UNIVERSITY OF GENOA

PHD PROGRAM IN BIOENGINEERING AND ROBOTICS

CURRICULUM BIOENGINEERING AND BIOELECTRONICS

Thesis submitted for the degree of

Doctor of Philosophy in Bioengineering XXX cycle

Towards a Learning Health System: a SOA based platform for data re-use in chronic infectious diseases

Barbara Giannini

February 2018

Thesis advisor: Prof. Mauro Giacomini

Contents

Abstract

Information and Communication Technology (ICT) tools can efficiently support clinical research by providing means to collect automatically huge amount of data useful for the management of clinical trials conduction. Clinical trials are indispensable tools for Evidence-Based Medicine and represent the most prevalent clinical research activity. Clinical trials cover only a restricted part of the population that respond to particular and strictly controlled requirements, offering a partial view of the overall patients' status. For instance, it is not feasible to consider patients with comorbidities employing only one kind of clinical trial. Instead, a system that have a comprehensive access to all the clinical data of a patient would have a global view of all the variables involved, reflecting real-world patients' experience. The Learning Health System is a system with a broader vision, in which data from various sources are assembled, analyzed by various means and then interpreted. The Institute of Medicine (IOM) provides this definition: "In a Learning Health System, progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and health care".

The final goal of my project is the realization of a platform inspired by the idea of Learning Health System, which will be able to re-use data of different nature coming from widespread health facilities, providing systematic means to learn from clinicians' experience to improve both the efficiency and the quality of healthcare delivery.

The first approach is the development of a SOA-based architecture to enable data collection from sparse facilities into a single repository, to allow medical institutions to share information without an increase in costs and without the direct involvement of users. Through this architecture, every single institution would potentially be able to participate and contribute to the realization of a Learning Health System, that can be seen as a closed cycle constituted by a sequential process of transforming patient-care data into knowledge and then applying this knowledge to clinical practice. Knowledge, that can be inferred by re-using the collected data to perform multi-site, practice-based clinical trials, could be concretely applied to clinical practice through Clinical Decision Support Systems (CDSS), which are instruments that aim to help physicians in making more informed decisions. With

this objective, the platform developed not only supports clinical trials execution, but also enables data sharing with external research databases to participate in wider clinical trials also at a national level without effort. The results of these studies, integrated with existing guidelines, can be seen as the knowledge base of a decision support system.

Once designed and developed, the adoption of this system for chronical infective diseases management at a regional level helped in unifying data all over the Ligurian territory and actively monitor the situation of specific diseases (like HIV, HCV and HBV) for which the concept of retention in care assumes great importance. The use of dedicated standards is essential to grant the necessary level of interoperability among the structures involved and to allow future extensions to other fields.

A sample scenario was created to support antiretroviral drugs prescription in the Ligurian HIV Network setting. It was thoroughly tested by physicians and its positive impact on clinical care was measured in terms of improvements in patients' quality of life, prescription appropriateness and therapy adherence. The benefits expected from the employment of the system developed were verified. Student's T test was used to establish if significant differences were registered between data collected before and after the introduction of the system developed. The results were really acceptable with the minimum p value in the order of 10^{-5} and the maximum in the order of 10^{-3}. It is reasonable to assess that the improvements registered in the three analysis considered are ascribable to this system introduction and not to other factors, because no significant differences were found in the period before its release.

Speed is a focal point in a system that provides decision support and it is highly recognized the importance of velocity optimization. Therefore, timings were monitored to evaluate the responsiveness of the system developed. Extremely acceptable results were obtained, with the waiting times of the order of 10^{-1} seconds.

The importance of the network developed has been widely recognized by the medical staff involved, as it is also assessed by a questionnaire they compiled to evaluate their level of satisfaction.

List of abbreviations

AIDS	Acquired Immune Deficiency Syndrome
API	Application Program Interface
ARCA	Antiretroviral Resistance Cohort Analysis
ASCO	American Society of Clinical Oncology
ASL	Azienda Sanitaria Locale
ATC	Anatomical Therapeutic Chemical
CancerLinQ	Cancer Learning Intelligence Network for Quality
CCR	Continuity of Care Record
CDA	Clinical Document Architecture
CDISC	Clinical Data Interchange Standards Consortium
CDMS	Clinical Data Management System
CDS	Clinical Decision Support
CDSS	Clinical Decision Support System
CIG	Computer-Interpretable Guidelines
CISAI	Italian Coordination Study for Allergies and Infections from HIV
CTS2	Common Terminology Services Release 2
DBA	DataBase Administrator
DSS	Decision Support Systems Release 1
DSTU	Draft Standard for Trial Use
EBM	Evidence-Based Medicine
EDP	Electronic Data Processing
EHR	Electronic Health Record
EPR	Electronic Patient Record
ESB	Enterprise Service Bus
FSE	Fascicolo Sanitario Elettronico
GEM	Guideline Elements Model
GLIF	Guideline Interchange Format

HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HeD	Health eDecisions
HIMSS	Healthcare Information and Management Systems Society
HIS	Hospital Information System
HIV	Human Immunodeficiency Virus
HL7	Health Level 7
HL7 V2	Health Level 7 Version 2
HL7 V3	Health Level 7 Version 3
HSSP	Healthcare Services Specification Project
HTS	Health Terminology Service
ICD	International Classification of Diseases
ICONA	Italian COhort Naïve Antiretroviral
ICT	Information and Communication Technology
II	Integrase inhibitors
IOM	Institute Of Medicine
ISO	Identification Service
ISO	International Organization for Standardization
IT	Information Technology
IXS	Cross-Reference Service Release 1
JSON	JavaScript Object Notation
KM	Knowledge Module
LAN	Local Area Network
LHS	Learning Health System
LHSNet	Patient-Centered Network of Learning Health Systems
LIS	Laboratory Information System
LOINC	Logical Observation Identifiers Names and Codes
MLM	Medical Logic Modules

NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
ODBC	Open DataBase Connectivity
OID	Object Identifier
OMG	Object Management Group
PCORI	Patient Centered Outcomes Research Institute
PCORnet	National Patient-Centered Clinical Research Network
PEDSnet	Pediatric Learning Health System
PI	Protease inhibitors
PSM	Platform Specific Model
RIM	Reference Information Model
RLUS	Retrieve, Locate and Update Services Release 1
SDM	Study Design Model
SFM	Service Functional Model
SNOMED	Systemized Nomenclature of Medicine Clinical Terms
SOA	Service Oriented Architecture
SOAP	Simple Object Access Protocol
SQL	Structured Query Language
STM	Service Technical Model
TB	Tuberculosis
UML	Unified Modeling Language
US	United States
USA	United States of America
WCF	Windows Communication Foundation
WHO	World Health Organization
WSDL	Web Service Description Language
XML	eXtensible Markup Language
XPDL	XML Process Definition Language
XSD	eXtensible Markup Language Schema Definition

1 Introduction

1.1 Context

In the last years, worldwide National Health Institutes are becoming always more aware of the importance of ICT in healthcare [1]. Consequentially, the government of many countries have planned remarkable investments in the implementation of ICT solutions in the healthcare setting [2]. In particular, Italy is doing significant efforts to develop a federated Electronic Health Record (EHR) called Fascicolo Sanitario Elettronico (FSE). The EHR is a computer-based record of patients' health information that includes information about patients' demographics, medications, vital signs, clinical history, immunizations, laboratory results, and reports of diagnostic procedures [3]. On September 3rd 2015 the Italian Minister of Health Lorenzin has signed the national directives and guidelines for FSE. According to these directives, the Regions have to set up the implementation of the infrastructures needed to guarantee the correct level of interoperability for FSE. The subsequent amendments introduced to Legislative Decree n. 179/2012 with the Legislative Decree of June 21st 2013, n. 69, entitled "Urgent Provisions for the Recovery of the Economy" (converted, with amendments, from the Law of August 9th 2013, No.98), established the deadline for the activation of the FSE at the Regions and Autonomous Provinces on June 30th 2015. The most recent Legislative Decree of August 4th 2017 defines the technical modalities and the telematics services made available by the national infrastructure for the interoperability of the FSE [4].

Despite the deadline, most regions are presently developing the infrastructure to support FSE (November 2017), and in the last two years, only few regions already provide citizens with a complete and operating FSE, as reported in figure 1.1 and 1.2.

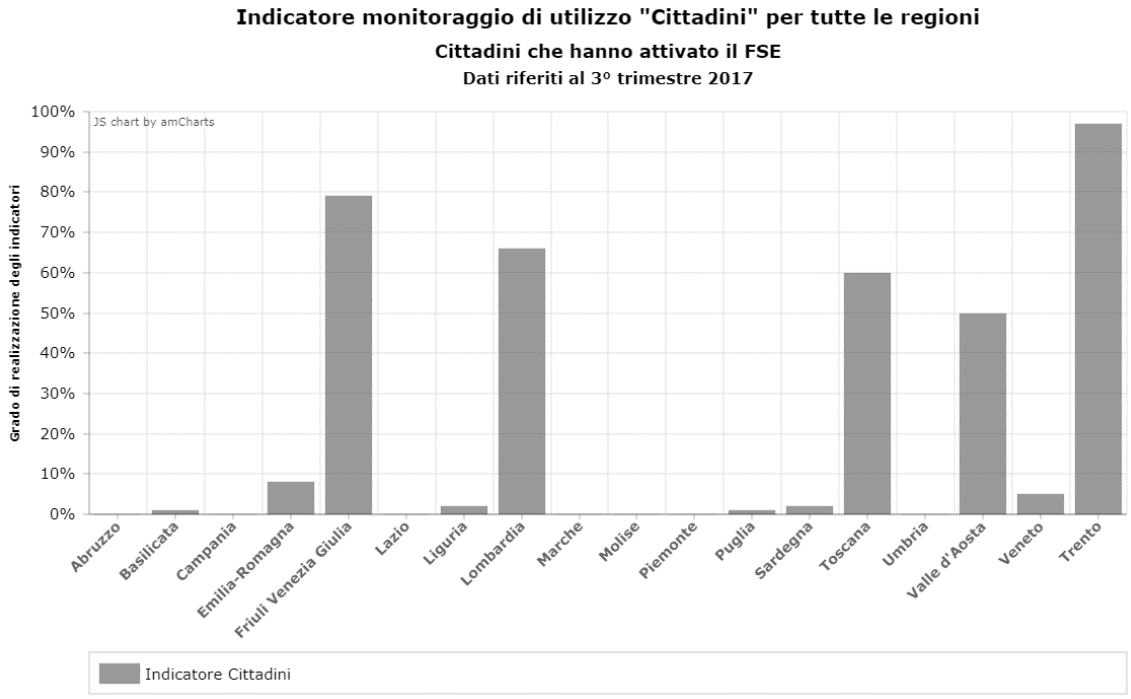


Figure 1.1: Indicator of the percentage of citizens that have access to their personal FSE, distributed per regions. Statistics from the official Italian FSE web site, last update November 2017.

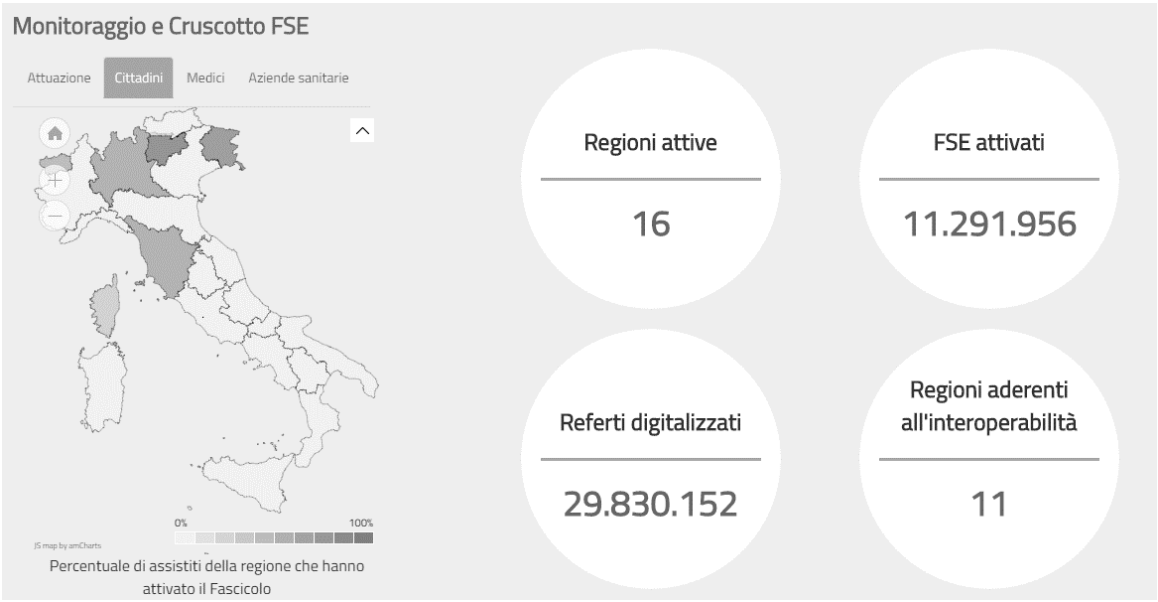


Figure 1.2: Data about the territorial distribution of infrastructures supporting FSE and the related adoption by citizens. 16 regions have adopted infrastructures to support FSE, but only 11 can support interoperability. About 11 thousand FSE were activated by citizens corresponding to about 30 thousand of digital reports created. Statistics from the official Italian FSE web site, last update November 2017.

The Legislative Decree of October 18th 2012 n.179 converted with amendments by Law December 7th 2012 n. 221 on "Further Urgent Measures for Growth of the Country" states in Article 12 the legal provision prepared by the Ministry of Health, which governs the FSE at national level. In particular, paragraph 2 of that article states that it is set up by the

Regions and Autonomous Provinces, not only for clinical care purposes but also for scientific research purposes. Systematic research mainly consists in clinical trials, which are essential tools for the conduction of focused surveys. Clinical trials give a partial vision of patients' status, since the population considered is a restricted part that respond to particular and strictly controlled requirements. For these reason, it is not feasible to consider patients with comorbidities employing only one kind of clinical trials. A system that have a comprehensive access to all the clinical data of a patient would have a global view of all the variables involved, reflecting real-world patients' experience.
Federated FSE should be based on medical standards to grant interoperability among different Regions, in order to share data at a national level. The Ministry of Health suggest the use of Health Level 7 (HL7) Clinical Document Architecture Release 2 (CDA r2).

Liguria region does not supply complete FSE functionalities yet. Nevertheless, physicians have expressed their need to employ a computerized infrastructure that supports data collection from different healthcare institutions of the territory to enable the conduction of multicenter clinical trials.

1.2 Objectives

The main issue addressed by this thesis is the lack of interoperability between different healthcare institutions at intra-regional level, resulting in communication problems and difficulties in data exchange. Fixing that problem, would allow the creation of a common framework for data sharing that, similarly to the described FSE, can support data re-use for research purposes.
In this view, the final goal of my project is the realization of a platform inspired by the idea of Learning Health System [5], applied to the chronic infectious disease field. The LHS can be seen as a closed cycle constituted by a sequential process of transforming patient-care data into knowledge and then applying this knowledge to clinical practice. A concrete application of this concept would involve a standardized framework that allows clinical data collection from widespread health facilities, creating a common data base suitable for data re-use. In this vision, data from everyday clinical care are available for clinical studies, thus enabling integration between clinical care and medical research worlds. Within this relationship, systematic means to learn from clinicians' experience can improve both the efficiency and the quality of the healthcare delivery.

The first step for the implementation of such a system is the development of a SOA-based architecture to enable data collection from sparse facilities into a single repository, to allow medical institutions to share information without an increase in costs and without the direct involvement of users. Through this architecture, every single institution would potentially be able to participate and contribute to the realization of a Learning Health System. Knowledge, that can be inferred by re-using the collected data to perform multi-site, practice-based clinical trials, could be concretely applied to clinical practice through Clinical Decision Support Systems (CDSS), which are instruments that aim to help physicians in making more informed decisions. With this objective, the second step of the development of my project was the realization of a platform that not only supports clinical trials execution, but also enables data sharing with external research databases to participate in wider clinical trials also at a national level without effort. The results of these studies, integrated with existent guidelines, can be seen as the knowledge base of a decision support system, which development consisted in the third step of the project. Once designed and developed, the adoption of this system for chronical infective diseases management at a regional level helped in unifying data all over the Ligurian territory and actively monitor the situation of specific diseases (like HIV, HCV and HBV) for which the concept of retention in care assumes great importance [6].

The use of dedicated standards is essential to grant the necessary level of interoperability among the structures involved and to allow future extensions to other fields and participants.

1.2.1 Learning Health System

The Institute of Medicine (IOM) provides this definition: "In a Learning Health System, progress in science, informatics, and care culture align to generate new knowledge as an ongoing, natural by-product of the care experience, and seamlessly refine and deliver best practices for continuous improvement in health and health care" [7].

This emerging idea was born in the USA and developed until now importing successful experiences coming from other sectors. It aims at the formation of a knowledge starting from data that can be shared through ICT tools, with the purpose of re-evaluate and improve processes and activities, thus ensuring a greater effectiveness of care when applied in the healthcare context [8].

In Europe even if the efficacy of this vision is widely recognized [9], there are only scattered islands of innovation ready to constitute an initial core of an European learning health system, but at a central policy level, its adoption as an organizational approach is not considered one of the imminent goals. The main cause of this organization delay is due to European history in which language and cultural differences are extremely relevant. This reasons result also in technical differences like clinical formats and units of measure that make the automatic sharing of data contained within Electronic Patient Record (EPR) extremely difficult. The use of standards at any level of the sharing process would significantly improve the feasibility of this operation [10].

The use of ICT (Information and Communication Technology) tools (e.g. electronic record systems, data transmission infrastructures and clinical networks) represents one of the prerequisites for the development of a learning health system, whose main goal is to adopt structured knowledge in order to improve activity and processes in medical field [10].

In LHS, the strong integration between medical research and patient-care practice is a key concept.

The learning health system can be seen as a closed cycle constituted by a sequential process of transforming patient-care data into knowledge and then applying this knowledge to clinical practice. In my project, this kind of knowledge is meant to be concretely applied to clinical practice through a Clinical Decision Support System, which is an instrument that aims to help physicians in making more informed decisions. Different types of CDSS exist, basing on the different ways of inferring knowledge from patient's specific data: rule-based CDSS or inferential CDSS [11]. A rule-based CDSS rest on the knowledge that could be extracted from existent clinical guidelines combined with the inferences from the results of experimental research and clinical trials performance [12].

The flux diagram in figure 1.3 shows the cycle of LHS. The CDSS is integrated into the care environment to provide support in care practice, based on real time patients data coming from the computer based patient's record. The experimental research conducted through practice-based research networks provides knowledge that is published in the literature. This knowledge combined with those coming from guidelines forms the knowledge base of the CDSS.

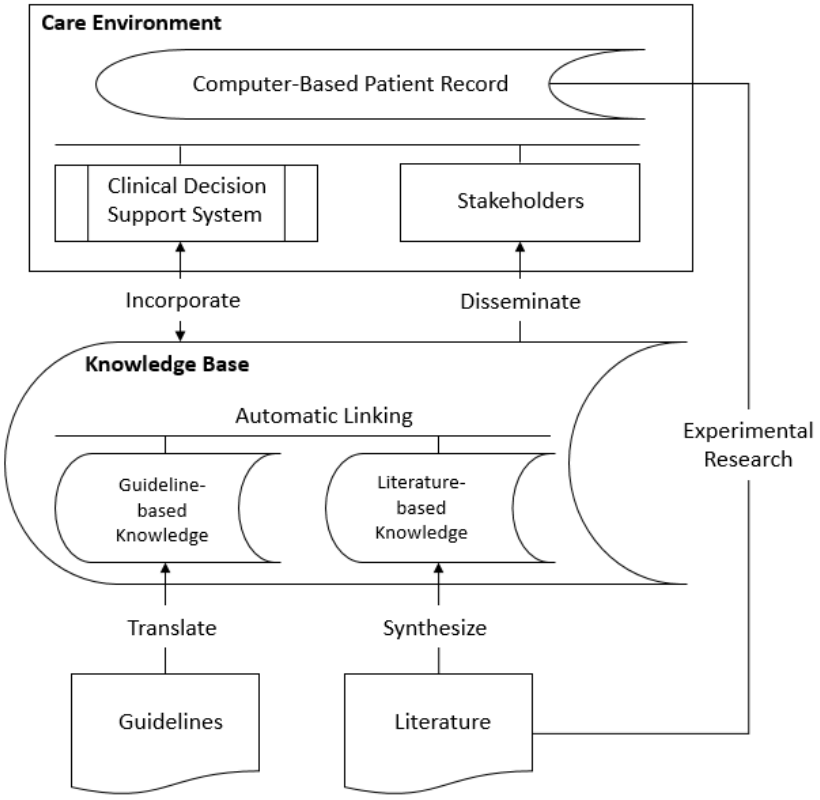


Figure 1.3: Diagram showing the cycle of LHS. Data from guidelines and literature are translated and synthesized into knowledge that is incorporated into the Clinical Decision Support System and in parallel disseminated to stakeholders. The care environment benefits from these tools. Data from clinical practice are collected through computer-based patient record and re-used for experimental research, serving as base for new publications, thus closing the cycle.

In a health system that "learns" every consenting patient's characteristic and experiences are, in principle, available for study and best practice knowledge is immediately available to support decisions. Improvement is continuous through ongoing studies while learning happens routinely, economically and almost invisibly.

1.3 State of the art of Learning Health System

In the United States, Friedman et al laid the foundations to the vision of the Learning Health System, which main goal is to adopt structured knowledge in order to improve activity and processes in the medical field [8]. Since its first definition in 2007, the LHS has evolved from an intriguing idea to a nascent reality. In the United States in the last few years, many networks of institutions that aim at achieving the principal LHS capabilities aroused. In 2014, the Patient Centered Outcomes Research Institute (PCORI) invested more than $250 million in the development of the National Patient-Centered Clinical Research Network (PCORnet), which is a "network of networks" that collects data routinely gathered in a

variety of healthcare settings all spread among the US [13]. The aim is the re-use of these data, in order to enable people to make informed healthcare decisions by efficiently conducting clinical research relevant to their needs. PCORnet includes 13 Clinical Data Research Networks, 20 People-Powered Research Networks, and 2 Health Plan Research Networks. Among these, two important PCORI funded LHS projects that are still in development are the "Patient-Centered Network of Learning Health Systems" (LHSNet) in Minnesota [14] and the "Pediatric Learning Health System" (PEDSnet) in Pennsylvania [15], both started in 2015 with an expected duration of three years.

The Scalable Collaborative Infrastructure for a Learning Health System (SCILHS) is a Clinical Data Research Network that participates in the PCORnet. SCILHS includes 12 health centers across the United States that use i2b2 (Informatics for Integrating Biology and the Bedside) software to collect and analyze patient data for clinical research. I2b2 is a data warehouse funded by the National Institute of Health (NIH) to re-use clinical data for research purposes [16]. This system allows the exchange of information between clinic and research fields, facilitating the testing of research results through clinical trials and using data generated by clinical practice for research purposes. The i2b2 software consists of a collection of independent modules called "cells" that constitute the so-called "hive". Each cell interact with the others using web services and XML messages.

An important LHS project already developed that focuses on the study of a single disease is Cancer Learning Intelligence Network for Quality (CancerLinQ), a LHS in oncology designed by the American Society of Clinical Oncology (ASCO) [17] [18]. It was formally launched in 2015 and presently it has more than one million patient records in the system from the main US states.

These are examples of working Learning Health System projects. There are also diffuse architectures that support clinical data sharing across different institutions, above which a Learning Health System could be built. In 2008 Harvard started a project with the aim to enable collaboration across the Harvard schools and affiliated hospitals and institutions [19]. The main issue was sharing patient data using a federated model where each institution would maintain control over their local databases. I2b2 software was used at each site. Shared Health Research Information Network (SHRINE) was built to link their respective i2b2 instances for the sharing of data [19]. SHRINE is currently in play at other

sites in USA such as i2b2-CICTR (Cross-Institutional Clinical Translational Research project) [16] and CARRAnet (Childhood Arthritis and Rhematological Research Alliance) [20].

A proof-of-concept architecture for a network-based LHS has also been realized in the chronic diseases field, with the aim of predicting models from data collected through which deliver the best possible treatments [21]. In this paper, Marsolo et al. assert that knowledge generated by the huge amount of data coming from chronic patients can be applied in routinely patient care through decision support systems. The use of standards at any level of the sharing process significantly improves the feasibility of such a system. In their work, Marsolo et al. propose the introduction of standards as a future development, and in particular, they suggest the use of Health eDecisions (HeD) standards. The Health eDecisions (HeD) initiative, supported by HL7 (Health Level 7) International and OMG (Object Management Group).) is an initiative of the Office of the National Coordinator‘s Standards & Interoperability Framework [22][23]. HeD does not aim to create a new standard, but its intent is to identify, define and harmonize already existing standards involved in clinical decision support field.

While in the US during the last few years the concept of LHS was increasingly consolidated, in the rest of the world there are only scattered islands of innovation ready to constitute an initial core of a Learning Health System, even if the efficacy of this vision is widely recognized [24]. In the last years, some projects about repurposing clinical data collected in the Electronic Healthcare Record (EHR) for use in clinical research are diffusing in Europe. EHR4CR (Electronic Health Records for Clinical Research), is an European project funded by Innovative Medicines Initiative (IMI) and the European Federation of Pharmaceutical Industries and Associations (EFPIA) which aims to provide adaptable/reusable and scalable solutions for reusing EHR data for clinical research [25]. It involves 34 academic and private partners and 11 hospital sites in France, Germany, Poland, Switzerland and the United Kingdom. The EHR4CR platform supports distributed querying to assist in clinical trials feasibility assessment and patient recruitment. Software connectors offer the possibility to use the EHR4CR reference implementation with an i2b2 clinical data warehouse [25].

In Europe the only example of LHS reported in literature is the TRANSFoRm project, an EU funded large scale project, which aims to develop and evaluate a LHS for European Primary Care [26] [27]. TRANSFoRm project has three main areas of application: facilitation of multiple site genotype-phenotype studies, enabling multi-site practice-based clinical trials and improvement of diagnosis by provision of a diagnostic decision support system linked to Electronic Health Records (EHR). In this project CDISC (Clinical Data Interchange Standards Consortium) SDM (Study Design Model) standard was adopted for study design. TRANSFoRm project involves 10 European countries, but Italy is not included. Italy is doing significant efforts to develop a federated Electronic Health Record (EHR) called Fascicolo Sanitario Elettronico (FSE). With this tool, Italian regions have to set up infrastructures that guarantees interoperability and data sharing at inter-regional level. Actually, such a comprehensive system has not been already achieved since data cannot be shared in a standardized way between regions because each of them has its own architecture. The concept of learning health system needs to be eradicated into a fully linked system to be significant. The development of this project could be the starting point for such approach, especially because its standardized and innovative solution can easily open the system to other regions.

The learning health system is a closed cycle in which medical knowledge is extracted from patient-care data and then it is applied to clinical practice. In my project, this kind of knowledge is meant to be concretely applied to clinical practice through Clinical Decision Support Systems (CDSS).

