, such as adverse events that followed that procedure. The type of relationship (cause, effect, part-of, etc.) between the procedure and the related events is represented by the coded field *targetRelationshipToSource*.

The whole structure is represented in Figure 5.9.

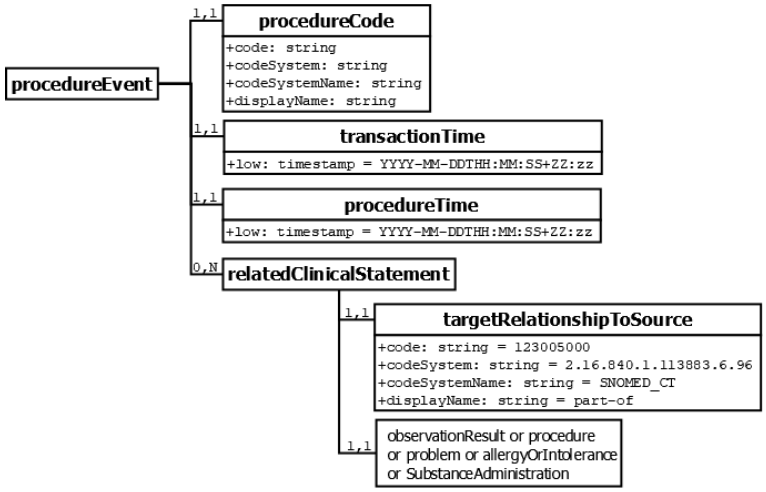


Figure 5.9: **Diagram of the XML *procedureEvent* tag.**

SubstanceAdministrationEvent

Children tags:

- *substanceCode*: coded field representing the administered substance;

- *transactionTime*: date and time of the insert transaction into the database;
- *administrationTimeInterval*: date and time of administration;
- *dose*: how the substance is administered (oral, intravenous, etc.);
- *doseQuantity*: quantity of substance that was administered. It could be an interval but, for the purposes of this work, only a single value was considered (tag *low*).

The whole structure is represented in Figure 5.10.

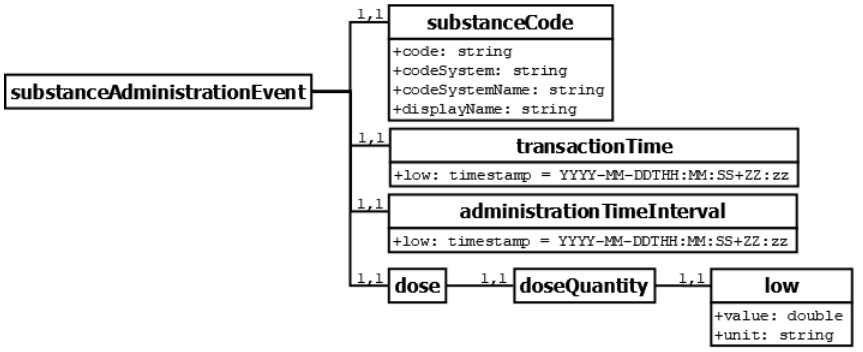


Figure 5.10: **Diagram of the XML *substanceAdministrationEvent* tag.**

5.3 Design of the Mobile Application

The design for a generic configurable mobile app tries to include the functional requirements listed in Chapter 4 and makes the most of the experiences described in Chapter 6. The idea is to provide an app as much configurable as possible, both in the textual contents

and in the clinical parameters, questionnaires, monitoring frequencies, and reportable symptoms. The adopted solution was to exploit the sync adapter framework provided by the Android operating system, for the reasons stated in Chapter 2.2 and 2.3 and because of lack of experience with other mobile operating systems. This framework allows to synchronize data between two mirror databases, one hosted on the mobile phone and a twin one hosted on a remote server. If the entire app configuration depends on data saved in those databases, it is sufficient to modify the data in the server database and synchronize it back into the mobile phone to change the app configuration as desired.

Besides the remote reconfiguration of the app, a manual configuration is still allowed in case doctors already know which data they would like to collect and with which frequency.

5.4 Design of the Web Application for the Physician

The analysis of functional requirements in Chapter 4 reveals the clinicians' need for visualizing patients' data as soon as they are synchronized to the server, in order to promptly intervene in case an adverse event occurs. Moreover, the clinicians need access to a decision support system. For these reasons, a web application has been designed to run on top of the clinic backend server, retrieving patients' data from the data integrator, making them available for visualization by the doctors, and raising alarms when needed. Moreover, the application allows invoking the Alium execution engine through the exploitation of the Alium Client Engine (Section 5.1) and shows the resulting recommendations to the clinicians. Finally, the application should also allow changing the configuration of the mobile app remotely, making use of a two-way synchronization.

According to the design, the web application should allow the clinician to start the execution of a CIG on a specific patient. The doctor, at the enrollment, associates the patient with one of the available clinical guidelines and the associated guideline for the proper personalization of the monitoring app. Once the execution of one of the guidelines for the selected patient starts, if that guideline includes decisions that have to be taken by the doctor, the interface shows all the possible options, with arguments in favor and arguments against, so that the doctor can make a considered choice. At the end of the execution, the resulting recommendations are shown on the same interface, together with an explanation for each one of them. The doctors can then select the recommendations they decide to accept, and those recommendations will be written in the data integrator, in order to keep track of their compliance to the guidelines. If the selected recommendations regard the app configuration, appropriate modifications will be applied to the database and, consequently, to the patient's mobile app at the next scheduled synchronization.

5.5 Guidelines Formalization with Alium

The formalization of all the information contained in a guideline is a complex process, whose steps depend on the text itself. For example, a guideline could be more or less descriptive, it could provide literature citations, or it could provide synthetic diagrams or figures summarizing its contents. Within this work, a formalization process was followed that should be general enough to allow addressing most of the existing clinical guidelines. The process is shown in Figure 5.11 and includes the following steps:

- Reading the guideline and comprehending the text: this phase involves both the engineer and the doctors, who could help in the formalization by adding any implicit knowledge the guideline

might imply and clarifying any obscure point. During this phase, each passage of the guideline is classified according to three axes: (i) type of text (e.g., simple information, generic recommendation, recommendation based on patients' data, etc.); (ii) temporal phase (e.g., if the text refers to prevention, treatment, diagnosis, follow-up, etc.); and (iii) recipient (e.g., general practitioner, professional, nurse, patient, etc.). This classification is useful for different purposes, such as addressing the recommendations to the proper recipients in due time, providing a better and clearer visualization of results, or, as a long-term goal, simplifying the evaluation of the doctors' compliance to the guidelines;

- Drafting semi-formal recommendations: the engineer writes the recommendations in a pseudo-natural language, easily understandable by the medical counterpart, but at the same time without any ambiguity and referring to the three axes mentioned above;

- Identifying the minimum patient's data set, which is the set of data necessary and sufficient for the guideline execution. These data might be raw data (e.g., body temperature), or abstractions based on raw data (e.g., anemia is defined according to gender and hemoglobin presence in blood). Abstractions might then be calculated automatically by the system, or directly inserted into the system through the EHR (when raw data are not considered indispensable) or through the interaction with the CIG (when they are not available through the two previous ways);

- Codifying concepts through a standard terminology;

- Formalizing the recommendations in a formal language through an authoring tool, finally obtaining the CIG.

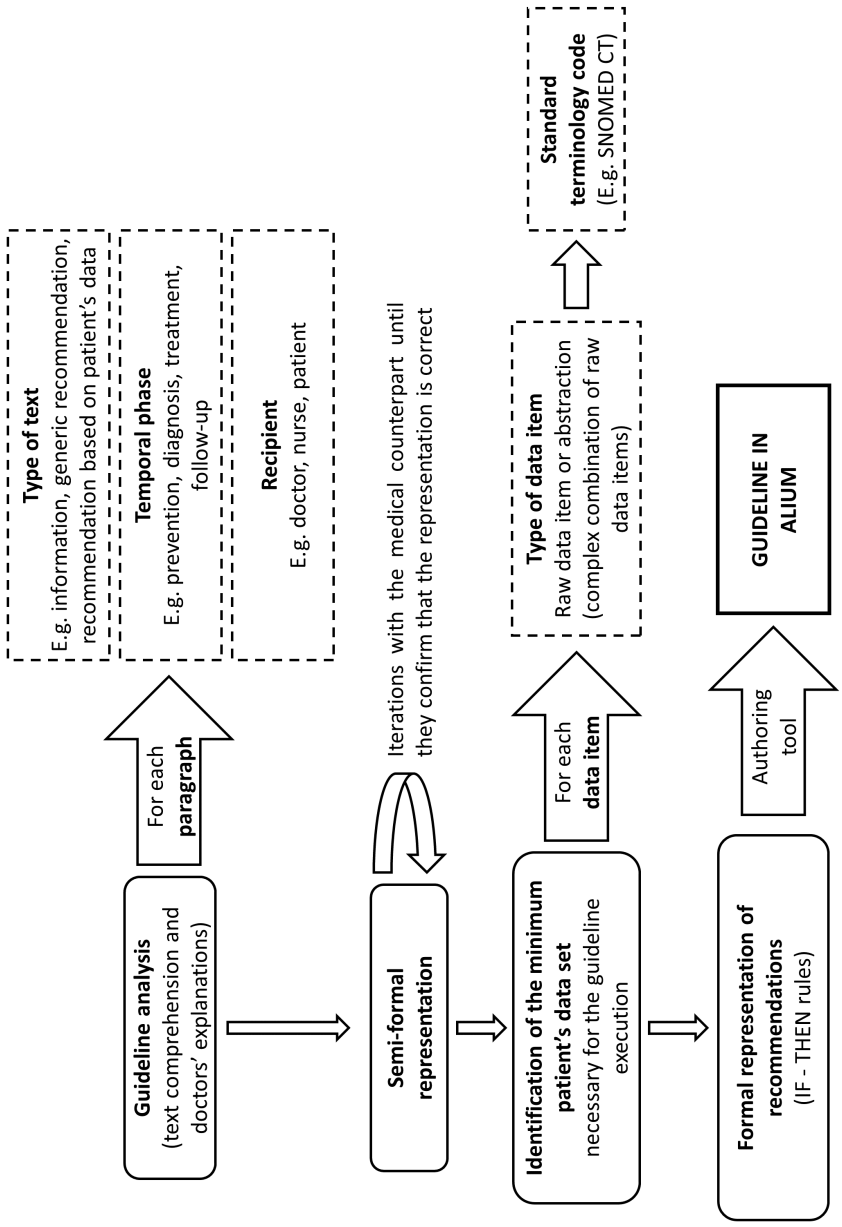


Figure 5.11: **Diagram of the guideline formalization process.**

The development of the personalized components described in the previous sections required some extensions to the basic properties of Alium tasks and data items. The extensions were possible thanks to a section of *metaproperties*, available in Alium for both data items and tasks, which allows to attach additional properties to those items in a key-value fashion (both keys and values are text fields). These additional properties are ignored by the engine during the execution of the guideline, but they allow to pass structured information to external systems. This is useful, for example, to provide information to the Alium Client Engine (Section 5.1) about data items to retrieve from the data integrator and to transform according to the guideline requirements. The metaproperties added to data items within this work are:

- *validity*: represents the period in which a data item is considered valid and can be used in the guideline execution. It can be a numeric value or the value "inf" (i.e. infinite), if that data item is always valid and does not change over time (e.g., the date of birth);

- *validity_unit*: the unit of measurement of validity. Possible values are: year, month, week, day, hour, minute, second. This property is added only if the validity is different from "inf";

- *mandatory*: true if the data item is necessary to the execution of the guideline, false otherwise;

- *category*: the data item type, to facilitate data retrieval from the data integrator. Possible values are:

  - diagnosis;
  - therapy;

- observation (if the data item to retrieve is a point value (e.g., a symptom, a clinical parameter measurement, a clinical observation, etc);
- abstraction (if the data item to retrieve is an abstraction of other clinical information (e.g., loss of weight).

The separation of point-value observations from abstractions is required because observations can be directly extracted from the data integrator, while abstractions must be computed from several observations. Since Alium does not provide adequate structure to compute abstractions, especially on temporal series of data, it was necessary to assume that abstractions would be computed before the execution of the guideline, and inserted into the data integrator. Then, at the guideline execution, an abstraction can be retrieved from the data integrator as is, with the final result of the computation (e.g., "loss of weight of more than 5% over one month" = "yes" or "no").[1]

Only one metaproperty was added to tasks of type Action: *pre-condition*, that is the user-friendly description of the preconditions on the task execution. In fact, Alium only allows to indicate a logic condition for the task activation, This metaproperty allows to transfer the information also to the doctors' web application, so that doctors can see a textual explanation for each recommendation.

[1]Please note that temporal abstractions, although being of utmost importance, have not been faced in this thesis work.

Chapter 6

Applications

This chapter presents two different use cases that involved the implementation of at least one part of the architecture described in Chapter 5.

6.1 Case 1: The HeNeA Experience

The first experience regards an intervention within a collaboration with the IRCCS Foundation National Cancer Institute (Istituto Nazionale dei Tumori (INT)) in Milan for patients affected by Head and Neck Cancer (HNC) undergoing Concurrent Chemo-Radiotherapy (CCRT).

6.1.1 The Medical Problem

Head and neck cancer is the sixth most common malignancy worldwide, often diagnosed in a locally advanced stage [2]. A 2015 report of the Italian Network of Cancer Registries (AIRTUM) confirms this

figure also for Italy [104]. In this setting, multidisciplinary treatments offer the best curative results combining surgery, radiation and systemic therapy [105]. Although being quite effective, these treatments generate important acute toxicities, which deeply and negatively affect both patients' quality of life and treatment compliance [106]. In fact, the treatment-related mortality for CCRT is as high as 2% [107]. Furthermore, it has been shown how the dose intensity of chemotherapy and radiotherapy, as well as the conformance with the scheduled duration of the treatment, are of paramount importance in securing the curative effect of CCRT [108, 109, 110]. Supportive care delivered throughout curative therapy is essential to address treatment-related symptoms and toxicities.

6.1.2 The Intervention

Considering the architecture in Figure 5.1, its application in this case study consists of:

- The formalization of the clinical guideline through the Alium editor;
- The implementation of a mobile app that synchronizes data to a server hosted in INT;
- The implementation of a web application as client interface for the oncologists.

There were some limitations to the development of the entire architecture in this context. The ETL processes to transform hospital EHRs into the format required by the data integrator could not be implemented, because no access to the hospital information system was available. For this reason, the evaluation concerned mainly the feasibility and usability of a system composed of a mobile app for patients

and a web app for clinicians to visualize patients' data. Although for the stated reasons no proper evaluation of the DSS technical aspects could be performed, the correctness of the formalized guideline was evaluated simulating patients' data.

