Original Articles

An Environment for Guideline based Decision Support Systems for Outpatients Monitoring

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Summary
Objectives: We propose an architecture for monitoring outpatients that relies on mobile technologies for acquiring data. The goal is to better control the onset of possible side effects between the scheduled visits at the clinic.
Methods: We analyze the architectural components required to ensure a high level of abstraction from data. Clinical practice guidelines were formalized with Alium, an authoring tool based on the PROforma language, using SNOMED-CT as a terminology standard. The Alium engine is accessible through a set of APIs that may be leveraged for implementing an application based on standard web technologies to be used by doctors at the clinic. Data sent by patients using mobile devices need to be complemented with those already available in the Electronic Health Record to generate personalized recommendations. Thus a middleware pursuing data abstraction is required. To comply with current standards, we adopted the HL7 Virtual Medical Record for Clinical Decision Support Logical Model, Release 2.
Results: The developed architecture for monitoring outpatients includes: (1) a guideline-based Decision Support System accessible through a web application that helps the doctors with prevention, diagnosis and treatment of therapy side effects; (2) an application for mobile devices, which allows patients to regularly send data to the clinic. In order to tailor the monitoring procedures to the specific patient, the Decision Support System also helps physicians with the configuration of the mobile application, suggesting the data to be collected and the associated collection frequency that may change over time, according to the individual patient's conditions. A proof of concept has been developed with a system for monitoring the side effects of chemo-radiotherapy in head and neck cancer patients.
Conclusions: Our environment introduces two main innovation elements with respect to similar works available in the literature. First, in order to meet the specific patients' needs, in our work the Decision Support System also helps the physicians in properly configuring the mobile application. Then the Decision Support System is also continuously fed by patient-reported outcomes.

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1. Introduction

During the last decades, due to the increase in life expectancy and consequently in the number of people affected by chronic diseases, healthcare policy makers shifted the focus from acute hospital care to home care. As a result, nowadays a large number of patients are treated most of the time at home, and go to the hospital only for treatment assessment and for the follow-up visits. Different care models have been proposed and experimented for that purpose. For example, a Cochrane review [1] reported on the effects of early discharge with "hospital at home", a service that provides active treatment by healthcare professionals at the patient's home. An implementation of such a model for cancer patients is reported by Font et al. [2]. Other organizations focused 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 with no additional costs [3].

Nevertheless, homecare is still particularly critical when patients undergo heavy treatment regimens. For example, the benefits of chemo- or radio-therapy 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. In order to avoid those consequences, the prevention and treatment of toxicity become an essential task.

Clinical practice guidelines have been developed for helping physicians in properly monitoring outpatients and undertaking corrective actions upon the occurrence of any remarkable event. However, to be effective, they rely on a suitable interaction with the patients for acquiring any information useful to early detect or possibly prevent those events.

Data provided by patients are called Patient-reported outcomes (PROs), and have been proved very useful to assess the patients' conditions, enhance the clinician awareness and improve symptom management. They usually include physical parameters (e.g., pain, weight and blood pressure), psychosocial symptoms (e.g., fatigue, anxiety and depression), functional assessment scores [4, 5], or Quality of Life (QoL) scores [6, 7]. 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, systems called electronic PROs (ePROs) are becoming popular to collect those data, analyze them, and summarize the results to patients and doctors. Compared to the conventional paperpencil approach, ePROs are more efficient and also increase data quality [8]. Various technologies including speech recording [9] and web based forms [10] have been used as effective means for acquiring ePROs with promising results. As for the best way of collecting ePROs, we observe that the "Digital in 2016" report shared by the global agency "We Are Social" in January 2016 stated that 51% of adults across 30 surveyed countries reported owning a smartphone, with a peak in developed countries. In the same survey, Italy reported a 62% of smartphones owners and a 21% of tablet owners. Moreover, in Italy the average daily use of the Internet via mobile devices is 2 hours and 10 minutes and 79% of the adult population uses the Internet every day [11]. These data suggest that ePROs may be successfully acquired through applications running on mobile devices (apps) [12].

In this work we propose a general architecture for acquiring and exploiting PROs, as we believe that there is a strong need for a methodology simplifying and speeding up that process and also optimizing its outcomes. Our architecture aims at supporting clinicians and patients in each step of the process, starting with the initial definition of the information to be acquired from each patient, the configuration of the mobile device, the subsequent synchronization of any PRO entered by the patient and the ensuing analysis of the collected data. The whole process may then be reiterated

according to the new assessments reached on the patient status. The suitability of the proposed architecture has been tested with a training example addressing the home monitoring of patients with head and neck cancer.

The paper is structured as follows. After this Introduction, in the Methods section we initially perform a requirement analysis and then review the chief methodologies that we considered for the implementation of the proposed architecture for managing PROs. The architecture itself is described in the Results section, along with a test case that has been used for assessing its effectiveness, while in the Discussion we review some strengths and limitations or our approach.