The importance of decision support systems is highly acknowledged as a key strategy to improve medical safety and quality of care [28]. In the past, cultural and technological barriers have prevented a broad application of CDSS across the healthcare setting. The evolution in the adoption of health IT during the years, together with the resulting increase of availability of digital data from Electronic Health Records (EHR) have played an important role in the evolution and adoption of CDSS [29]. Different kind of CDSS exist: guideline-based clinical decision support systems can offer to physicians patient-specific advices based on guideline recommendations. In the literature a great number of CDSS implementations are described for different medical fields [30] [31] [32] [33] [34]. Specifically, there are CDSS implementations also in HIV field, which have the potential

to improve specialty medical care by monitoring laboratory results and patients follow-up [35].

Most studies on the efficacy of the current CDSS implementations reveal that only the process outcomes benefit from these systems, while little improvements are registered in clinical outcomes [30] [32] [36]. To improve clinical outcomes, the automated decision support should be strictly interconnected with the process of care. Among the great number of computerized CDSS arousing in every medical field, a recent review shows that only few CDSSs delivered their recommendations at the point of care [37]. Therefore, these stand-alone systems need to be integrated into clinical practice. This should be done through the implementation of a Learning Health System, that applies the knowledge generated from the patient-care data to clinical practice through Clinical Decision Support Systems (CDSS).

A strong interoperability between the hospital EHR and the CDSS is the key to reach a most reliable decision support, that could aid in better diagnosis, reduce medication errors and improve practitioner performances [29]. A problem that arouses in the coupling of EHR and CDSS is the heterogeneity of clinical data sources and, as asserted by Kawamoto in 2010, the lack of a common information model and standardized clinical terminology force CDSS interfaces to have custom mappings between systems [38]. Different kind of standards are needed for data mapping and representation, for knowledge representation, re-use and transfer and for system intercommunication [39]. According to a review published in 2016, only 22% of the systems considered use standards for guidelines representation, 63% use clinical information standards, 46% outline the use of standard terminologies, and 32% report the use of web services to offer CDS functionalities [40].

Healthcare standards such as OpenEHR, ISO 13606-1:2008 and HL7 standards are used to enhance the communication between EHRs and clinical applications or middleware components [41]. The knowledge base of the decision support system in LHS is a combination of the evidence coming from clinical trials and clinical guidelines. Many standards are available to represent clinical guidelines in computable format, with the aim to simplify updating and sharing [41].

In accordance with the CDSS implementation needs, there is a great variety of standards that can facilitate implementation, but each of them has different gaps and challenges. In

their review, Kawamoto et al recommend that efforts should be made to harmonize and recommend the use of existing standards [39]. Health eDecision is such an initiative which intent is to identify, define and harmonize already existing standards involved in clinical decision support field [23]. During the very last years the first implementations of CDSS relying on the standards defined by the HeD initiative are rising. Besides the pilot study [42] and its applications [43], Zhang et al developed an infrastructure that is entirely based on these standards [44], assessing that, compared with other CDSS systems, their approach improves system maintainability, scalability and efficiency and saves time and cost in system development and implementation.

Speed is a focal point in a system that provides decision support and it is highly recognized the importance of velocity optimization [45].

2 Materials

2.1 Existing scenario

In 2011 the regional research network called Ligurian HIV Network (LHN) was implemented by some colleagues in Medinfo laboratory [46] [47]. The LHN was originally conceived as a mere web platform to enable the collection of data from HIV patients using a web interface, in order to perform multi-centric clinical trials at a regional level. The system relies on a relational database, which has a high data structuring through a meta-description approach, which permits the archiving of various types of clinical information. The web platform was developed in Microsoft VB .NET and visualization is standardized through the use of Microsoft .ascx templates, through which the web pages are loaded dynamically based on a specific tables structure.

The instrument developed provides a complete clinical vision of patients, granting data integration between the different types of clinical studies hosted on the platform and granting flexibility in data extraction through specific instruments that allow user customization.

For the first years, the platform was consistently used for its initial scope, supporting about half a dozen local studies. Routine use of the platform, together with the intention to address the well-known problem of errors due to manual data input into web interfaces, led to a consecutive gradual evolution of the system. The leading idea was that clinical data, already available in digital format in the LIS (Laboratory Information System) and other components of the Hospital Information System (HIS), could be extracted and automatically exported to the LHN database. In this way, patients' laboratory data could be updated daily without human intervention. In the previous works on the first prototype of LHN, the lack of integration between medical informatics and clinical research was pointed as one of the main critical point to be addressed.

2.2 Hospital EHRs network

The leading idea was to connect the main hospitals involved in the LHN in order to create a network to share information about patients. This network should allow the management of patients in a comprehensive way, granting the ability to track their clinical path in the regional territory. The EHR of each hospital has to be connected to the LHN database and a program has to organize data updating without human intervention.

The idea was submitted to the judgment of the Ligurian Ethics Committee that approved the proposed architecture and its functionalities.

Three hospitals agreed to connect to the network and provided access to their Hospital Information System. The three hospitals are Ospedale Policlinico San Martino of Genova, Ospedali Galliera of Genova and Ospedale di Sanremo of Sanremo (IM). Each hospital has a different informative system, so two different ways to make data accessible have been developed. Galliera offers several services to access patients' clinical data, including a data management service to access laboratory exams results. After authentication, data are available on demand in XML or JSON format. Data can be queried by the patient identification code and can be furtherly filtered using the date of the exam. Contrariwise, San Martino and Sanremo do not have services so the only way to access data is to directly extract them from the Electronic Health Record (EHR). A VPN connection is necessary to reach the hospital server, while an ODBC connection has to be used to achieve its database. San Martino and Sanremo hospitals created a custom account providing read-only access to some views. One of the views supplies administrative data, while the others allow access to clinical data, in particular those coming from laboratory tests, microbiological tests and antibiotic resistance tests.

In all cases, only a restricted part of the hospital information system is accessible, and sensitive patients' data are not visible, according to privacy issues. The management of patients' identity will be done in a pseudo-anonymous way through hospital identification codes. When a patient is registered into a hospital for the first time, he is given an alphanumeric identification code and every action related to the patient will be registered associated to this ID. The association between the patient's identity and the identification code is registered only in the hospital's demographic and cannot be accessed from outside. Each hospital associates a different identification code for the same patient.

The main clinical information that was made available by the three hospitals concerns laboratory tests, microbiological tests, therapies, serology and resistance patterns. Each hospital uses its own terminology and no standard vocabularies are employed in their systems. Thus, the hospital HIS administrators provided a complete schema of all the exams supported, mapped with local codes and descriptions.

The immunization administered to patients involved in the LHN with the related information of injection date, typology and dose are of interest too. Immunization data are not stored into hospital databases: there is a unique computerized immunization registry that manages immunization data storage in the Genoa metropolitan area and province. The company responsible of the administration of this system developed a web service to provide access to its content through standard CVX codes.

2.3 Clinical trials in chronical infectious diseases

Evidence Based Medicine (EBM) is the process of research, evaluation and systematic use of the results of contemporary research as a basis for clinical practice. Clinical trials are indispensable tools for Evidence-Based Medicine [48]. They are used in many clinical areas to evaluate the effectiveness of a specific protocol of treatment or drug therapy in a group of patients in order to be able to infer the possible treatment. There are different types and stages of clinical trials but all share similar characteristics [49]. The main classification consists in observational and interventional trials. During observational studies, the researchers simply observe the patients and register the outcomes. In interventional studies, the researchers administer the drug under study or other kind of intervention and compare the outcomes with those of non-treated patients. Observational studies divide into two sub-categories: cohort studies and case-control studies. In cohort studies, a population is observed in a certain period of time to detect potential risk factors or other communal characteristics. This inspection can be carried on considering only past data or collecting oncoming data. The first one is called retrospective study, the second one is called prospective study. Case-control studies compare a group of subjects with a particular disease with a group of healthy subjects to evaluate the exposure to certain risk factors.

Pre-clinical studies in vitro or in vivo on animals generally precede interventional studies. Interventional studies are in vivo tests on human that pass through different phases. Usually they start from phase 0, which consists in pharmacodynamics and pharmacokinetics

evaluation in human. Phase 1 is a screening for safety and allows evaluating the quantity of drug that is administrable to a restricted sample of subjects without registering serious adverse events. Phase 2 establishes the efficacy of the treatment administered to a bigger sample of subjects (usually 20-300 subjects). Case-control studies could be conducted in parallel to evaluate the treatment effects. Phase 3 provides a general evaluation on a bigger sample of subjects (usually 300-3000 subjects). After phase 3, the treatment can be commercialized. Phase 4 is a post marketing surveillance phase, called pharmacovigilance.

The results of the research will be much better as the quality of the data collected and analyzed is accurate. Data management is a critical point during the planning of a trial steps. Clinical trials may involve only one specialist center or group of centers. In the latter case, a larger amount of data will be collected and it will be easier to generalize samples as a global population rather than a single center. Information technology can facilitate clinical trials conduction in different phases such as data entry, database deployment and management, statistical and inferential processing, and data transfer.

In multicentric clinical trials, use of Clinical Data Management Systems (CDMS), such as the LHN, has become essential to handle a huge amount of data. The LHN web platform coordinates the conduction of different regional clinical trials in HIV field based on the amounts of data collected from the hospitals involved. Different types of clinical trials are managed on the LHN: those focused primarily on clinical aspects and therapy, which is a key trait for HIV patients and those focused on managerial and economical aspects [47].

At a national level, there are different databases that collect data from different institutions on the national territory to perform wider clinical trials. The ARCA (Antiretroviral Resistance Cohort Analysis) [50], ICONA (Italian COhort Naïve Antiretroviral) [51] and CISAI (Italian Coordination Study for Allergies and Infections from HIV) [52] databases constitute the most important clinical cohorts for HIV studies in Italy.

ARCA was started in 2002 by the HIV Monitoring Service at the University of Siena. It is a public database developed to investigate resistance to antiretroviral drugs used against the human immunodeficiency virus. The database contains patients' treatment data, variations in the viral genome and the corresponding inferred susceptibility to the antiretroviral drugs, and the main infection markers such as plasma HIV-RNA load and CD4 cell counts.

ICONA was constituted as Foundation in 2007, but it began in 1997 as an observational study conducted on a wide cohort of HIV-positive individuals. Presently more than 14.500 antiretroviral naïve patients are enrolled by the 50 institutions operating throughout Italy.

The CISAI group was born in 1995 with the aim of studying clinical manifestations and the pathogenesis of allergic reactions to drugs, that in subjects with HIV infection occur with higher frequency than the general population. Since September 2002, CISAI SCOLTA is the first online pharmacovigilance program for new antiretroviral drugs.

A fundamental aspect in clinical trials is the importance of communication between different research databases in order to expand the population under study, allowing the possibility of drawing on a broader set of information, to improve the knowledge about the disease, therapy or scope considered. In this perspective, interoperability between clinical structures with different architectures assumes great importance. The three hospitals involved in the Ligurian HIV network participate also in the three mentioned national clinical trials, by filling the platform through the dedicated web interfaces. In this way, when a patient undergoes a clinical test, all the research databases has to be manually updated; multiple manual input is time wasting and it may cause input errors affecting data quality.

2.4 Clinical Decision Support System

Decision support systems are tools that combine mathematical models and analysis techniques with traditional data processing functions in order to support decision makers. A decision support system includes two modules called EDP (Electronic Data Processing) and MIS (Management Information Systems). The EDP is the data processing system that is used to obtain information, while the MIS handles that information to provide references and possible choices in the decision options. A decision support system uses both these modules to elaborate the decision with the decision maker in interactive mode. Therefore, it does not attempt to provide the optimal solution, but the idea is to guide the decision maker through the best options in order to put him in the condition to make the optimal choice.

In the medical field, the decision support is based on the information set that can help physicians to diagnose or to treat a patient's health problem.

In clinical decision support systems, various methods are used to assemble information used for the process of decision-making, such as statistical method, neural network, rule-based method, fuzzy logic rule-based, genetic algorithms. CDSS are classified into two major groups: knowledge based and non-knowledge based. Knowledge based CDSS use rules mostly in the form of if–then statements. Ruled-based CDSS exploit knowledge acquisition tool that facilitate the creation and maintenance of a knowledge base made of condition–action rule templates [11]. Non-knowledge based CDSS are implemented with the support of artificial intelligence, using machine learning algorithms to extract knowledge from a large number of data [53]. In this thesis I will focus on knowledge based CDSS.

Knowledge based Clinical Decision Support Systems assemble the knowledge base with specific patient's data by a dedicated engine, that uses a peculiar logic, to provide clinicians with guidance based on real-time data. Innovative clinical decision support systems work as clinical advisory systems that use epidemiological data together with expert knowledge (scientific evidence, guidelines and others) to provide real-time support to clinicians. These kind of systems are applied to different clinical situations, such as warning service for potential adverse drug interactions, interpretation of results of blood gas analysis and automated diagnostic medical programs. CDSS can contribute specifically to the improvement of the quality of care by providing the clinician with the best possible information easily and quickly accessible, helping him to choose between alternative tests and treatments for a specific problem to solve. A CDSS system is designed to help directly or indirectly in clinical decision making, in a situation where the data of a given patient are crossed to a computerized knowledge database with the purpose of generating a specific evaluation for that patient, or to produce specific recommendations that are offered to the clinician as suggestions and advices. A Clinical Decision Support System can be defined as a system composed by a knowledge database and an inference engine that is able to use data to provide advices on specific cases. A knowledge database includes a set of systematically organized knowledge stored on a computer to make decisions or solve problems, while an inference mechanism indicates a procedure that operates on the representation of knowledge to complete new propositions. As already mentioned, Information and Communication Technology has become a fundamental tool for medicine, and the decision support system is essentially based on information technology. The main

information is that about the patient and that about the kind of problem and the relative knowledge. Traditional sources of patient information rely on paper files and have a long list of restrictions: illegibility, lack of completeness, lack of accuracy, lack of uniformity, inaccessibility, slow and unreliable transmission, lack of security and excessive physical volume of this documentation. To go beyond these shortcomings, the role of information technology, with its range of solutions, is definitely important, because of the potential to improve the accuracy of the information needed in making clinical decisions, to reduce the amount of time required to retrieve that information and finally to ensure that the information is accessible in the administration point of care. The key technology to improve the patient information is the aforementioned electronic medical record that stores complete information from a variety of sources (clinical, laboratory, from radiology, the pharmacy etc.). A fundamental feature that arouses from literature on this matter is that CDSS, to be truly efficient, should be smoothly integrated within the clinical information system, interacting with other components, in particular with the hospitals electronic health record, to avoid data manual entry, exploiting data already available in digital format. This kind of systems needs to directly interface with the electronic health record to access all the clinical data required [54]. This fundamental interaction between CDSS and EHR is deeply analyzed in the paragraph "Interoperability of CDSS and EHR".

The Information Technology is also used to retrieve, store and maintain scientific knowledge that will be used as base for the decision process. Electronic resources are generally easier to find and more up-to-date in respect of paper sources. The topic of knowledge representation is deeply analyzed in the dedicated paragraph.

The process of healthcare information retrieval from hospitals EHR and the procedure of appropriate knowledge finding from clinical guidelines are not easy, because they require a correct integration of data coming from heterogeneous sources. Without the use of appropriate standards, errors could affect this operations, jeopardizing all the system. Moreover, without the use of healthcare standards, each user should implement specific interfaces to access the knowledge made available by the CDSS. The interoperability with external consumers should be facilitated through the adoption of a standardized service.

In the literature a great number of CDSS implementations are described for different medical fields [30] [31] [32] [33]. Specifically, there are CDSS implementations also in

chronic infective diseases and in particular in HIV field, which have the potential to improve specialty medical care by monitoring laboratory results and patients follow-up [29] [35]. CDSS provide timely and efficient review of important new laboratory values and scheduling patient follow-up, generating alerts to notify HIV outpatient provider of adverse events. Alerts should effectively capture the attention of providers in a timely manner and they should be correctly rationed in order to avoid over-alerting that leads providers to ignore it. In the study conducted by Robbins et al [35] static alert and interactive alert have been compared on two groups of subjects, respectively the control group and the intervention group to control the suboptimal follow up. The figure 2.1 shows that the interaction alerts significantly improved the follow up control.

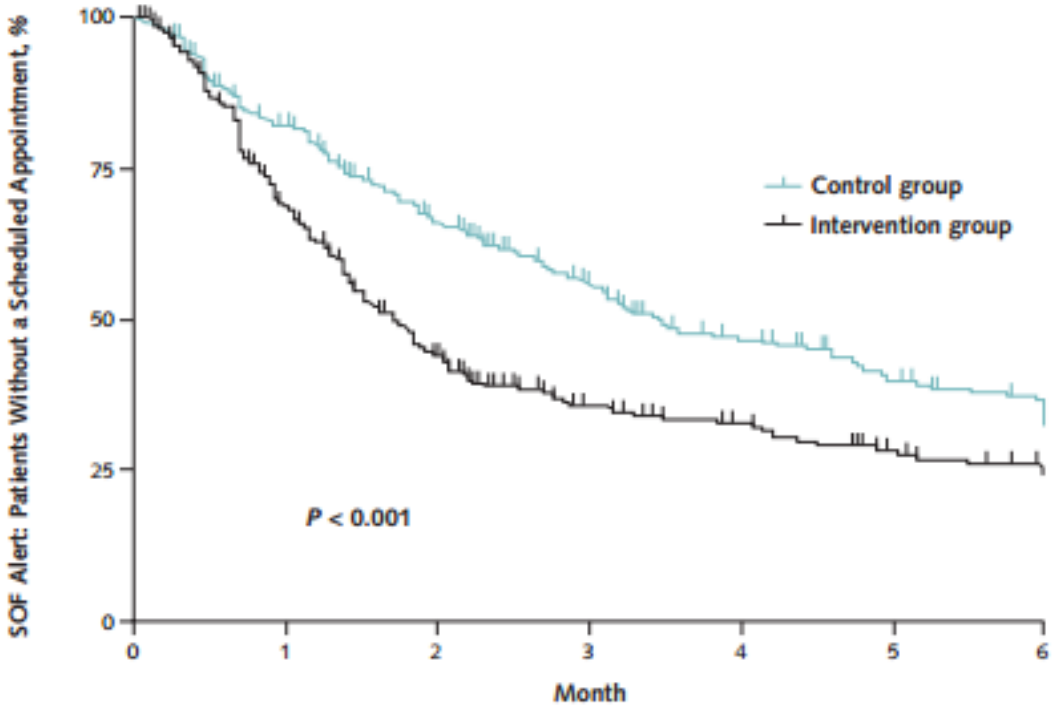


Figure 2.1: Sub-Optimal Follow-up alerts were introduced by Robbins et al to improve retention in care in HIV infected patients. The Kaplan-Meier analysis of time to next scheduled appointment after the first Sub-Optimal Follow-up alert in the intervention group reveals that the interaction alerts significantly improved the follow-up control.

The importance of decision support systems is highly acknowledged as a key strategy to improve medical safety and quality of care. Despite the recognized potential to improve healthcare outcomes, examples of effective CDSS in routine clinical care are lacking, due to technical and social aspects [55].

2.4.1 Interoperability of CDSS and EHR

As before mentioned, CDSS assume great recognized importance as a mean to measure and control the quality of care, and the employment of computer-based CDSS has significantly improved clinical practice [38]. During the last years, CDSS has become increasingly important, raising clinical relevance [28] but, in the past, cultural and technological barriers have prevented a broad application of CDSS across the healthcare setting. The evolution in the adoption of health IT during the years, together with the resulting increase of availability of digital data from Electronic Health Records have played an important role in the evolution and adoption of CDSS. The avoid of manual data input that is error prone in respect to the re-use of digital available data on which infer decisions about patients assures better quality of the care delivered. This gave more confidence about this kind of systems among physicians that initially were suspicious about them. To re-use digital data already entered in the Hospital Information System, an interaction with other components, in particular with the Electronic Health Record, to access all the clinical data is required. A strong interoperability between the hospital EHR and the CDSS is the key to reach a most reliable decision support, that could aid in better diagnosis, reduce medication errors and improve practitioner performance [29]. A problem that arouses in the coupling of EHR and CDSS is the heterogeneity of clinical data sources and, as asserted by Kawamoto in 2010, the lack of a common information model and standardized clinical terminology force CDSS interfaces to have custom mappings between systems [38]. Moreover, CDSS require data at a higher abstraction level in respect to those contained into EHR. This problem is named “Impedance mismatch”. To overcome these problems, a virtual interface could be used between the EHR and the CDSS, in order to define mappings between it and the CDSS only once [54]. In this way, when a CDSS has to be connected to a new EHR system, only the mappings between the EHR system and the virtual interface are needed, without the need to modify the CDSS.

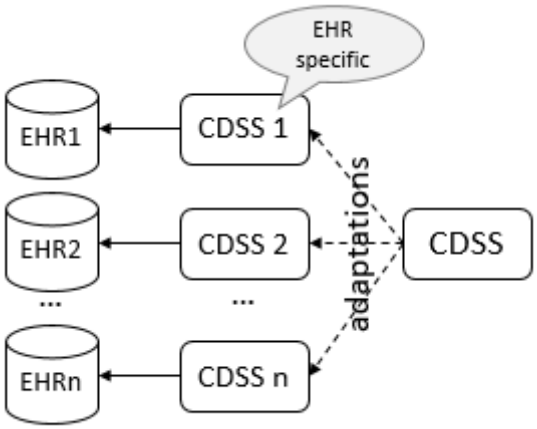


Figure 2.2: Linking a CDSS to different EHRs adapting the CDSS to each EHR

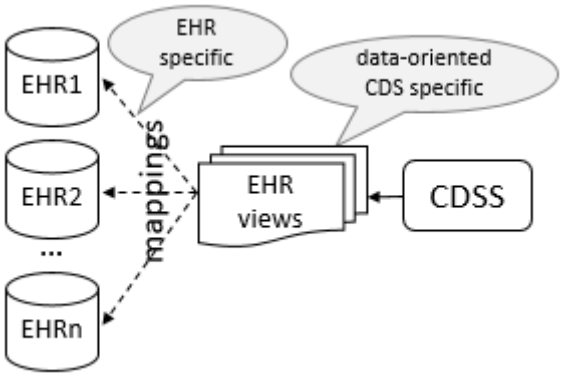


Figure 2.3: Linking a CDSS to different EHRs through data views

The specification for such a virtual interface have been developed by HL7 and it is named Virtual Medical Record (vMR). The HL7 vMR is a data model for representing clinical data relevant to CDSS, which entails providing clinicians or patients with clinical knowledge and patient-related information, intelligently filtered or presented at appropriate times, to enhance patient care [56]. The vMR aims to model and capture the totality of the clinical concepts that are relevant for CDSS in a simplified way and to omit non-influential concepts that are present in the EHR.

3 Methods

3.1 Architectural approach

3.1.1 Service-oriented architecture (SOA)

Service-oriented architecture (SOA) is an architectural approach based upon the use of web services. A service is a piece of functionality made available by a service provider in order to deliver end results for a service consumer. These services communicate with each other: the communication can involve simple data passing or it could involve two or more services. A service consumer sends a request to a service provider, which returns a response containing the expected results. SOA emphasizes on breaking business processes into smaller blocks (services), thus addressing issues related to re-use, maintenance and integration [57].

SOA is increasingly utilized as an integration paradigm for HIS (Healthcare Information Systems). Healthcare organizations demonstrate ongoing efforts to reduce costs and improve the quality of their services through systems integration. The emphasis on standards based interface is a critical success factor for SOA.

The number of interfaces grows exponentially as the number of connected systems increases, rising the economical expense for interface design, development and maintenance. SOA paradigm adoption reduces the number of point-to-point interfaces, thus reducing costs. Another advantage of SOA approach is the facilitation in software design and implementation, due to the decomposition of complex problems into smaller ones [58]. Software reusability is also a crucial point that can be achieved using Service Oriented Architecture, reusing existing IT resources and improving adaptability to new requirements. Among the recognized benefits of SOA, the improve in quality of data is one of the most important, especially in the medical field. In fact, the enhanced interoperability allows to produce more accurate and up to date information that are essential for the healthcare decision-making process [57].

Considering all the benefits described, a number of organizations have adopted SOA approach in health care environment, and in particular in Clinical Decision Support. and a literature review about it has been reported in 2014 by Salvador Rodriguez Loya et al [41].

There are different possibilities for SOA-based architectural approaches, in particular six general architectural themes has been highlighted in this review:

1. point to point
2. enterprise service bus (ESB)
3. service registry
4. clinical guideline engine
5. rule based engine
6. service choreography and orchestration

The review shows that all the architectural approaches presented can coexist within a SOA based implementation of a Clinical Decision Support.

Contract standardization and scalability are both characteristics for which SOA integration can be seen as a process that enables interoperability. According to The Healthcare Information and Management Systems Society (HIMSS), interoperability is "the ability of different information technology systems and software applications to communicate, exchange data, and use the information that has been exchanged" [59]. There are three levels of interoperability:

- *Foundational interoperability:* it allows data sharing, so that data sent by one system can be received by another system, but it does not imply that the receiving system can interpret it.
- *Structural interoperability: it* is an intermediate level that defines the format of the data exchange and it focuses on the packaging of the data into standard messages. Specific standards, such as Health Level 7 for the healthcare field, provide guidance on how messages should be structured.
- *Semantic interoperability*: it is the ability of two or more systems not only to successfully exchange information, but also to meaningfully interpret the information exchanged. It is granted only when both systems refer to a common information reference model. In healthcare field, the most known and used information model is RIM (Reference Information Model) of HL7.

A SOA architecture itself does not guarantee complete interoperability. Semantic interoperability is essential for SOA architectures to grant consistency in the data exchange among service providers and service consumers. To address interoperability challenging in the context of SOA architectures, the Healthcare Services Specification Project (HSSP)

was formed in 2005 within a collaboration among Health Level Seven (HL7) and the Object Management Group (OMG) standards groups.

3.1.1.1 Windows Communication Foundation (WCF) services

Windows Communication Foundation (WCF) is a framework for building service-oriented applications in .NET. WCF combines different technologies by providing a unified programming model (and its API) for the implementation of interoperable applications, all based on shared standards, enabling the exchange of information even between non-heterogeneous platforms. This new unified programming model was based on the SOA architecture guidelines.

3.2 Standards

3.2.1 Data sharing in clinical context

The healthcare domain is very large, complex, and in continuous changing. During the process of data sharing through different healthcare institutions, many problems can arouse in the interpretation of the identities exchanged due to different formats, domains and geographical locations. Effective communication requires that both information sender and receiver share a common reference framework that enables all interactions to be unambiguously understood providing uniformity in the definition. One possible solution should be the developing of custom interface solutions for each problem, but in this way, it is difficult to adapt to new requirements. The heterogeneity of the clinical data sources should be overcome by the creation of a sharing framework through dedicated standard services in order not to modify the hospital systems architectures. Different methodologies exist to implement an interoperable system such as Health Level 7 standard.

Interoperability includes two components: syntactic or functional interoperability and semantic interoperability. Syntactic refers to the structure of the communication, while semantics refers to the meaning of the communication, as dictionaries or thesaurus. To represent clinical concepts and constructs within the HL7 framework, a standard vocabulary is needed to populate the model with meaningful data. A standard list of codes represents many different clinical concepts. Without semantic interoperability, information may be interchanged but there is no certainty that the receiver can understand it. Terminology only provides a standardized set of terms, there is the need to provide a

standard structure for data and specifications about the correct use of these terms in this structure.