6.1.3 The Clinical Guideline

The CPG analyzed during this study concerns the prevention, diagnosis, and treatment of side effects in patients with HNC undergoing CCRT. This guideline was developed during a multidisciplinary panel of experts, who met in Milan on February 17th and 18th 2013 with the aim of achieving a shared opinion on the management of those side effects. The panel included 37 experts, among which radiotherapists, physicians, oncologists, dentists, radiologists, nurses, and a group of coordinators, experts in different clinical disciplines. The Delphi rating method was used for consensus development; this method allows obtaining a shared opinion on the theme subject of the study [111]. According to this method, the study coordinators identify through a literature review some recommendations, which are then voted by each expert with a score from 1 to 4. These scores are analyzed afterwards during a second meeting, in order to identify which recommendations the experts reached consensus upon, and to approve the final version. The results of the panel were described in a series of publications containing different sections of the guideline, divided by area of expertise [112, 113, 114, 115, 116, 117, 118].

The different types of consequences of CCRT were divided according to three axis:

1. The damaged anatomical region or functional structure. The areas of interest identified by the experts are *skin*, *oral cavity*, *swallowing*, *nutrition and hydration*, *septic syndrome*, *haematologic effects* and *pain*. For each area of interest, the experts

identified one or more side effects. For example, the section concerning oral cavity care discusses mucositis, osteoradionecrosis, xerostomia and trismus;

2. The time each recommendation refers to: *before*, *during*, or *after* the treatment;

3. The recipient of each recommendation (the *oncologist*, the *nurse*, the *patient*, the *dentist*, or other professionals).

The final guideline is therefore structured as shown in Table 6.1, according to the first axis:

Table 6.1: **Structure of the guideline about the management of CCRT side effects.**

Area of Interest	**Side Effect**
Skin Care	Radiodermatitis
Oral Cavity Care	Mucositis Tooth care and osteoradionecrosis Xerostomia Trismus
Swallowing Care	Swallowing dysfunction (Dysphagia)
Nutrition - Hydration	Malnutrition Dehydration
Septic Syndrome	Septic Syndrome
Haematologic Toxicity Care	Febrile Neutropenia Anemia

The side effects are defined as follows:

- *Radiodermatitis*: a finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation. It can also be caused by exposure to biologically effective levels of ionizing radiation in addition to biological therapies (e.g., Cetuximab) [112].
- *Mucositis*: inflammation of the oral mucosa [113].
- *Osteoradionecrosis (ORN)*: necrotic process occurring in the bone (mandible or maxilla). ORN is a late adverse event of radiotherapy, persisting for 3 months or longer and worsening slowly, which cannot heal spontaneously. Clinical presentation includes pain, drainage and fistula formation (to mucosal or skin surface) in an area of exposed, irradiated bone [114].
- *Xerostomia*: decrease in salivary output and a change in salivary composition, resulting in the sense of a dry mouth and sticky saliva [114].
- *Trismus*: lack of ability to fully open the mouth due to a decrease in the range of motion of the muscles of mastication [114].
- *Dysphagia*: disorder characterized by difficulty in swallowing [115].
- Moderate or severe *malnutrition*: presence of unintentional loss of weight, i.e. 5% weight loss over prior 1 month or >10% in over 6 months [119].
- *Dehydration*: disorder characterized by an excessive loss of water from the body.
- *Septic syndrome*: the panel adopted the nomenclature and definitions for terms used by 2001 International Sepsis Definitions Conference (i.e., Systemic Inflammatory Response Syndrome (SIRS),

infection, sepsis, severe sepsis, and septic shock). *SIRS* is defined as an inflammatory state derived from the body (the system) response to an infecting pathogen. Sepsis is a suspected or documented infection with a systemic manifestation of the infection itself. Severe sepsis occurs in the presence of sepsis and tissue hypoperfusion, or evidence of organ dysfunction. In patients with HNC, any kind of tissue damage can induce a systemic inflammatory response. When this response is prolonged and associated with infection, it can result in severe sepsis and its complications [118]. This definition, however, changed after the guideline publication, and the most recent definition in the clinical practice refers to the use of qSOFA [120]. Sepsis is then defined as a "life-threatening organ dysfunction caused by a dysregulated host response to infection". The Sequential [Sepsis-related] Organ Failure Assessment (SOFA) Score allows determining the level of the patient's organ dysfunction and it is based on the evaluation of six different clinical systems (respiratory, coagulation, liver, cardiovascular, renal, and central nervous system). Quick SOFA (qSOFA) is a simplified version of the SOFA Score used for a first identification of patients with suspected infection at high risk of poor outcomes (hospitalization or death). qSOFA criteria for suspected sepsis are:

  - respiratory rate $\geq$ 22 breaths/min;
  - alteration in mental status;
  - systolic blood pressure $\leq$ 100mmHg.

  After consultation with some of the experts that authored the guidelines, in this work the presence of SIRS was evaluated using the qSOFA criteria.

- *Febrile Neutropenia*: disorder characterized by an absolute neu-

trophil count < 1000/mmc and a single temperature of more than 38.3 °C (100.4 °F) for more than one hour.

- *Anemia*: a reduction in the amount of hemoglobin (< 13 g/dL in male patients and < 12 g/dL in female patients).

- Oral, throat or tumor *pain*: marked discomfort in the mouth, throat, or from a neoplasm that may be pressing on a nerve, blocking blood vessels, inflamed or fractured from metastasis [116]. Pain can also be an adverse event of CCRT (e.g., pain due to mucositis or dermatitis).

Main Workflow

The described guideline is destined to provide decision support mainly during the visits. The main workflow in Alium, reported in Figure 6.1, starts with an enquiry collecting:

- treatment phase: the allowed values are "before", "during" and "after". This data item is mandatory for the execution of the guideline;

- current cancer treatment: the treatment that the patient is undergoing (chemotherapy, radiotherapy, monoclonal antibody, Cetuximab, or steroid therapy). More than one choice is possible.

The flow, then, follows a different branch according to the treatment phase. If the patient is in the *pre-treatment* phase (top branch), an assessment is performed ("Risk Factors Assessment" task), evaluating generic information (e.g., age, comorbidities, gender, etc.) and data specific for each possible side effect, in order to identify if the patient is at risk of developing one or more of the side effects considered in the guideline. Then, a series of recommendations for this phase is shown ("Pre-treatment" task). If the patient is already undergoing

treatment (middle branch), some scales and questionnaires are considered ("Scales and Generic Data"), before providing both generic ("Always valid recommendations") and side-effect specific ("Treatment") recommendations. Finally, if the patient is in the *post-treatment* phase (bottom branch), only recommendations specific for this phase are shown.

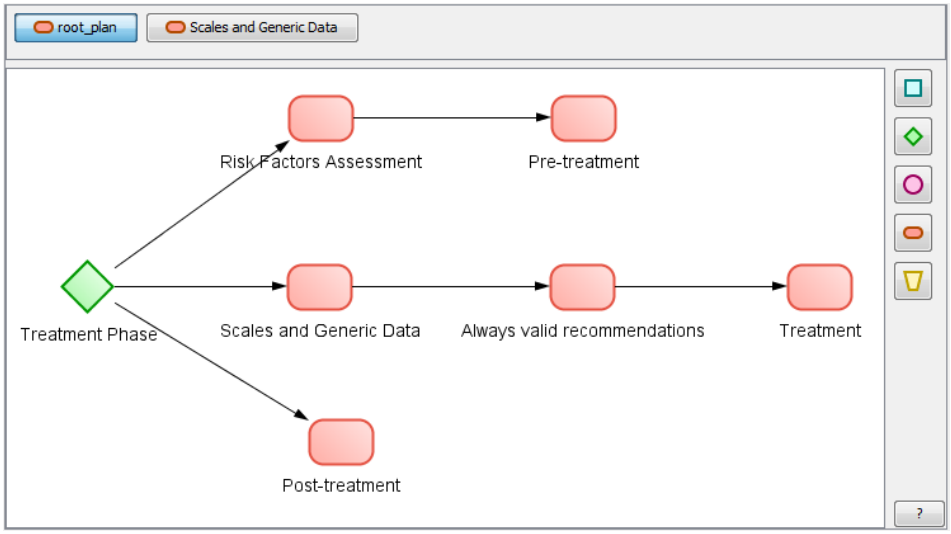


Figure 6.1: **The main workflow in Alium for the clinical guideline.**

Risk Factors Assessment

The plan "Risk Factors Assessment" in Figure 6.1 contains the subnetwork shown in Figure 6.2.

This workflow includes three enquiries:

- Generic Assessment, collecting:

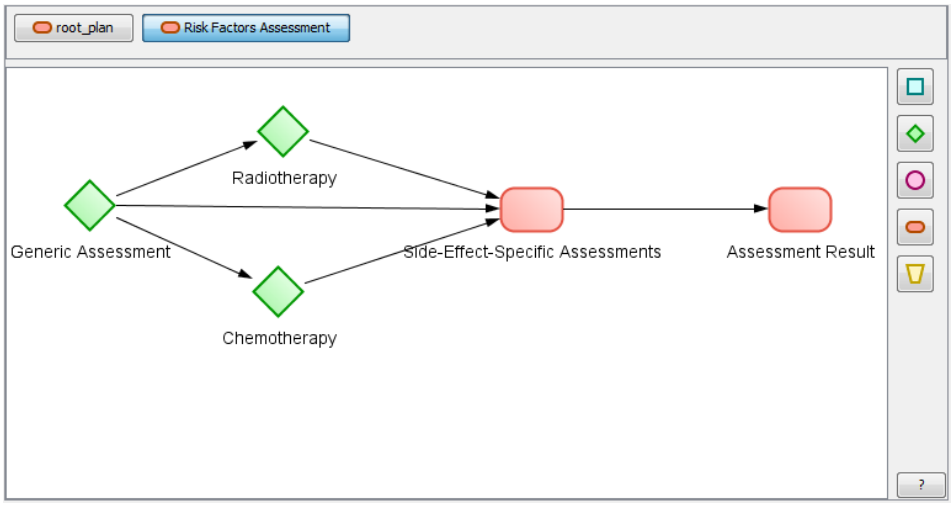


Figure 6.2: **Subnetwork of the plan "Risk Factors Assessment".**

- comorbidities: concomitant pathologies that could become risk factors for the treatment side effects (e.g., psoriasis could increase the risk of developing radiodermatitis). More than one choice is possible;
- date of birth;
- excessive alcohol consumption: it represents a risk factor for septic syndrome and febrile neutropenia;
- gender: it could represent a risk factor for some side effect (e.g., mucositis risk is higher for female patients);
- glycemia;
- basal height and basal weight: used to compute the Body Mass Index (BMI);
- nutritional status: a compromised nutritional status before

the beginning of the therapy increases the probability of occurrence of pathologies, such as febrile neutropenia. Allowed values are ”nutritionally compromised”, ”emaciated”, ”well nourished”, and ”undernourished”;

- race and ethnicity: people with dark complexion are at higher risk of developing radiodermatitis [121]. Allowed values are, therefore, reduced to ”white” and ”black”;
- smoking: a risk factor independent of the quantity, allowed values are ”smoker” and ”non-smoker”;
- unintentional weight loss: defined as a severe weight loss, before the beginning of the treatment, of 5% over a month or of 10% over 6 months. This data item is an abstraction calculated by the Alium Client Engine from the weight measures found in the data integrator. allowed values are, therefore, ”yes” or ”no”.

- Radiotherapy (executed only if this treatment was selected in the main flow), collecting:
  - concomitant therapies;
  - previous radiotherapy on head and neck: abstraction, allowed values are ”yes” or ”no”;
  - radiotherapy fractionation: ”altered” or ”not altered”;
  - radiation total dose on oral cavity and oropharingeal mucosa.
- Chemotherapy (executed only if this treatment was selected in the main flow), collecting:
  - chemotherapy dosage;
  - chemotherapy duration.

The workflow continues with the plans "Side-Effect Specific Assessments" and "Assessment Result", which contain subnetworks as well.

Side-Effect-Specific Assessments The subnetwork of the plan "Side-Effect-Specific Assessment" handles the collection of data that are specific to each side effect. Figure 6.3 shows that this workflow is composed only of enquiries without any temporal constraint, since the order of execution is not important and the tasks can be executed in random order. Some of the side effects are assessed based on the scores obtained in scales and questionnaires; however, the guideline does not require that these scores are above a threshold, they just provide a general evaluation of the patient's conditions.

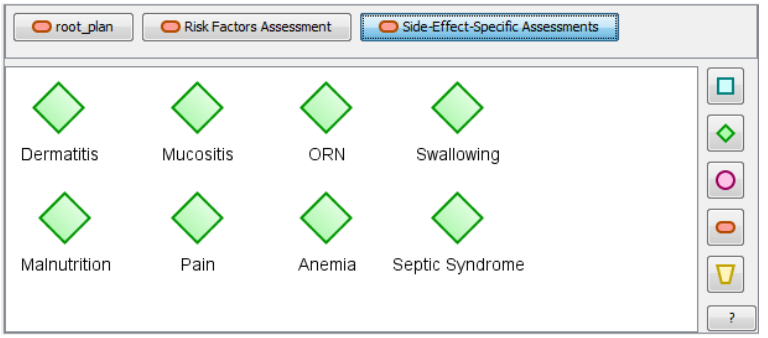


Figure 6.3: **Subnetwork of the plan "Side-Effect-Specific Assessments".**

The list below reports the data required by each enquiry.

- Dermatitis
  - basal Skindex-16 scale score [122];

  - personal risk factors for radiodermatitis (e.g., skin friction or abrasion, excessive sun exposure, etc.);
  - diagnosis of gene repair disorders (i.e., hereditary defects in DNA repairing capabilities, for example xeroderma pigmentosum, Fanconi anemia, ataxia-telangiectasia, etc.).

- Mucositis
  - personal risk factors for mucositis (e.g., poor oral hygiene, periodontal diseases, or immunosuppression).

- ORN
  - personal risk factors for ORN (e.g., poor oral hygiene, dental or periodontal diseases, extractions, etc.).

- Swallowing
  - presence of symptoms for dysphagia: the guideline does not specify these symptoms. Therefore, given also the high subjectivity in this field for lack of a clear clinical evidence, this data item expects as answer only ”yes” or ”no”, according to the doctors’ evaluation.

- Malnutrition
  - Mini Nutritional Assessment (MNA) [123];
  - Malnutrition Screening Tool (MST) [124];
  - Malnutrition Universal Screening Tool (MUST) [125];
  - Patient-Generated Subjective Global Assessment (PG-SGA) [126].

- Anemia

  - hemoglobin levels in blood (g/dL).