2. Methods

Since the main purpose of our work is the definition of a general architecture for acquiring PROs through mobile devices, smartphones and tablets play a key role in its design. Thus we started our work with a requirement analysis aimed at identifying the different levels of support that those devices provide in the healthcare context, and then we moved to the definition of the functionality of the backend. We accomplished the analysis from both the viewpoints of patients and physicians.

2.1 Requirement Analysis

A starting point for the requirements definition has been the paper by Klasnja and Pratt [13] that classifies the different intervention types in healthcare exploiting mobile phones. Based on that work and taking into account our previous experiences in collecting patient information [14, 15] and supporting therapy compliance [16] using mobile devices, we came up with the following set of requirements for the mobile component:

- Include educational material, 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.);
- Provide suggestions for the prevention of complications and the treatment of side effects, contextualized to the specific PRO being entered or the whole patient history;
- Support the patient with advices on healthy diet and habits, contextualized to his specific conditions;
- Issue reminders for taking the prescribed medications;
- Acquire PROs in terms of both biomedical parameters and questionnaires for functional assessment, and issue reminders for entering those data according to the plan configured by the doctor;
- Support wireless/USB connections with sensors or wearable devices for automatically collecting clinical parameters;
- Synchronize PROs to a hospital server, so that they are added to the patient's Electronic Health Record (EHR) and become immediately available for perusal.

Asking a patient to provide PROs in terms of symptoms [17] and questionnaires [4] 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 may be used either to adjust the treatment or to prepare and support a shared decision-making process during the next scheduled visits [18].

To provide the abovementioned functionalities at best, we argue that the doctor should be supported by a suitable tool in providing an initial configuration for the mobile device of each single patient according to his/her 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 the PROs. Based on the above discussion such configuration translates into which parameters and questionnaires should be collected as well as their collection frequency.

The support for the doctor is provided by a service at the clinic backend that is best implemented as a web application integrated into the Hospital Information System (HIS) [19]. Also in this case, based on the literature [20, 21] and on our research experience in developing report systems for physicians [22, 23], we were able to define the following set of requirements with the aim of making the most of the PROs that are regularly added by patients between scheduled visits:

- Oversee the patients' disease evolution through temporal plots and aggregation charts (e.g., bar and pie charts);
- Make available a Decision Support System (DSS) with 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 re-configuring the mobile device to continue the provision of suitable advices 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 we envision the exploitation of a computerized clinical practice guideline embedded into the DSS for generating standard recommendations for doctors, based on both data collected at the hospital and PROs.

The following sections shortly introduce the methodological foundation upon which the design of the proposed architecture for monitoring outpatients relies.

2.2 Guideline Formalization

Clinical practice guidelines are usually available in paper format, so, in order to be used by a DSS platform, they need to be rendered into a computer-interpretable format. An authoring tool is advisable in this case, since it is a software explicitly designed to help users in speeding up and simplifying this task through the use of a dedicated graphical user interface. A number of authoring tools have been developed in the past [24] but only few achieved the necessary stability for being used in the clinical practice. Among those there is Alium, developed by Deontics Ltd (London, UK), which is based on PROforma, a formal language combining logic programming and object-oriented modeling [25]. 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 their authors to support guideline design and dissemination in the form of DSSs and workflow management systems. Given that in our proposed architecture the modeling of clinical practice guidelines is instrumental for the implementation of a DSS, PROforma seemed to be a suitable choice [26].

The Alium editor allows creating a clinical pathway using PROforma to define processes, data, clinical logic and decisions. PROforma defines processes as a set of components [27], the most frequently used being tasks and data items. There are four classes of tasks: Action, which represents a procedure that needs to be executed in the external environment (e.g., a surgical procedure); Enquiry, which represents a point of information acquisition from an external person or system; Decision, which represents a point at which a choice has to be made; Plan, which is a collection of tasks grouped together [28]. Therefore, a guideline is initially formalized through a series of flowcharts and then implemented through Alium.

In addition to the editor, Alium also provides a reliable execution engine that can be accessed through a specific set of Application Programmer Interfaces (APIs) made available by their implementers. Those APIs may be invoked from an external environment to supply all the data

required as input by the guideline, activate the execution of the inferential processes encapsulated within the guideline itself and finally collect the outputs. This possibility accounts for a straightforward implementation of an architecture based on two separate components. Mobile devices are used as the patient component for collecting data, while the enterprise component running on the clinic server stores all those data into a data base repository. The same enterprise component becomes also responsible for activating the Alium guideline engine, and eventually showing the results to the doctors.

2.3 Use of Terminological Standards

Guideline recommendations often include general concepts and terms. 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 and indicate the specific disease, not its generic category. Thus, in order to properly match the active substance name with the term “immunosuppressive drugs” or the specific disease with “autoimmune disease”, an additional inferential process is required external to the guideline. To this aim, we exploited the SNOMED-CT terminology.

As an example, Figure 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.