The existing healthcare standards address both components of interoperability and are grouped into the following categories [41]:

- **Terminology standards**: vocabularies provide specific codes for clinical concepts such as diseases, medications, allergies, and diagnoses. Examples of terminology standards are LOINC (Logical Observation Identifiers, Names and Codes) for laboratory results, SNOMED (Systematized Nomenclature of Medicine) for clinical terms, ICD (International Classification of Diseases) for diseases and ATC (Anatomical Therapeutic Chemical) codes for drugs.
- **Document standards**: to structure information in clinical documents. Examples are The Continuity of Care Record (CCR), the Virtual Medical Record (vMR) of HL7 to structure patient's data for decision support and the HL7 Clinical Document Architecture (CDA) r2 which specifications are subdivided according to the type of document to be developed (discharge letters, referrals, consultation notes and image or laboratory reports). The CDA semantics is based on the HL7 V3 RIM, the HL7 V3 methodology and controlled vocabularies. CDA documents have a header and a body. The header set the context of the document for management and communication purposes. The body of the document may be unstructured (NonXMLBody) which could contain any content or structured (StructuredBody) which contains coded sections and the narrative block. In the header are distinguished the various participants (author, authenticator, performer, custodian and subject of the performance). The body may also contain external attachments.
- **Conceptual standards**: provide a framework to model and describe clinical data and the surrounding context. For example the HL7 Reference Information Model. The reference model is used by all local applications to map their structures in order to successfully communicate with other local applications.
- **Architecture standards for web services and exchange of clinical documents**: to define the processes involved in data distribution and storage. Examples include the standards developed within the Healthcare Services Specification Project described in the next paragraph.

3.2.2 Healthcare Services Specification Project (HSSP)

The Healthcare Services Specification Project (HSSP) was formed in 2005 within a collaboration among Health Level Seven and the Object Management Group standards groups [60]. The objective of the HSSP project is to produce standards that define the services' interfaces, functions and behavior supportive of the healthcare sector based on SOA principles. HSSP aims at the standardization of services involved in health processes, facilitating the development of a set of standard interfaces. The HSSP standardization cycle produces two specific levels of service: Service Functional Model (SFM), managed by HL7 International and the Service Technical Model (STM), managed by OMG. The SFM is a specification of the functionality of a service; it does not specify any technology or platform because it is implementation-independent. The "business capabilities" and "profiles" sections provide the core normative service description. Each business capability describes a specific action that the service must perform, resulting in one or more operations. A set of profiles are defined to cover specific functions (functional profile), semantic information (semantic profile) and overall conformance (conformance profile). The functional profile consists of a list of all the operations defined within the service; the sematic profile defines the meaning of the entities and their properties, and could provide cross-references to the RIM based domain models; the conformance profile is a machine testable specification of all conformance issues. As displayed in the diagram in figure 3.1, after the development of a Service Functional Model, the next step is the adoption of the SFM as a Draft Standard for Trial Use. To be adopted as a draft standard, the HL7 specification has to be presented to the HL7 national membership for the ballots. After the adoption of an SFM as an HL7 draft standard, a Request for Proposals (RFPs) for a technology-neutral Platform Independent Model and one or more technology-specific Platform Specific Models for the service are generated under the supervision of OMG group. The final step is the revision of the adopted standards based on real implementations. Presently, there are some HSSP products for which SFM and STM has been developed.

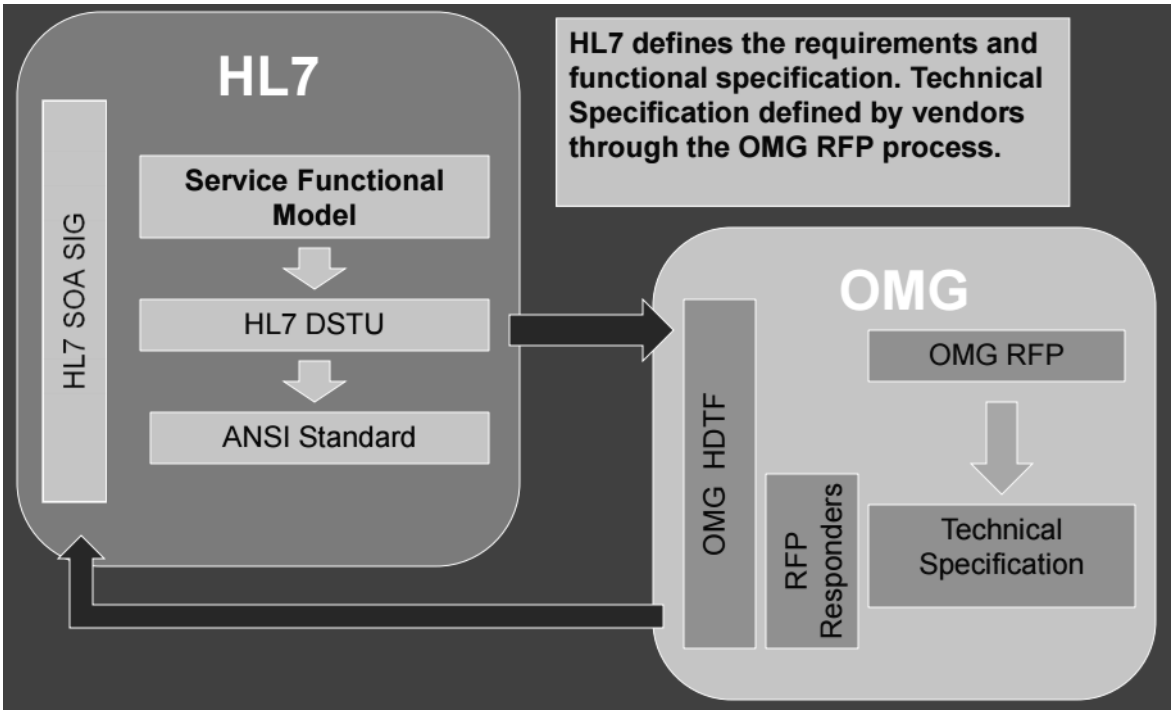


Figure 3.1: HSSP standardization cycle. Two specific levels of service are defined: the Service Functional Model (SFM) is managed by HL7 International and the Service Technical Model (STM) is managed by OMG group.

3.2.2.1 Identification and Cross-Reference Service (IXS)

The Identification Service (IS) also known as the Identification and Cross-Reference Service (IXS), manages the identifying information for different kind of entities, such as people, organizations, devices and others. It provides means for managing, defining and updating identities and systems that share a standards interface to maintain a common description of each entity. The Service Functional Model specifications refer mainly to patients as entity, because it is the most common entity that generates problem to a wide audience, but similar functionalities and scenarios are relevant also to other types of entities. The main problem on which this standard is focused is the merging of all the identification codes (IDs) that are assigned to a person by each healthcare facility during lifetime. Having a standard for the process of identification of a patient considerably improves the quality of care.

3.2.2.2 Retrieve, Locate, Update Service (RLUS)

The Retrieve, Locate, Update Service Release 1 (RLUS) provides means for interacting with a system that exposes the data of interest, providing a standardized way of location, update, and retrieval of that content. RLUS objective is the definition of service interfaces for the creation, registration, update, search, discovery, retrieval and query of clinical and

health resources. The main operations involved are to locate, get, list, put, initialize and discard resources.

3.2.2.3 Decision Support Service (DSS)

The Decision Support Service Release 1 (DSS) is a service that provides decision support to clinicians based on real-time patients' data. Decision support systems could be highly effective and improve clinical practice. A DSS contains many "knowledge modules", which are able to drive machine-interpretable conclusions about a patient basing on his data. When requesting for evaluation, the client specifies the knowledge modules to be used, and provides the patient's data that are required by the knowledge modules. The DSS returns the evaluation made on the patient in a format that is pre-defined for the used knowledge modules.

3.2.2.4 Common Terminology Services Release 2 (CTS2)

The Common Terminology Services Release 2 (CTS2) is a terminology service that should provide a standardize interface for the usage and the maintenance of terminologies. The service interface allows the query, definition and modification of the different terminology components, establishing a common model. It specifies the interactions between terminology providers and consumers, managing revisions, corrections and extensions through versioning.

3.2.3 Knowledge representation in CDSS

The CDSS relies on the data stored in a database to drive conclusions about a patient's problem basing on a knowledge base. The type of logic to be used derives from the kind of knowledge base implied. Ruled-based CDSS use some knowledge acquisition tool that facilitate the creation and maintenance of a knowledge base made of condition–action rule templates [11].

The knowledge used as basis for decision support should have an adequate scientific evidence, and any deficiency in the quality or relevance of it could affect the CDSS effectiveness. Therefore, knowledge basis should be extracted from the research literature, guidelines and up-to-date practice-based sources [12]. Once extracted from the most appropriate sources, most frequently from clinical guidelines, knowledge has to be made easily accessible in machine interpretable format to be computationally digested by the

software. A knowledge management system is therefore needed to extract, maintain, update and share computer interpretable evidence-based knowledge.

3.2.3.1 Computer interpretable clinical guidelines

Clinical Practical Guidelines are "systematically developed statements that can be used to assess the appropriateness of specific health care decisions, services, and outcomes", as defined in 1990 by the Institute of Medicine [61].

According to [62] clinical guidelines should accomplish 5 tasks:

1. Making of decision: one of the main purposes of the clinical guidelines is the support to be provided to physicians in making a decision
2. Sequencing of actions, that is to support the structuring of actions and decisions and, therefore, suggest the temporal order of the actions or the possible sequence
3. Setting of goals: indicates the ability of the physician to identify, through the guideline, the goals to be pursued in applying a specific treatment to a clinical case
4. Interpretation of data: the application of a guideline to an individual always requires customization of the abstract and general concepts described
5. Refinement of actions.

These five tasks are interdependent, and the links among them are represented in figure 3.2: the continuous line arrows indicate the sequence of actions and decisions, the arrows in dashed line indicate the choice between different alternatives, while the rounded arrows indicate data flow.

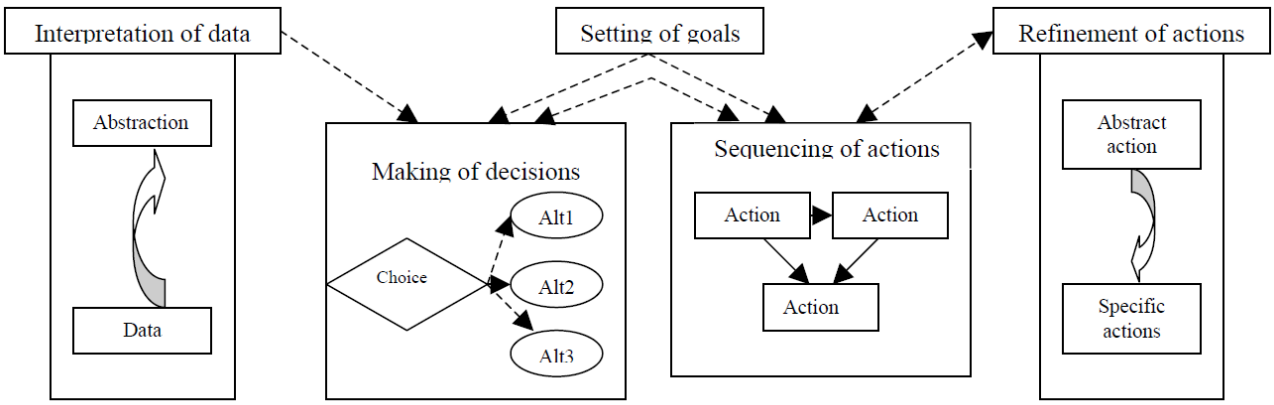


Figure 3.2: Schema representing the five tasks that a clinical guideline have to accomplish. These five tasks are interdependent: the continuous line arrows indicate the sequence of actions and decisions, the arrows in dashed line indicate the choice between different alternatives, while the rounded arrows indicate data flow.

Computer-interpretable clinical practice guidelines (CIGs) are text-based clinical guidelines converted to machine executable CDSS rules through the use of a guideline representation model. Guideline representation models are representation languages and frameworks that can be used to model guidelines and protocols in a computer interpretable and executable format. Different kind of guideline representation models have been developed in the last decades, as represented in figure 3.3.

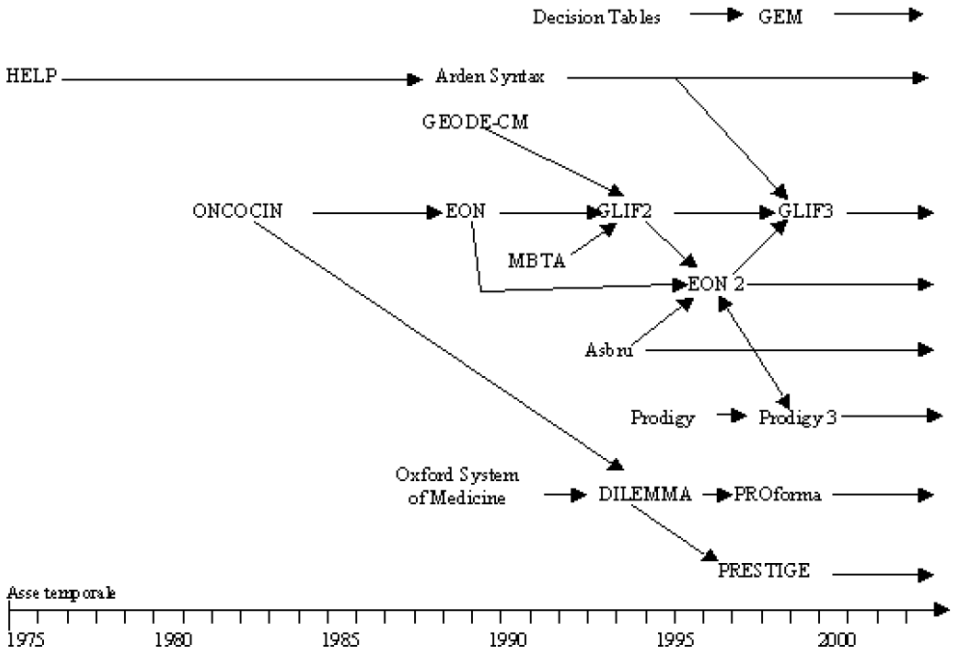


Figure 3.3 Time evolution and conceptual links between the different guideline representation models

The guideline representation models mentioned in figure 3.3 are designed for the same goal, and they have many common points, but each of them has a different approach.

In the following paragraphs, a brief description of the most popular guideline representation models is reported.

3.2.3.1.1 Arden Syntax

The Arden Syntax for Medical Logic Modules (MLM) is a language for encoding medical knowledge bases that consist of independent modules [63]. A MLM is a software module that, when implemented on a clinical information system works on a database and provides warnings and alerts for physicians. The purpose of an MLM is to provide the knowledge required to start an action on data available in a database. An MLM is an ASCII file with the slots grouped into three categories: maintenance, library and knowledge. The maintenance slot defines the name, author, origin, version, and the validation information.

The library slot defines the connections with other sources of knowledge, comments, and keywords for searching. The slot knowledge, which is the substance of MLM, contains the current medical knowledge.

The Arden Syntax adopts a procedural paradigm, in which each independent module does not provide a list of facts, but it contains the necessary procedures to recover, filter and analyze data, make a decision or carry out a specific action. The procedural modules, therefore, do not indicate what to do but how to do it. The Arden Syntax uses a frame made in blocks, without the use of loops and therefore the structure to be used is the classic if-then-else. The data types are those fundamentals of the most common programming languages, such as integer, real, char, pointers, strings, arrays and lists. Lists cannot be nested. A key assumption is that the data come from an existing electronic clinical database, without interactive input.

3.2.3.1.2 GLIF

"The Guideline Interchange Format (GLIF) was created by the InterMed collaboration, a joint project of biomedical informatics groups at Harvard, Columbia, and Stanford universities, to serve as a common representation format for CIGs" .[64]. The researchers analyzed the implementation of MLM Arden Syntax, and other previous systems in order to seek what were the possible common characteristics and to analyze those that best correspond to the optimization criteria. The first version of GLIF was rather limited and it was not widely disseminated.

GLIF2 [65] was designed to support guideline modelling as a flowchart of structured steps which represented clinical actions and decisions. GLIF2 was published in 1998 and consists of two main parts: a model to GLIF objects and GLIF syntax.

The GLIF2 model allows specification of a guideline as a flowchart of steps ordered temporally. The steps represent actions or clinical decisions and, at the same time, ramifications and synchronization steps are used. There are four types of steps:

1. Action steps: specify clinical actions that has to be undergone during the care process
2. Decision steps: could be conditions or branches
3. Conditional steps: contains a condition, or criterion, which is a logical statement that may be evaluated to true or false

4. Branch steps: direct flow to multiple guideline steps

GLIF2 presents a few limitations, for example some important attributes do not have a structured representation and some concepts and flow-control constructs are missing.

GLIF3 is the last revision that overcomes the previous difficulties. In particular, object-oriented expressions and query language were added and the flow-control was improved [64]. The GLIF3 model consists of classes, their attributes, and the relationships among the classes, all of which are necessary to model clinical guidelines.

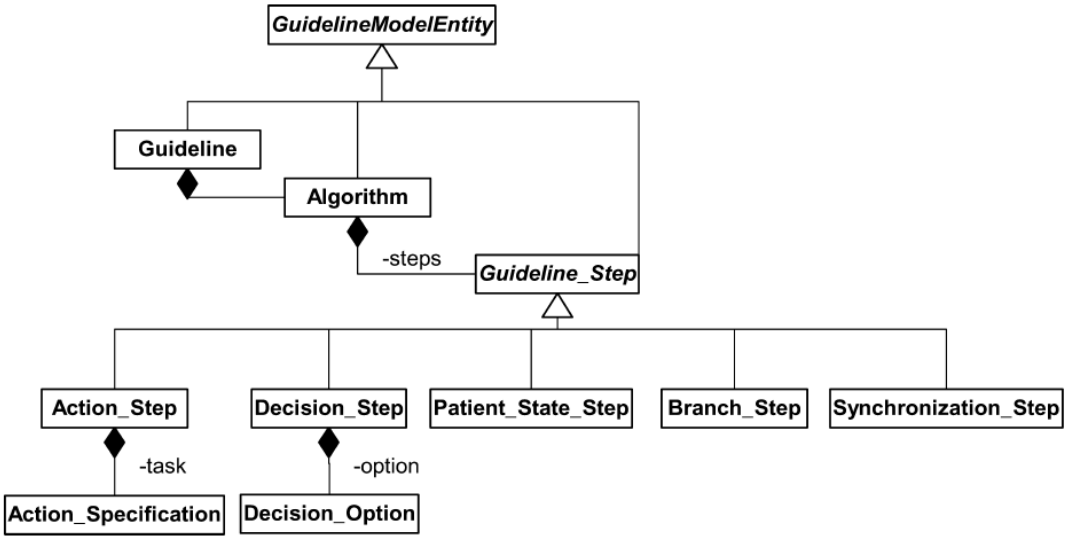


Figure 3.4: A high-level view of the major classes in GLIF. The lines between the classes denote relationships: a diamond-shape arrowhead indicates an aggregation or containment relationship, and a triangle shape indicates inheritance.

GLIF3 supports representing clinical guidelines in three levels of abstraction:

1. Conceptual level: the guideline is represented as a flowchart.
2. Computable level: completeness and logical consistency of the guideline can be checked. The expression syntax, the medical actions and the algorithm flow are defined.
3. Implementable level: the guideline is ready to be incorporated within environments of institutional information systems.

Action and decision classes of the GLIF ontology reference patient data items and medical concepts. These concepts are formally defined by standard controlled vocabularies (e.g., UMLS, LOINC, SNOMED CT) and standard medical data models. A reference information model defines the basic data model for representing medical information and

it is essential for guideline execution and data sharing among different applications and different institutions. The default reference information model that GLIF3 supports is HL7's Reference Information Model (RIM) version 1. Core GLIF defines how medical data items are structured and how they relate to medical concepts.

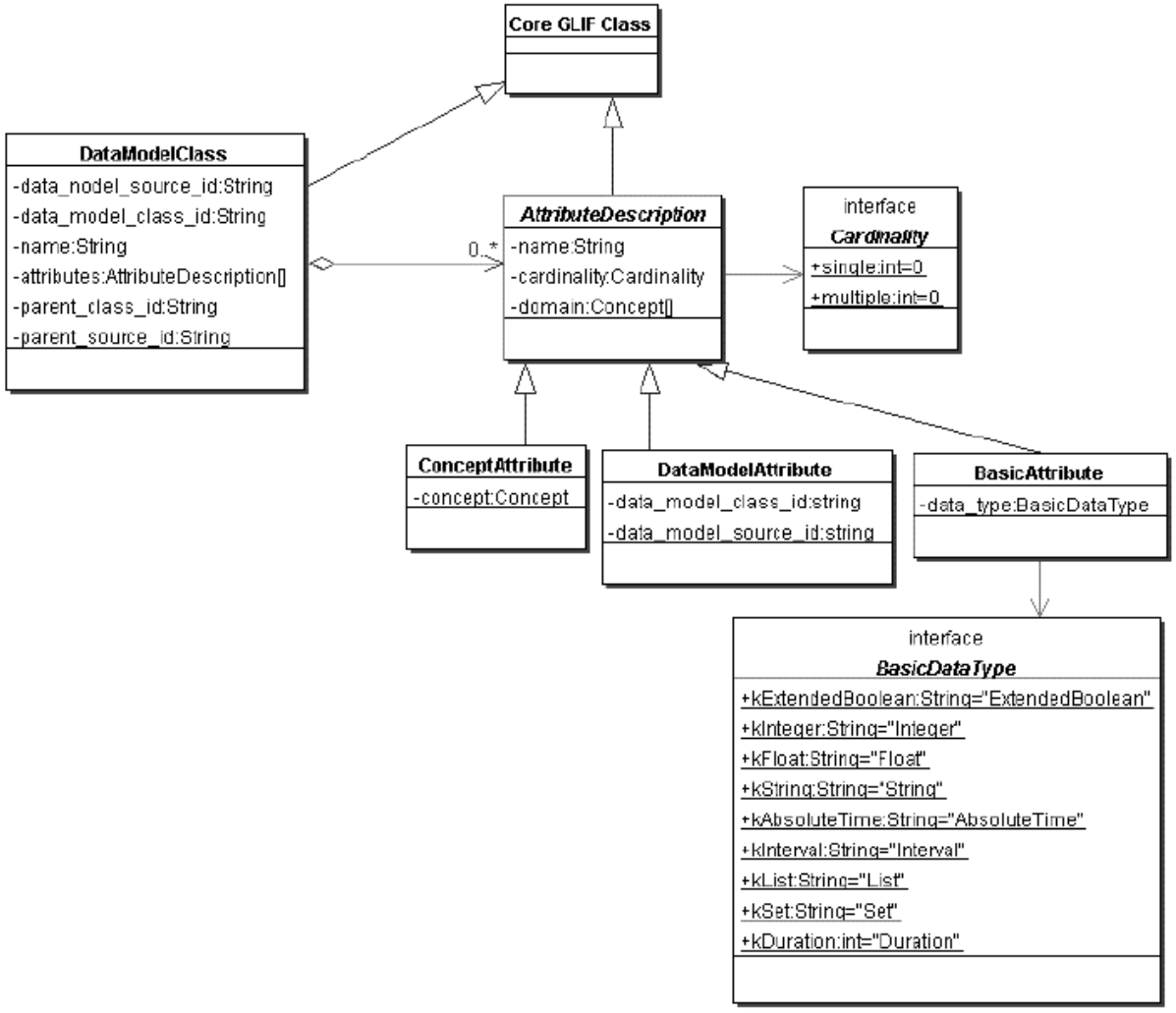


Figure 3.5: Core GLIF class diagram

The Guideline class of GLIF ontology is used to model clinical guidelines and sub-guidelines. GLIF's guideline class specifies the algorithm, which is a flowchart of guideline steps, maintenance information such as author, guideline status, last modification date, and version. The intention of the guideline, the eligibility criteria, didactics, and the set of exceptions that interrupt the normal flow of execution are specified too. The guideline also defines patient data items that are accessed by it and parameters that the guideline passes in and out to other sub-guidelines. Figure 3.6 reports all this information.

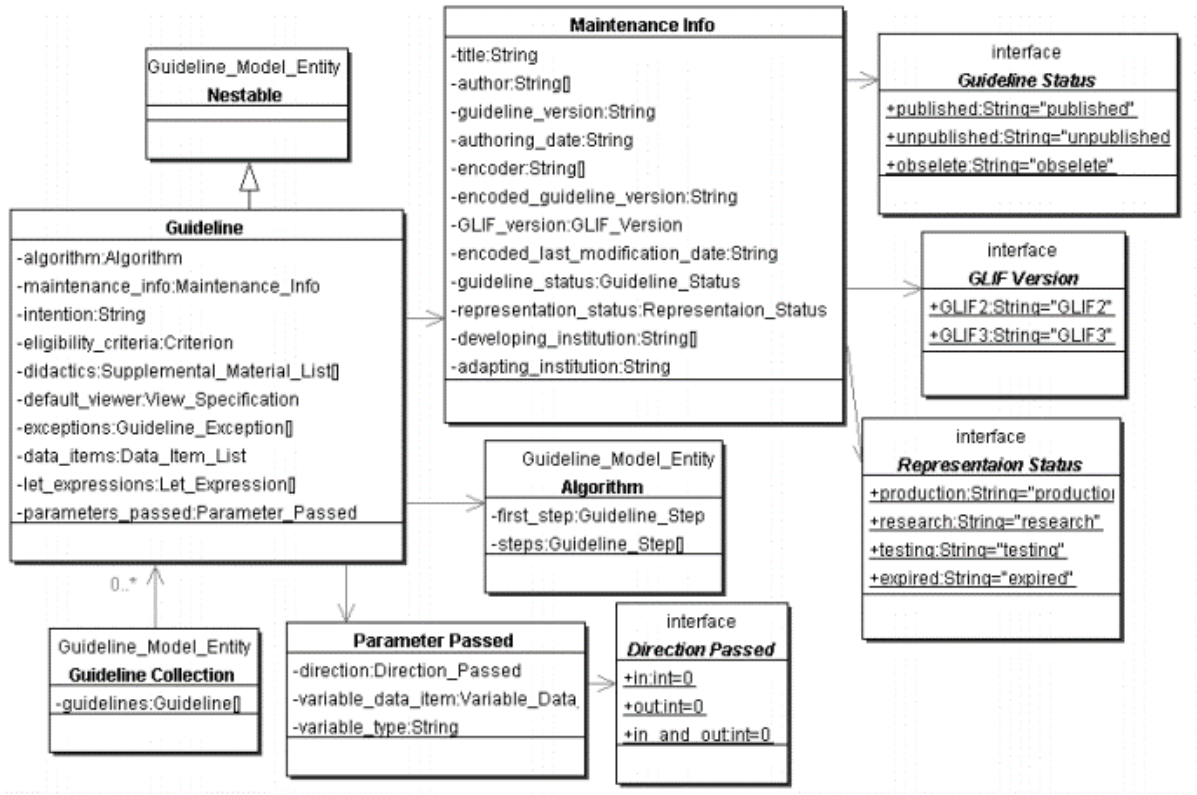


Figure 3.6: The GLIF guideline package

3.2.3.1.3 ASBRU

Asbru has been developed by the Asgaard project led by the Vienna University of Technology and Stanford Medical Informatics and it was first introduced in 1998. Asbru is a task-specific and intention-based language to represent clinical guidelines as time-oriented skeletal plans [66]. Skeletal plans provide a powerful way to re-use existing domain-specific procedural knowledge. Clinical guidelines can be seen as a set of schematic plans for the treatment of patients who have a peculiar clinical condition. In Asbru, the following parts of a plan can be specified: preferences, intentions, conditions, effects, and plan body (actions). Plans might be executed in sequence, or in parallel (all of

them or some), or in a particular order, or periodically. Explicit intentions and preferences can be stated for each plan separately.