- Septic Syndrome

  - personal risk factors for septic syndrome (e.g., swallowing problems, chemotherapy-induced neutropenia, presence of gastrostomy or tracheostomy, etc.).

Assessment Result After all the necessary data have been collected, by extracting information from the data integrator or prompting the doctors, the workflow proceeds with the evaluation of the patient's risk to suffer from one or more side effects. If the patient is at risk, the system displays this information to the doctors exploiting tasks of type Action, which allow to show information or recommendations that do not require an answer. This plan contains 5 recommendations about the evaluation of risk factors.

Pre-Treatment

This subnetwork of the main workflow is executed if the data item "treatment_phase" has value "before". It shows 27 recommendations about suggested pre-treatment actions to prevent the onset of side effects.

Scales and Generic Data

This subnetwork of the main workflow is executed if the data item "treatment_phase" has value "during". It contains eight enquiries, as shown in Figure 6.4.

The list below reports the data required by each enquiry.

- Generic Data

  - comorbidities;

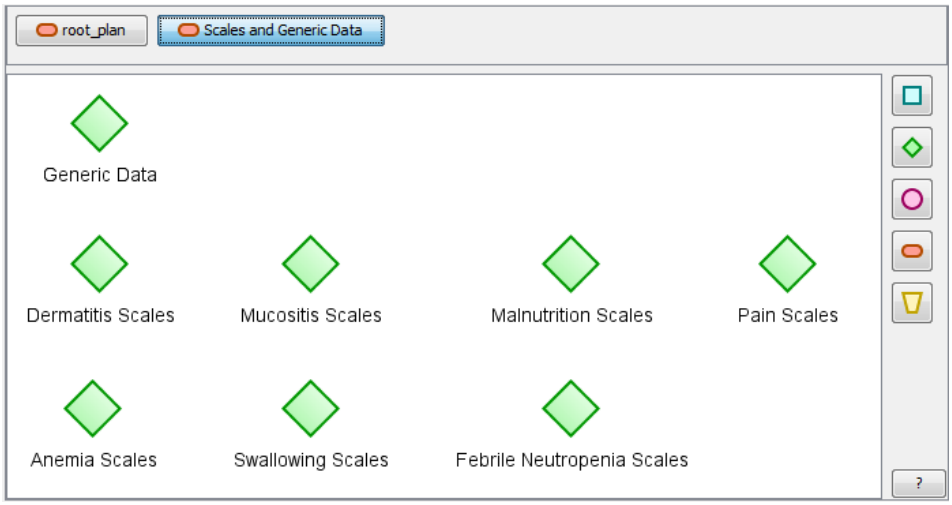


Figure 6.4: **Subnetwork of the plan "Scales and Generic Data".**

  - gender;
  - hemoglobin;
  - nutritional status.

- Dermatitis Scales
  - RISRAS scale score [127];
  - Skindex-16 scale score [122].

- Mucositis Scales
  - M.D. Anderson Symptom Inventory Head and Neck Cancer Module (MDASI HN) [128];
  - National Cancer Institute (NCI) Common Toxicity Criteria (CTC) version 4 [129];

  - Oral Mucositis Assessment Scale [130];
  - OMQD Scale Score;
  - RTOG toxicity criteria [131];
  - World Health Organisation (WHO) toxicity criteria [132].

- Malnutrition Scales
  - Mini Nutritional Assessment (MNA) [123];
  - Malnutrition Screening Tool (MST) [124];
  - Malnutrition Universal Screening Tool (MUST) [125];
  - Nutritional risk screening (NRS 2002) [133];
  - Patient-Generated Subjective Global Assessment (PG-SGA) [126].

- Pain Scales
  - numerical rating scale: allowed values are integer numbers ranging from 1 to 10. If the pain is greater than 4, the system recommends to consider therapies for pain management;
  - verbal rating scale: allowed values are ”absent”, ”weak”, ”moderate”, ”high”, ”very high”. If the pain is ”moderate” or higher, the system recommends to consider therapies for pain management;
  - visual-analog scale: allowed values and threshold are the same as for the numerical rating scale.

- Anemia Scales
  - Common Terminology Criteria for Adverse Events (CTCAE) for anemia [134].

- Swallowing Scales
  - Common Terminology Criteria for Adverse Events (CTCAE) for dysphagia [134];
  - M.D. Anderson Dysphagia Inventory (MDADI) [135].
- Neutropenia Scales
  - Common Terminology Criteria for Adverse Events (CTCAE) for neutropenia [134].

Always Valid Recommendations

This subnetwork of the main workflow follows "Scales and Generic Data" and is, therefore, part of the branch that is executed if the patient is undergoing treatment. It shows 26 recommendations that are always valid in case the treatment has already started. Some of these recommendations might have a precondition based on previously acquired data, but they are all independent of the onset of side effects. For example: if assessment scales scores were never inserted, the system might suggest evaluating the patient using one or more scales; if comorbidities were reported, the system might suggest keeping them under control.

Treatment

This subnetwork of the main workflow is executed after "Always valid recommendations" and contains recommendations for patients undergoing the treatment who manifested one or more side effects. The workflow is shown in Figure 6.5 and it starts with an enquiry collecting the side effects manifested by the patient. Then, on the base of those side effects, specific recommendations are shown for their management. For some side effects, further enquiries collect more details, in order to

generate more precise recommendations. In particular, the following paragraph reports a list of those enquiries and the data items they ask for.

- Dermatitis enquiries
  - amount of exudate (allowed values are "excessive" and "normal");
  - crust exudation (allowed values are "present" and "absent");
  - dermatitis characteristics (e.g., ulcer, itching, crust on skin);
  - CTCAE grade of dermatitis;
  - Glasgow Coma Scale score: used to evaluate the patient's conscious state [136];
  - microbial culture (allowed values are "positive" and "negative");
  - respiratory rate;
  - systolic blood pressure.

  The values of systolic blood pressure, respiratory rate, and the Glasgow Coma Scale score are used to dynamically calculate the qSOFA score, cited in the definition of the septic syndrome.
- Mucositis enquiries
  - painful mouth (allowed values are "yes" and "no").
- Malnutrition enquiries
  - food intake less than 50% for more than 5 days (allowed values are "yes" and "no").
- Septic Syndrome enquiries

  - blood culture (allowed values are ”positive” and ”negative”);
  - date of clinical presentation: when the patient manifested the first symptoms of a possible septic syndrome (both date and time are important);
  - empirical antibiotic therapy (allowed values are ”started” and ”not started”);
  - Glasgow Coma Scale score [136];
  - needle aspirate culture;
  - oral infection;
  - organ failure;
  - respiratory rate;
  - systolic blood pressure;
  - sputum culture;
  - stool culture;
  - skin-lesions swabs culture;
  - urine culture.

  The allowed values for all the cultures are ”positive”, ”negative”, or ”requested” (if the culture has already been requested but the result is still unknown). If no value has been assigned to a culture, it is supposed that the culture has not been ordered yet.

- Pain enquiries
  - musculoskeletal pain;
  - odynophagia (pain when swallowing);
  - WHO analgesic ladder [137].
- Swallowing enquiries

– enteral nutrition (allowed values are ”yes” and ”no”).

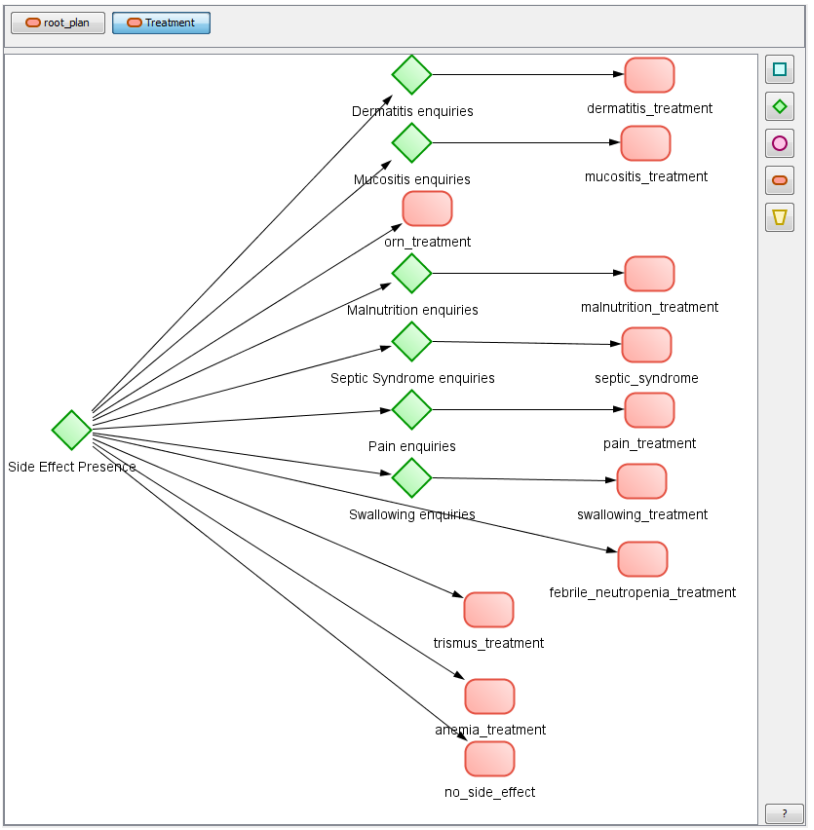


Figure 6.5: **Subnetwork of the plan ”Treatment”.**

The ”Treatment” plan contains in total 77 recommendations: 11 for dermatitis, 17 for mucositis, 4 for ORN, 4 for malnutrition, 6 for septic syndrome, 4 for sepsis, 2 for SIRS, 18 for pain, 3 for swallowing problems, 1 for trismus, 4 for febrile neutropenia, 2 for anemia, and 1 if no side effect is present.

Post-Treatment

The subnetwork of the main workflow is executed if the data item "treatment_phase" has value "after". This plan contains 18 recommendations about the post-treatment phase and the follow-up, especially for those side effects that can last months after the end of the treatment (e.g., ORN).

Overall Summary

Overall the CIG contains 153 recommendations: 5 recommendations for the evaluation of risk factors, 27 valid in the pre-treatment phase, 26 always valid during treatment, 77 side-effect-specific during treatment, and 18 valid in the post-treatment phase.

6.1.4 The App Configuration Guideline

From the same CPG, other 42 recommendations destined to patients or regarding the acquisition of PROs were extracted (6 valid in the pre-treatment phase, 24 in the treatment phase, and 12 always valid). These recommendations were included into a detached CIG for the proper configuration of the mobile app, in terms of which clinical parameters and questionnaires should be collected, with which frequency, and which tips about the prevention of side effects should appear into the patient's mobile app. The analyzed CPG was not very detailed in terms of collection frequencies. When no frequency is recommended, the choice is entrusted to the doctors.

The clinical parameters mentioned in the guideline are:

- glycemia (no recommended frequency), to be collected if the patient is affected by diabetes or if the last measure of glycemia exceeded 120 mg/dl;

- weight (no recommended frequency or precondition);
- blood pressure (no recommended frequency), to be collected if the patient is affected by a hypertensive disorder;
- temperature(no recommended frequency).

The questionnaires:

- EuroQoL [138];
- M.D. Anderson Dysphagia Inventory (MDADI) [135];
- M.D. Anderson Symptom Inventory Head and Neck Cancer Module (MDASI HN) [128];
- European Organisation for Research and Treatment of Cancer Quality of Life (EORTC QoL) [139];
- Big Five Inventory (BFI) [140, 141].

Main Workflow

The main workflow of this CIG in Alium, reported in Figure 6.6, is very similar to the previous CIG for the management of patients' side effects to the treatment. In fact, it starts with the same assessments of the patient's status ("Treatment Phase" enquiry followed by the "Risk Factors Assessment" plan).

These assessments are followed by a set of tips that patients should always be able to see in the app ("Always valid recommendations"). These are suggestions about good habits that will help patients avoiding or reducing the onset of side effects to chemo- or radiotherapy (e.g., "Avoid micro-traumas or tapes/adhesives in irradiated areas"). Some of these tips might have preconditions. For example, the tip "Shave with a sharp, disposable multi-blade wet razor or with a non-traumatizing

electric razor" is destined to male patients, while "Avoid smoking" is destined to smokers.

The flow, then, proceeds into different subnets according to the treatment phase. In this case, no *post-treatment* phase is considered, because the CPG did not present any recommendation for the patients' behavior at home during the treatment follow-up.

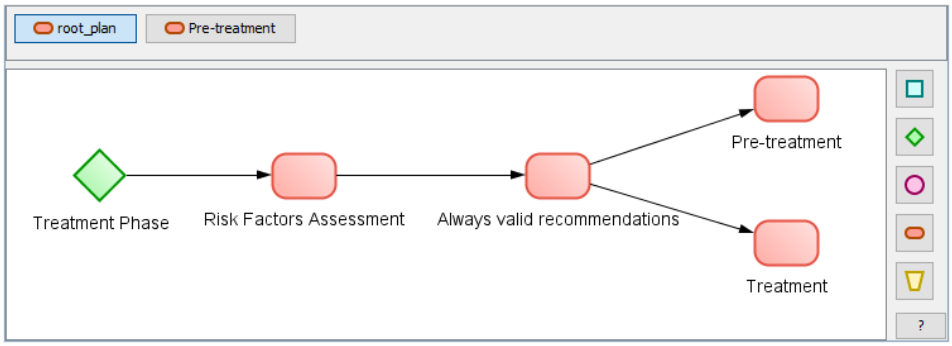


Figure 6.6: **The main workflow in Alium for the app configuration guideline.**

Pre-Treatment

Since the app is mainly for monitoring purposes and patients' behaviors during treatment, if the patient is in the *pre-treatment* phase the only recommended tips are about the prevention of ORN, suggesting that the patient undergoes a dental examination before starting the radiation therapy.

Treatment

If the patient is already undergoing *treatment*, recommendations about which clinical parameters and questionnaires to collect and which

tips to include in the app are shown to the doctors.