Since we do not know a priori which of the children will be entered by the doctor in the patient’s record, we have to explicitly add knowledge to handle this situation. The Alium editor facilitates this task by supporting the integration of terminologies

Figure 1 General terms “Immunosuppressant (substance)” and “Autoimmune disease (disorder)”

SNOMED-CT dominates ICF [32] and there are ongoing efforts to harmonize ICF and SNOMED-CT [33].

2.4 Design of the Application for the Physician

We developed an application on top of the clinic backend server including a module that communicates with the Alium engine through its APIs. This module is used to retrieve the patients’ data, render them in the required format, invoke the Alium guideline execution engine and collect the resulting output. It has been designed at an abstract level in order to maximize its reusability and avoid the implementation of a new client for every different guideline.

To allow the physician to easily start the execution of the computerized guideline on a specific patient, we implemented a graphical interface in terms of a web application. Through this interface the doctor, at the enrollment, can associate the patient with one of the available guidelines. Moreover, every clinical practice guideline is also associated with another guideline for the configuration of the monitoring app. Once the Alium engine starts the execution of a guideline for the specific patient, if the guideline foresees decisions that have to be taken by the doctor, the interface shows all the possible choices, with arguments in favor and arguments against, so that the physician can make a considered choice. At the end of the execution, the resulting recommendations are shown on the same interface. In addition, the doctor can see an explanation for each recommendation, by selecting it in the list.

2.5 Use of Standards for the Integration of Data from Different Sources In order to effectively use DSSs, they need to be coupled with the patients’ EHRs [34, 35]. However, in the phase of DSS design the access to the

data model is 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

and their children in SNOMED-CT terminology.
and ontologies into the PROforma model [29]. 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 about immunosuppression, we could use the rule shown in Figure 2 to detect if the patient is actually immunosuppressed.
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 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, we can easily navigate the taxonomy to detect if the patient is immunosuppressed. In the same way, we created rules using terms as generic as possible in the ontology hierarchy, to develop a lexicon related to the clinical problem considered.
The choice of using SNOMED-CT as the main terminology standard was a natural consequence of the fact that Alium natively interfaces with the BioPortal web service provided by the National Center for Biomedical Ontology [30]. As a matter of fact, Alium supports three different terminology standards: LOINC, SNOMED-CT and ICD9-CM, but SNOMED-CT better depicts the complexity of reality. Conversely, classification systems such as ICD 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 reports, rather than as inputs for a DSS [31]. In addition, the fact that ICD does not include drugs would require the use of other terminologies, not managed by Alium, to feed that information to the DSS. For the same reason, in this first implementation we did not use other classifications, such as the International Classifications of Functioning, Disability and Health (ICF). Despite ICF seems more suitable for functional outcomes, there is some evidence that, in specific domains,

```
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 2
Example of a rule in the Alium Expression Editor for navigating the SNOMED-CT terminology.