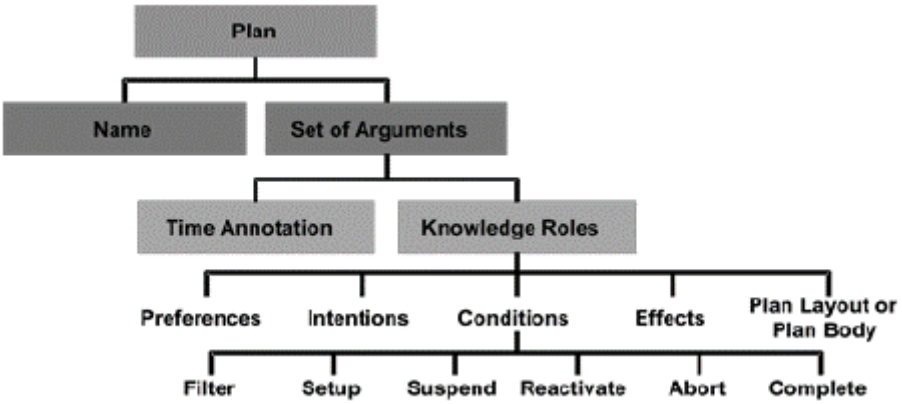


Figure 3.7: The Asbru plan ontology structure

3.2.3.1.4 GEM

The Guideline Elements Model (GEM) is an XML- based guideline document model that can store and organize the information contained in practice guidelines. GEM offers a translation of documents, written in natural language, in a computer-processable format. GEM is structured in a hierarchy with more than 100 elements with 10 major branches: Identity, Developer, Purpose, Intended Audience, Target Population, Method of Development, Testing, Revison Plan, Implementation Plan, and Knowledge Components.

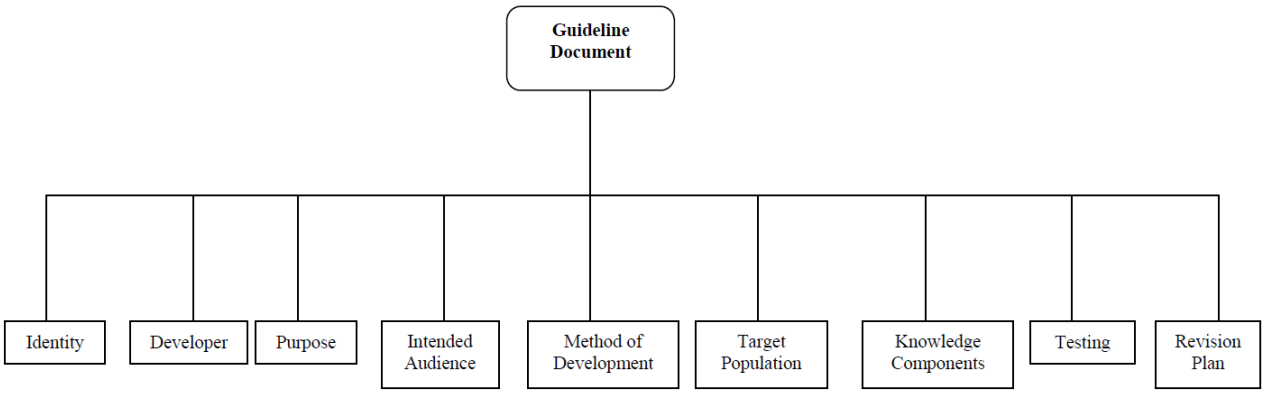


Figure 3.8: GEM hierarchy structure

3.2.3.1.5 PROforma

The PROforma System, designed by Fox in 1998, to represent Guideline, using a logic-based approach. The Guidelines are modeled in terms of an ontology task (task, action), consisting of decisions, actions, inquiries and plans, which, in turn, can be further decomposed into more detailed tasks. All the PROforma system tasks have the following

attributes: trigger, goal, precondition and postcondition. Tasks are described by their scheduling constraints (list of limitations), preconditions and postconditions. A task manager that performs a task can write new facts from a global database, and then perform the activation of other tasks, through evaluation of their preconditions. Any number of tasks can be activated simultaneously.

3.2.3.1.6 GELLO

GELLO is a standard object oriented query and expression language for clinical decision support [67]. It is a language to write expressions and make queries on medical data. GELLO expressions can be shared among institutions with different systems without the need of rewriting. GELLO programs refers to an environment that contains a list of predefined classes which can be used with their properties and methods (attributes and operations).In general, the data model supplied to the GELLO program will have a number of classes which represent components of the data model.

GELLO expressions can be embedded at any point where decision rules, eligibility criteria, patient state specifications or guidelines are needed. For example, decision points in the GLIF flowchart run automatically by using GELLO to evaluate computable decision criteria on patient's loaded data. GELLO is compatible with the Reference Information Model RIM of HL7.

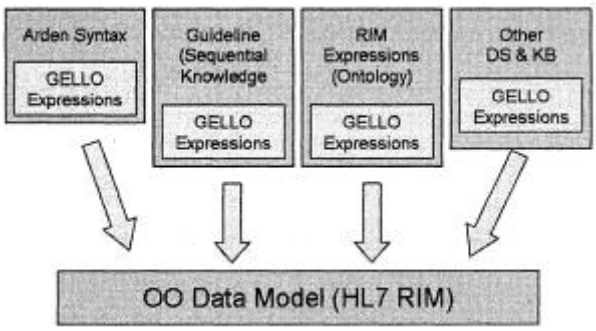


Figure 3.9: GELLO and its relation to Arden Syntax, GLIF, RIM and other DSs and KBs. GELLO query and expression languages can be embedded into various tools to provide the mechanisms for access and manipulation of Object Oriented data.

There are two phases in embedding GELLO code into decision support system: the pre-execution phase, which consists in parsing and compiling, and the execution phase, which consists in requesting and evaluating patient's data. The execution phase consists of three steps, which are reported in figure 3.10. In the first step, GELLO expression is considered.

If it is an evaluation then it goes to step three, while if it is a request of patient's data it goes to step two. In the second step, the expression is an internal call to the DBMS requesting information about a patient. The DBMS is an intermediary database compatible with HL7 RIM (such as vMR) that handles the request, retrieves the information and returns it to the application. Ad-hoc mapping software extracts data from the institution database and stores it into the DBMS. Institution's databases where patients' data are stored are organized in specific ways that may not be compatible with other institution's data organization. In the third step, if all needed information is available, the engine evaluates the expression and returns the result to the application.

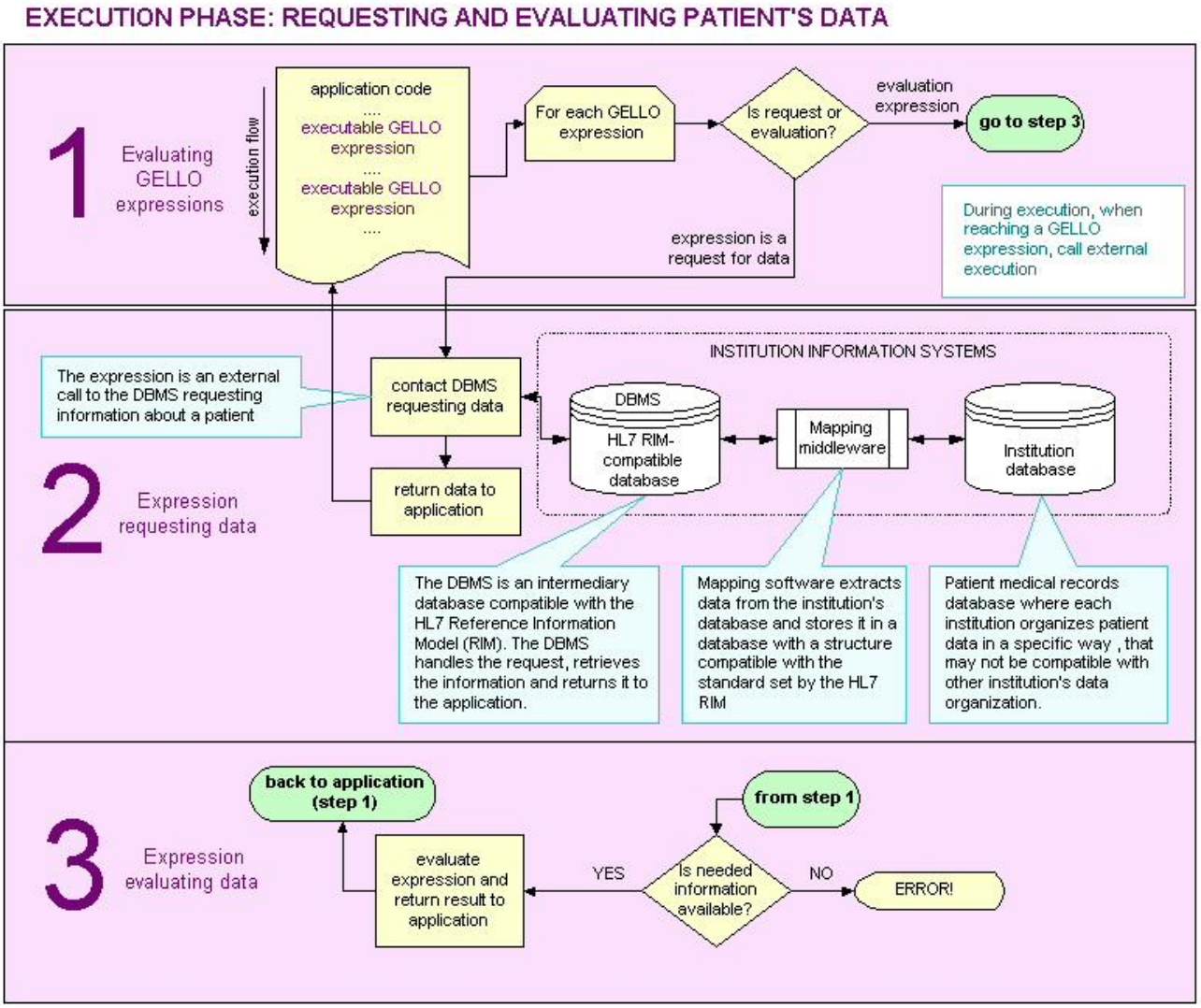


Figure 3.10: The execution phase of GELLO consists into three steps: evaluating GELLO expressions, requesting data and evaluating data.

3.2.3.2 Lifecycle

To be effective, clinical guidelines have to be integrated into the clinical workflow, to assist physicians in real time providing patient specific advices. Clinical guidelines are inferred by a systematic review of the evidence coming from the results of the most recent clinical trials. The lifecycle of the computer interpretable guideline shall consider the periodic revision of the related clinical guideline, as the requirements change over time because new information sources become available and new experience is gained. According to Mor Peleg [68] the lifecycle of the development of clinical computer interpretable guidelines passes by three phases "Analysis and design", "Deployment and usage" and "Maintenance" which in total consist of eight steps:

1. Definition of modelling language
2. Knowledge acquisition and specification
3. Integration of computer interpretable guideline into EHR
4. Validation and verification (the testing phase is usually supported by execution engines)
5. Use of computer interpretable guidelines in CDSS to deliver decision support
6. Exception handling
7. Maintenance
8. Sharing

In figure 3.11 the interconnections between these steps are presented.

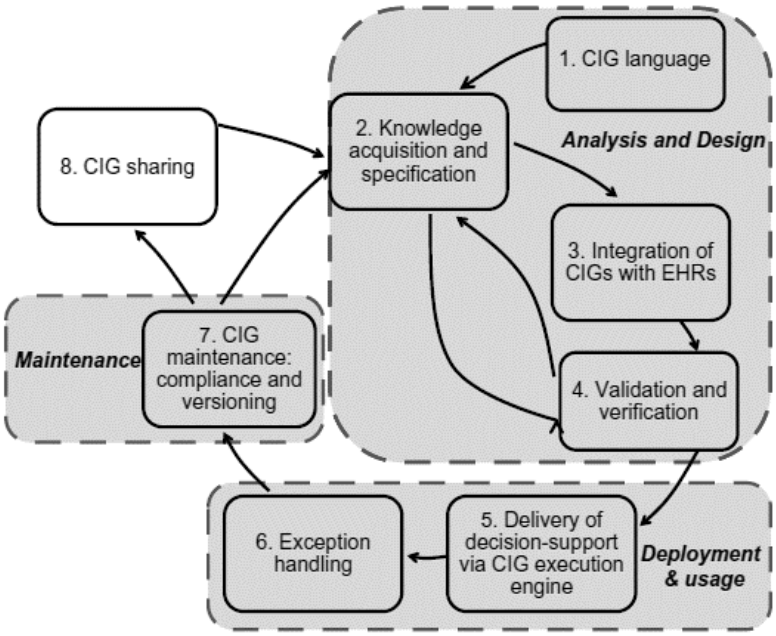


Figure 3.11: Clinical guidelines lifecycle

The representations of clinical practice guidelines can be classified into three categories: document models, decision trees and probabilistic models, and task-network models [68]. The Guideline Elements Model is the best known example of the first category, and it is an XML-based knowledge model for guideline documents. Guideline representation that belongs to the second category represents the guideline's algorithmic knowledge as a decision tree, which is a graph that uses a branching method to illustrate every possible outcome of a decision, sometimes applying a probabilistic model. The third category allows to execute the represented knowledge against patient data by means of an execution engine. A variety of task-network languages have been developed such as GLIF and PROforma.

The critical phase is the development and usage phase. The development of computer interpretable guidelines is facilitated by the use of a guideline editor. Some guideline editors have been realized to facilitate the process of describing clinical guidelines by means of a graphical interface using flow charts to describe the logical sequence of action and rules. Guideline editors translate the flow charts edited by the users into a hidden code usually in a standard language as XML, since standard format enables to better share the clinical knowledge embedded within guidelines. RetroGuide [69] is an analytical framework that has a graphical flowchart and a hidden code layer. Also users with low computer skills can design flowcharts. The code is hidden behind the nodes and arrows of the flowchart and points to EHR data through references to modular applications. Together

Workflow Editor produces XML files based on the XPDL (XML Process Definition Language) specification, and supports every workflow engine that knows how to interpret standard XPDL, for example Together Workflow Server.

Before its release, the computer interpretable guidelines produced with the editor has to be successfully validated. The validation phase can be performed using an execution engine that interprets and executes the clinical guidelines created. Some editors have intrinsic guideline execution engine that allows to test the condition-action-rules described in the graphical interface on real data, also available in standard formats. This is the case of GLIF Editor that was developed by Medical-Objects. The GLIF Editor provides clinicians with an intuitive flowchart interface. Decision points in the GLIF Editor can run automatically by adding GELLO code to evaluate computable decision criteria by querying patient's data. In this way, queries and expressions share a common object-model because the results of queries are used in decision criteria and other expressions. GLIF Editor allows to test the guideline automatic decisions steps which encapsulate GELLO code by loading patient's test data in HL7 v2 format. Patients' data loaded are mapped according to the RIM model and can be accessed by GELLO code:

let Hb_code = factory.codedvalue('718-7','LN')

let Hb_obs = observation->select(code = Hb_code)->sortby(absolutetime)->last()

GELLO is the execution language of GLIF editor. The execution language is an important issue of the executable representation of guidelines to formalize expressions. According to Kolesa [70], an execution language consists of four sublanguages with different roles: the arithmetic expression sublanguage, the query sublanguage, the data manipulation sublanguage and the date related functions.

3.2.4 Standards for CDSS: HED initiative

Health eDecision (HeD) is an initiative of the Office of the National Coordinator‘s Standards & Interoperability Framework [23]. HeD does not aim to create a new standard, but its intent is to identify, define and harmonize already existing standards involved in clinical decision support field. The main standards considered are:

- **HL7 Virtual Medical Record (vMR)**, a data model for representing patient's data that are analyzed and/or produced by CDS engines

- **HL7 CDS Knowledge Artifact**, for knowledge artifact specifications
- **HSSP HL7 Decision Support Service (DSS)**

This initiative actually supports two general use cases. The first use case "CDS Artifact Sharing" is about knowledge artifact exchange and it specifies how to structure medical knowledge in a sharable and executable format. The second use case "CDS Guidance Service" relates to the exchange of information that allows the delivery of the results derived from the execution of clinical decision support, focusing on how a clinical decision support system receives data and returns conclusions and recommendations.

3.2.4.1 vMR

The virtual Medical Record is a standard for the representation of medical knowledge for CDS developed by the HL7 group. It is a RIM based data model that represents the data that are analyzed and/or produced by CDS engines, thus allowing interoperability between different CDS and medical data sources.

González-Ferrer et al. assert that the vMR model is bi-dimensional, in which one dimension represents the type of clinical information (Procedure, Observation, Problem, Substance Administration, Goal, Encounter) and a second one the workflow moment (Proposal, Order, Event) [71].

The vMR can be considered a simplified representation of the clinical record that is suitable for a CDS knowledge engine to directly manipulate in order to derive patient-specific assessments and recommendations. With respect to the CDA, it avoids multiple nesting of concepts. It uses a simplified version of the HL7 version 3 data types release 2, with a particular attention to the management of the null flavors. It employs a more intuitive representation of concepts, using alternate methods to express the concepts of mood codes, negation indicators and inversion indicators.

The vMR class diagram is represented in figure 3.12. Substantially, the vMR class can refer to a particular template, among those listed in the draft standard for trial use "HL7 Version 3 Standard: Virtual Medical Record for Clinical Decision Support (vMR-CDS) Templates, DSTU Release 1". The class vMR has an EvaluatedPerson type attribute, which is a Person (inherits from Person class) which, in turn, inherits from Entity class. The EvaluatedPerson can have an indefinite number of ClinicalStatement attributes. The ClinicalStatement class is a concrete class that can be used as it is or it can be specialized as needed into more

specific clinical statements, such as ObservationResult, SubstanceAdministrationEvent and Problem.

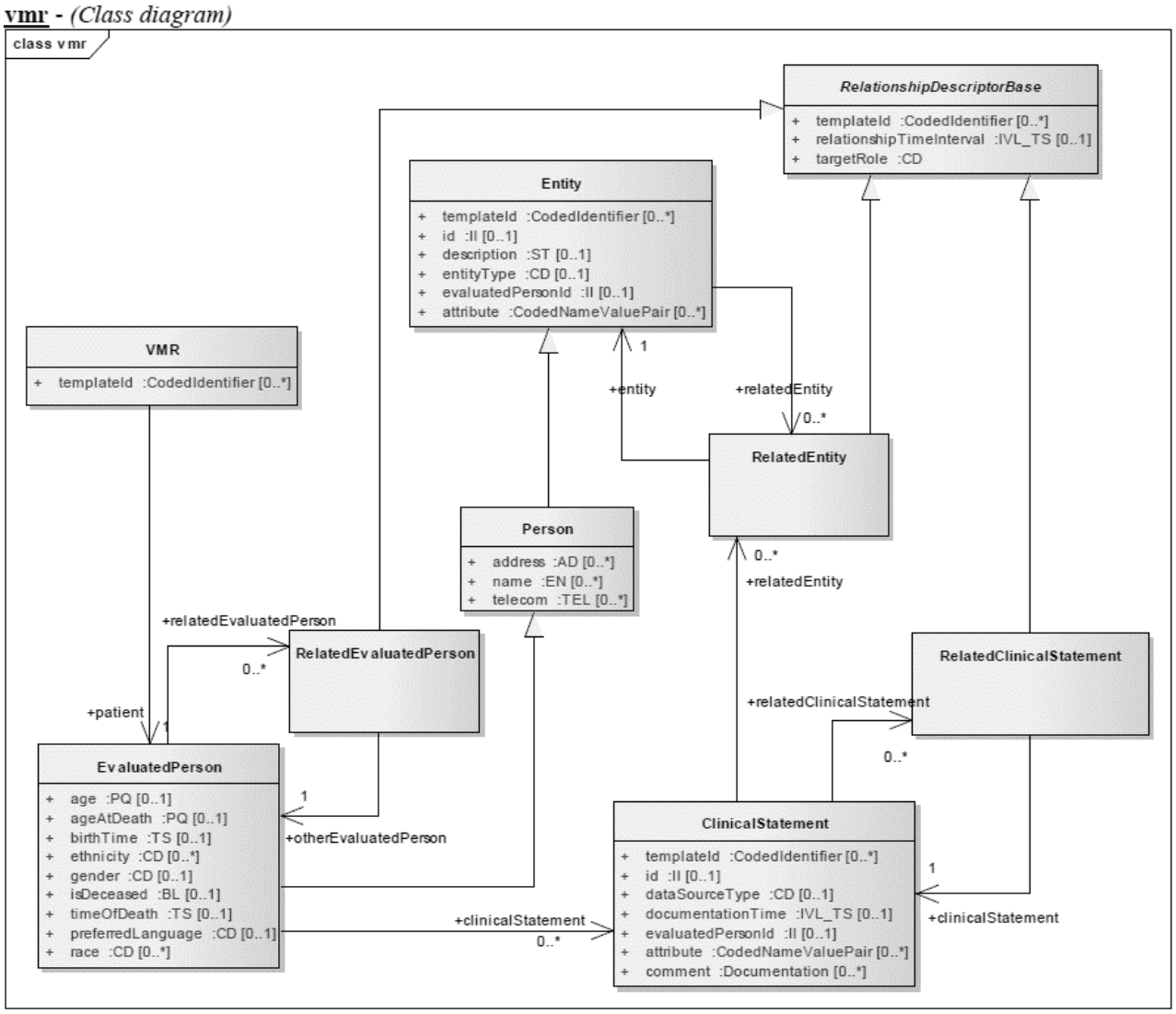


Figure 3.12: vMR class diagram

3.2.4.2 HSSP HL7 Decision Support Service (DSS)

A decision support service receives patient data as input and returns patient-specific conclusions as output. HL7 DSS is part the Healthcare Service Specification Project, as already mentioned in the HSSP paragraph. The DSS is a custodian of knowledge modules (KM); a knowledge module is a package of knowledge that can be applied to patient's data to derive conclusions about the patient under evaluation. The DSS is called by a client application, which specifies the knowledge module which is interested in, and supply the

related patient's data. In return, the DSS sends its conclusions in a specified format. Each knowledge module takes part in the related lifecycle according to its status. Status are:

- DRAFT: when a KM is created and can be modified. Every time the status changes to draft, a new version is created.
- DEFINED: the KM is in unit test.
- REJECTED: the KM has been tested unsuccessfully. A new draft is required.
- APPROVED: the KM has been tested successfully and can be deployed.
- PROMOTED: the KM has been deployed.
- RETIRED: the KM was deployed or approved but is no longer active.

The diagram in figure 3.13 represents the lifecycle.

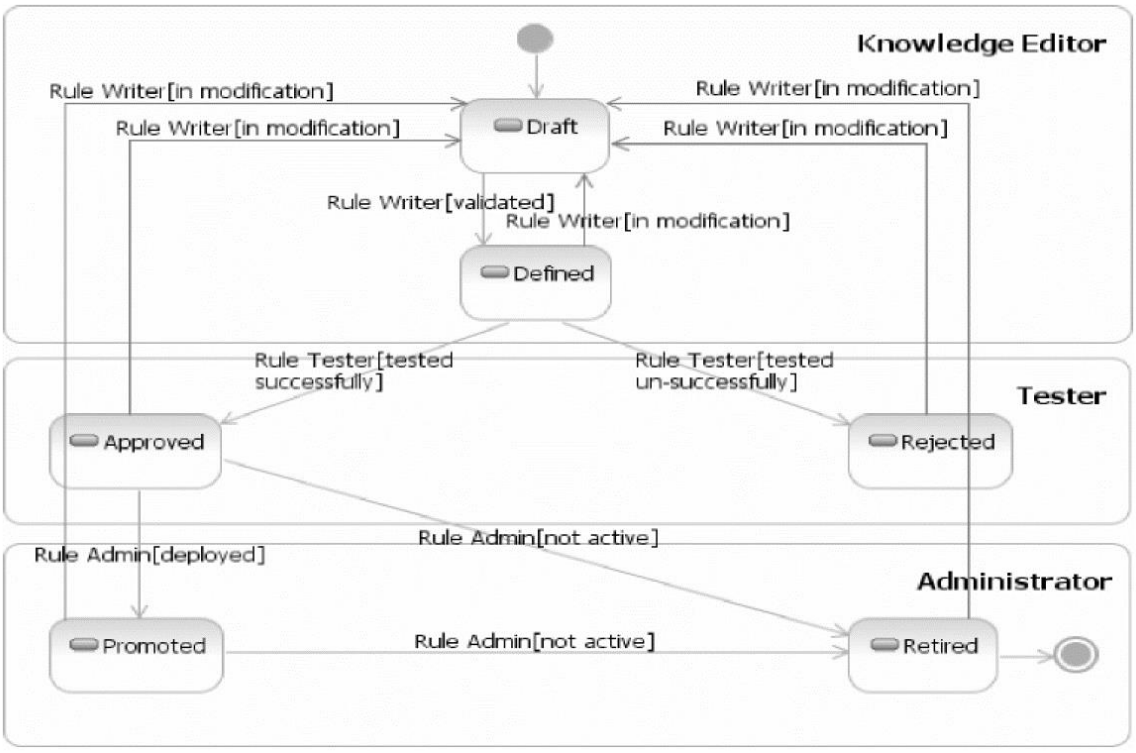


Figure 3.13: knowledge modules lifecycle

The DSS service is called by a client that requires a patient evaluation, specifying which knowledge modules to use. The logic sequence of calls are reported in the diagram in figure 3.14.

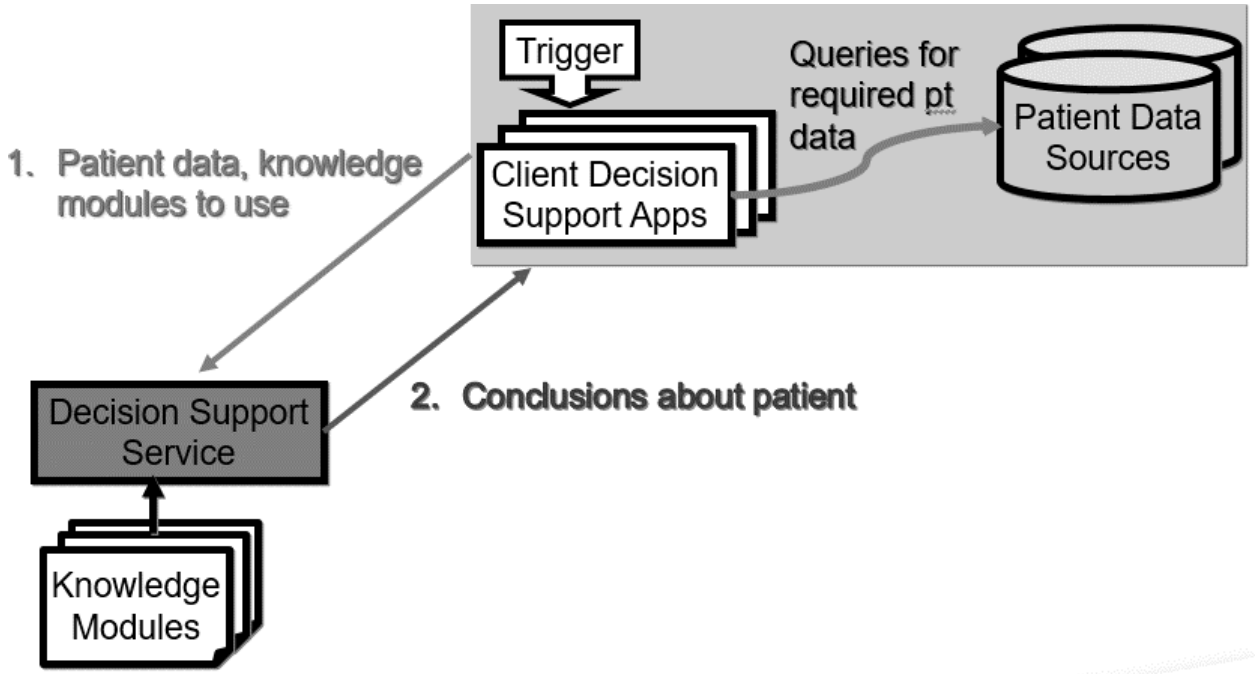


Figure 3.14: Logic sequence of calls to the DSS service

The normative provides a WSDL (Web Services Description Language) and associate XSD files that describe the Platform Specific Model (PSM) for SOAP XML Web services. The WSDL is a formal language in XML format used to describe the public interface of a web service. A WSDL document contains information about *operations* provided by the service, the communication *protocol* to use to access the service, the size of accepted messages for *input* and *output* returned by the service and related data, the constraints (*bindings*) of the service and the service endpoints which usually correspond to the addresses in URI format.