Figure 6.7 shows that this subnetwork is composed of actions without any temporal constraint, since the order of execution is not important. Each action corresponds to a recommendation about a clinical parameter, a questionnaire, or a tip for patients about the prevention or treatment of a side a effect. The execution of these actions consists in the visualization of their descriptions/recommendations. Some of these actions are always activated, because the tip they contain is valid for all patients; for example, the suggestion to "Use oral care products not containing alcohol and without intense flavour" helps avoiding the onset of mucositis. Other activities are activated based on the guideline rules described above. For example, the recommendation about collecting the patient's glycemia is shown if the patient is affected by diabetes or if the last measure of glycemia exceeded 120 mg/dl. In Alium this rule becomes:

('comorbidities_relevant_list' term_includes "SCT:73211009 [Diabetes mellitus] || Diabetes mellitus") or glycemia > 120

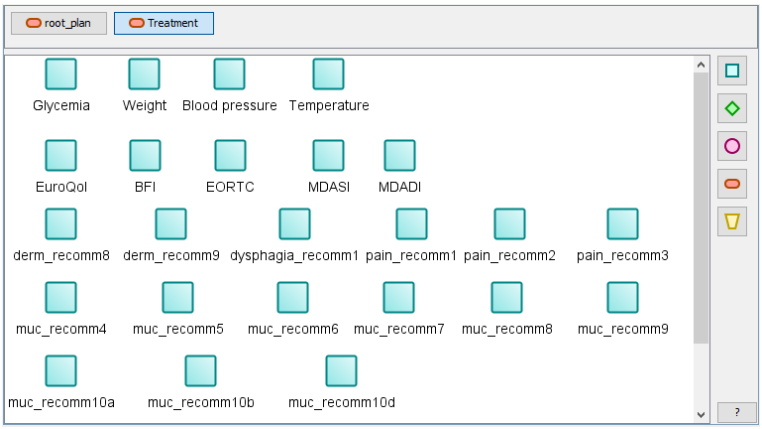


Figure 6.7: **Subnetwork of the plan "Treatment" in the app configuration guideline.**

6.1.5 The Mobile Application

The mobile app developed within this experience is called HeNeA (Head and Neck Application) [142]. HeNeA runs on Android and it is designed to collect patients' symptoms, clinical parameters, and questionnaires in a proactive manner. In a dedicated and password-protected area of the app, doctors are able to manually configure the frequency and type of clinical parameters and questionnaires that a specific patient is asked to report. According to the configuration guideline describe above, the doctors are recommended to monitor up to four parameters and up to five questionnaires. Since the guideline does not specify collection frequencies, for both clinical parameters and questionnaires the possible acquisition frequency in HeNeA ranges from "every day" to "every six months", and reminders are automatically issued to patients in due time. Moreover, HeNeA allows reporting on three symptoms: nausea, vomiting, and pain. These symptoms are entered on a voluntary basis only. Patients can also report the symptom severity on a discrete scale from 0 to 10, and if any medication was taken to mitigate the symptom. For pain, also its location can be reported. HeNeA regularly (once a day) synchronizes all the data to a private server hosted by INT and, therefore, subject to their strict privacy policy.

In addition to the reporting functionality, HeNeA offers:

- Educational material about the diagnosis of HNC, the possible treatments and their side effects, and dietary suggestions for the patients who are fed through nasogastric tube;
- "Tips of the day" (derived from the guideline), which are daily suggestions about the prevention and self-treatment of side effects caused by CCRT;
- The possibility of keeping track of the costs related to the therapy

(e.g., visits fees, oral hygiene products the patient had to buy, etc.);

- Embedded maps with location markers for pharmacies and hospitals with a radiotherapy unit;
- The possibility to subscribe to a dedicated social network and interact with peer patients;
- The possibility to interact with the medical staff via e-mail, attaching the report of the clinical parameters and questionnaires. Patients can use this functionality when they want to send data immediately, instead of waiting for the automatic daily data synchronization.

Figure 6.8 shows some screenshots of HeNeA. As it can be deduced from the previous description, HeNeA is not remotely configurable, as its development started prior to the design of the architecture described in this dissertation. However, the implemented DSS provides some recommendations for the manual configuration of the app. Moreover, the data synchronized to the hospital server are available to the doctors through a dedicated website.

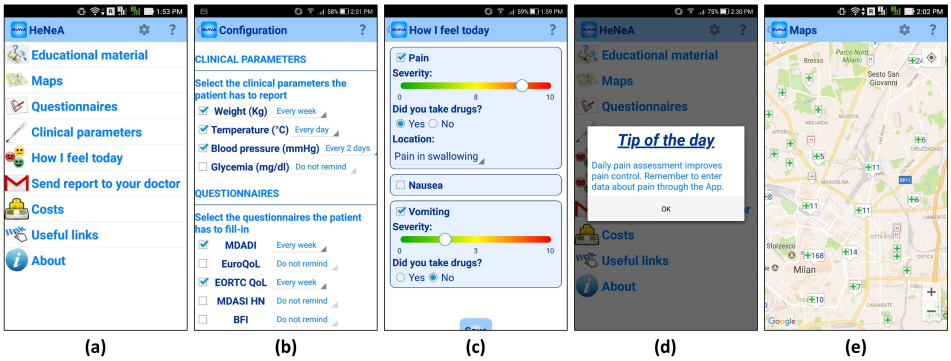


Figure 6.8: **Screenshots of HeNeA.** (a) The homepage; (b) setting of parameters and questionnaires to be collected; (c) symptoms reporting; (d) tip of the day; (e) maps showing points of interest.

6.1.6 The Doctors' Web Application

The website dedicated to doctors shows temporal plots and qualitative charts (bar charts and pie charts) for the clinical parameters, questionnaires, symptoms, and costs inserted by the patients. For example, Figure 6.9 reports a screenshot of the website with the symptoms reported by the patient John Doe. Alerts are generated if any clinical parameter exceeds predefined thresholds, for example if the weight decreases of more than 10% from its basal measure (taken before starting the treatment), or if the body temperature is greater than 38 °C.

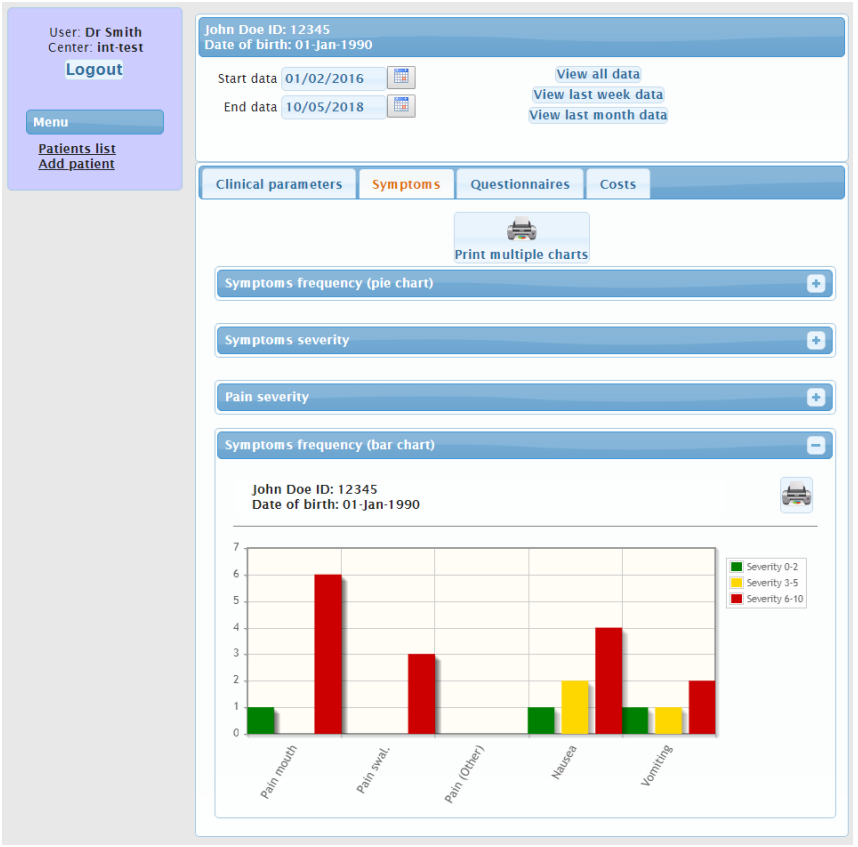


Figure 6.9: **Screenshot of the doctors' website.** Visualization of patients' data

For hospital- and time-related reasons, the evaluation of the system concerned only the parts of HeNeA described until this point. However, another section of the website implementing the DSS has been recently added. Figure 6.10 shows some recommendations generated for a patient undergoing CCRT who developed radiation-related dermatitis and who experienced moderate pain: the guideline suggests a series of

possible treatments for these side effects. The figure also shows that when a specific recommendation is selected a brief explanation of why it is shown appears at the bottom of the page.

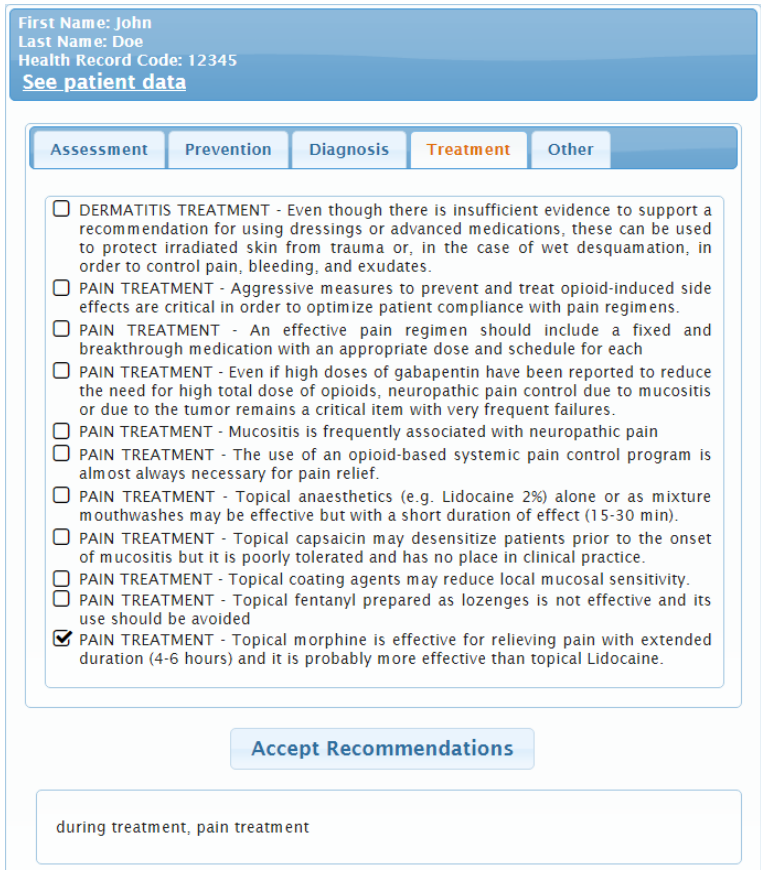


Figure 6.10: **Screenshot of the doctors' website.** Recommendations from the clinical guideline.

Figure 6.11 shows some recommendations about the app configuration. The patient is undergoing CCRT and no completed questionnaire

was found in the database, thus the guideline suggests which questionnaires could be useful for estimating the patient's status. As reported in the description of the CPG (Section 6.1.4), the collection of weight and temperature is always suggested, entrusting the doctor with the decision about the frequency.

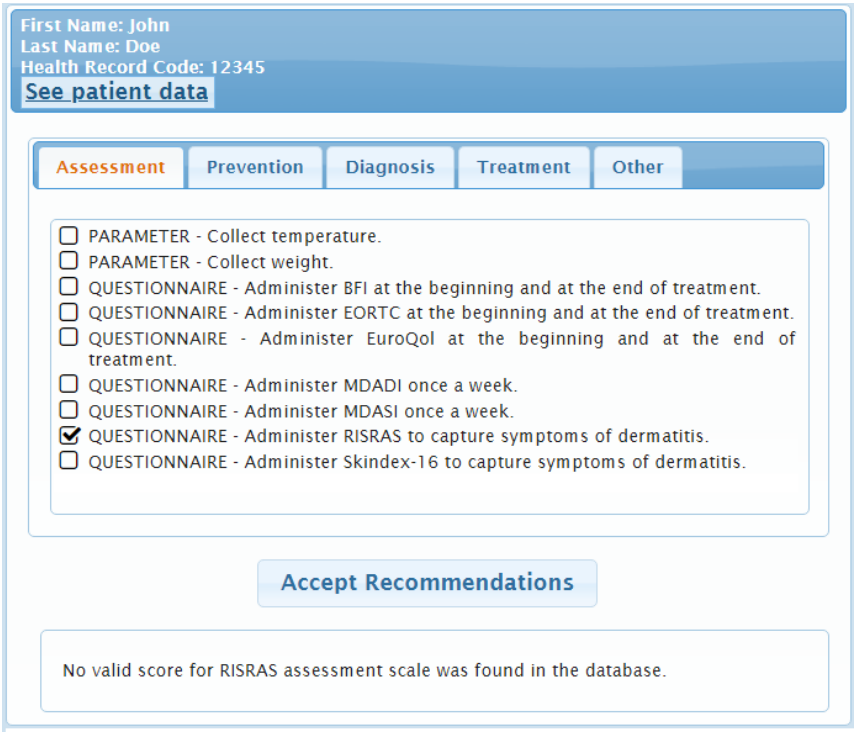


Figure 6.11: **Screenshot of the doctors' website.** Recommendations from the app configuration guideline.

As mentioned, at the moment, the doctors may consult the guideline for the app configuration, but the configuration itself must be performed by accessing the app locally in the patient's mobile. The web interface

for the remote app configuration is still a work in progress. A mockup is shown in Figure 6.12.

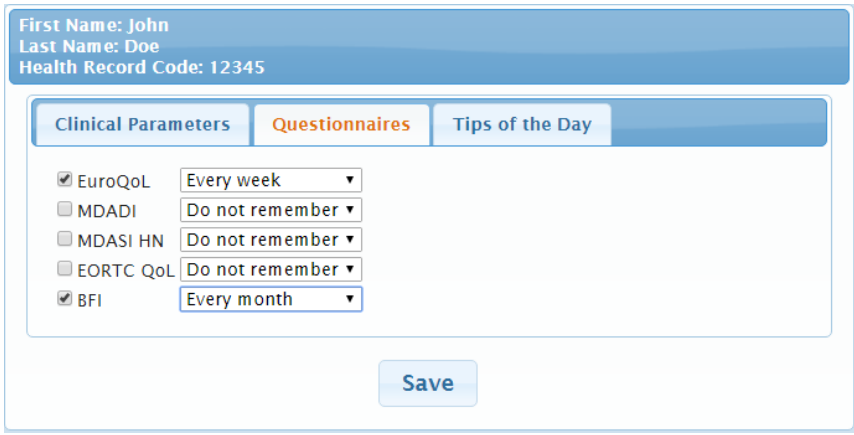


Figure 6.12: **Mockup of the doctors' website section for the app configuration.**

6.1.7 The Evaluation

HeNeA (the mobile application and the part of the doctors' website for the data visualization) was tested on patients undergoing CCRT at the INT, and the INT internal Ethics Committee approved the pilot study (N.INT 14/16 on Jan 28th, 2016).