```
<vmr xmlns="org.opencds.vmr.v1_0.schema.vmr"
xmlns:ns4="org.opencds.vmr.v1_0.schema.datatypes"
xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance" xsi:schemaLocation="
        file:schemas/vmr.xsd file:schemas/datatypes.xsd   ">
<patient xmlns:ns2="org.opencds.vmr.v1_0.schema.vmr">
<id root="patient_n"></id>
<clinicalStatements>
<encounterEvents>
<encounterEvent>
<id root="visit1"/>
```

<encounterEventTime low="2016-10-24T12:20:00+02:00" high="2016-10-24T12:40:00+02:00"/>
<relatedClinicalStatement>
<targetRelationshipToSource code="123005000" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="part-of" />
<procedureEvent>
<procedureCode code="5880005" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="Physical examination" /> <procedureTime
low="2016-10-24T12:20:00+02:00" high="2016-10-24T12:40:00+02:00" />
<relatedClinicalStatement>
<targetRelationshipToSource code="123005000" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="part-of" />
<observationResult>
<transactionTime low="2016-10-24T12:20:00+02:00" high="2016-10-24T12:20:00+02:00"/>
<observationFocus code="365873007" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="Gender Finding" /> <observationEventTime
low="2016-10-24T12:20:00+02:00" />
<observationValue>
<concept code="703117000" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="Masculine Gender"></concept>
</observationValue>
</observationResult>
</relatedClinicalStatement>
<relatedClinicalStatement>
<targetRelationshipToSource code="123005000" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="part-of" />
<observationResult>
<transactionTime low="2016-10-24T12:20:00+02:00" high="2016-10-24T12:20:00+02:00"/>
<observationEventTime low="2016-10-24T12:20:00+02:00" />
<observationFocus code="365981007" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="Tobacco smoking behaviour - finding"/>
<observationValue>
<concept code="77176002" codeSystem="2.16.840.1.113883.6.96"
codeSystemName="SNOMED_CT" displayName="Smoker"></concept> </observationValue>
</observationResult>
</relatedClinicalStatement>
</procedureEvent>
</relatedClinicalStatement>
<encounterEvent>
</encounterEvents>
</clinicalStatements>
</patient>
</vmr>
Figure 3 Example of an XML file for a patient including observations about gender and smoking behaviour.

app for outpatients are usually not enough to generate useful recommendations, since they lack the information concerning the patient's background that is 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 integrating all the data sources available at each setting. In order to conform to current standards, we adopted the HL7 Virtual Medical Record (vMR) for Clinical Decision Support (CDS) Logical Model, Release 2 [36], which originates from academic research [37].

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 patients' safety and 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 one 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., Proposal, Order, Event) [38].

Since HL7 provides a set of XML Schemas as examples of a potential platformspecific implementation of the vMR, we followed a similar approach storing patients' data in a middleware XML database, 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, we avoided storing every single answer, but we saved only the summary scores, extending the class ObservationResult. Thus, according to this design, data coming from different sources are integrated through a layer of conversion and adaptation, including ETL processes, to adjust them to the format re- quired by the DSS.

An example of an instance of a medical record for a patient who underwent a physical examination is shown in Figure 3. During the examination, the doctor registered that the patient was a male and a smoker. The observations about gender and smoking status (represented through the class ObservationResult) are entities related to the physical examination (class ProcedureEvent), which is a part of the encounter (class EncounterEvent). The relation "a part of" is represented through the class RelatedClinicalStatement, while the ClinicalStatement itself records anything of clinical relevance for the patient.

As shown in Figure 3, the concepts "male" and "smoker" are identified by a SNOMED-CT code (when no SNOMED-CT code is available, especially for abstractions related to the guideline context, it was necessary to introduce customized codes).

3. Results

Considering all the requirements identified in the previous sections we were able to define a prototypical architecture that is described in the following paragraph and that has been tested on the specific use case of head and neck cancer that is introduced later.

3.1 The Proposed Architecture

All the components introduced so far are shown in Figure 4 that describes how they are coupled together and the typical workflow of the monitoring environment proposed.

Once a care pathway has been authored in Alium by the knowledge engineer (a) and made available through a library, the doctor can start the engine from the client interface (b) in order to launch the execution of the guideline (c), obtaining the possible decision options and/or actions to be performed. Patient's data are taken from the middleware database (d), which integrates information from different sources, among which the EHR (e) and the data sent by the patient's monitoring application (f). The resulting recommendations are presented in the doctor's interface as a list of selectable items, so that the clinician can choose the ones he decides to follow and discard the others (see Figures 6 and 7). In the end, the selected recommendations can be exported in different formats, such as PDF, XML or JSON (g). It is important to highlight that the

DSS produces two sets of recommendations, one for the patients' management (diagnosis and treatment) and one for the configuration of the monitoring app.