The DSS WSDL provides three endpoints: query, evaluation and metadata discovery.

Metadata discovery interface: allows a consumer to get the list of all the profiles supported by the DSS and then to use the other operations to identify the capabilities of the service.

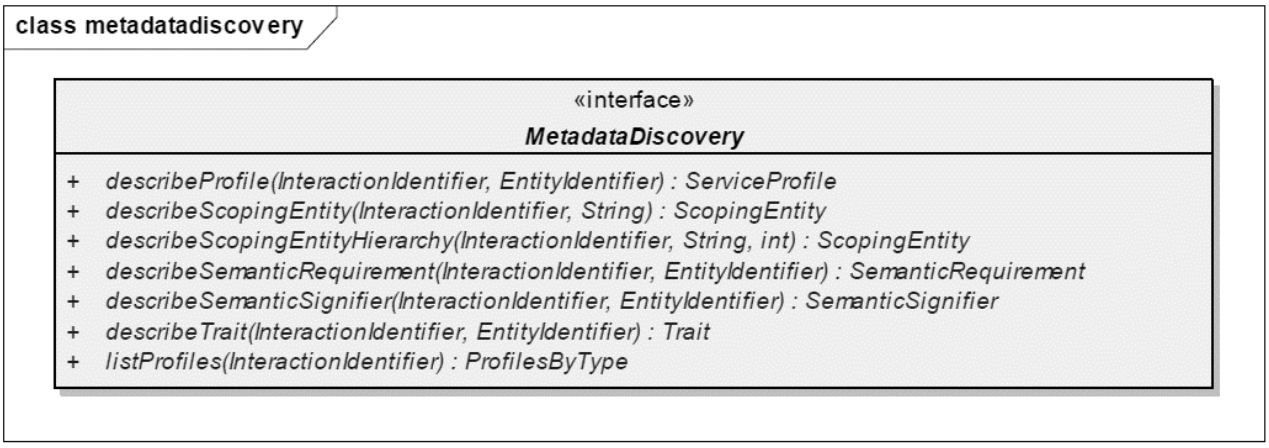


Figure 3.15: Operations defined in the MetadataDiscovery interface of DSS service

The query interface enables the characterization and discovery of all knowledge modules in the platform.

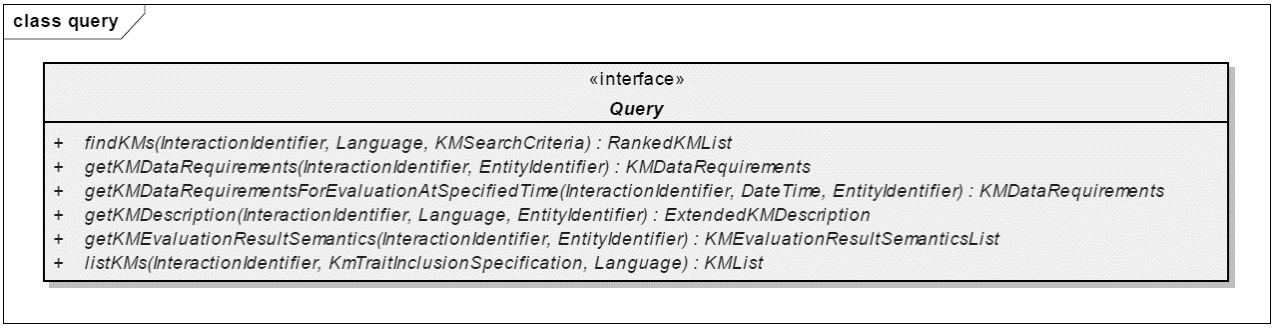


Figure 3.16: Operations defined in the Query interface of DSS service

The evaluation interface enables data evaluation using knowledge modules.

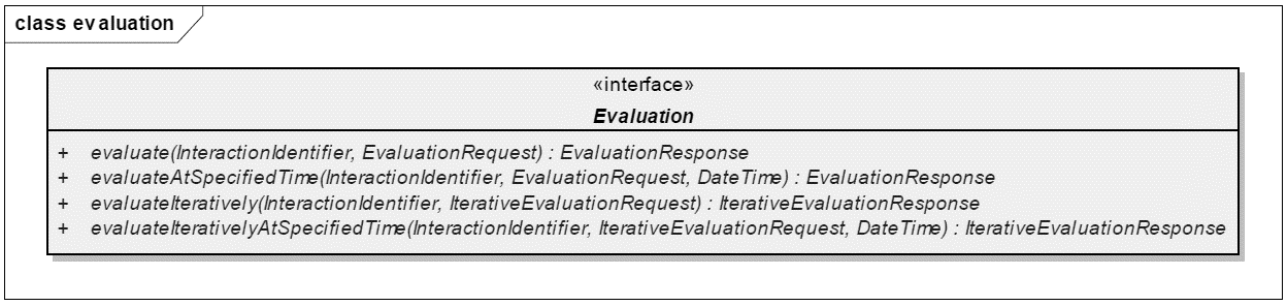


Figure 3.17: Operations defined in the Evaluation interface of DSS service

To ensure a minimum level of interoperability two functional profiles are defined in the normative [72]: HSSP Simple Evaluation DSS Functional Profile and HSSP Complete DSS Functional Profile. Figure 3.18 reports the operations supported by those functional profiles.

Operation	Supported by HSSP Simple Evaluation DSS Functional Profile	Supported by HSSP Complete DSS Functional Profile
describeProfile		X
describeScopingEntity		X
describeScopingEntityHierarchy		X
describeSemanticRequirement		X
describeSemanticSignifier		X
describeTrait		X
listProfiles		X
findKMs		X
getKMDataRequirements		X
getKMDataRequirementsForEvaluation AtSpecifiedTime		X
getKMDescription		X
getKMEvaluationResultSemantics		X
listKMs		X
evaluate	X	X
evaluateAtSpecifiedTime		X
evaluateIteratively		X
evaluateIterativelyAtSpecifiedTime		X

Figure 3.18: Operations supported by HSSP Simple Evaluation DSS Functional Profile and HSSP Complete DSS Functional Profile

In the normative, two separate WSDLs are provided to correspond with the two functional profiles.

Evaluate is the main operation of the DSS service. It takes a complex Evaluate type as input called evaluateRequest and returns a complex EvaluateResponse type object. The payload for the request is the clinical data that is evaluated by the DSS. The payload for the response is the guidance provided by the DSS. In both cases the data model that could be used is the vMR. Moreover, compliant DSS implementations shall use HL7 vMR templates as defined in [73] when an appropriate template is available.

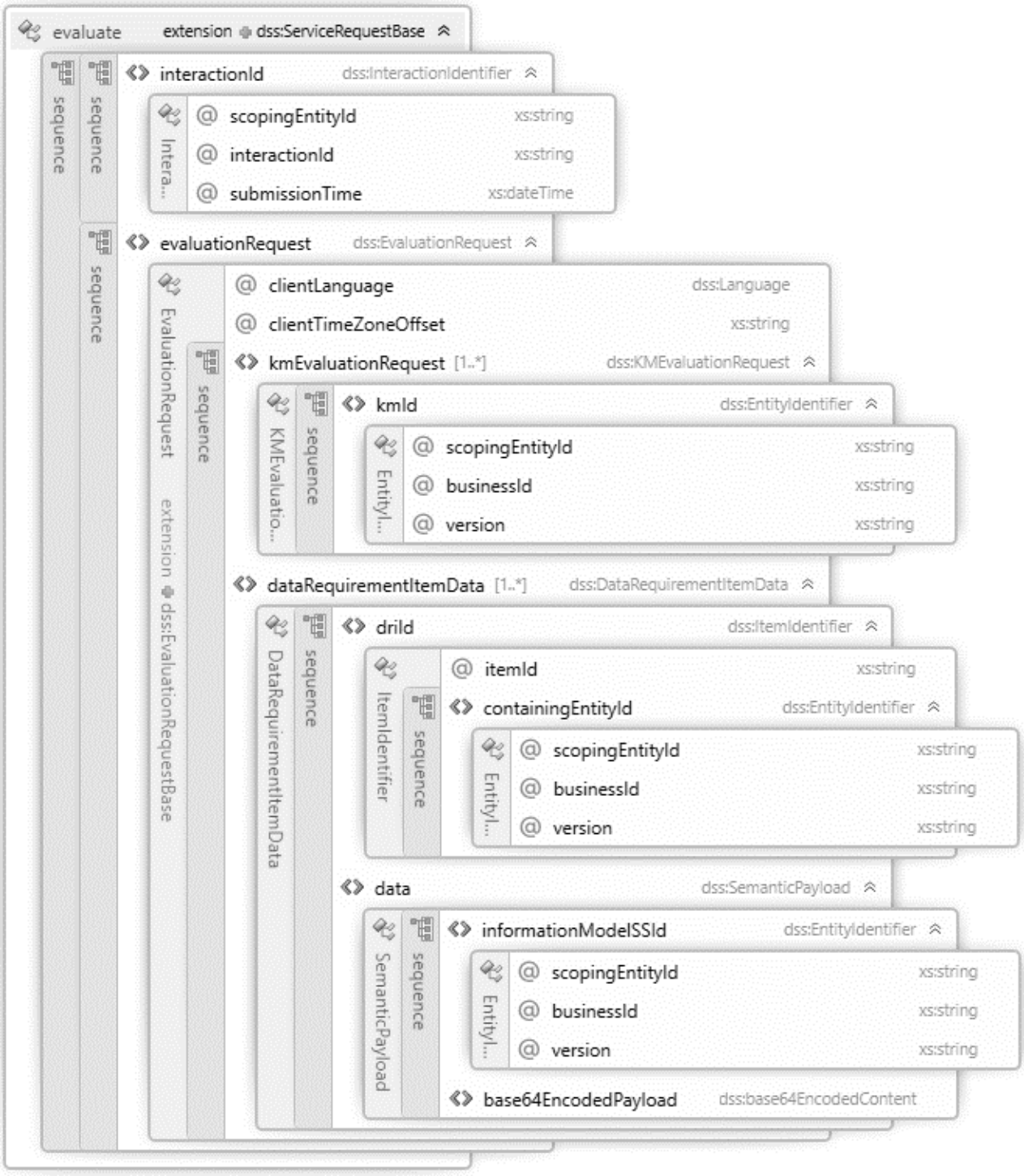


Figure 3.19: Evaluate is the complex type that is given as input to the Evaluate operation. The figure reports the Evaluate class composition.

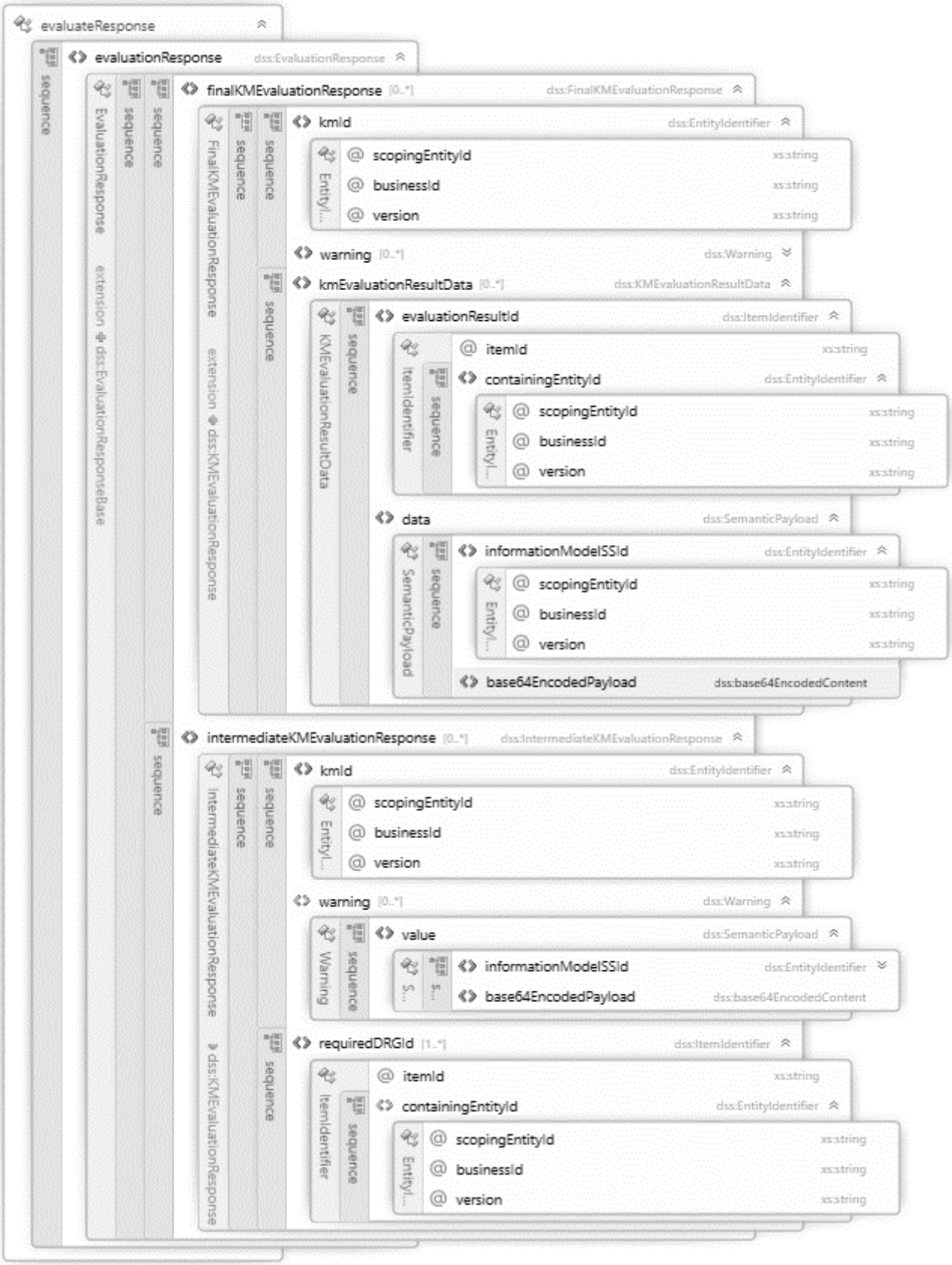


Figure 3.20: EvaluateResponse is the complex type that is returned by the Evaluate operation. The figure reports the EvaluateResponse class composition.

4 Results

My PhD project is inspired by the innovative idea of LHS. It could be seen as a composition of three layers, where each layer is developed above the previous one. The first one consists in the setting-up of a SOA-based architecture to enable data collection from sparse facilities into a single repository. This would allow medical institutions to share information without an increase in costs and without the direct involvement of users. The second layer uses the data collected from the healthcare institutions involved to perform multi centric clinical trials at regional and national level. The third layer relies on the knowledge acquired through the conduction of clinical trials, put together with clinical guidelines directions to drive decision support. The benefits of using a decision support system in clinical practice should affect the quality of the care delivered, thus closing the LHS cycle.

The architecture built allows the integration of many healthcare facilities into a larger system, ready to data sharing. In order to allow interoperability among different healthcare facilities, suitable medical informatics standards were applied to the system developed. Thanks to this system, real-time learning from patients' experience can be reached, because the system can achieve all historical data irrespective of their physical location.

It is evident how this system could be of peculiar importance in chronic diseases, where a significant amount of data is periodically collected and analyzed. Specifically, I put in practice this system in chronic infectious diseases data management in the Ligurian setting, where it is fundamental to enroll large number of patients in order to implement clinical trials.

In this and other domains, all the collected data will provide wide and scientifically valid samples that can then be used to infer knowledge, in order to support chronic care management and treatment decisions. The overall architecture of the system developed is displayed in figure 4.1.

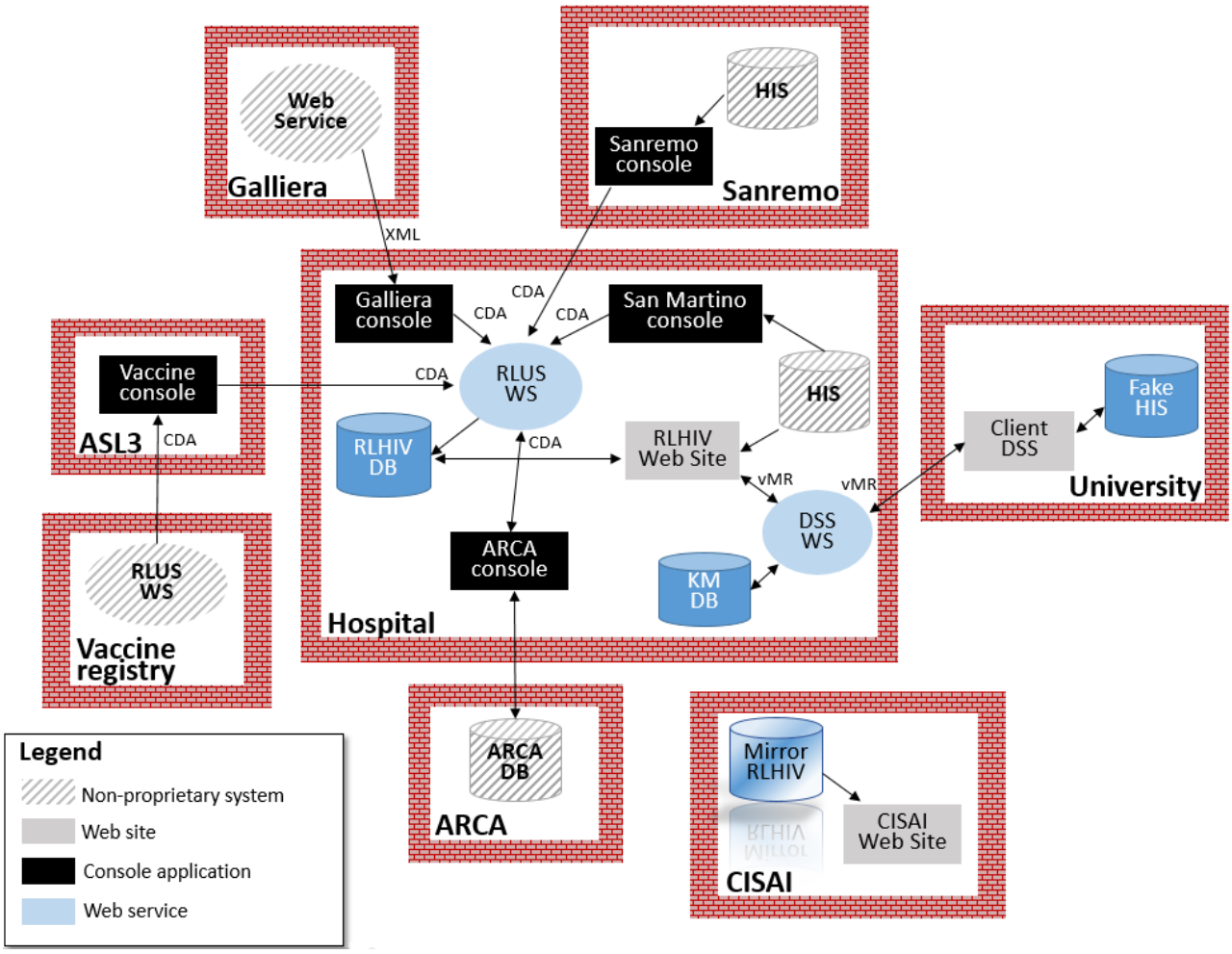


Figure 4.1: Recap of the architecture developed. The red-bricked squares represent the firewalls of hospitals and institutions involved. Non-proprietary systems are highlighetd with grey bars. The software applications developed within this project are of three types: Web Sites (in grey), Console Applications (in black) and Web Services (in lightblue). Single arrowheads represent monodirectional data-flow (read-only permissions), double arrowheads represent bidirectinoal data flow (read and write permissions). Details about the system developed and the communication among the components involved are explained in the next paragraphs.

4.1 First layer: automatic clinical data flow in the Ligurian HIV Network

The first layer of this project has seen the finalization of a prototype of interoperability at an intra-regional level through the development of an infrastructure based on standardized services starting from the LHN architecture.

The LHN was originally conceived as a mere web platform to enable the collection of data from HIV patients using a web interface, in order to perform multi-centric clinical trials at a regional level. For the first year, the platform was consistently used for its initial scope, supporting about half a dozen local studies. Routine use of the platform, together with the intention to address the well-known problem of errors due to manual data input into web interfaces, led to a consecutive gradual evolution of the system. The leading idea was that clinical data, already available in digital format in the LIS (Laboratory Information System) and other components of the Hospital Information System (HIS) could be extracted and automatically exported to the LHN database. In this way, patients' laboratory data could be updated daily without human intervention. For this purpose, the architecture developed supports a standardized and automatic transfer of data from hospitals EHRs towards a central repository. With this system, data collected in hospitals' EHRs can be electronically transferred to a single registry, thus eliminating double data entry and reducing the resources required for care centers to participate in single clinical trials.

This automatic data retrieve architecture currently involves the chronic infection diseases wards of three hospitals in Liguria, but thanks to standardization, it is ready to new enrollments. The achieved structure allows clinical data to be shared between the authorized healthcare facilities.

The adoption of standardized solutions allows interoperability among the healthcare facilities involved in the project. The current architecture is an implementation of the Healthcare Services Specification Project (HSSP) proposed by HL7 and OMG (Object Management Group) standard groups, which is based on SOA (Service Oriented Architecture) approach. HSSP Retrieve, Locate, and Update Service (RLUS), is used at present to manage patients' data; HSSP Common Terminology Services - Release 2 (CTS2) is currently under construction by some colleagues in the laboratory and, when

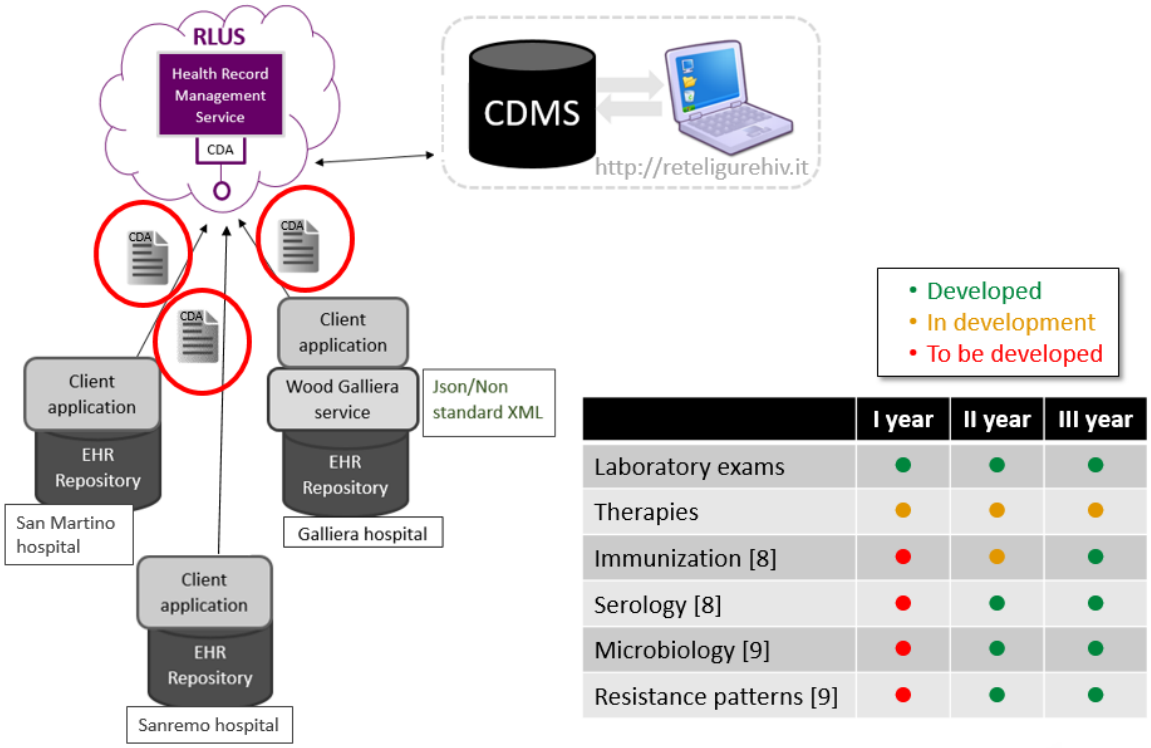
finished, it will be usefully integrated in the actual architecture to administrate the definition of semantics and syntax.

To manage patient administrative data, the Patient Topic within the Patient Administration domain of HL7 v3 was taken into account; in particular, information about patients was mapped through a "PRPA_MT201301UV.PRPA_MT201301UV02Patient" object. To share clinical data between the healthcare facilities the HL7 v3 Clinical Document Architecture R2 (CDA R2) standard was adopted.

To support semantic interoperability among different care facilities, waiting for the CTS2 service to be ready, a harmonization of hospital local terms was manually performed. In particular, the LOINC (Logical Observation Identifiers Names and Codes) vocabulary was adopted to translate laboratory terms. To univocally identify diseases the International Classifiers of Disease (ICD10) was used, as indicated by World Health Organization (WHO).

In order to connect the authorized Hospital Information Services (HIS) to this architecture, technically different client applications were implemented, because each hospital had different access policies. Specifically, each HIS adopted its own strategy to provide access to its content: through a web service or by direct access to the database.

In the first case, after authentication and authorization control, data were made available on demand in different formats (e.g. XML (eXtensible Markup Language), JSON (JavaScript Object Notation)). In the second case, the database administrator (DBA) created a specific user profile with reading permissions to access database or a restricted part of it, so that information could be directly extracted thought queries or store procedures. In this case, the client application needs to be installed within the hospital LAN (Local Area Network) for security policies.



	I year	II year	III year
Laboratory exams	●	●	●
Therapies	●	●	●
Immunization [8]	●	●	●
Serology [8]	●	●	●
Microbiology [9]	●	●	●
Resistance patterns [9]	●	●	●

Figure 4.2: Qualitative schema of the architecture developed to support automatic data collection from the LIS of the three hospitals involved. The table reports the list of the categories of clinical data extracted from LIS and the related year of PhD in which the single functionality was employed.

The Galliera Hospital offers several services to access patients' clinical data, including a data management service to access laboratory test results. After authentication, data are available on demand in XML or JSON proprietary format. On the other hand, IRCCS AOU San Martino IST and Sanremo hospitals do not share data through services, thus the only way to access data is to extract them directly from the LIS, installing the console application inside the hospital firewall.