According to the study protocol, at least ten patients had to be recruited by three oncologists of the Head and Neck Unit of INT. The inclusion criteria considered only adult patients with HNC in anticipation of CCRT. To be included, patients had to be able to use a tablet. The observation period was supposed to be nine weeks, seven for the treatment and two for the follow-up. At the enrollment, the doctors acquired the patients' informed consent and provided them

with a tablet (Android version 4.4.4) on which HeNeA had already been installed and properly configured. The tablet configuration consisted in the patient-personalized definition of the clinical parameters and questionnaires to be collected, and the related collection frequency. Patients were then instructed about HeNeA functionalities, but they also received a paper manual in case of further doubts about the app functioning. The aim of the pilot study was evaluating the usability of HeNeA and the feasibility of continuous symptoms monitoring during CCRT in HNC patients.

In order to assess the usability, perceived usefulness, and user acceptance of HeNeA, both patients and doctors have been administered a paper-based questionnaire in Italian, composed of 8 questions. Figures 6.13 to 6.16 report the English translation.

Since, as pointed out in a recent review [143], no definite guidelines exist yet about the selection of questionnaires for evaluating mobile apps, a questionnaire was developed purposely for evaluating HeNeA, adapting the Telehealth Usability Questionnaire [144] to this context. The questionnaire was administered anonymously to patients. Each questionnaire resulted in a score ranging from 0 to 25, obtained by summing up the answers to all questions. The overall satisfaction with the app was decided to be acceptable if the median score of the questionnaires, separately computed for patients and doctors, was equal to or greater than 16 (i.e., approximately 2/3 of the maximum obtainable score, similarly to the threshold adopted by other questionnaires [145, 146]). However, the individual constructs of usability, perceived usefulness and acceptance, were also considered separately, analyzing the answers to the corresponding questions (1-2, 3-5, and 6-8, respectively).

In this study, feasibility is meant as the actual patient's willingness to use the app for the main purpose it was intended to, i.e. remote data collection. To this aim, the following measures were defined:

- *Percentage of dropouts*: patients who interrupted the use of HeNeA before the end of their treatment, for reasons unrelated to the worsening of their medical condition or death. This percentage had to be less than 30%, which appears to be the average dropout rate across all clinical trials [147].

- *Percentage of noncompliance with assignments*: number of clinical parameters (CP) or questionnaires (Q) actually inserted, with respect to the number expected from the doctors' configuration (e.g., if the doctor set a frequency of "every day" for the clinical parameter "weight" and the patient's treatment lasted 4 weeks, 28 measures of weight were expected. If the patient only inserted 20 measures, the number of noncompliance events was 8, leading to a noncompliance percentage of 28.5%). To be acceptable, again it was established that the percentage had to be less than 30%. Based on this definition, the noncompliance percentage was calculated according to this general formula:

$$noncompliance(\%) = 100 - \frac{insertedCP + insertedQ}{expectedCP + expectedQ} * 100$$

QUESTIONNAIRE FOR EVALUATING THE SATISFACTION WITH THE APP FOR PATIENTS

Please, evaluate your experience with this App (HeNeA).

Please, answer the questions to the best of your possibility. All your answers will be confidential.

Please, mark only one answer for each of the following questions.

		Poor	Discrete	Good	Very Good	Excellent
1	How did you consider the **ease of use** of the App? (ease of filling, clear instructions, access to contents, filling reminders)	0	1	2	3	4
2	How did you consider the **comfort of use** of the App? (use at home or in the hospital, choice of the moment of filling)	0	1	2	3	4

		No, not at all	Yes, to some extent	Yes, quite a lot	Yes, very much
3	Did this App help you **recognize and better describe the side effects (toxicities) of your therapy**?	0	1	2	3
4	Did this App help you in the **prevention and treatment of side effects (toxicities)**?	0	1	2	3
5	Did this App help your **relationship with the Doctors** that cured you?	0	1	2	3

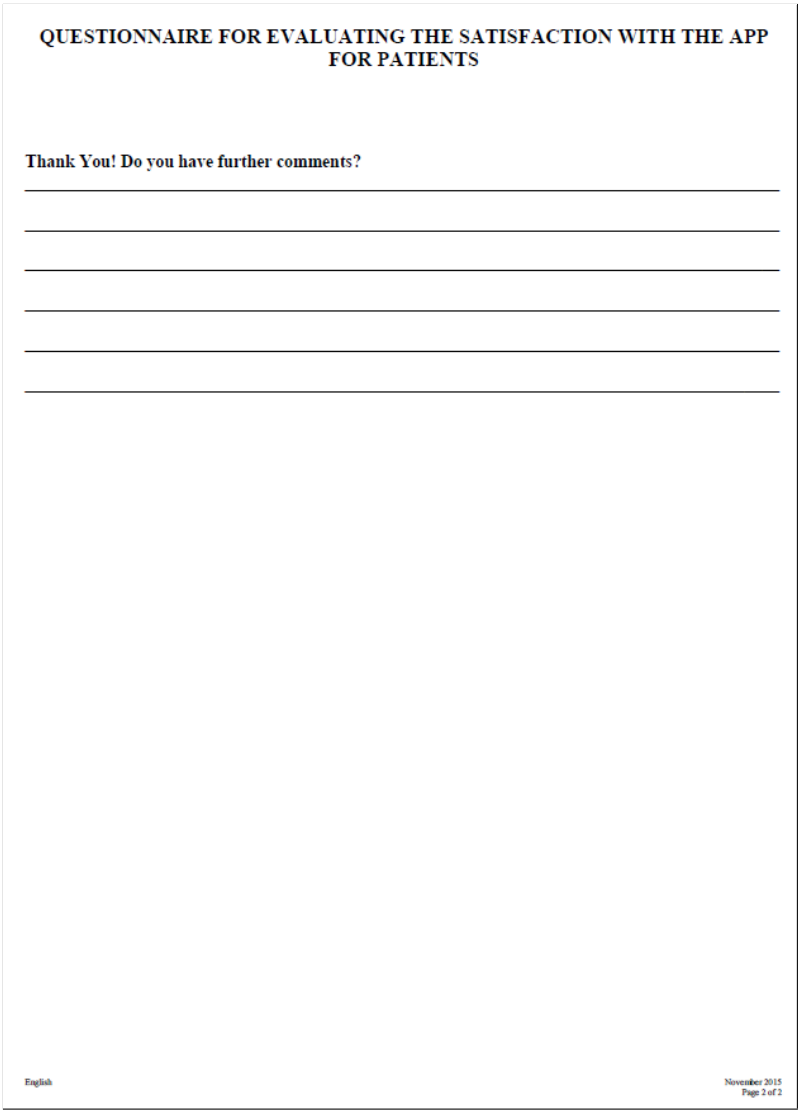
		No	Maybe	Yes
6	**Would you suggest** this App to other people who have the same disease as you have?	0	1	2
7	**Would you choose** this App **again**?	0	1	2

		Poor	Discrete	Good	Very Good	Excellent
8	Overall, **how do you rate** this App?	0	1	2	3	4

English

November 2015
Page 1 of 2

Figure 6.13: **Questionnaire for evaluating patients' satisfaction with HeNeA (Page 1).**



QUESTIONNAIRE FOR EVALUATING THE SATISFACTION WITH THE APP FOR PATIENTS

Thank You! Do you have further comments?

English

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Page 2 of 2

Figure 6.14: **Questionnaire for evaluating patients' satisfaction with HeNeA (Page 2).**

QUESTIONNAIRE FOR EVALUATING THE SATISFACTION WITH THE APP FOR DOCTORS

Please, evaluate your experience with this App (HeNeA).

Please, answer the questions to the best of your possibility. All your answers will be confidential.

Please, mark only one answer for each of the following questions.

		Poor	Discrete	Good	Very Good	Excellent
1	How did you consider the **ease of use** of the App? (ease of filling, clear instructions, access to contents, filling reminders)	0	1	2	3	4
2	How did you consider the **comfort of use** of the App? (use at home or in the hospital, choice of the moment of filling)	0	1	2	3	4

		No, not at all	Yes, to some extent	Yes, quite a lot	Yes, very much
3	Did this App help you **evaluate the effects of the treatment on your patients**?	0	1	2	3
4	Did this App help you in the **management and treatment of side effects (toxicities)**?	0	1	2	3
5	Did this App help your **relationship with the Patients** that you cured?	0	1	2	3

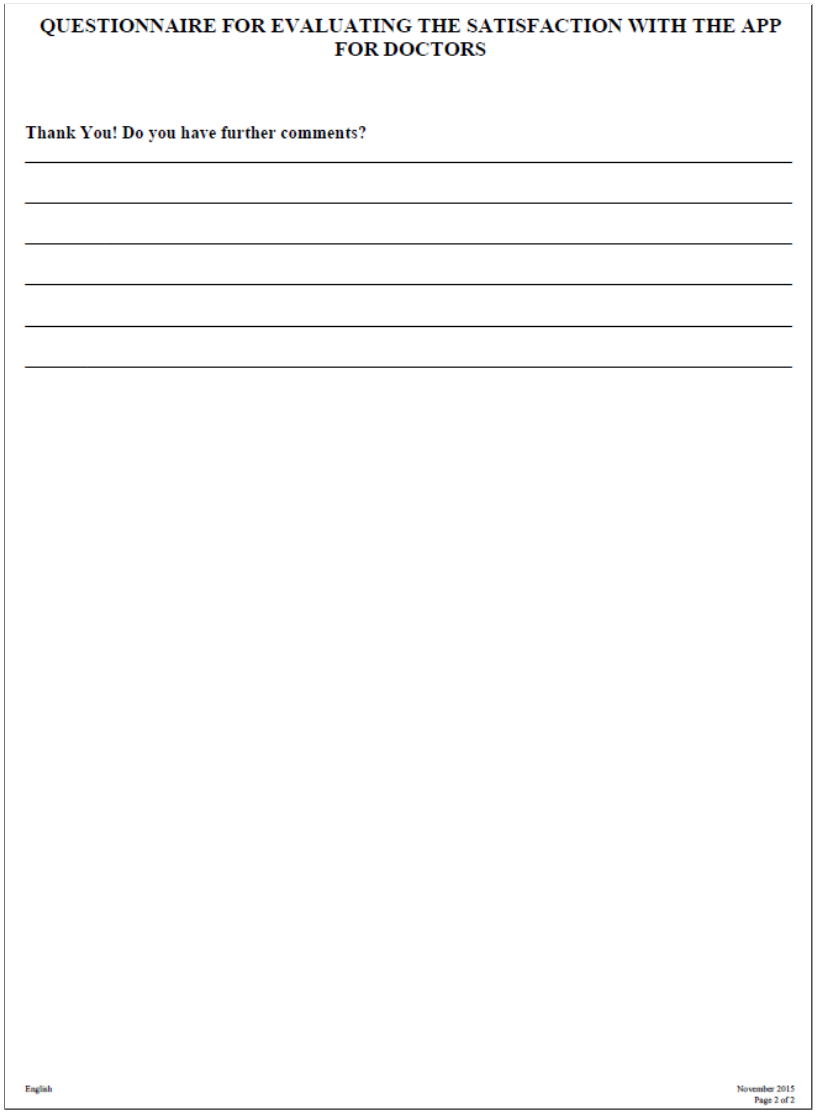
		No	Maybe	Yes
6	**Would you suggest** this App to other Patients who have the same disease?	0	1	2
7	**Would you choose** this App **again** to monitor the side effects in your patients?	0	1	2

		Poor	Discrete	Good	Very Good	Excellent
8	Overall, **how do you rate** this App?	0	1	2	3	4

English

November 2015
Page 1 of 2

Figure 6.15: **Questionnaire for evaluating doctors' satisfaction with HeNeA (Page 1).**



QUESTIONNAIRE FOR EVALUATING THE SATISFACTION WITH THE APP FOR DOCTORS

Thank You! Do you have further comments?

English

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Page 2 of 2

Figure 6.16: **Questionnaire for evaluating doctors' satisfaction with HeNeA (Page 2).**

For the analysis of patients' and doctors' questionnaires, at first the raw sum of the answers was calculated for both groups. Summary statistics were then performed, to provide information about the overall satisfaction with the app. To cope with non-normal distributions and small sample sizes, median and interquartile range (i.e., 25th and 75th percentiles) have been preferred to mean and standard deviation for all the following descriptive statistics. In order to get a detailed visual insight on each aspect, histograms of the answers to each question were considered. Finally, summary statistics have been calculated also for each construct separately (usability, perceived usefulness, and acceptance) and the association among them was investigated. In particular, it was considered interesting to check (i) if usability was a predictor of perceived usefulness (as a matter of fact, a system could be easy to use but perceived as ineffective) and (ii) to which extent usability and perceived usefulness affected acceptance. Moreover, symptom severity was evaluated as a predictor of quality of life. For testing those hypotheses, Kendall-Theil Sen Siegel non-parametric linear regression [148] has been used for simple regressions. Multiple regression has also been performed, using a robust linear model [149]. Root Mean Squared Error (RMSE), i.e. residual standard error, has been used as a goodness-of-fit measure.

Concerning feasibility, the data collected through HeNeA were analyzed to compute the percentage of dropouts and noncompliance.

Microsoft Excel has been used to tabulate the data collected through HeNeA and produce graphs, while the R environment for statistical computing [150] has been used for all the data analyses (function "mblm" of the mblm package [151] for the Kendall-Theil Sen Siegel non-parametric linear regression, and function "rlm" of the MASS package [152] for the robust regression).

A total of 11 patients treated with CCRT and 3 caring doctors agreed to start the study. However, one of the patients withdrew the consent soon after the enrollment, so he was not considered in

the analysis. Another patient kept the tablet until the toxicities worsened too much for him to continue the study, but he was included in the statistics since he returned the tablet after 20 days, which was considered a satisfactory period for him to evaluate the application. This accounts for a final sample size of 10 patients and 3 doctors. The patients' age ranged from 44 to 59 years (median: 53.50 years, interquartile range: 45-57.7 years) and 90% of them were males. Sixty percent of patients were diagnosed with nasopharyngeal cancer, while the remaining 40% with HPV-related oropharyngeal cancer.

Table 6.2 shows the results about the usage of tablets for each patient, with respect to the time that the tablet was lent to them (loan time). Summary statistics are shown in the last row.