3.2 The Head and Neck Application Use Case

We evaluated the effectiveness of our environment by representing and running a guideline about prevention, diagnosis and treatment of the side effects of concurrent chemo-radiotherapy (CCRT) for head and neck cancer (HNC). CCRT is one of the most effective treatments for unresectable HNCs in high risk patients [39]. Cetuximab added to radiotherapy is another effective option for locally advanced HNCs [40]. To standardize the process of optimally adjusting the treatment for the patients, controlling the complications and reducing their management costs, the Italian Association of Medical Oncology (AIOM), the Italian Association of Oncologic Radiotherapy (AIRO) and the Italian Head and Neck Oncologic Society (IHNS) joined efforts to implement a comprehensive clinical practice guideline [41].

Within a collaboration with the IRCCS Foundation National Cancer Institute in Milan, we had already developed a mobile application called HeNeA (Head and Neck Application) for collecting PROs [42]. Our organizational model foresees that HeNeA is configured by the physician when it is first handed to the patient (e.g., at discharge or at a control visit). ▶ Figure 5 shows some snapshots from HeNeA. The home page for accessing the main functionalities is shown in ▶ Figure 5a. According to the guideline and depending on the therapy (radiotherapy alone or combined with systemic therapy), the oncologist defines which clinical parameters have to be collected (e.g., weight, temperature, blood pressure), which questionnaires have to be filled in by the patient (e.g., MDADI for dysphagia, EuroQoL for quality of life) and the data collection frequency (▶ Figure 5b). HeNeA embeds a library of 5 possible questionnaires, each one characterized by a variable number of questions (from 6 questions for the EuroQoL to 65 questions for

Figure 5 Some screenshots of the HeNeA mobile application for acquiring Patient Reported Outcomes.

the EORTC QoL), and generating one or more scores.

PROs are collected through a simple graphical interface (▶ Figure 5c) and are automatically sent to the hospital server, through which the oncologists may oversee the patient evolution in terms of temporal plots and aggregation charts (e.g., bar and pie charts). Moreover, HeNeA supplies some educational material, to provide all the information that the patients might need about their disease and the possible side effects of the treatment. Some educational tips are also shown as soon as the app is accessed (▶ Figure 5d). Finally, HeNeA offers the possibility of keeping in touch with "peer" patients showing their locations on a map which also includes pharmacies and hospitals with radiotherapy services (▶ Figure 5e).

Initially, HeNeA was structured as a standalone monitoring system, implemented as a mobile application for the patient and a web application for the doctor, and lacked the dynamic integration of the guideline recommendations. We included HeNeA into the architecture described in ▶ Figure 4, integrating it with two separate DSSs. To simplify its adoption and make its use more straightforward for the physicians, the first DSS helps in properly configuring HeNeA with the most appropriate parameters, questionnaires and tips for the actual patient. Conversely, the second DSS supports the doctors in optimizing the prevention, diagnosis and treatment of the CCRT side effects, also considering the

PROs sent through HeNeA. The two DSSs encapsulate knowledge concerning the seven areas considered by the guideline: Skin Care, Oral Cavity Care, Swallowing Care, Nutrition-Hydration,

Septic Syndrome, Haematologic Toxicity Care and Pain; each area includes different CCRT side effects. For each side effect, the guideline involves (i) risk factors assessment, (ii) evaluation of the patient's answers to specific questionnaires and (iii) clinical evaluation. After this diagnostic assessment of the side effect, a set of actions for its prevention and/or treatment is suggested.

The guideline workflow for HeNeA customization is shown in Figure 6: after a step of demographic data collection and assessment, general recommendations (i.e., valid for any patient) are chosen to be included in the app, in order to provide the patient with tips about the prevention of side effects. Additional recommendations are then set based on the specific patient's data (e.g., recommendations for smokers).

Figure 6 A part of the workflow of the decision support system developed for customizing HeNeA.
Figure 7 The doctor's interface showing the recommendations for configuring the app.

Finally, the evidence about side effects or risky situations triggers a set of rules dedicated to the generation of suggestions about which questionnaires the patient should fill-in and with which frequency.

Figure 7 shows the doctor's interface with the suggested configuration for the app to be delivered to a fictitious Mr. Mario Rossi. For example, since the patient is a male, the eighth tip suggests avoiding traumatizing razors, in order to prevent dermatitis. Moreover, since this patient is a smoker, the fifth tip recommends stopping smoking. The other tips are quite general and applicable to any patient; however, the physician may decide to discard some of them, according to the patient's characteristics. For example, the ninth tip could be not appropriate for a patient with low health literacy who could be confused by such a huge list of active ingredient names.