During the second year, the network on which the learning health system is based has been widened: the automatic and daily updated flow of data have been enriched with microbiologic tests, antibiotic resistance tests to bacteria, serology data and immunization administration.

To monitor immunization administration, it is essential to collect data in a unique regional vaccine registry. However, in Liguria there is no such system. Each of the five local health units ASLs (Azienda Sanitaria Locale) relies on a different private company to manage immunization information. The “Ligurian Vaccination in HIV Project” was developed in collaboration with the Department of Health Sciences (DiSSal) for the monitoring of vaccination coverage in HIV population [74]. Vaccine administration data such as injection

date, typology and dose are extracted from the ASL vaccine registry, structured according to indications present in the immunization section of the HL7 CCD document and then recorded into the LHN.

The supervision of immunization coverage can be evaluated through the association between the immunization information and the antibody titers and serological data gathered from the hospitals' LIS. The process of data extracting is shown in figure 4.3.

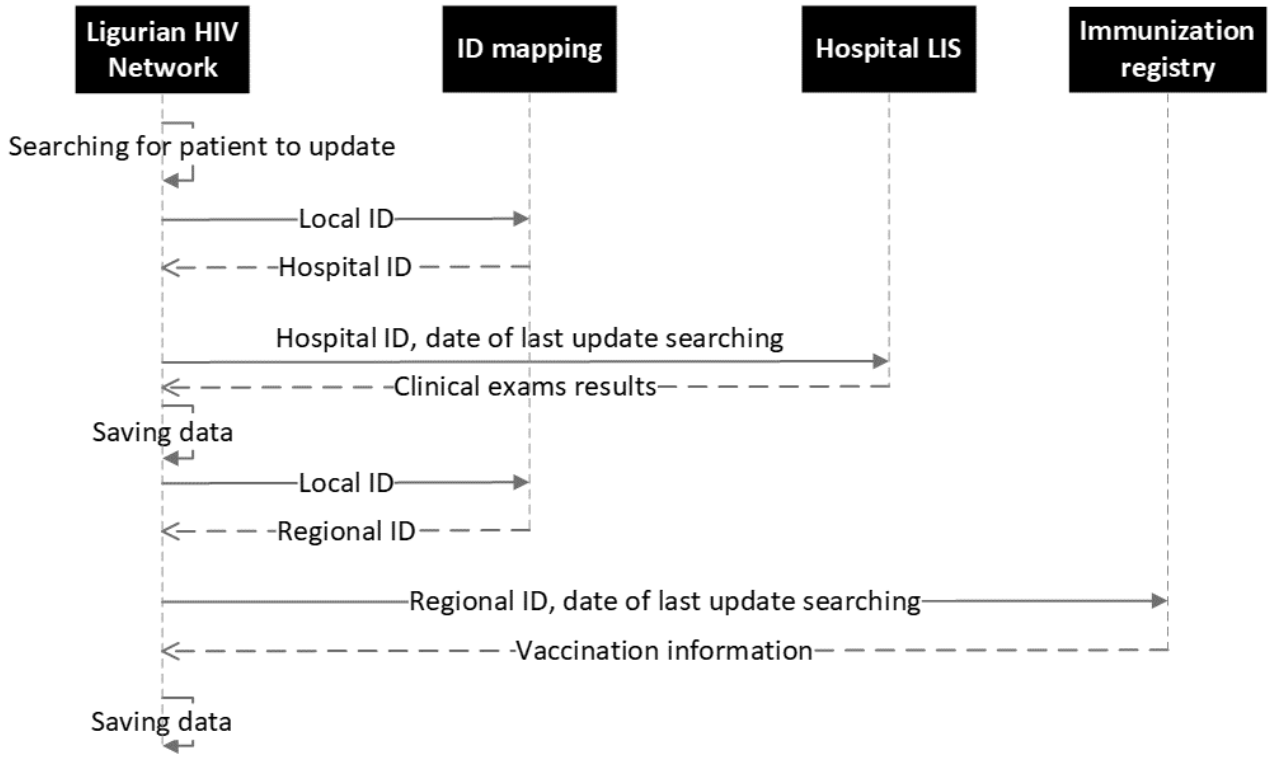


Figure 4.3: UML sequence diagram showing update of LIS data and vaccination information

One problem, faced within this project, was the harmonization of patients' identification from separate systems. Specifically, each hospital has its own administration system, where patients are identified by a tax code, a hospital ID and a regional ID. The hospital ID is used for intra-hospital data exchange, for example to identify patients' laboratory exam results. The regional ID is used when data needs to be exported outside the hospital, for instance to make periodical regional reports. Even if using both IDs, it is not possible to infer patient identity, without a direct link to the hospitals' demographic system. In order to properly identify patients without knowing the related identity, the region Liguria should implement an identification web service. Waiting for the region to implement such a system, I developed a repository with the mappings of patients' IDs.

Currently 4338 patients from eight different hospitals are involved in the LHN. Among them, data from 1851 patients from San Martino hospital, 1241 from Galliera hospital and 267 from Sanremo hospital are automatically updated using the described tool.

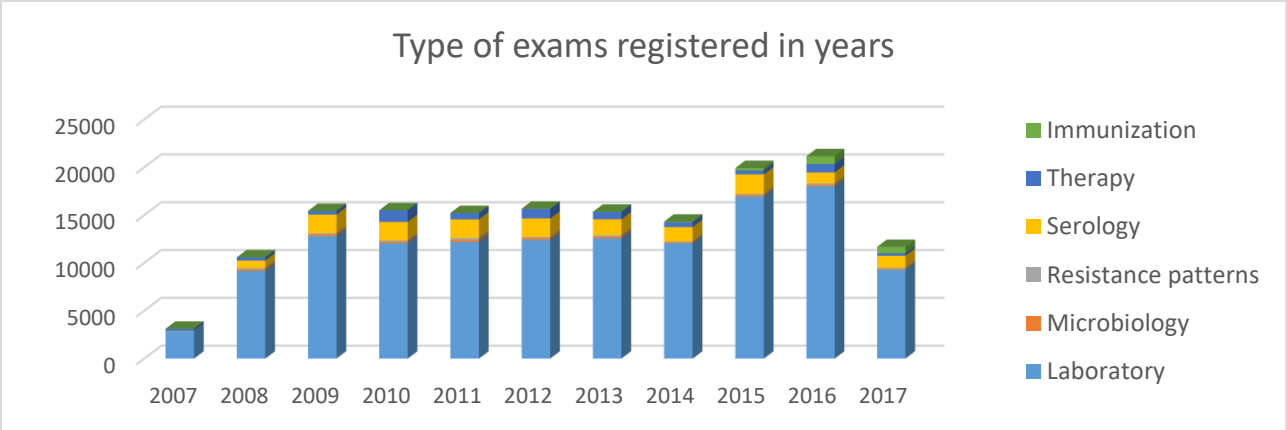


Figure 4.4: Number of exams registered in the Ligurian HIV Network distributed per type and years.

The difference between the data collected automatically and the data collected manually through the web interface, regarding the mean number of laboratory tests registered each year and the mean number of parameters registered in a single laboratory test is shown in table 4.1.

	Mean no. of lab tests per year	Mean no. of parameters per test
Automatized centers	10679	41
Non automatized centers	1910	31

Table 4.1: Difference in the quantity of data registered between the two scenarios

Without automatic data transfer, a complete report of the laboratory activity for all the patients involved in a web network such as the LHN is only achievable due to a strenuous human effort and the allocation of great resources, as the numbers in table 4.1 attest. Using this tool, anonymized data were automatically transferred from the Electronic Health Records (EHR) towards the Clinical Data Management System (CDMS). This enhanced clinical trials conduction on chronic viral infections.

A project about clinical data re-use applied to tuberculosis management was developed too, to consider a different approach to infectious diseases. Indeed, tuberculosis is not chronical but could have relapses if not properly treated [75] [76]. The platform allows TB patients' surveillance by tracking their transfers to other hospitals or outpatient departments: a complete surveillance could be reached with a total adherence of hospitals to the network.

4.2 Second layer: Clinical trials automatic feed

The huge amount of data collected can be re-used to perform multi-centric clinical trials. The former architecture already allowed to perform regional clinical trials. Clinical studies are very important to conduct focused surveys, especially in chronic diseases management. Several clinical studies have been conducted with the support of the LHN; initially data entry was manually executed, but the last clinical trials performed benefit from the automatic data sharing.

Presently nine regional studies are supported by the platform [77] [78] [79] [80] [81] [82] as they are listed in table 4.2. They are all observational studies, except for AIFA HCV, which is a phase 4 study about new HCV drugs pharmacovigilance funded by Italian Medicines Agency (AIFA) in which Liguria is the pilot region.

Each study has a specific interface and role based access control, but they share the same database in order to re-use the clinical information and avoid multiple data input.

Studies	Description	Patients	Centers involved
MARHIV	Study on Maraviroc therapy	120	8
Long-Term	Study on HIV long term non-progressor patients	35	2
ACTeA-I	Analysis of the costs for patients in antiretroviral therapy	208	4
Vertical transmission	Study on mother-to-child transmission of HIV	51	2
IANUA	Study on antiretroviral prescription appropriateness in HIV	2245	4
T reg	Determination of regulatory T lymphocytes as a new biomarker for HIV monitoring	93	5
VELA	Effectiveness and sustainability strategies in the management of long-term HIV patient quality of life	275	6
AIFA HCV	AIFA pharmacovigilance project for HCV therapy prescription in mono-infected and co-infected patients	1504	8
SCUDI	Study on therapeutic failure in HIV patients	389	2

Table 4.2: Clinical trials available on the LHN

Other professional figures has been involved in the conduction of clinical trials and periodical meetings were organized with physicians, economists and psychologists. For example, in IANUA study the overall annual economic expense in Liguria region for HIV+ patient management and the related improvement in patients' health were compared. Economists were employed for the cost effectiveness analysis and psychologists were designated to collect data related to patients perceived health status as marker of clinical quality.

Another example of a regional study conducted on the platform is VELA (Valore Esiti Liguri per l'Appropriatezza della terapie HIV), whose main objective is the evaluation of

the appropriateness of HIV therapy prescribed in the Ligurian centers of infectious diseases during 2015 and 2016 according to guidelines.

In an ever-evolving scenario like that of HIV infection, characterized by long-term therapy and burdened with multiple comorbidities, it is increasingly important an optimal prescription of the HAART therapies. Optimization in this case means having the opportunity to offer everyone the best pharmacological combination for his or her clinical situation. The first therapeutic lines are decisive in this context, as they are responsible for immune-virological success as well as possible side effects.

In HIV treatment, the therapy is a crucial point: the currently available anti-HIV drugs cannot completely cure HIV, but treatment with a combination of these drugs can reduce the amount of the viral load and prevent the virus from reproducing. This allows the immune system to fight off infections and other illnesses, granting an almost normal life. There are currently more than 20 approved antiretroviral drugs; taking two or more antiretroviral drugs at a time is called combination therapy. The way to choose which drugs to be combined is highly difficult and it depends on many factors. The efficacy of HAART treatment is reached only with a complete adherence of the patient at the therapy prescribed, otherwise drug resistances arise. At the beginning of the treatment, the combination of drugs that a person is given is the first line therapy. If HIV becomes resistant to this combination, or if side effects are particularly bad, then a change to second line therapy is usually recommended; higher the current line, less the probability of next therapeutic success. Thus the adherence is a key factor in avoiding treatment failure, and the concept of retention in care assumes great importance. In figure 4.5 shows VELA main page interface.

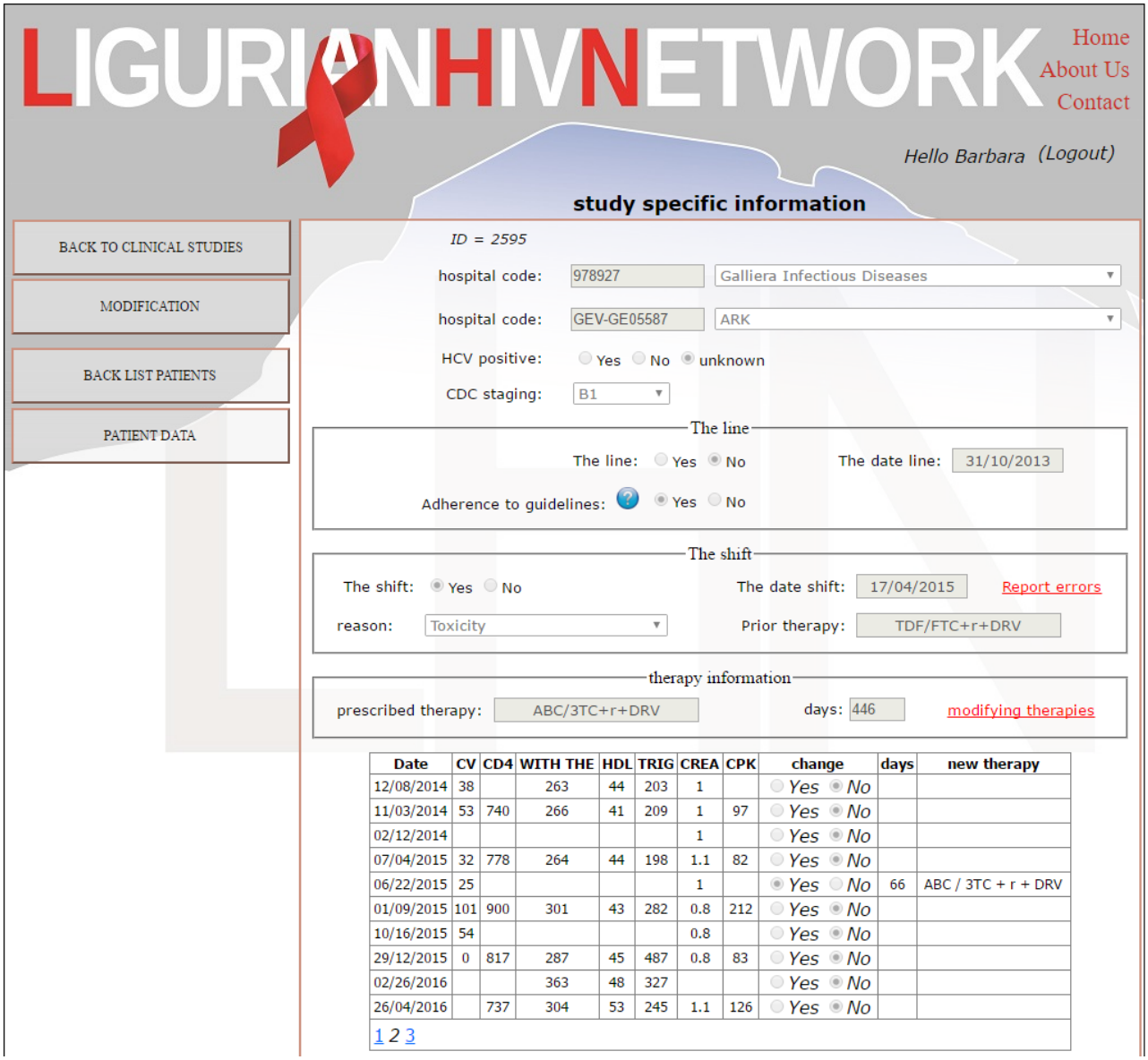


Figure 4.5: An example of the web interface showing the main page of VELA study with the principal information

Even if the clinical trials implemented have different purposes and procedures, their belonging to a single platform allows to integrate common information among trials. In this way, the clinical information that were recorded to monitor the follow up for a particular study can be available for other studies. Consequently, a patient can be involved in multiple trials simultaneously but clinical data have to be recorded only once.

Appreciating the low effort in participating in these clinical trials, physicians of connected centers requested an extension of this mechanism to facilitate the participation to external trials too. In chronical infectious diseases field, as mentioned in the material section, many research databases collect data at national level. Solutions to fulfill this request have been

set up for ARCA and CISAI databases. A semi-automatic solution has been set to enable physicians to connect from CISAI web site to the network, asking for the data of interest, in a specific time interval. This solution is not fully automatable, due to intrinsic complications in the trial structure that requires human supervision. The connection with ARCA database, that was developed within a master degree thesis under my supervision, enables a complete automatic and bidirectional data exchange between the two platforms (but on a limited number of parameters).

In both cases, the first step was an initial matching of the anonymous codes used by the two systems to identify patients. The second step consisted in a manual matching of the clinical parameters involved in both sites, which do not employ terminology standards, and their translation into standard LOINC codes according to their meaning, measurement units and properties.

An intermediate solution was adopted for ICONA database, because the system administrators did not allow access to the database structure. To feed ICONA database without data manual copy, Excel files containing the information of interest of the patients involved are presently downloaded from the network and reloaded into ICONA database by their technicians. A fully automated system will be set up when bureaucratic constraints will permit it.

At present, 1243 LHN patients are registered in the ARCA database, 590 in CISAI and 458 in ICONA. A program has been developed to continuously update the ARCA database with CD4+, CD8+, CD3+, HIVRNA and genetic sequence data for all patients included in the LHN. The CISAI study also involves HCV infected subjects and collects a greater amount of data.

The interchange of data at a national level ensures a wider vision that grants greater stability in statistical elaborations and knowledge inference.

In chronic infectious diseases data management, where a significant amount of data is periodically collected and analyzed, this system assumes great importance. In this and other domains, all the collected data will provide wide and scientifically valid samples.

To estimate the impact of the application of the platform developed in clinical practice, a fast anonymous questionnaire was set. It was developed as an indicator of progress, stalling or failure, and it could give an evaluation of the improvement in the effort to merge clinical practice and medical research. The questionnaire is anonymous since only the user age, the

experience with the platform and the frequency of use are requested. Two different sets of questions were asked, depending on which scenario the user's hospital belonged to. Two scenarios were depicted: the first one includes the hospitals that do not allow external agents to access data from LIS (that insert data into the LHN only manually through the web interface). The second scenario includes the hospitals that are automatically connected to the LHN architecture (San Martino, Galliera and Sanremo). In the first scenario case, a few questions are addressed to investigate if the user perceives differences with the use of paper-based case report forms, and if he thinks that the adoption of the second scenario would improve his way of working. To automated system users, questions are focused on evaluating the level of satisfaction in terms of time and quality. Moreover, in this second scenario users should indicate if they appreciate less workload in the participation to regional and national studies thanks to the automatic support. In both cases, at the end of the questionnaire, users had to specify if they would like to integrate a decision support system to the platform and if they would suggest the adoption of the platform to their colleagues. The questions can have numeric answers on a scale 0 to 5.

Sixteen questionnaires were collected at the end of 2015, 5 in the first scenario and 11 in the second. The user's average age was 37 with a standard deviation of 11. All 16 users (100%) asserted that they would recommend adoption of the platform to their colleagues and 14 (88%) appreciated the idea of integrating a decision support system. The questions and the results of the questionnaires are summarized in table 4.3.

	Average values		
Questions (on a scale of 0 to 5, with 0 being poor and 5 being excellent)	**I scenario**	**II scenario**	**Weighted average**
How much did the platform improve data input in respect to paper-based collection?	4,4	4,1	**4,2**
How much did the platform simplify clinical trials conduction?	4,2	3,4	**3,6**
To what extent do you think the automatic import of LIS data has lightened the workload and reduced the time spent entering data manually?	-	4,7	**4,7**
To what extent do you think the automatic import of LIS data has facilitated the export process towards national databases?	-	4,4	**4,4**
To what extent do you think the automatic import of LIS data has improved the quality of the data collected?	-	4,0	**4,0**
To what extent do you think the automatic import of LIS data could lighten the workload?	4,8		**4,8**
Weighted average	**4,4**	**4,1**	**4,2**

Table 4.3: Questions asserting the satisfaction level of the platform, with numeric answers on a scale 0 to 5

4.3 Third layer: CDSS

The flexibility and the capability to continuously evolve is the key points of the structure, in order to follow the typical LHS cycle, which consists on learning from data and applying knowledge to clinical practice. The evidence abstracted by clinical trials results, integrated with existing guidelines, can be used as the knowledge base for a clinical decision support system.

A fundamental feature that arouses from literature is that CDSS, to be truly efficient, should be smoothly integrated within the clinical information system, interacting with other components, in particular with the electronic health record. Since data stored in EHR are of heterogeneous nature, differing in the data models, schemas and semantic, there is the need of standardized solutions. The choice of joining the HeD initiative instead of using other cited standards for CDSS is driven by the already existing platform, which involves other HSSP specifications, as already described.

To fully comprehend theoretical in-depth analysis, I considered a useful attitude to have a more practical approach to the matter in parallel of literature researches. I searched for a restricted field in which apply an initial draft of CDSS and, during a meeting with infectious diseases physicians, the whole team agreed to implement decision support to HIV-infected patients drug prescription. In HIV treatment, the therapy is a crucial point: the currently available anti-HIV drugs cannot completely cure HIV, but treatment with a combination of these drugs (called HAART – Highly Active AntiRetroviral Therapy) can reduce the amount of the viral load and prevent the virus from reproducing. This allows the immune system to fight off infections and other illnesses, granting an almost normal life. There are currently more than 20 approved antiretroviral drugs, subdivided into four main classes: NRTI (Nucleoside reverse transcriptase inhibitors), NNRTI (Non-nucleoside reverse transcriptase inhibitors), PI (Protease inhibitors), and II (Integrase inhibitors); taking two or more antiretroviral drugs at a time is called combination therapy. The way to choose which drugs to be combined is highly difficult and it depends on many factors. The efficacy of HAART treatment is reached only with a complete adherence of the patient at the therapy prescribed, otherwise drug resistance arises. At the beginning of treatment, the combination of drugs that a person is given is the first line therapy. If HIV becomes resistant to this combination, or if side effects are particularly bad, then a change to second line therapy is usually recommended; higher the current line, less the probability of next

therapeutic success. Thus the adherence is a key factor in avoiding treatment failure, and the concept of retention in care assumes great importance [6]. Therefore, CDSS would be very useful in HAART prescription, with the aim not to substitute the physician with a computerized tool, but to aid him by providing patients' historical data on adherence, prescription, resistances acquired and comorbidities.

The first step to the development of this tool was to collect data about therapies and integrate it in the current architecture, using the Italian AIC standard codes for drugs and the international ATC codes to identify active ingredients. HAART drug sale is not allowed in pharmacies, so patients withdraw their drugs in the hospital every month. The register of patients' ambulatory withdraws in excel format was the first way we accessed data. In the last few months, a direct network towards San Martino hospital drug management system has been performed, thanks to the collaboration with the appointed company Ingegneria Biomedica Santa Lucia S.p.A.

The second step consisted in the consideration of existing clinical guidelines regarding HAART therapy prescription and the standardization of the related control-flow engine using the GLIF model. The GLIFeditor developed by Medical Objects has been used to draw the logical flux that describes the "BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015" of the British HIV Association [83]. This guideline, together with the national "Linee guida italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostica-clinica delle persone con infezione da HIV1" [84] has been used in VELA project. VELA (Valore Esiti Liguri per l'Appropriatezza della terapie HIV) is one of the regional studies conducted on the platform, whose main objective is the evaluation of the appropriateness of HIV therapy prescribed in the Ligurian centers of infectious diseases during 2015 and 2016, according to guidelines. Using GLIF editor, patients' states, decisions, actions and the related links were descripted in a computer interpretable way. To embed automatic decision steps, scripts in GELLO language has been used, to query archetype data.

After the learning phase, the implementation of a CDSS through which apply the knowledge to clinical practice has been performed exploiting the standards described by HeD Initiative.

4.3.1 Clinical guideline representation

The initial idea was to create a computer interpretable code to describe the workflow of clinical guideline and integrate it into a custom informatics program. GLIF was chosen as guideline representation format mainly because it is based on HL7's Reference Information Model (RIM). GLIF editor provides a user-friendly interface to describe clinical guideline through a flow chart. The blocks of the flow chart represents different classes of the GLIF model. The first implementation of this tool was to describe the part of clinical guideline "BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015" that is related to therapy prescription for naïve patients, that are patients that are new to this kind of therapy. I decided first to concentrate on this restricted group of subject, mostly because VELA project involves this kind of people. Moreover, the management of patients who have already undergone HAART therapy is more complicated, because also possible resistances to some active ingredients previously swallowed need to be taken into consideration. In figure 4.6 six different sub-guidelines organized into different layers are represented. The starting layer is the one describing the patient state. Action steps are represented using green rectangles. From the action step "Naïve" the arrow brings to the second layer, which considers two sub-guidelines embedded into two corresponding action steps, concerning the starting time and the kind of drugs to start. The first sub-guideline considers clinical parameters of the patients to evaluate the urgency of starting HAART. The second leads to a third layer in which the details about the kind of therapy are exploited. According to the guideline, a naïve patient has to take a therapy composed by two NRTI agents and a third agent from another class. In this third layer, two different sub-guidelines are dedicated to the choice of the three active ingredients that most suits the patient's clinical profile.

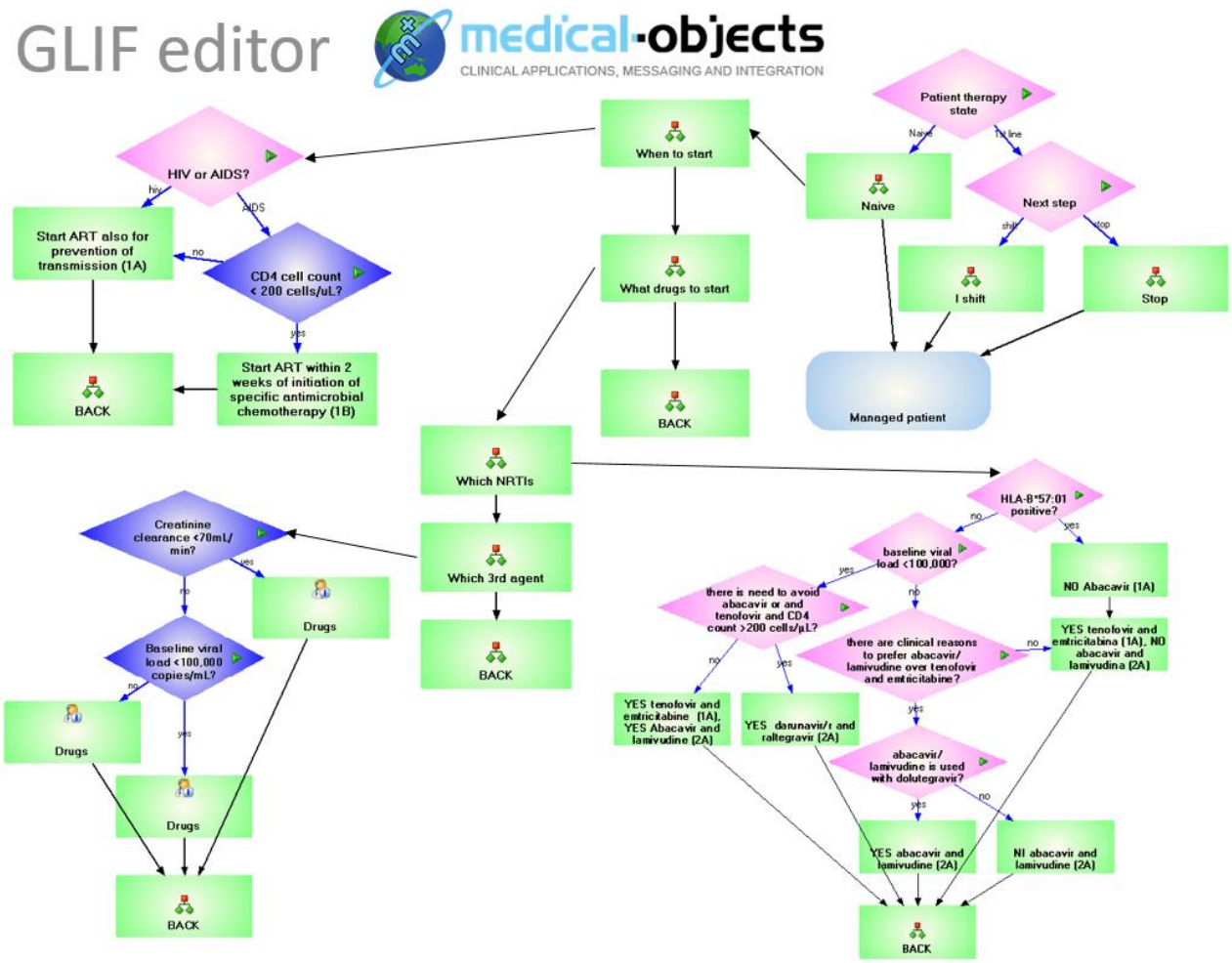


Figure 4.6: Definition of BHIVA clinical guidelines on HAART prescription in naive patients developed with GLIF Editor of Medical Objects

The decision steps are represented as pink or blue rhombuses. GLIF Editor can be used as an execution engine too, to test if the logic data flux described by the flux diagram is correct. A decision choice can be expressed manually by the user in testing phase, or it can be derived automatically by the editor basing on patient's data. In the first case the rhombus is pink, in the second one it is blue. To automatize a decision block, a code in GELLO language expressing the choice logic should be integrated. During the running phase, the GELLO code evaluates this logic against patient's data that can be loaded inside GLIF Editor. Patient's data can be loaded in standard HL7 v2 format. To test the diagrams created, instructions in GELLO language have been embedded into some decision blocks. For example, in figure 4.7 there are two blue decision blocks that leads to different paths of the diagram to suggest a list of drugs suitable for the patient. The first one evaluates if the last available value of creatinine clearance is less than 70 mL/min. If the answer is no, the second block evaluates if the baseline viral load is less than 100000 copies/mL. In figure

4.8 the GELLO code for the evaluation of the first block is reported. In the second line of this GELLO code, a variable that describes the entity “creatinine clearance” is declared. The type of this variable is CD (Coded Value) that is a type derived from the RIM (Reference Information Model) model of HL7 that has been imported (figure 4.9). The coded value 2163-4 is the standard LOINC code for the entity creatinine clearance, as it is appreciable from screenshot in figure 4.10. In the following instruction, the program searches for this code among the patient’s data imported, sorted by time to take the last available value. After, it compares the value found with the threshold to provide the final answer that will drive the flux towards one of the two available options (Yes/No). This answer is expressed according to the type GLIFDecisionResult of GLIF entity class model that was imported too.