Table 6.2: **Tablets usage and loan time.**

Patient	**Usage (days)**	**Loan Time (days)**	**Usage / Loan (%)**
P1	31	53	58.5
P2	54	56	96.4
P3	18	20	90.0
P4	18	30	60.0
P5	39	52	75.0
P6	37	59	62.7
P7	4	49	8.2
P8	63	65	96.9
P9	27	40	67.5
P10	27	43	62.8
Median (Interquartile Range)			
	29 (20.2-38.5)	50.5 (40.7-55.2)	65.1 (60.7-86.2)

As shown in the table, 9 patients out of 10 had the tablet turned

on for more than 50% of the time. Despite this good result, this information is not enough to confirm that they used the app consistently and with satisfaction. Thus, the following paragraphs will report findings about the effective usage of the app and the users' judgment about it.

Users' Satisfaction

Table 6.3 reports the answers to the questionnaire administered anonymously to the 10 patients, ordered according to the total score, from negative to positive rating. Since the questionnaires could no be attributed to the patients' identities, a different enumeration has been used for the patients: [P_A...P_J] instead of [P1...P10]. Note that questions 1-2 concern usability, 3-5 concern perceived usefulness, and 6-8 concern acceptance. The table shows an overall positive result (for 6 patients out of 10 the final score is greater than 16), while question 4, representing a usefulness item, turned out to be the most critical one.

Legend for Table 6.3: Questions of the patients' questionnaire

1	How did you consider the ease of use of the App? (ease of filling, clear instructions, access to contents, filling reminders)
2	How did you consider the comfort of use of the App? (use at home or in the hospital, choice of the moment of filling)
1+2	Usability partial score per patient
3	Did this App help you recognize and better describe the side effects (toxicities) of your therapy?
4	Did this App help you in the prevention and treatment of side effects (toxicities)?
5	Did this App help your relationship with the Doctors that cured you?
3+4+5	Perceived usefulness partial score per patient
6	Would you suggest this App to other people who have the same disease as you have?
7	Would you choose this App again?
8	Overall, how do you rate this App?
6+7+8	Acceptance partial score per patient

Table 6.3: **Answers to the questionnaire given by the 10 study patients.** Median and interquartile range (IQ range) are reported for each partial score and for the total score.

Question (Score Range)	$\mathbf{P_A}$	$\mathbf{P_B}$	$\mathbf{P_C}$	$\mathbf{P_D}$	$\mathbf{P_E}$	$\mathbf{P_F}$	$\mathbf{P_G}$	$\mathbf{P_H}$	$\mathbf{P_I}$	$\mathbf{P_J}$
1 **(0-4)**	0	2	2	3	3	4	3	4	3	3
2 **(0-4)**	0	2	2	2	3	4	3	4	4	4
1+2	0	4	4	5	6	8	6	8	7	7
Median (IQ Range)	**6 (4.2 - 7)**									
3 **(0-3)**	1	1	1	1	2	2	2	2	2	3
4 **(0-3)**	1	0	1	1	1	1	2	1	2	3
5 **(0-3)**	0	1	1	2	2	1	2	2	3	3
3+4+5	2	2	3	4	5	4	6	5	7	9
Median (IQ Range)	**4.5 (3.2 - 5.7)**									
6 **(0-2)**	1	1	1	2	2	2	2	2	2	2
7 **(0-2)**	1	1	1	2	2	2	2	2	2	2
8 **(0-4)**	1	1	1	2	3	3	3	4	3	4
6+7+8	3	3	3	6	7	7	7	8	7	8
Median (IQ Range)	**7 (3.7 - 7)**									
Total Score per Patient	**5**	**9**	**10**	**15**	**18**	**19**	**19**	**21**	**21**	**24**
Median (IQ Range)	**18.5 (11.2 - 20.5)**									

Concerning the associations among the scores, Figure 6.17 shows that perceived usefulness is positively associated with usability (β=1, p=0.01) (a). Moreover, the user acceptance is positively associated with both perceived usefulness (β=0.896, p=0.006) (b) and usability (β=0.8334, p=0.006) (c); thus, perceived usefulness and usability, at univariate analysis, contributed to the user acceptance with the same statistical significance. The multiple regression analysis showed that usability and perceived usefulness are also independent significant predictors of acceptance (β=0.479 with p=0.012 and β=0.416 with p=0.046, respectively; RMSE= 0.99).

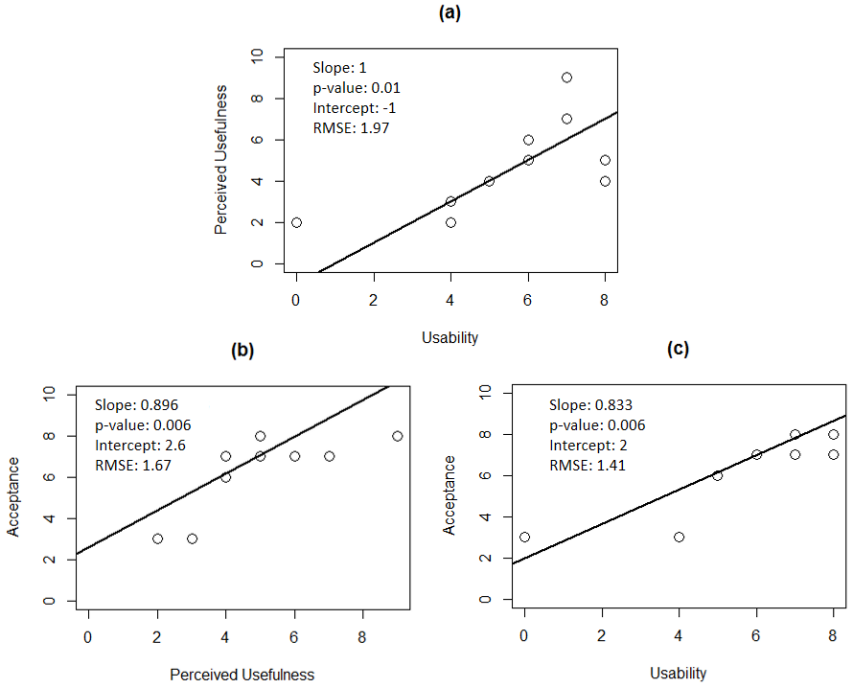

Figure 6.17: **Relationships among the patients' questionnaires partial scores.** (Non-parametric linear Siegel regression lines are shown)

Table 6.4 reports the answers to the questionnaire administered to doctors, who considered both the mobile app and the website functionalities. Summary statistics were not performed on doctors' answers, since they were only 3 individuals.

Legend for Table 6.4: Questions of the doctors' questionnaire

1	How did you consider the ease of use of the App? (ease of filling, clear instructions, access to contents, filling reminders)
2	How did you consider the comfort of use of the App? (use at home or in the hospital, choice of the moment of filling)
1+2	Usability partial score per doctor
3	Did this App help you evaluate the effects of the treatment on your patients?
4	Did this App help you in the management and treatment of side effects (toxicities)?
5	Did this App help your relationship with the patients that you cured?
3+4+5	Perceived usefulness partial score per doctor
6	Would you suggest this App to other patients who have the same disease?
7	Would you choose this App again to monitor the side effects in your patients?
8	Overall, how do you rate this App?
6+7+8	Acceptance partial score per doctor

Table 6.4: **Answers to the questionnaire given by the 3 doctors.**

Question (Score Range)			
1 **(0-4)**	4	3	3
2 **(0-4)**	2	4	3
1+2	6	7	6
3 **(0-3)**	2	2	1
4 **(0-3)**	1	2	1
5 **(0-3)**	1	2	1
3+4+5	4	6	3
6 **(0-2)**	1	2	1
7 **(0-2)**	1	2	0
8 **(0-4)**	3	3	1
6+7+8	5	7	2
Total Score per Doctor	**16**	**20**	**11**

Feasibility

One patient out of 11 (9%) interrupted the use of HeNeA for reasons unrelated to the worsening of his medical condition (consent has been withdrawn). Thus, the percentage of dropouts is significantly less than the previously established threshold of 30%.

Table 6.5 summarizes the number of clinical parameters and questionnaires actually inserted by patients with respect to their expected number, and the resulting noncompliance percentage. The table shows that 6 patients have less than 30% of noncompliance with assignments, 5 of which reached 0%. The patients who had 0% of noncompliance ac-

tually inserted even more parameters or questionnaires than expected, entering from 5 to 44 reports in excess. The median noncompliance is 10% (interquartile range 0 - 49.5).

Table 6.5: **Number of clinical parameters (CP) and questionnaires (Q) inserted vs. expected and noncompliance (NC) percentage.**

	Inserted CP (number)	**Expected CP (number)**	**Inserted Q (number)**	**Expected Q (number)**	**NC (%)**
P1	55	80	12	16	30.21
P2	60	16	6	6	0.00
P3	9	27	3	5	62.50
P4	6	20	5	5	56.00
P5	42	52	22	28	20.00
P6	27	30	48	38	0.00
P7	1	17	10	10	59.26
P8	97	87	10	15	0.00
P9	39	20	5	10	0.00
P10	30	44	30	10	0.00

Additional Insight: Symptoms, EuroQoL, Free-text Comments

While patients received reminders for entering clinical parameters and for filling-in questionnaires, no reminders were planned for symptoms, expecting patients to insert them proactively upon their occurrence. This was done by all patients but one. In particular, the total number of symptoms inserted by each patient was: **P1**: 15 symptoms, **P2**: 8 symptoms, **P3**: 3 symptoms, **P4**: 6 symptoms, **P5**:

0 symptoms, **P6**: 2 symptoms, **P7**: 9 symptoms, **P8**: 47 symptoms, **P9**: 63 symptoms, **P10**: 10 symptoms.

The reliability of data collected at home is a well-known issue. In fact, the risk that a patient provides "random" answers because of lack of interest in the application or because of reminder fatigue is high. Thus, post-hoc analyses are necessary to check data reliability. This may be accomplished, for example, by testing correlations among data that, in principle, should be correlated. In the case of HeNeA, the reported severity of these symptoms was compared with the scores of the EuroQoL questionnaire for those patients who compiled it at least once in the whole treatment period. To obtain sensible statistics, only the symptoms reported *in proximity* of each EuroQoL compilation were considered (meaning 6 to 0 days before they filled-in the EuroQoL). Figure 6.18 shows the results of the regression analysis: a negative association (β=-0.0249, p=0.007) between the quality of life measured with EuroQoL and the symptoms severity can be highlighted.

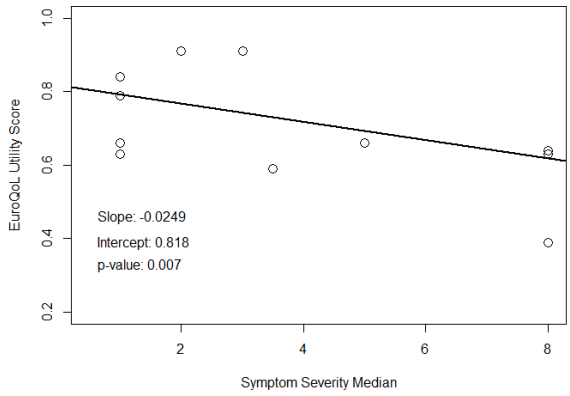

Figure 6.18: **Regression analysis of the quality of life on reported symptoms severity.**

Table 6.6 shows the raw data used for deriving the relation shown in Figure 6.18. Each row in this table corresponds to a separate compilation of the EuroQoL questionnaire by a patient, thus the same patient may be referenced multiple times. For each submission, the number of symptoms reported by that patient in the preceding 6 days is indicated, along with some information concerning their severity (i.e., min, max, median). Note that the numbers of symptoms referenced in this table are much less than the total number of symptoms mentioned above, since the majority of symptoms were not reported in proximity of a submission of the EuroQoL questionnaire.

Table 6.6: **Symptoms reported by patients "in proximity" of a EuroQoL questionnaire.**

Patient	Symptom Severity Min, Max (Median)	Number of symptoms	EuroQoL Score
P4	1, 1 (1)	3	0.84
P6	3, 3 (3)	1	0.91
P6	8, 8 (8)	1	0.63
P6	8, 8 (8)	1	0.64
P7	1, 3 (1)	6	0.79
P7	1, 10 (8)	3	0.39
P8	1, 5 (3.5)	8	0.59
P9	1, 5 (2)	15	0.91
P10	1, 10 (3)	3	0.91
P10	1, 6 (1)	3	0.66
P10	5, 5 (5)	1	0.66
P10	1, 3 (1)	3	0.63

Both patients' and doctors' questionnaires allowed free-text non-mandatory comments.

Patients' Comments The English translations of the comments provided by 6 patients are reported below, grouped by theme.

1. **Usability.** Table 6.3 shows an overall satisfaction of patients (n=10) with the app. One patient argued that the usability might need improvement; however, he did not specify which functionalities were critical, only mentioning that the user manual was too cumbersome:

   "First of all I think that an app conceived to bridge the communication gap (and/or ease the communication) between a doctor and a patient is an excellent idea, but as it is designed right now, it does not get the job done. The app is not very intuitive, requires a lot of effort from the patient to read the manual. The app has to be simple, intuitive, and graphical." [P_A]

2. **Reporting Symptoms.** Two patients complained about the poor flexibility of the symptom reporting function (the section "How I feel today"), because the app allowed reporting only pain, nausea, and vomiting, but they would have liked to report also other symptoms experienced during the treatment:

   "It is not very flexible to the patient's needs (e.g., symptoms: why cannot I insert other symptoms besides those suggested by the app?)." [P_A]

   "Some functionalities are unnecessary (according to me). The section 'How I feel today' could be improved." [P_I]

   One of those patients also argued that doctors should check if patients could actually measure all the required clinical parameters:

   "You need to ensure that patients own all the tools necessary to measure the required clinical parameters." [P_A]

3. **Contents and Functionalities.** Three patients asked for integration with therapeutic prescriptions, also with reminders, and results of laboratory tests:

   "It would be interesting to add as a new functionality the therapy prescriptions, with reminders notified to patients." [P_A]

   "It would be useful to see the results of your own laboratory tests directly from the app and to have the medical prescriptions and the referrals." [P_C]

   "According to me, it would be very useful to add the drugs that the patient is taking every day." [P_H]

   Finally, four patients highlighted the need for further and personalized content:

   "I would start with a study of what patients and doctors need for themselves and from each other, in order to ease every kind of monitoring and communication. I would redesign the app based on this 'user-centric' approach, maybe providing a section for the doctor and one for the patient." [P_A]

   "The links present in the app are already very common online." [P_C]

   "[The app] could be enriched with more contents, maybe personalized for the individual case." [P_E]

   "A section with 'Small remedies' (in a more holistic point of view) could be added." [P_I]

4. **Technology.** Two patients commented on the technology used for the app. One of these patients suggested the possibility to expand/prolong the use of the app after the end of the treatment and to port the app also to different mobile operating systems:

"The potential is remarkable, a lot still to reach fully. I would suggest a prolonged use for monitoring beyond the end of therapies, even without tablet loan. It would be enough to provide an app for Android and iOS downloadable on any device." [P_I]

The other patient provided a generic comment on today's technology:

"[The app] could be improved more, considering the technological possibilities and the social networks." [P_D]

Doctors' Comments Doctors, unlike patients, did not feel the need to express many comments, possibly because two of them participated in the app development, thereby shaping the app according to their wishes. One comment included two suggestions, one about the app graphics that should be more captivating, and another one about the possible integration of PRO-CTCAE [153], i.e., the patient-reportable version of the Common Terminology Criteria for Adverse Events scale. The only other comment emphasized the usefulness of alerts in the website, which efficiently capture the doctor's attention, in contrast with notifications based on e-mails, since with the latter "the risk is to open a lot of e-mails, overlooking the active and relevant issues among a lot of data that are within the thresholds".