Figure 8 shows the workflow for prevention, diagnosis and treatment of a gen- eric side effect considered in the guideline (its PROforma representation is shown in Figure 9). The first step is, again, the risk factors assessment, followed by a check for the presence of the side effect. If the side effect is already present, then it must be treated, otherwise it must be prevented. Since patients, while not hospitalized, access the radiotherapy service almost every day, the guideline is intended for them as well as for the healthcare personnel. Patients already receive recommendations, mostly related to prevention, through the app. Thus the computerized guideline provides doctors and nurses with recommendations about prevention and treatment of the side effects through the website interface. Figure 8 shows a general workflow that must be instantiated for every side effect, as each of them has specific recommendations for prevention and treatment.

Finally, Figure 10 shows the doctor's interface with the recommendations about

diagnosis, prevention and treatment of chemoradiotherapy side effects for Mr. Rossi. For example, since the patient already had a hereditary cancer-predisposing syndrome (in particular, xeroderma pigmentosum), he was diagnosed to be at risk of skin toxicity and dermatitis.

3.2.1 Preliminary Evaluation of the System

During the design and implementation phases of HeNeA, we performed a technical assessment with 15 healthy volunteers, in order to identify and fix possible shortcomings. Then a preliminary validation has been accomplished enrolling five volunteer patients that were asked to express their feelings about the functionality of the app and its usability. We also asked two medical doctors that were not involved in the app design to provide their own independent comments. All the suggestions received have been used for improving the functionality and usability of the app [43].

4. Discussion and Conclusion

Integration of information from different sources has been addressed since many years through the adoption of shared ontologies, semantically linking systems running on separate servers [44]. Also the “separation of concerns” paradigm, which is considered as a foundation in ICT [45], has been ported to the DSS context for the implementation of flexible DSSs [46], and is now pursued using new technologies [47] based on standards to represent data, medical knowledge and inferential knowledge. In our work data are represented through HL7 vMR; medical knowledge is represented through Alium that is a general-purpose tool for guideline authoring; SNOMED-CT is used to share terminology; while inferential knowledge is managed by proper client-server interactions leveraging the Alium APIs.
Another issue, related to the generalized use of m-health apps, is due to the fact that most of those found on Google Play Store or on the App Store are not customized and cannot change their configuration over

time according to the specific patient’s clinical status. As a consequence, the information provided to the patient is often general and imprecise or, at least, not fitting his/her case. In fact, during the design phase of HeNeA we also tried to compare its functionality with that of similar apps. Indeed we found several apps addressing cancer, even developed in collaboration with prestigious institutions such as the American Society of Clinical Oncology, or addressing HNC that we selected as our test case. However those apps are only meant as informational or educational tools, even though some also included detailed information about guideline procedures. In summary, none of them were actually meant to establish an active link with the physicians which is the core feature of our approach. This made such a comparison effort almost useless.
Nevertheless, attempts to personalize applications do exist. For example the EU project MobiGuide [48], developed an app for patients’ monitoring, which needs an initial configuration about the most frequent “contexts” a patient may live in, and the changes induced by those contexts in the patient’s 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, and no explicit recommendations about the app configuration are delivered. As a matter of fact, to our knowledge there are no examples of dynamic configuration of apps based on guidelines. This is also witnessed by Ventola in his recent discussion about future trends of m-health [49], where he points out that mobile apps, in order to evolve into efficient clinical DSSs, should incorporate artificial intelligence–oriented algorithms. He also added that there is a need to develop standards for mobile apps so that they can seamlessly contribute to ad-
Figure 8
The generic workflow of the DSS for side effect management.
Figure 9
The PROforma rendering of the workflow for side effect management shown in ▶ Figure 8.

Figure 10 The doctor’s interface showing some recommendations about diagnosis, prevention and treatment.

vanced patient monitoring systems that are custom-designed for each patient. Accordingly, our effort goes exactly in those directions.

Our study is also affected by some limitations. In this first attempt, our purpose was to show that our 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). We still have to develop a layer of conversion from a real database to our middleware. Accordingly, the next step will consist in fetching both the data stored into the EHR of our medical partners and those acquired through the mobile application and converting them into the data format adopted by the middleware through an ETL (ExtractTransform-Load) process. Another step will be enabling the remote configuration of the monitoring app directly from the doctors' web application. Moreover, all the recommendations chosen by the doctor should be stored in the database and integrated with other data sources, in order to be exploited for analysing the doctors' compliance to guidelines. Finally, even though we accomplished a preliminary evaluation of the solution enrolling patients, doctors and healthy volunteers, that assessment was performed on the monitoring app alone and not on the whole architecture.