To test this program inside GLIF Editor, I imported a hand-written example of HL7 v2 message (figure 4.11) that contains some clinical observations of a fake patient. In particular, in this message, the creatinine clearance assumes value 80 mL/min. While executing the test, after loading patient’s data, the results and the values assumed by the variables involved are shown by the editor (figure 4.8). In this case, the final answer correctly assumes false value. Similarly, the second decision block was realized with GELLO code inside, and tested against the patient’s data imported. In the same HL7 v2 message, HIVRNA assumes value 100 copies/mL, so in this case the final answer should be yes. Figure 4.12 shows the final execution of this sub-guideline, highlighting the effective data flow that occurs, which is the one expected.

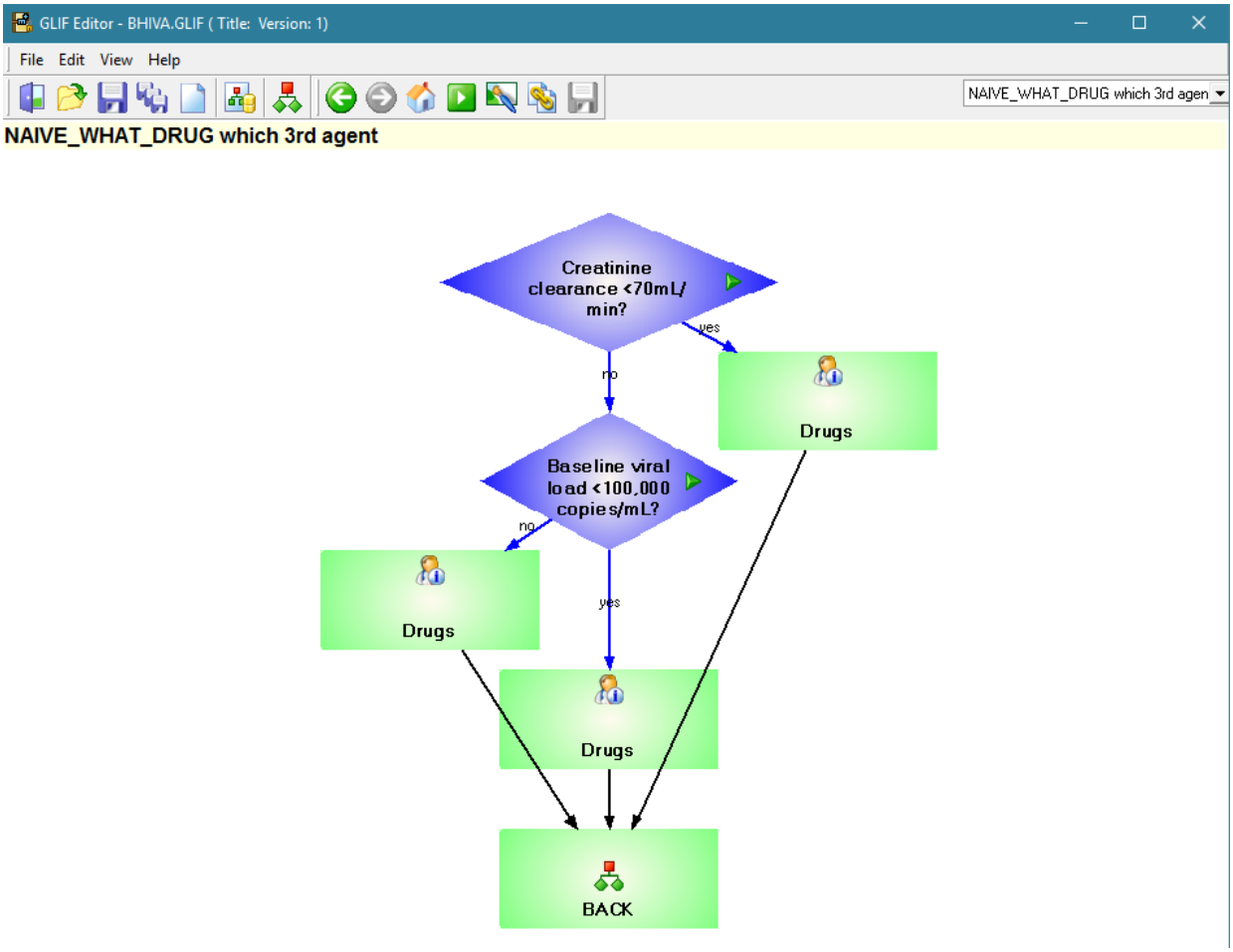


Figure 4.7: GLIF Editor blocks to define the third agent of HAART therapy with GELLO code embedded to automatize the two decisions steps execution.

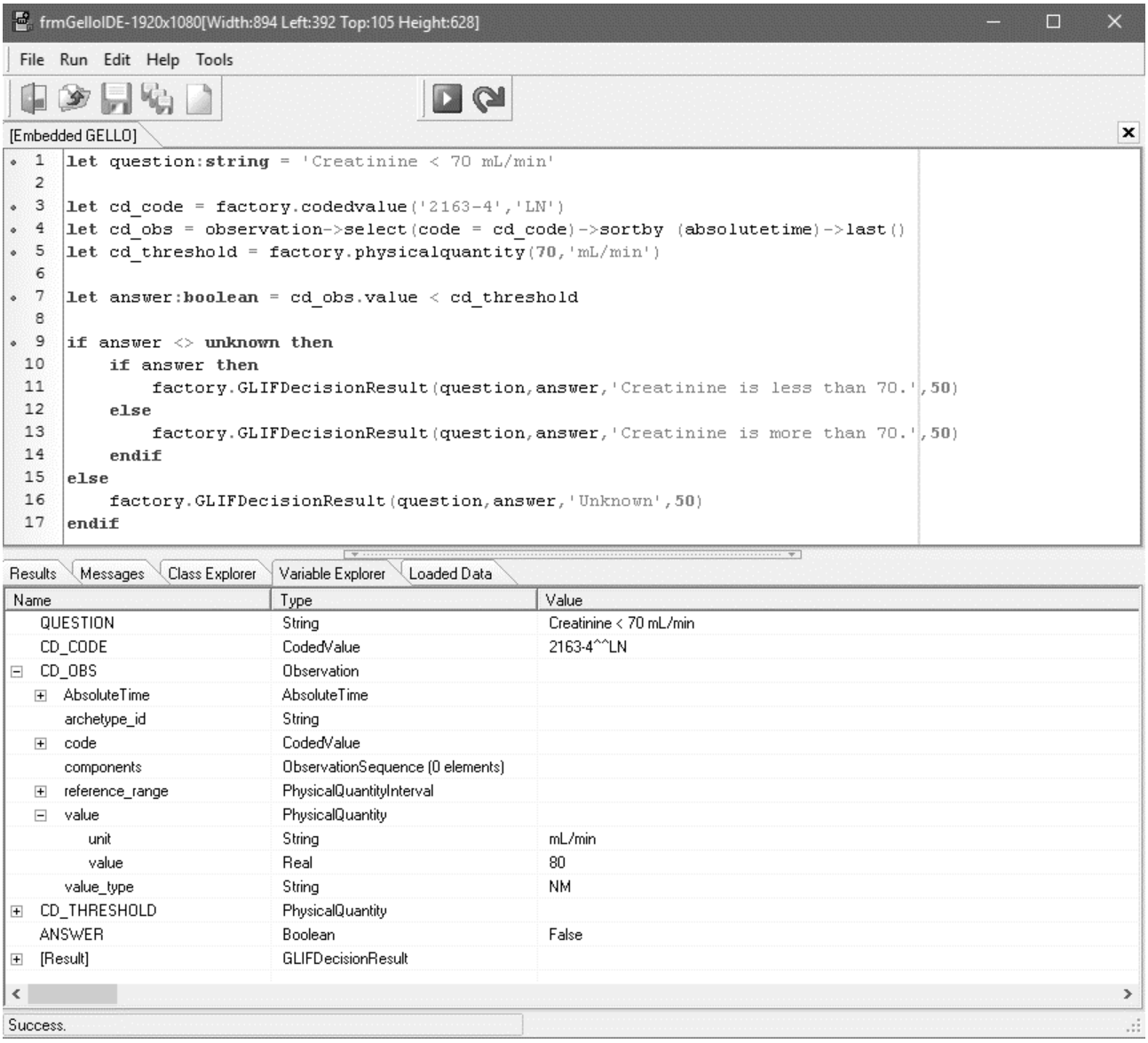


Figure 4.8: GELLO code execution in GLIF decision node. The GELLO code related to the first decision step evaluates if the last value of creatinine clearance of the patient considered is lower than the set threshold (70 mL/min). LOINC code is used to identify the parameter.

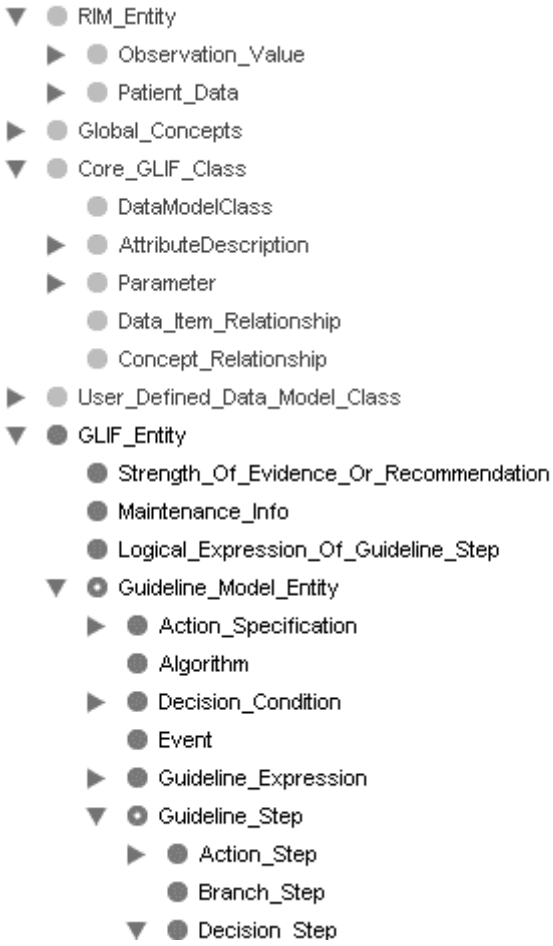


Figure 4.9: Brief overview of the object oriented models imported.

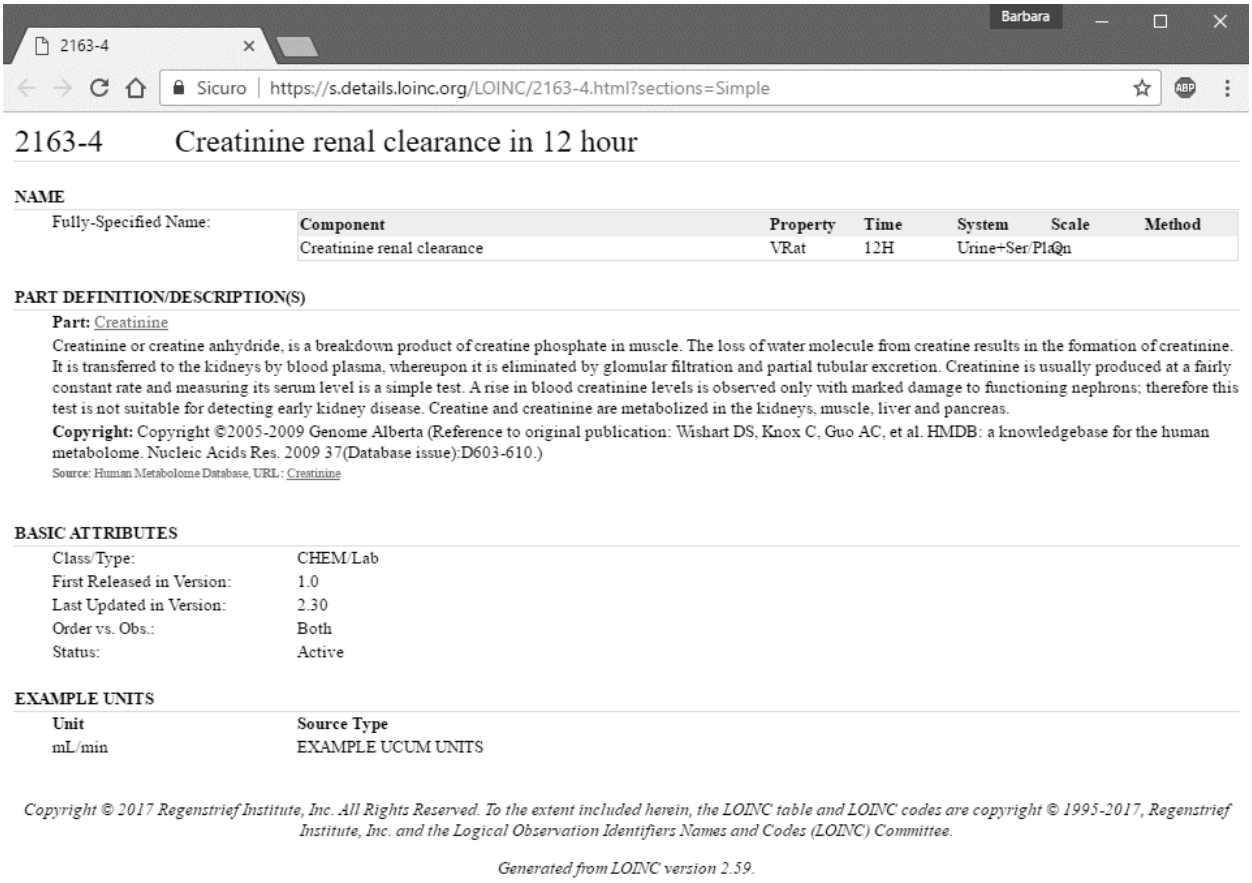


Figure 4.10: Creatinine renal clearance parameter definition in LOINC code

```
FHS|^~\&|SNP|NATA^1964^N|PRSLT|1150A|201702301537+1000||SN693804.ORU||112
BHS|^~\&|SNP|NATA^1964^N|PRSLT|1150A|201702301537+1000||SN693804.ORU||112
MSH|^~\&|EQUATORDXTRAY^EQUATORDXTRAY:2.20.2 (Build 977)^L|San Martino GE Centre^7C3E3681-91F6-11D2-8F2C-4445
PID|1||00901115||M^L||19710711|M|||
OBR|1||306523580-C-GENCHEM^NATO^1971^N|C-GENCHEM^_ROUTINE CHEMISTRY^1971||201603021636+0100|20160303163614||
Pathology"SNPG022201.oru"
30.08.2006||LN=306523580||20160303173614+0100||CH|F||^^^201603021636+0100^^R|0135505X^ANDERSON^PITRE^^^DR^^^
OBX|1|NM|NA^Sodium^1964^2951-2^Sodium^LN||143|mmol/L^mmol/L|135-145||||F
OBX|2|NM|K^Potassium^1964^2823-3^Potassium^LN||4.5|mmol/L^mmol/L|3.5-5.0||||F
OBX|3|NM|CL^Chloride^1964^2075-0^Chloride^LN||106|mmol/L^mmol/L|96-109||||F
OBX|4|NM|CO^Bicarb.^1964^2028-9^Bicarb.^LN||23|mmol/L^mmol/L|23-32||||F
OBX|5|NM|ND1^Ca (corr)^1964^29265-6^Ca (corr)^LN||2.33|mmol/L^mmol/L|2.10-2.60||||F
OBX|6|NM|PO^Phosphate^1964^14879-1^Phosphate^LN||1.2|mmol/L^mmol/L|0.8-1.5||||F
OBX|7|NM|BN^Urea^1964^22664-7^Urea^LN||7.2|mmol/L^mmol/L|3.5-7.5||||F
OBX|8|NM|RA^Uric Acid^1964^14933-6^Uric Acid^LN||0.32|mmol/L^mmol/L|0.25-0.50||||F
OBX|9|NM|CR^Creatinine^1964^14682-9^Creatinine^LN||80|umol/L^umol/L|40-120||||F
OBX|10|NM|GLF-R^Random Glucose^1964^14749-6^Random Glucose^LN||4.9|mmol/L^mmol/L|3.6-7.7||||F
OBX|11|NM|TP^Total Protein^1964^2885-2^Total Protein^LN||69|g/L^g/L|63-80||||F
OBX|12|NM|AB^Albumin^1964^1751-7^Albumin^LN||41|g/L^g/L|35-50||||F
OBX|13|NM|GOB^Globulin^1964^10834-0^Globulin^LN||28|g/L^g/L|20-40||||F
OBX|14|NM|BL^Bilirubin^1964^14631-6^Bilirubin^LN||11|umol/L^umol/L|3-20||||F
OBX|15|NM|BD^C Bilirubin^1964^14629-0^C Bilirubin^LN||3|umol/L^umol/L|0-7||||F
OBX|16|NM|AP^Alk Phos^1964^12805-8^Alk Phos^LN||61|U/L^U/L|30-115||||F
OBX|17|NM|AS^AST^1964^1920-8^AST^LN||22|U/L^U/L|5-40||||F
OBX|18|NM|AL^ALT^1964^1742-6^ALT^LN||40|U/L^U/L|5-40||||F
OBX|19|NM|TN^Gamma GT^1964^2324-2^Gamma GT^LN||22|U/L^U/L|5-65||||F
OBX|20|NM|LD^LDH^1964^2532-0^LDH^LN||350|U/L^U/L|100-225||||F
OBX|21|NM|CHOL^Chol.^1964^14647-2^Chol.^LN||4.1|mmol/L^mmol/L|3.9-5.5||||F
OBX|22|NM|TR^Trigs.^1964^14927-8^Trigs.^LN||2.7|mmol/L^mmol/L|0.6-2.0|H|||F
OBX|23|NM|FE^Iron^1964^14798-3^Iron^LN||25|umol/L^umol/L|9-29||||F
OBX|24|NM|CRC^Creatinine Clearance^1964^2163-4^Creatinine Clearance^LN||80|mL/min^mL/min|70-120||||F
OBX|25|NM|HIVRNA^Viral Load^1964^10351-5^HIVRNA^LN||100|UI/mL^UI/mL|||||F
```

Figure 4.11: HL7 v2 message used to test the GELLO code execution in GLIF decision node. The creatinine clearance value measured is 80 mL/min, which is greater than the threshold set in the decision node.

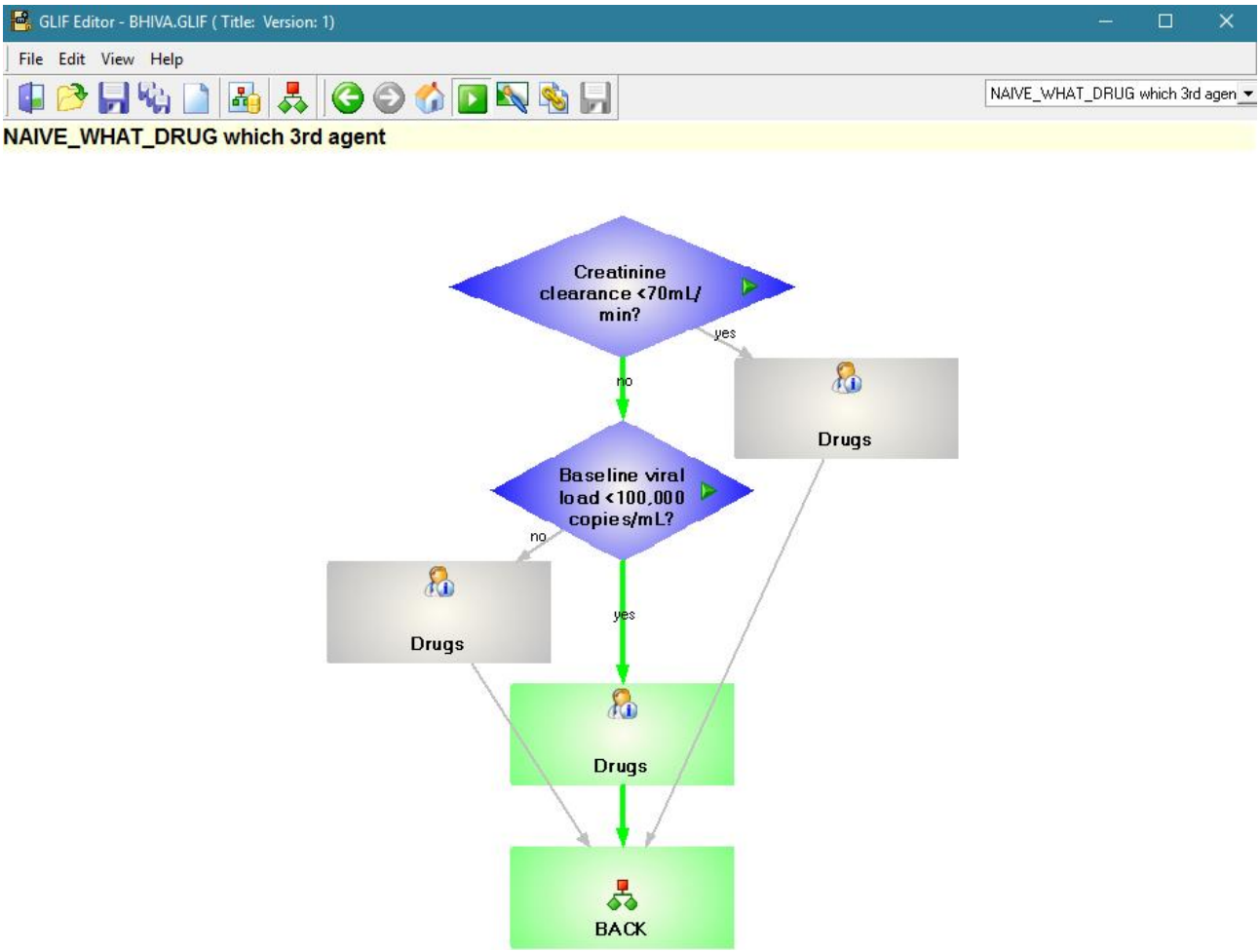


Figure 4.12: Automatic execution results. The HL7 v2 message in figure 4.11 was uploaded in GLIF Editor and the created algorithm evaluates the GELLO code against patient's data read in the HL7 v2 message.

The editor translates the flow chart edited by the user into a hidden code in XML standard language. As mentioned above, the initial idea was to create a computer interpretable code to describe the workflow of clinical guidelines and integrate it into a custom informatics program. In this way, that program should be able to evaluate flow chart decision steps against patients' data, providing a custom interface to physicians. For this reason, I tried to re-use the created XML, but I came across some difficulties in embedding this code into a software program. (figure 4.13)

Figure 4.13: XML representation of the block diagram developed with GLIF Editor.

4.3.2 Knowledge Modules

After representing the acquired knowledge using GLIF, in order to use this knowledge as the basis of the decision support system, I developed a database structure suitable to store it and to make it available to a computer program. Each "package" in which knowledge is stored is called "Knowledge Module" (KM). Maintenance and versioning of knowledge modules are very important and should be considered in database development. The database structure should be very flexible in order to easily allow the management of knowledge modules changing according to new versions of the guidelines involved and new literature publications. A flexible structure should consider normalization. To reproduce the GLIF flux diagram logic, I assumed that each KM should have an ordered collection of criteria that have to be evaluated according to a specific comparison operator. The diagram of the database developed is shown in figure 4.14. Table "Combo_Evaluations" contains the list of criteria that are to be evaluated for each KM. Criteria are expressed through standard vocabularies codes, such as LOINC for clinical parameters, ICD9 for diagnosis and ATC for the active ingredients of drugs. Evaluations

for each criteria in KM will be done using comparison operators that are defined into table “Comparison_Operators”. In case of two-way operators, the comparison value is specified in column “Comparison_Value” of table “Evaluation”. The list in “Combo_Evaluations” is not ordered; this table only contains reference to which is the first evaluation of a KM. In fact, the chain is not fixed, but has to be dynamically created, according to the evaluations results, as in a flux diagram. The order of the evaluations is therefore defined into table “Results_Combo_Evaluation”. In this table, each comparison is related to the two possible answers (0 or 1) and to the related next step, that is the id of the table “Combo_Evaluations”. With this logic, the path to follow is dynamically drawn according to evaluations results and ends when the next step id is null. The implementation choice was to consider the possibility of providing guidance not only at the end of the path, but also gradually at each step. This could be specified in table “Combo_Criteria_Tip”, in which from 0 to N tips can be provided at each step (that is for each row of the table “Results_Combo_Evaluation”). The system is capable of dealing with generic advices, such as pharmacological prescriptions, diagnostic procedures, blood test recommendations etcetera. Each advice is associated with a weight that indicates the level of strength established by the guideline for the action proposed. In the program code, during the execution of the recursive function that iteratively evaluates the criteria for the involved KM, all the advices suggested at each step are recorded into a list. At the end of this function, this list is checked. Discordant tips are analyzed and the one with the lowest weight is taken into consideration.