6.2 Case 2: The ImmunApp Experience

The second use case regards an intervention within a collaboration with INT and the Academic Medical Center (AMC) in Amsterdam for patients affected by cancer and undergoing immunotherapy.

6.2.1 The Medical Problem

Immunotherapy is one of the latest cancer treatments and relies on the ability of the immune system to recognize tumor cells and contrast their growth [154]. Immunotherapy uses antagonistic antibodies that block specific immune checkpoint molecules, which tumor cells employ to down-regulate immune response. So far, several categories of immune checkpoints inhibitors have been developed (e.g., anti-CTLA-4, anti-PD-1 and anti-PD-L1), all relying on the same mechanism of action: they block immune checkpoints, interfering with the normal functioning of the immune system, which consequently usually develops an immune reaction against tumor cells. Unfortunately, these inhibitors might unbalance the immune system, favoring the development of a wide spectrum of autoimmune manifestations, also referred to as Immune-related Adverse Events (IRAEs) [13], some of which are well-known [155], while others are still to be assessed. Since IRAEs are caused by an excessive immune response, they are usually managed by anti-cancer treatment interruption, high dose corticosteroids, antihistamines and antitumor necrosis factor medications [156]. However, the problem is more or less the same as with other cancer treatments: the later adverse events are detected, the longer they need to be treated, compromising the treatment efficacy. Thus, an early detection becomes essential.

6.2.2 The Interface Terminology of Adverse Events

In order to properly monitor patients and early detect the occurrence of adverse events, a first step consists in the collection of patients' data in a structured form. To facilitate this task, within a collaboration with the Department of Medical Informatics of the AMC in Amsterdam, a patient-oriented interface terminology was developed, with symptoms that patients can self-report [157].

An interface terminology is defined as a *systematic collection of health care related phrases (terms) that supports clinicians' entry of patient-related information into computer programs and decision support tools* [158]. In general, interface terminologies are controlled vocabularies, which provide the translation from the natural language that professionals or patients use in their daily practice into more structured representations, processable by computers.

The work presented in [157] started with a research of all the possible authoritative sources of information about adverse events. Clinical trials from literature were found to include only the frequencies and onset times of generic categories of adverse events (e.g., skin, gastrointestinal, hepatic, etc.). Then, the U.S. Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) was taken into account, but it contained adverse events that were not patient-reportable (e.g., hyperthyroidism) or events that seemed co-occurrent but unrelated to the administration of the drug (e.g., alcohol abuse or pregnancy).

For this reason, the final choice was to exploit the information contained in the Patient / Package Information Leaflets (PILs) of the five immunotherapy drugs approved by the FDA as of January 2018, as PILs contain a significant amount of information about the possible side effects reported by patients in clinical trials. The drugs considered in the work are: an anti-CTLA-4 antibody, Ipilimumab (trade name Yervoy®), approved in 2011 [159, 160]; two anti-PD-1 monoclonal antibodies, Nivolumab (Opdivo®, approved in 2014 [161]) and Pembrolizumab (Keytruda®, approved in 2014 [162]); two anti-PD-L1 monoclonal antibodies, Avelumab (Bavencio®, approved in 2017 [163]) and Atezolizumab (Tecentriq®, approved in 2016 [164]). Both the English and the Italian versions of the PILs were considered, since the intention was to perform a first pilot study with Italian patients. Unfortunately, the PILs usually present the information in an unstructured form, as free text. Therefore, some kind of formalization was needed in order to exploit their contents.

Initially, the work consisted in a manual extraction of a list of adverse events from the English version of the PILs, trying to separate the symptoms that could be directly reported by patients (e.g., nausea, pain, fever, urine color) from the conditions that could only be detected by the physicians or through laboratory tests (e.g., hypo- or hyperthyroidism). In a second step, the symptoms of those clinical conditions were extracted from another section of the PILs, where they were better described. These symptoms were added to the list of patient-reportable adverse events, avoiding repetitions. Finally, the resulting concepts were mapped to reference terminologies, in order to obtain a standardized vocabulary and facilitate data reuse. Two collections of health-related vocabularies were evaluated: the Unified Medical Language System (UMLS) Metathesaurus [165] and the Observational Health Data Sciences and Informatics (OHDSI) Standard Vocabulary [166]; both the collections included many terminologies, among which SNOMED CT and Medical Dictionary for Regulatory Activities (MedDRA). In addition to the preferred terms, for some of the concepts extracted from the PILs the synonyms present in the PILs themselves were added to the terminology, both in English and Italian, to provide a better match with the patients' expectations.

The final terminology contains 151 unique concepts, described by 424 terms, considering both English and Italian and including synonyms in the count. The whole set of concepts is published in [157], together with the complete process of extraction. The issue with these numbers is that, even if they are far less than the number of concepts contained in any existing standard terminology, the concepts are, however, too many to be presented to patients as a flat list. According to The User Interface Design Guidelines for Canada Health Infoway [167] prepared by Healthcare Human Factors [168], the best way to present interface terminologies with more than 100 concepts to patients within an application is through a search bar. In fact, the presentation of the terms as a list, even if it is navigable and hierarchical, could

be less straightforward to the patients if they are not familiar with the organizational structure of the concepts. In any case, the hierarchical structure of the interface terminology is intrinsically provided by the mapping of the terms to UMLS Metathesaurus. Moreover, a hierarchical list would assume that the patients are also familiar with the preferred terms chosen by the developers of the terminology, while patients might prefer synonym terms, which inherently requires the possibility to search using free text. The guidelines also suggest that the search should be facilitated by implementing progressive matching and by showing symptoms ordered according to their incidence, i.e. showing as first the most frequently reported ones. In the case of this interface terminology, a more patient-oriented search could be implemented leveraging on the specific patient's treatment drug and clinical status. Some of the package leaflets address also the issue of interaction with other drugs administered in combination. For example, the package leaflet of Nivolumab reports also the side effects identified in clinical trials with Nivolumab in combination with Ipilimumab, and a slight change in the frequency of occurrence can be noticed. However, unfortunately, not all the combinations of these drugs have already been the subject of clinical trials. Thus, the incidence of side effects with most of the combinations is not known yet. The same issue affects also the interaction with other drugs, since immunotherapies are quite recent and not thoroughly tested in combination with other treatments. For these reasons, within this work, only the frequencies stated in the package leaflets have been considered.

6.2.3 The Intervention

Considering the architecture in Figure 5.1, its application in this case study consists of:

- The implementation of a mobile app that synchronizes data to

and from a server hosted in INT;

- The future implementation of a web application as a client interface for the oncologists, which allows not only the visualization of the patients' data, but also the remote configuration of the app.

In this context, no evidence-based guidelines for the management of IRAEs were available, so it was not possible to implement a decision support system for clinicians.

6.2.4 The Mobile Application

As anticipated, a mobile app was developed for the collection of ePROs such as clinical parameters, questionnaires, and symptoms of adverse events. The mobile app, called ImmunApp, adopts the general structure that was found successful in HeNeA, but enhances some features:

1. Patients can report all the symptoms they experience (not only pain, nausea, and vomiting, since it was criticized by patients in the HeNeA pilot study). In order to acquire structured data, a terminology close to patients' vocabulary is provided.

2. The synchronization between the app and the hospital server is two-way, so that the app can synchronize data to the server, but it can also download data, such as new and personalized educational material, or a change in its configuration.

Therefore, considering also the requirement analysis in Chapter 4, ImmunApp provides:

- Educational material about day-by-day practical information, such as prevention and first remedies for the most common side

effects (diarrhea, pain, fatigue, mucositis, nausea or vomiting, itching, skin toxicity, nails toxicity, xerosis);

- Tips of the day, appearing once a day, containing simple recommendations extracted from the educational material, and referring to that section for more details. These are meant to provide simple tips to the patients, while encouraging them to read the extended material;

- Reporting of clinical parameters (e.g., weight and temperature), as required by the clinicians;

- Questionnaires to be filled-in as required by the clinicians (e.g., EuroQoL for the quality of life). The questionnaires are not hard-coded into the app, but the questions and the related answers and scores are loaded from XML files;

- Reminders and notifications to remind the patients to report the clinical parameters and fill-in the questionnaires with the frequency required by the clinicians;

- Reporting of symptoms. The search bar (a screenshot in Figure 6.19) presents the results following a sorting algorithm, outlined in Figure 6.20. First, the resulting terms are sorted according to their affinity to the search string: the first to be shown are the terms that begin with the search string and, then, it shows the remaining ones that contain the search string within them. If two or more terms contain the search string in the same position, they are ordered depending on their probability of occurrence for the drug administered to the patient; to this purpose, the probability levels ("very common", "common", "uncommon" and "rare") found in each drug leaflet were used. Finally, if two or more symptoms containing the search string at the same position

also belong to the same probability level for that drug, they are sorted alphabetically. This sorting algorithm ensures that the patients can quickly find the symptom they are looking for;

- Possibility to describe the symptoms through attributes such as:
  - Severity, according to the Common Terminology Criteria for Adverse Events (CTCAE) grading scale;
  - Onset time and whether the symptom is ongoing, or its end time;
  - Whether the patient took any drugs to soothe the discomfort and the drugs names (in free text);
- Visualization of reported symptoms, clinical parameters charts, and completed questionnaires;
- Possibility to contact the hospital secretariat via e-mail;
- Possibility to contact the healthcare professionals via e-mail, attaching the summary of reported symptoms and completed questionnaires and the charts of reported clinical parameters;
- Reporting of costs the patients had to meet due to the therapy and its adverse events.

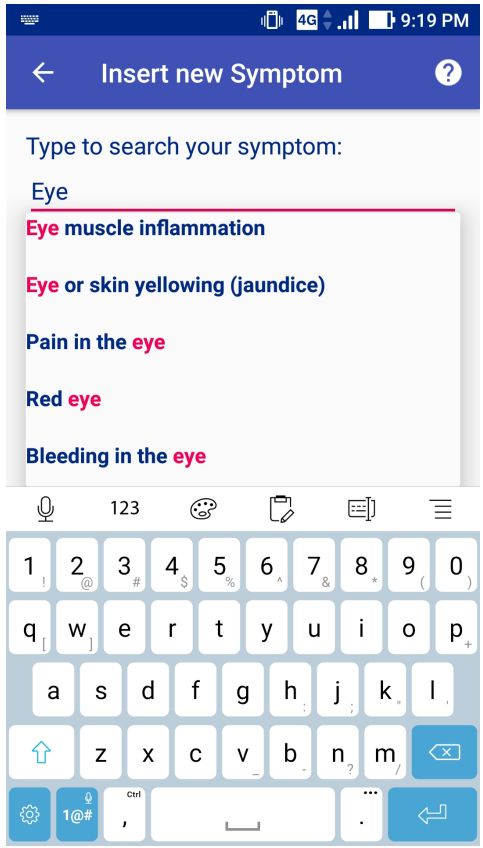

Figure 6.19: **Screenshot of the search bar and the results of searching the term "eye".**

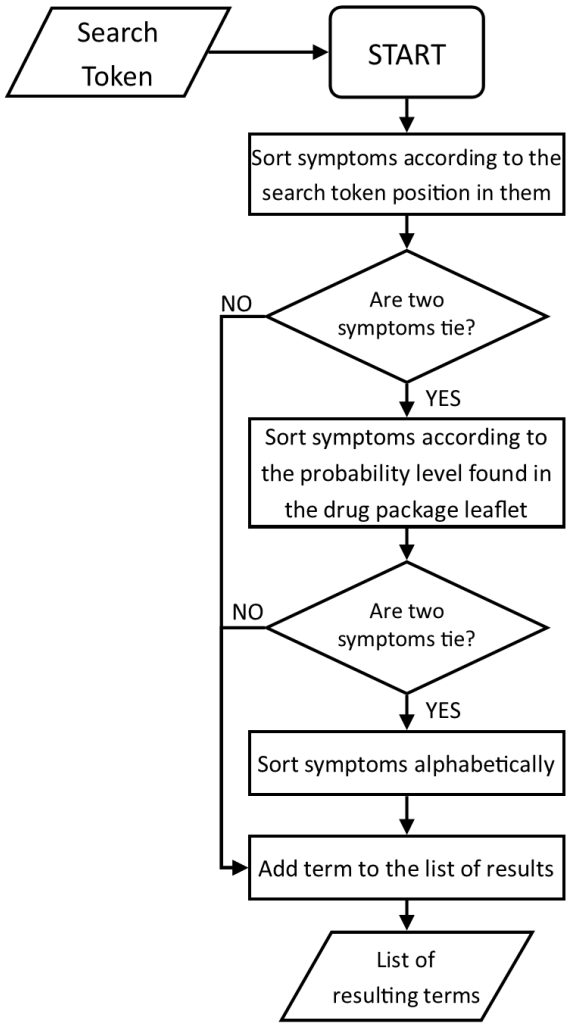

Figure 6.20: **Sorting algorithm for the list of results in the search bar.**

It may happen that a patient cannot find through the search bar the specific symptom he/she is experiencing. In this case, the patient can decide to add the symptom as a new term in free text. The new symptom will be signaled to the healthcare professionals, in order to turn it into structured information: they can decide if the new symptom is a new concept, which will have to be linked to the related UMLS unique identifier, or if it is a synonym of a concept that is already present in the interface terminology with a different phrasing. In this case, it could be sensible to add the term as a new synonym of that concept. Meanwhile, the patient can keep using the concept in the app, which stores it in the patient's personal terminology, so that it can be showed in future searches.

Besides the enhancement of the symptom reporting functionality, ImmunApp also provides an improved synchronization to the hospital server. In fact, the app not only synchronizes all the ePROs to a hospital server so that they can become immediately available for perusal, but it can synchronize information back from the server to the smartphone. In this way, clinicians can remotely change the configuration of all of ImmunApp functionalities. They can modify the educational material and the "tips of the day", or change the choice of clinical parameters, questionnaires and collection frequencies according to the individual patient's needs. Moreover, they can change the concepts and terms of the interface terminology, adding new concepts if patients report any new significant symptom. Figure 6.21 shows some screenshots of the app.