The aim of this work was the design of a general architecture for speeding up the acquisition of PROs, re-using as much as possible already experimented methods and available software components. This was required by the need to easily integrate some prototypical applications that we are developing so that they could be tested in trials at the clinical centers that are collaborating with us. Unfortunately the information technology infrastructure at those centers is varied and quite often relies on commercial solutions and proprietary technologies. As a consequence we were forced to avoid depending on emerging standards for the deployment of our architecture. If it were not for this constraint, the SMART on FHIR approach proposed by Mandel [50] would have perfectly fit as an infrastructure for our architecture. Nevertheless, since in developing applications we rely on currently consolidated web standards both on the mobile side as well as on the server side, we might consider such an integration as a future task once we have experimentally validated the architecture. A future evolution could also envision the use of additional standard classifications for improving the characterization of PROs. For example, ICF-based questionnaires about functional outcomes, such as the one proposed for HNC [51], could be integrated into our architecture.

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References

1. Shepperd S, Doll H, Broad J, Gladman J, Iliffe S, Langhorne P, Richards S, Martin F, Harris R. Early discharge hospital at home. Cochrane Database Syst Rev 2009; (1): CD000356.
2. Font C, Fernández-Avilés F, Calderon C, GarcíaFernández T, Arab N, Pineda E, Buxó E, Ayora P, Carreño M, Pereira V, Viladot M, Moreno C, Gallego C, Hernando A, Creus N, Barrera C, Alcaraz R, Sanchez J, Prat A, Tuca A. Home management of acute medical complications in cancer patients: a prospective pilot study. Support Care Cancer 2016; 24(5): 2129–2137.
3. MacAdam M. PRISMA: Program of Research to Integrate the Services for the Maintenance of Autonomy. A system-level integration model in Quebec. Int J Integr Care 2015; 15: e018.
4. Pickard AS, Jiang R, Lin H-W, Rosenbloom S, Cella D. Using Patient-reported Outcomes to Compare Relative Burden of Cancer: EQ-5D and Functional Assessment of Cancer Therapy-General in Eleven Types of Cancer. Clin Ther 2016; 38(4): 769–777.
5. Von Ah D, Tallman EF. Perceived cognitive function in breast cancer survivors: evaluating relationships with objective cognitive performance and other symptoms using the functional assessment of cancer therapy-cognitive function instrument. J Pain Symptom Manage 2015; 49(4): 697–706.

6. Holzner B, Giesinger JM, Pinggera J, Zugal S, Schöpf F, Oberguggenberger AS, Gamper EM, Zabernigg A, Weber B, Rumpold G. The Computerbased Health Evaluation Software (CHES): a software for electronic patient-reported outcome monitoring. BMC Med Inform Decis Mak 2012; 12: 126.
7. Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, Rogak L, Bennett AV, Dueck AC, Atkinson TM, Chou JF, Dulko D, Sit L, Barz A, Novotny P, Fruscione M, Sloan JA, Schrag D. Symptom Monitoring With Patient-Reported Outcomes During Routine Cancer Treatment: A Randomized Controlled Trial. J Clin Oncol 2016; 34(6): 557–565.
8. Tsai J, Bond G. A comparison of electronic records to paper records in mental health centers. Int J Qual Health Care 2008; 20(2): 136–143.
9. Mooney KH, Beck SL, Wong B, Dunson W, Wujcik D, Whisenant M, Donaldson G. Automated home monitoring and management of patient-reported symptoms during chemotherapy: results of the symptom care at home RCT. Cancer Med 2017; 6(3): 537–546.
10. Cowan RA, Suidan RS, Andikyan V, Rezk YA, Einstein MH, Chang K, Carter J, Zivanovic O, Jewell EJ, Abu-Rustum NR, Basch E, Chi DS. Electronic patient-reported outcomes from home in patients recovering from major gynecologic cancer surgery: A prospective study measuring symptoms and health-related quality of life. Gynecol Oncol 2016; 143(2): 362–366.
11. Digital in 2016 – We Are Social. 2016 [cited 2016 Oct 16]. Available from: http://wearesocial.com/ special-reports/digital-in-2016.
12. Hochstenbach LMJ, Zwakhalen SMG, Courtens AM, van Kleef M, de Witte LP. Feasibility of a mobile and web-based intervention to support selfmanagement in outpatients with cancer pain. European Journal of Oncology Nursing 2016; 23: 97–105.
13. Klasnja P, Pratt W. Healthcare in the Pocket: Mapping the Space of Mobile-Phone Health Interventions. J Biomed Inform 2012; 45 (1): 184–198.
14. Lanzola G, Ginardi MG, Mazzanti A, Quaglini S. Gquest: modeling patient questionnaires and administering them through a mobile platform application. Comput Methods Programs Biomed 2014; 117(2): 277–291.
15. Losiouk E, Quaglini S, Visetti E, Perfetti F, Lanzola G. Ambulance Protocols: A Mobile Solution. Stud Health Technol Inform 2016; 225: 520–524.
16. Capozzi D, Lanzola G. An Agent-Based Architecture for Home Care Monitoring and Education of Chronic Patients. In: Proceedings of the 2010 Complexity in Engineering (COMPENG '10). IEEE Computer Society, Washington, DC, USA, 138–140.
17. Pearman TP, Beaumont JL, Paul D, Abernethy AP, Jacobsen PB, Syrjala KL, Von Roenn J, Cella D. Evaluation of Treatment- and Disease-Related Symptoms in Advanced Head and Neck Cancer: Validation of the National Comprehensive Cancer Network-Functional Assessment of Cancer Therapy-Head and Neck Cancer Symptom Index-22 (NFHNSI-22). Journal of Pain and Symptom Management 2013; 46(1): 113–120.
18. Kidane B, Sulman J, Xu W, Kong QQ, Wong R, Knox JJ, Darling GE. Baseline measure of healthrelated quality of life (Functional Assessment of Cancer Therapy-Esophagus) is associated with overall survival in patients with esophageal cancer. The Journal of Thoracic and Cardiovascular Surgery 2016; 151(6): 1571–1580.