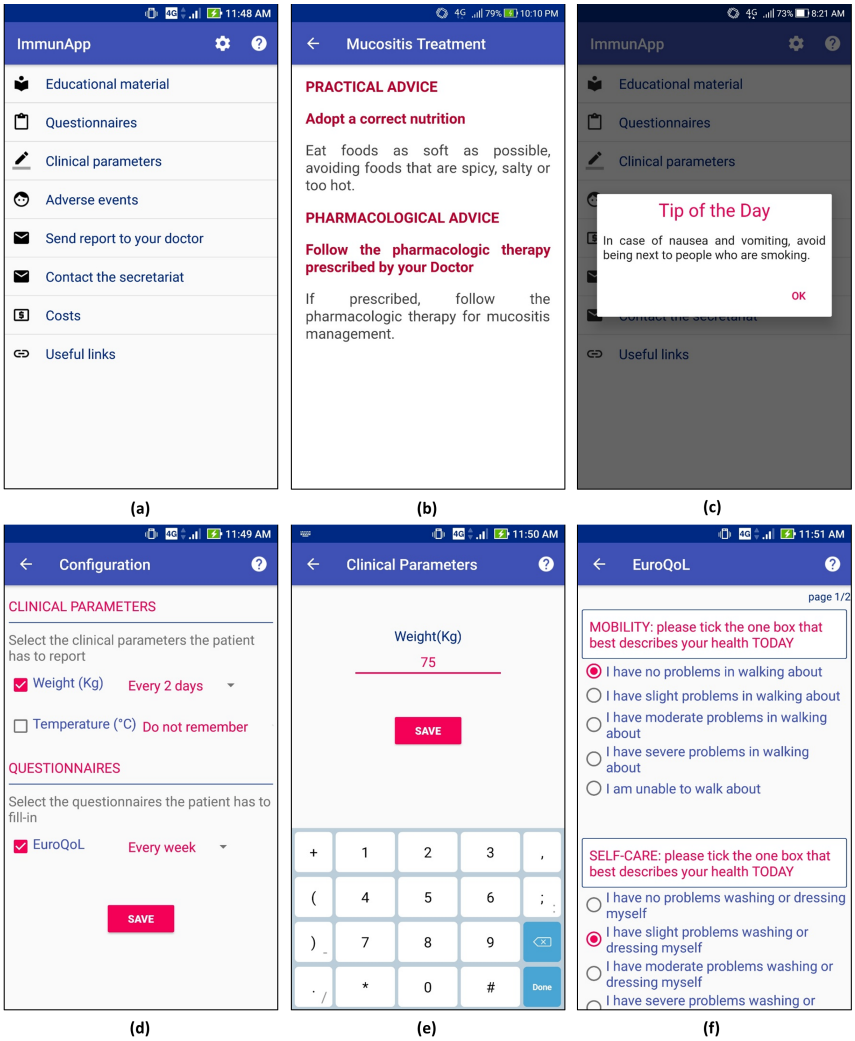

Figure 6.21: **Screenshots of ImmunApp.** (a) The homepage; (b) part of the educational material for the patient; (c) one of the "tips of the day"; (d) doctor's settings about the collection frequency of clinical parameters and questionnaires; (e) clinical parameter collection; (f) a questionnaire.

6.2.5 The Evaluation

The evaluation of the benefits arising through the use of ImmunApp requires a clinical trial. Thus, a study protocol is going to be presented to the Ethics Committee of INT in Milan and a new collaboration is being established with the Istituti Clinici Scientifici (ICS) Maugeri in Pavia. The study protocol proposes to evaluate, as a first step, the usability and perceived usefulness of ImmunApp with a small group of patients. As a matter of fact, these two parameters can deeply influence the compliance of patients with the reporting schedule and with the reporting of symptoms, compromising the potential benefits of such a system. The starting trial expects 20 patients, who, at the end, will be asked to answer a questionnaire composed of 18 questions:

- The first 10 questions belong to the System Usability Scale (SUS) [169] and will be evaluated accordingly;
- The last eight questions expect an answer according to a Likert scale (1-5):
  - Questions 11 and 12 investigate whether the terminology used in the search bar was familiar to the patients and adequate for their symptoms;
  - Questions 13 - 15 are about the perceived usefulness of the app in helping with the prevention, recognition, and treatment of side effects, and in improving the relationship with the doctors;
  - Questions 16 and 17 ask whether the patient would recommend the app to other patients who are following the same treatment and if he/she would choose the app again;
  - Finally, question 18 asks for an overall rating of the app.

The doctors will be asked to answer another questionnaire, composed of 10 questions:

- Questions 1 - 3 are about the perceived usefulness of the app in helping with the management and treatment of side effects, and in improving the relationship with the patients;
- Questions 4 and 5 ask whether the doctor would recommend the app to other patients following the same treatment and if he/she would choose the app again;
- Questions 6 and 7 are about the complexity of the app configuration and the adequacy of the results (charts and summaries);
- Questions 8 and 9 are about the frequency of alarms and e-mails by patients (too low, adequate, too high);
- Finally, question 10 asks for an overall rating of the app.

Questions 1-7 and 10 expect an answer according to a Likert scale (1-5).

Chapter 7

Conclusions and Future Work

The aim of the work described in this dissertation was to investigate a possible solution for speeding up the acquisition of PROs from cancer outpatients, re-using already experimented methods and available software components as much as possible. This was required by the need to easily integrate some prototypical applications under development, so that they could be tested in trials at the clinical centers that were collaborating with the Laboratory of Biomedical Informatics of the University of Pavia.

The integration of information from different sources has been addressed for many years through the adoption of shared ontologies, semantically linking systems running on separate servers [170]. In addition, the "separation of concerns" paradigm, which is considered as a foundation in ICT [171], has been ported to the DSS context for the implementation of flexible DSSs [172], and is now pursued using new technologies [173] based on standards to represent data, medical knowledge and inferential knowledge. In this work, data

have been represented through the HL7 vMR, medical knowledge has been represented through Alium, which is a general-purpose tool for guideline authoring, SNOMED CT has been used as reference terminology, while inferential knowledge has been managed by proper client-server interactions leveraging the Alium APIs.

Therefore, the novelty of this work is not on basic technologies for data or knowledge representation, nor in the development of new medical ontologies or terminologies, rather in the development of an architecture featuring novel functionalities and easily tailorable to different applications, as described in the following sections.

7.1 Original Contribution

Most of the apps found on the Google Play Store or on the Apple App Store are not customized and cannot change their configuration over time according to the specific patient's clinical status. Therefore, the information provided to patients is often general and imprecise or, at least, not fitting their case. Indeed, there are several apps addressing cancer, even developed in collaboration with prestigious institutions such as the American Society of Clinical Oncology. However, those apps are only meant as informational or educational tools, even though some also include detailed information about guideline procedures. In summary, none of them is actually meant to establish an active link with the physicians, which is the core feature of the approach presented in this dissertation. Nevertheless, attempts to personalize applications do exist and have been presented in Section 2.4, together with the review from Ventola [50] witnessing the lack of examples of dynamic configuration of apps based on guidelines. The attempt in the present work was to fill those gaps.

As a matter of fact, the developed architecture allows a physician to obtain recommendations both on the medical issues (e.g., how to treat

an adverse effect) and on the patient's app configuration (e.g., which questionnaires and clinical parameters to monitor and the monitoring frequency) through the same interface. It is worth noting that all recommendations are produced starting from data that comes from different sources (hospital and patient's home), which are integrated into a unique patient's record for a comprehensive analysis. Running guidelines on data that are continuously captured and integrated into a virtual patient record is also an original contribution of the thesis. A final novel contribution is the synchronization mechanism that allows the remote reconfiguration of the app, saving time for both patients and doctors, when face-to-face visits are not really necessary and patients should go to the hospital just for reconfiguring their app.

7.2 Generalization Issues

Although this dissertation focused on the management of cancer outpatients, it could be argued that the proposed approach is flexible enough to be adapted to other medical contexts, in particular chronic diseases requiring outpatients' monitoring. In order to apply the proposed architecture to a different context of use, the main effort would be: (i) locating and formalizing with Alium a guideline about patients with a disease of interest or undergoing a specific treatment requiring constant monitoring, and (ii) identifying the proper content for the mobile app: the list of symptoms (especially considering the configurable app used within the ImmunApp project) and clinical parameters to keep track of, the proper questionnaires for the evaluation of the patients' quality of life and health status, and the educational material. Nowadays, there is a wide availability of CPGs, but the ones to prefer should contain also recommendations with advice for the patients' monitoring and behavior at home. The knowledge engineer is then responsible for separating the recommendations directed to

doctors from the ones directed to patients and formalizing them into two different Alium workflows. Once the workflows are ready and loaded in the Alium library, they will be shown in the doctors' interface, to be started at need. Even in the absence of appropriate CIGs, the doctors can change the app configuration manually or through their interface. A generalization can be applied also to the list of reportable symptoms: they can be specific problems related to a disease or treatment, or the doctors can decide to provide patients with a wider list of terms. For example, in a recent evolution of the ImmunApp project, oncologists from the Istituti Clinici Scientifici (ICS) Maugeri decided to include in the app all the symptoms contained in the CTCAE. In this light, the app can also become a useful tool of pharmacovigilance.

7.3 Limitations

Nonetheless, this study is affected by some limitations. The purpose was to show that the proposed architecture and software solutions constitute a suitable system to represent and run guidelines in a distributed environment (encompassing the clinic and the patient's home). However, a layer of conversion from a real database to the proposed middleware has still to be developed. Accordingly, a future step will consist in fetching both the data stored into the EHR of our medical partners and those acquired through the mobile applications and converting them into the data format adopted by the middleware through an ETL process.

A second issue was that the validation phase of the two use-cases involved a small number of patients and physicians. These first validations allowed an improvement of the interface in terms of usability and user experience and their results will be taken into account for the next versions of the mobile app, in order to further increase patients' willingness to use it. However, a more extensive validation is necessary

to evaluate the effect of introducing such a system into the normal care flow. The new project involving ImmunApp and the oncologists of the ICS Maugeri aims also at this goal.

7.4 Future Developments

Based on the considerations above, future directions of the research described in this dissertation include an analysis of the doctors' compliance to the guidelines, logging the recommendations that they accept and refuse, and an assessment of the impact of the proposed architecture on the process of care of cancer outpatients. In fact, the evaluation accomplished until today concerns only the usability and perceived usefulness of the system in a specific setting.

Moreover, it would be interesting to investigate new emerging standards for the integration of data in the architecture. Unfortunately, the information technology infrastructure at the collaborating centers quite often relies on commercial solutions and proprietary technologies. Therefore, in this work it was necessary to avoid depending on emerging standards for the deployment of the architecture. If it were not for this constraint, the SMART on FHIR approach proposed by Mandel [174] or the OHDSI on FHIR approach with OMOP CDM [175] would have been taken into account as a standard for the integration of data. Nevertheless, since currently consolidated web standards were used in developing these applications both on the mobile side and on the server side, such an integration might be considered as a future task, once the architecture has been experimentally validated.

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List of publications

Articles in peer-reviewed journals

- E. M. Zini, G. Lanzola, P. Bossi, and S. Quaglini. An environment for guideline-based decision support systems for outpatients monitoring. *Methods of Information in Medicine*, 2017 Aug 11; 56(4):283-93. doi: 10.3414/ME16-01-0142.

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- E.M. Zini, G. Lanzola, S. Quaglini, P. Bossi, L. Licitra, and C. Resteghini. A pilot study of a smartphone-based monitoring intervention on head and neck cancer patients undergoing concurrent chemo-radiotherapy. *Under review at the International*

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Contributions to conference proceedings

- M. Gabetta, A. Malovini, M. Bucalo, E. Zini, V. Tibollo, S. Vettoretti, C. Larizza, R. Bellazzi, and N. Barbarini. Beyond cohort selection: an analytics-enabled i2b2. *Stud Health Technol Inform*. 2016; 228:572-576. doi: 10.3233/978-1-61499-678-1-572.

- E.M. Zini, G. Lanzola, P. Bossi, L. Licitra, and S. Quaglini. A decision support system for managing chemoradiotherapy side effects in patients with head and neck cancer. Poster and oral presentation at the *V Italian National Bioengineering Group convention*, Naples, June 20th - 22nd 2016.

- E.M. Zini, G. Lanzola, and S. Quaglini. Detection and management of side effects in patients with head and neck cancer. *2017 IEEE 3rd International Forum on Research and Technologies for Society and Industry (RTSI)*, September 2017. doi: 10.1109/RTSI.2017.8065888.

- G. Lanzola, R. Boninsegna, E. Losiouk, E.M. Zini, S. Quaglini, V.V. Ferretti, and A.Corso. An mHealth app counseling patients and general practitioners about Multiple Myeloma. *2017 IEEE 3rd International Forum on Research and Technologies for Society and Industry (RTSI)*, September 2017. doi: 10.1109/RTSI.2017.8065889.

- E.M. Zini, A. Tagliabue, C. Trentani, C. Ferraris, R. Boninsegna, S. Quaglini, and G. Lanzola. An mHealth application for educating and monitoring patients treated with a ketogenic diet regimen. *Stud Health Technol Inform*. 2018; 247:481-485. doi: 10.3233/978-1-61499-852-5-481.

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- R. Bagarotti, G. Lanzola, E.M. Zini, L. Sacchi, E. Salvi, and S. Quaglini. Assessing the Performance of a Commercial Sensorized Mat for Estimating Gait Parameters. Poster at the *VI Italian National Bioengineering Group convention*, Milan, June 25th - 27th 2018.

- R. Bagarotti, E.M. Zini, E. Salvi, L. Sacchi, S. Quaglini, and G. Lanzola. An Algorithm for Estimating Gait Parameters through a Commercial Sensorized Carpet. *2018 IEEE 4th International Forum on Research and Technologies for Society and Industry (RTSI)*, September 2018. doi: 10.1109/RTSI.2018.8548404.

Awards

- Degree Award HL7 Italy (Second Edition) for the Master Thesis "Extension of the i2b2 framework for extraction of qualitative patterns from time series", received at the 16th International HL7 Interoperability Conference (IHIC 2016) in Genoa, June 13th-15th 2016

- "Young Researchers Award" of the Italian National Bioengineering Group (GNB) for the work "A decision support system for managing chemoradiotherapy side effects in patients with head and neck cancer", presented at the V GNB convention in Naples, June 20th-22nd 2016.