19. Kohane IS, Greenspun P, Fackler J, Cimino C, Szolovits P. Building national electronic medical record systems via the World Wide Web. J Am Med Inform Assoc 1996; 3(3): 191–207.
20. McCoy AB, Wright A, Eysenbach G, Malin BA, Patterson ES, Xu H, Sittig DF. State of the art in clinical informatics: evidence and examples. Yearb Med Inform 2013; 8: 13–19.
21. Quaglini S, Sacchi L, Lanzola G, Viani N. Personalization and Patient Involvement in Decision Support Systems: Current Trends. Yearb Med Inform 2015; 10(1): 106–118.

22. Capozzi D, Lanzola G. A generic telemedicine infrastructure for monitoring an artificial pancreas trial. Comput Methods Programs Biomed 2013; 110(3): 343–353.
23. Lanzola G, Parimbelli E, Micieli G, Cavallini A, Quaglini S. Data quality and completeness in a web stroke registry as the basis for data and process mining. J Healthc Eng 2014; 5(2): 163–184.
24. Peleg M, Tu S, Bury J, Ciccarese P, Fox J, Greenes RA, Hall R, Johnson PD, Jones N, Kumar A, Miksch S, Quaglini S, Seyfang A, Shortliffe EH, Stefanelli M. Comparing Computer-interpretable Guideline Models: A Case-study Approach. J Am Med Inform Assoc 2003; 10(1): 52–68.
25. Fox J, Johns N, Rahmanzadeh A. Disseminating medical knowledge: the PROforma approach. Artif Intell Med 1998; 14(1–2): 157–181.
26. De Clercq P, Kaiser K, Hasman A. Computer-Interpretable Guideline formalisms. Stud Health Technol Inform 2008; 139: 22–43.
27. Sutton DR, Fox J. The Syntax and Semantics of the PROforma Guideline Modeling Language. J Am Med Inform Assoc 2003; 10(5): 433–443.
28. Sutton DR, Taylor P, Earle K. Evaluation of PROforma as a language for implementing medical guidelines in a practical context. BMC Med Inform Decis Mak 2006; 6: 20.
29. Fox J. Cognitive systems at the point of care: The CREDO program. Journal of Biomedical Informatics 2017; 68: 83–95.
30. Noy NF, Shah NH, Whetzel PL, Dai B, Dorf M, Griffith N, Jonquet C, Rubin DL, Storey M-A, Chute CG, Musen MA. BioPortal: ontologies and integrated data resources at the click of a mouse. Nucleic Acids Res 2009; 37(Web Server issue): W170–173.
31. Steindel SJ. A comparison between a SNOMED CT problem list and the ICD-10-CM/PCS HIPAA code sets. Perspect Health Inf Manag 2012; 9: 1b.
32. Tu SW, Nyulas CI, Tudorache T, Musen MA. A Method to Compare ICF and SNOMED CT for Coverage of U.S. Social Security Administration's Disability Listing Criteria. AMIA Annu Symp Proc 2015; 2015: 1224–1233.
33. Karlsson D, Gongolo F, Robinson M, Millar J. ICFSNOMED CT Harmonization a gap analysis. Beijing, China: 2013.
34. Kawamoto K, Lobach DF. Clinical decision support provided within physician order entry systems: a systematic review of features effective for changing clinician behavior. AMIA Annu Symp Proc 2003; 361–365.
35. Garg AX, Adhikari NKJ, McDonald H, RosasArellano MP, Devereaux PJ, Beyene J, Sam J, Haynes RB. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. JAMA 2005; 293(10): 1223–1238.
36. HL7 Standards Product Brief – HL7 Version 3 Standard: Clinical Decision Support; Virtual Medical Record (vMR) Logical Model, Release 2. 2016 [cited 2016 Oct 16]. Available from: http://www.hl7.org/implement/standards/prod uct_brief.cfm?product_id=338.

37. Johnson PD, Tu SW, Musen MA, Purves I. A virtual medical record for guideline-based decision support. Proc AMIA Symp 2001; 294–298.
38. Marcos C, González-Ferrer A, Peleg M, Cavero C. Solving the interoperability challenge of a distributed complex patient guidance system: a data integrator based on HL7's Virtual Medical Record standard. J Am Med Inform Assoc 2015; 22(3): 587–599.
39. Pignon J-P, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACHNC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92(1): 4–14.
40. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally

advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010; 11(1): 21–28.
41. Bossi P, Russi E, Numico G, De Sanctis V, Denaro N, Ghi MG, Mirabile A, Moretto F, Ripamonti CI, Buglione M, Airoldi M, Vermorken JB, Murphy B, Langendijk J, Raber Durlacher JE, Licitra L. Defining best practices on supportive care during chemo-radiotherapy for head and neck cancer with a formal systematic methodology. Ann Oncol 2014; 25(suppl 4): iv342.
42. Buzzacchino S, Lanzola G, Bossi P, Licitra L, Quaglini S. A mobile application supporting outpatient treatment and follow-up. Stud Health Technol Inform 2015; 210: 788–792.
43. Buzzacchino S, Lanzola G, Bossi P, Licitra L, Quaglini S. A mobile application supporting outpatient treatment and follow-up. Stud Health Technol Inform 2015; 210: 788–792.
44. Falasconi S, Lanzola G, Stefanelli M. An ontologybased multi-agent architecture for distributed health-care information systems. Methods Inf Med 1997; 36(1): 20–29.
45. Reade C. Elements of Functional Programming. Boston, MA, USA: Addison-Wesley Longman
Publishing Co., Inc.; 1989.
46. Lanzola G, Stefanelli M. Inferential knowledge acquisition. Artif Intell Med 1993; 5(3): 253–268.
47. Isern D, Sánchez D, Moreno A. Ontology-driven execution of clinical guidelines. Comput Methods Programs Biomed 2012; 107(2): 122–139.
48. Sacchi L, Fux A, Napolitano C, Panzarasa S, Peleg M, Quaglini S, Shalom E, Soffer P, Tormene P. Patient-tailored workflow patterns from clinical practice guidelines recommendations. Stud Health Technol Inform 2013; 192: 392–396.
49. Ventola CL. Mobile devices and apps for health care professionals: uses and benefits. Pharm Ther 2014; 39(5): 356–364.
50. Mandel JC, Kreda DA, Mandl KD, Kohane IS, Ramoni RB. SMART on FHIR: a standards-based, interoperable apps platform for electronic health records. J Am Med Inform Assoc 2016; 23(5): 899–908.
51. Rogers SN, Forgie S, Lowe D, Precious L, Haran S, Tschiesner U. Development of the International Classification of Functioning, Disability and Health as a brief head and neck cancer patient questionnaire. Int J Oral Maxillofac Surg 2010; 39(10): 975–982.