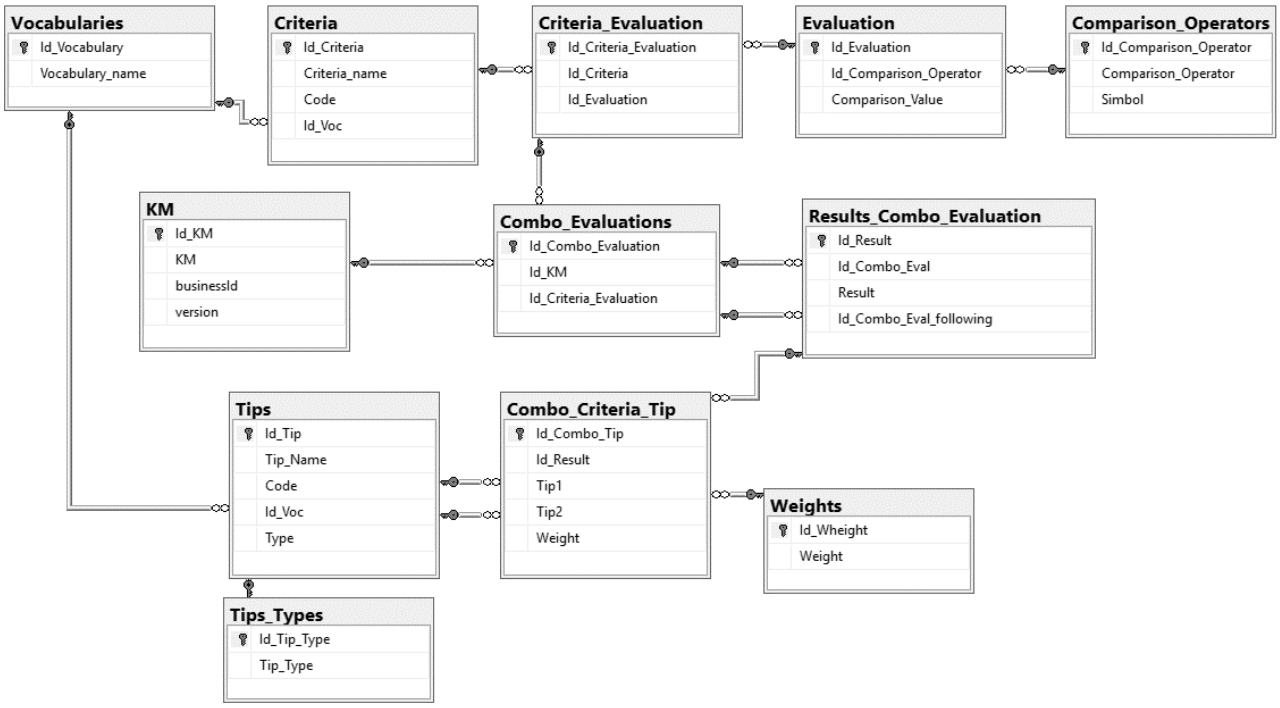


Figure 4.14: Knowledge Modules Database structure

The strength of this structure is that it is flexible and easily adaptable to different contexts and guidelines. The guidelines stored in such a database are prone to updating, since only the records in the tables have to be changed, while the structure of the database and the program code do not need to be modified. This generic and adjustable structure has been tested in the use case reported below.

4.3.3 Decision support service

The database structure described stores the knowledge modules that will be used by the decision support system as knowledge base. The decision support service has been developed according to the HL7 version 3 standard Decision Support Service (DSS) Release 1 (August 2011). The decision support service utilizes patients' data for the execution of the evaluation logic that is contained into the knowledge modules. The DSS service has to be used by a DSS client that is an external entity that interacts with the DSS to obtain its services. The client, querying the DSS service, has to specify the KM to be used in the evaluation phase, and has to provide patient's data. The DSS service returns inferences regarding the patient in a pre-defined format. A general schema describing the actors involved in the decision support is shown in figure 4.15.

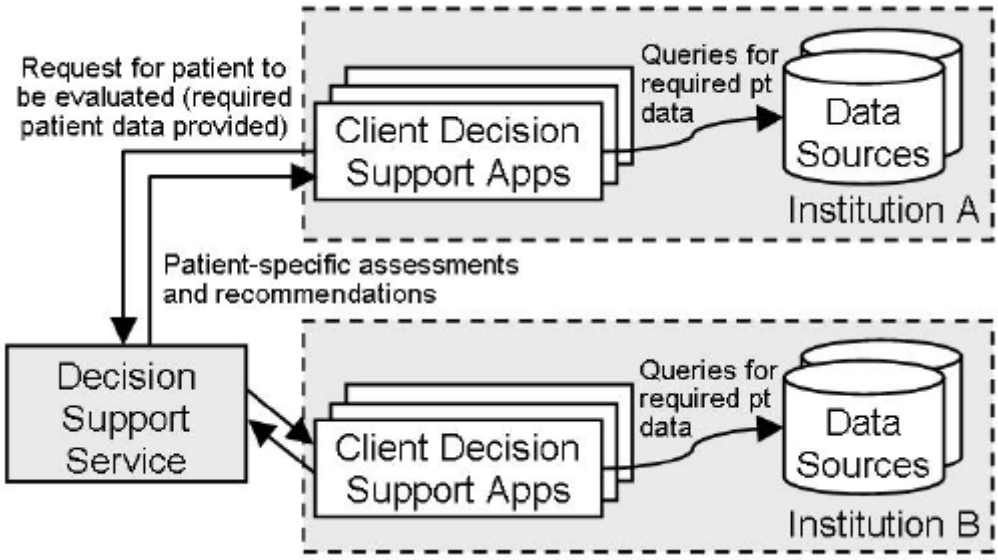


Figure 4.15: General schema describing the actors involved in the decision support

The primary functionality of a DSS service is to receive patient's data as input and returns patient specific conclusions as output. For both input and output, the HeD group suggests the use of the HL7 Virtual Medical Record (vMR). The aim of the designed system is to develop the service using a standard structure, so that an ad-hoc client can be built for each healthcare facility that wants to connect to the service. In this way, the interoperability problems described in the previous chapters that could limit the adoption of decision support tools are resolved. This architecture allows existing resources to be more readily re-used, as the main system does not have to be modified each time a new institution join the system. Moreover, since the DSS uses a standard interface, client implementers would be able to leverage CDS content from different DSSs in an easy manner. The normative specifications defined in the implementation guide [72] consist of two functional profiles: the HSSP Simple Evaluation DSS Functional Profile and the HSSP Complete DSS Functional Profile. Figure 3.18 provides a view of the operations supported by the two functional profiles. The conformance with the HSSP Simple Evaluation DSS Functional Profile version 1.0 is granted with the implementation and support of the service operation "evaluate" of the Evaluation interface. The evaluate operation evaluates one or more knowledge modules using the data provided as EvaluationRequest object and returns the results of the evaluation as an EvaluationResponse object. To describe the service interface, a common language exists: the Web Service Definition Language. WSDL documents have an associated XSD (XML Schema Definition) that describes the static structure of the

complex data types being exchanged by the service methods. A WSDL document and the associated XSD are provided by HL7 with the specification of the DSS. To develop a WCF web service starting from the WSDL I used WSCF.blue tool. This approach is named schema-based contract-first design and it is schematized in figure 4.16.

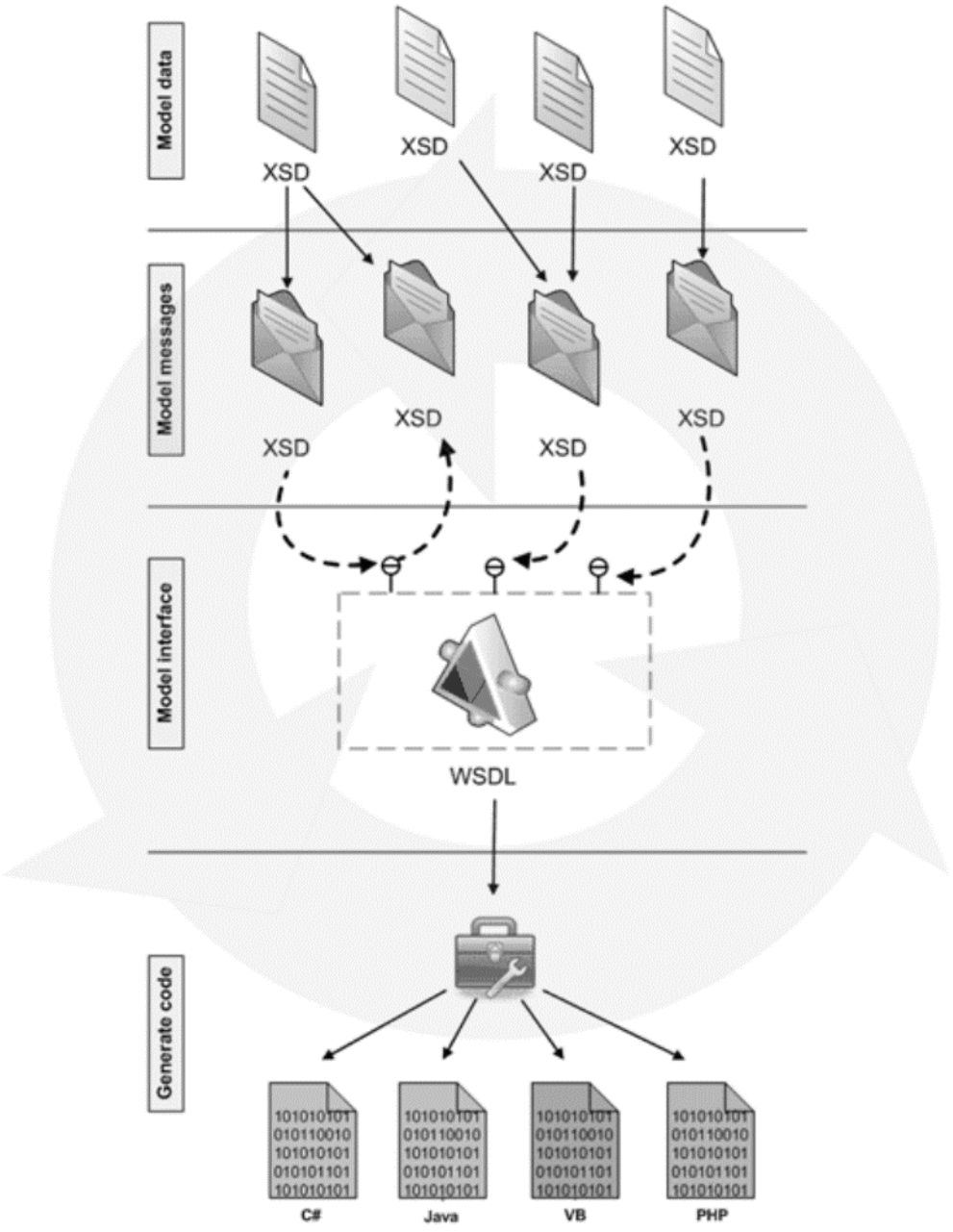


Figure 4.16: Schema of WSCF.blue schema-based contract-first design

WSCF.blue provides a user interface to define the options to create the classes' code, both client and service side (shown in figure 4.17).

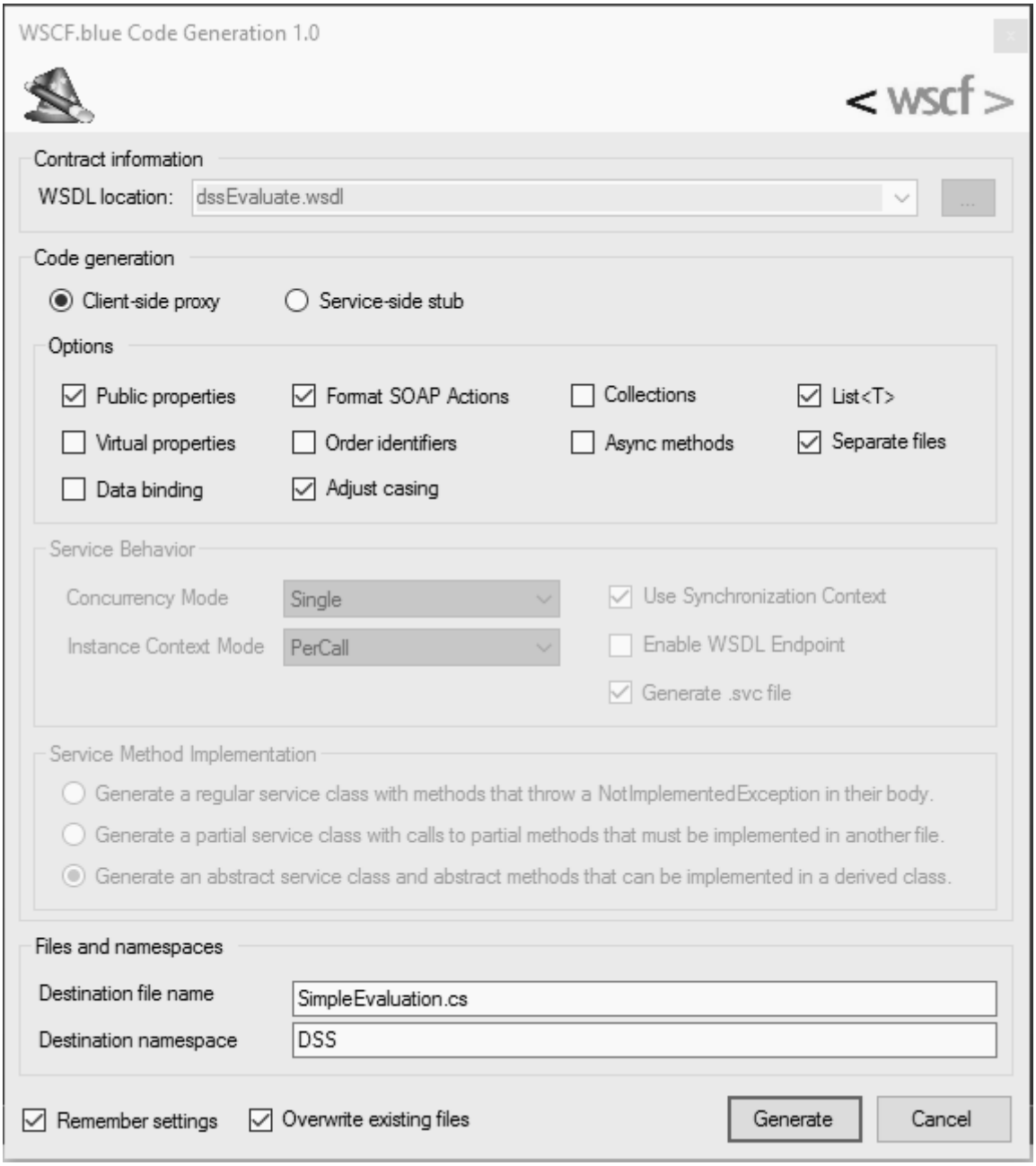


Figure 4.17: WSCF.blue user interface to define the options to create class code, both client and service side

The Platform Specific Model content of the specification includes three WSDLs: one is the "dssBaseComponents.wsdl" that defines the type and the message elements that are shared by the two functional profiles; the others are "dssEvaluate.wsdl" and "dss.wsdl" that contain the portType, binding and service elements of the simple evaluation and the complete functional profiles respectively. To develop a web service compliant to the simple evaluation profile, I blended the "dssBaseComponents.wsdl" with the "dssEvaluate.wsdl" in a single file.

The first attempt to generate code with WSCF.blue tool from the created file failed, because the first part of the WSDL provided was not correct. Some <part> parameters of different messages had the same name. After correction by renaming these parameters, the tool worked properly. Abother problem faced with WSCF.blue tool is that it is not compliant with Visual Studio versions after 2013. To use this tool, Visual Studio 2012 was installed on a virtual machine. The code for both client and service sides has been generated. The main classes generated from the XSD files has been collected into a library called DSS.dll. This library was enclosed into both the service and the client projects. The interface developed is standard, and the WSDL is available for any institution that would like to build a client to connect to the service. Instead, the implementation of the service function "evaluate" is customizable. I developed this function according to the content of the knowledge database described in the previous paragraph. The input of the function is a standard "evaluate" element. In this element, the KMs (at least one) to be used and the patient's data needed for the evaluation are specified. The program first checks if the KMs specified are actually stored into the database (checking by BusinessId and version).

The patient's data are stored into the semantic payload of the element "evaluate" (exactly into <evaluate><evaluationRequest><dataRequirementItemData><data>

<base64encodedPayload>).

The payload for the request is the clinical and contextual data that is evaluated by the DSS. The payload for the response is the guidance, such as for clinical interventions, provided by the DSS. The implementation guide affirms that vMR format shall be used as request payload, and one of the following shall be used as response payload: vMR, data type, string name-value pairs or Action Group. I decided to use vMR for both request and response payload.

The service receives and interprets the vMR, and checks if all data requested by the selected KM have been provided. If so, the recursive function described in the previous paragraph is called to evaluate the KM against patient's data. The evaluation is then encapsulated as vMR into the payload of the standard element "evaluationResponse" and it is returned as the output of the evaluate function.

After implementing the service, I developed an ad hoc client for the Ligurian HIV Network users to test the system. The client shows a user friendly interface integrated on the Ligurian

HIV Network web site. The client application collects the clinical data of a patient selected by the clinician and calls the evaluate service function, specifying also a specific set of KMs available in the database. To test the system and to examine the SOAP messages exchanged between the client and the service, a tracing system was set. The XmlWriterTraceListener class from the library “System.Diagnostics” has been used to convert tracing and debugging information into an XML-encoded text stream. The Service Trace Viewer Tool (SvcTraceViewer.exe) has been used to display the XML output. An example of SOAP message traced by this tool during a service call operated by the developed client application is reported in figure 4.18. The body of the SOAP message reports the evaluate element, which points out to the namespace of the standard DSS specifications. The element <kmEvaluationRequest> contains the list of KMs that the client wants to use. In this view, the semantic payload is collapsed. In the next paragraph a specific example of the implementation of a specific set of KMs will be presented.

```
<MessageLogTraceRecord>
    <HttpRequest xmlns="http://schemas.microsoft.com/2004/06/ServiceModel/Management/MessageTrace">
        <Method>POST</Method>
        <QueryString></QueryString>
        <WebHeaders>
            <Connection>Keep-Alive</Connection>
            <Content-Length>3732</Content-Length>
            <Content-Type>text/xml; charset=utf-8</Content-Type>
            <Accept-Encoding>gzip, deflate</Accept-Encoding>
            <Expect>100-continue</Expect>
            <Host>localhost:27956</Host>
            <VsDebuggerCausalityData>
                uIDPo0kXycCdxs1KvE1uB26Ub4QAAAAApGr6Q2eF106JG5U4lNwyMoPXOMKaTfhGrHTdemE3IysACQAA
            </VsDebuggerCausalityData>
            <SOAPAction>
                "http://www.omg.org/spec/CDSS/201012/dssWsdl/ISimpleEvaluation/Evaluate"
            </SOAPAction>
        </WebHeaders>
    </HttpRequest>
    <s:Envelope xmlns:s="http://schemas.xmlsoap.org/soap/envelope/">
        <s:Header>
            <To s:mustUnderstand="1" xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">
                http://localhost:27956/SimpleEvaluation.svc
            </To>
            <Action s:mustUnderstand="1" xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">
                http://www.omg.org/spec/CDSS/201012/dssWsdl/ISimpleEvaluation/Evaluate
            </Action>
        </s:Header>
        <s:Body xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
        xmlns:xsd="http://www.w3.org/2001/XMLSchema">
            <evaluate xmlns="http://www.omg.org/spec/CDSS/201012/dss">
                <interactionId scopingEntityId="it.hsanmartino.cds"
                interactionId="979aa143ff8a4cb294b56afb988f2d32"
                submissionTime="2017-04-07T10:05:18.4763818Z" xmlns=""></interactionId>
                <evaluationRequest clientLanguage="it-IT" clientTimeZoneOffset="+01:00">
                    <kmEvaluationRequest>
                        <kmId scopingEntityId="it.medinfo.km" businessId="NAIVESceltaNRTI" version="1.0"/>
                    </kmEvaluationRequest>
                    <dataRequirementItemData>
                        <driId itemId="RequiredDataId"></driId>
                        <data>
                            <informationModelSSId scopingEntityId="org.hl7.cds"
                            businessId="cdsinput:r2:CDSInput" version="2.0"/>
                            <base64EncodedPayload>
                        </data>
                    </dataRequirementItemData>
                </evaluationRequest>
            </evaluate>
        </s:Body>
    </s:Envelope>
</MessageLogTraceRecord>
```


Figure 4.18: An example of SOAP message traced by the tool during a service call operated by the client application

4.3.4 Specific implementation of DSS client to evaluate HAART therapy prescription in naive patients

Exploiting the GLIF representation of the BHIVA guidelines on HAART prescription, I developed a HAART prescription support service for naïve patients. The first implementation only regards naïve patients because it is easier to manage patients that never had therapy failure and have never developed drug resistances. The structure of the system developed is generic and highly reusable for different purposes, so further additions are very easily manageable. It is not necessary for the service to be changed, thanks to the use of standard interfaces and standard format for both input and output. The database structure remains unchanged too. To add a new KM, it only takes to add new lines to

specific tables of the database. The client application is the only piece that changes, because it is the conjunction ring between the standard service and the custom hospital database.

The BHIVA guidelines suggest that a naïve patient has to take a therapy based on two NRTI class active ingredients and one INI or NNRTI or PI class active ingredient. Two different KMs have been developed to independently manage the two NRTI class active ingredient selection and the third one. In figure 4.19, a sketch of an intermediate passage using Excel towards the translation from GLIF to the database content is reported. The database logic has been explained in the previous paragraph. According to it, different criteria evaluation steps are recorded into the intermediate table shown in figure, each with the related output (the drug active ingredient suggested) and weight. According to the guidelines, four weights from -2 to +2 excluding 0 have been set to indicate respectively:

-2: avoid this drug

-1: be careful

1: acceptable alternative

2: recommended

	A	B	C	D	E	F	G	H	I
1	**Result**	**Next**	**First**	**Criteria**	**Sym**	**Value**	**Drug1**	**Drug2**	**Weight**
2	False	11	True	Creatinine renal clearance [mL/min]	<	70	Atazanavir	Ritonavir	2
3	False	11	True	Creatinine renal clearance [mL/min]	<	70	Darunavir	Ritonavir	2
4	False	11	True	Creatinine renal clearance [mL/min]	<	70	Dolutegravir		2
5	False	11	True	Creatinine renal clearance [mL/min]	<	70	Elvitegravir		2
6	False	11	True	Creatinine renal clearance [mL/min]	<	70	Raltegravir		2
7	False	11	True	Creatinine renal clearance [mL/min]	<	70	Rilpivirina		2
8	False	11	True	Creatinine renal clearance [mL/min]	<	70	Efavirenz		1
9	True	11	True	Creatinine renal clearance [mL/min]	<	70	Atazanavir	Ritonavir	2
10	True	11	True	Creatinine renal clearance [mL/min]	<	70	Darunavir	Ritonavir	2
11	True	11	True	Creatinine renal clearance [mL/min]	<	70	Dolutegravir		2
12	True	11	True	Creatinine renal clearance [mL/min]	<	70	Elvitegravir		-2
13	True	11	True	Creatinine renal clearance [mL/min]	<	70	Raltegravir		2
14	True	11	True	Creatinine renal clearance [mL/min]	<	70	Rilpivirina		2
15	True	11	True	Creatinine renal clearance [mL/min]	<	70	Efavirenz		1
16	False	12	False	HIV 1 RNA [#/volume] (viral load)	<	100000	Rilpivirina		-2
17	True	12	False	HIV 1 RNA [#/volume] (viral load)	<	100000			
18	False	13	False	Tubercolosi polmonare	+				
19	True	13	False	Tubercolosi polmonare	+		Dolutegravir		1
20	True	13	False	Tubercolosi polmonare	+		Efavirenz		2
21	False	14	False	Rifampicina	+				
22	True	14	False	Rifampicina	+		Raltegravir		-1
23	True	14	False	Rifampicina	+		Nevirapina		-2
24	True	14	False	Rifampicina	+		Ritonavir		-2
25	True	14	False	Rifampicina	+		Cobicistat		-2
26	False	15	False	Neurocognitive disorders	+				
27	True	15	False	Neurocognitive disorders	+		Efavirenz		-2
28	False	16	False	Rischio cardiovascolare	+				
29	True	16	False	Rischio cardiovascolare	+		Fosamprenavir	Ritonavir	-2
30	True	16	False	Rischio cardiovascolare	+		Lopinavir	Ritonavir	-2
31	True	16	False	Rischio cardiovascolare	+		Maraviroc		-2
32	False	17	False	ABC	+				
33	True	17	False	ABC	+				
34	False	END	False	3TC	+				
35	True	END	False	3TC	+		Dolutegravir		-1

Figure 4.19: Part of the guideline rules explicitation for KM database table immission

The next step was the insertion of this knowledge into the corresponding tables of the database. The normalized structure of the database avoids row fields' repetitions that are visible in the Excel file.

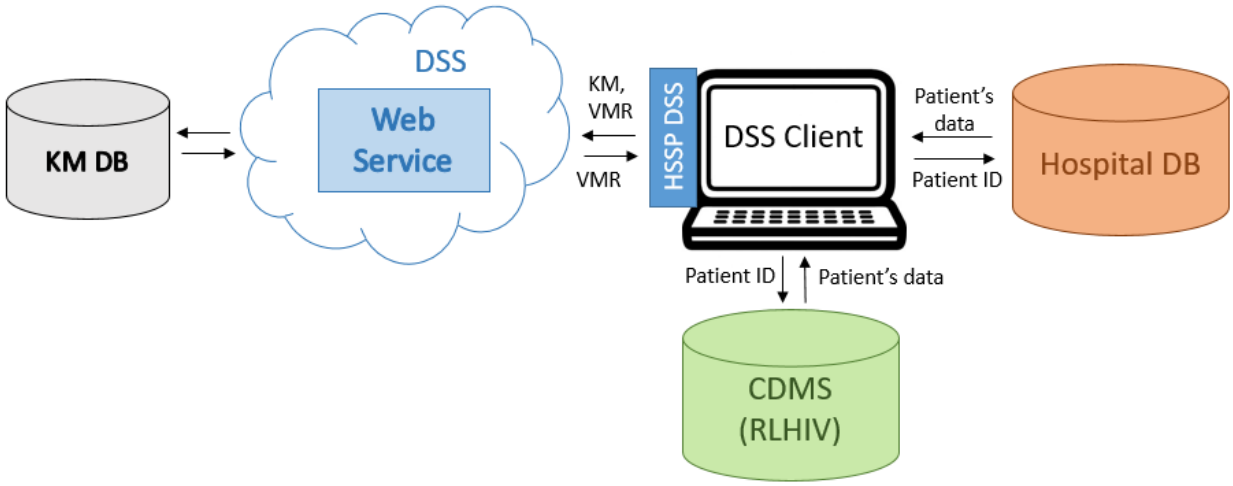


Figure 4.20: Schema of the communication between the main actors involved in the CDSS execution

To test the knowledge module created, I built a client embedded into the Ligurian HIV Network to support physicians of San Martino hospital in prescribing a new therapy to patients. A similar client application could be done also for Galliera and Sanremo hospitals, which have automatic connection to LIS, to retrieve data that are not available on the Ligurian HIV Network. The interface is simple and user friendly, as it is appreciable from figures 4.21, 4.22, 4.23. With the first screen of the program, the physician can choose the patient to be evaluated.

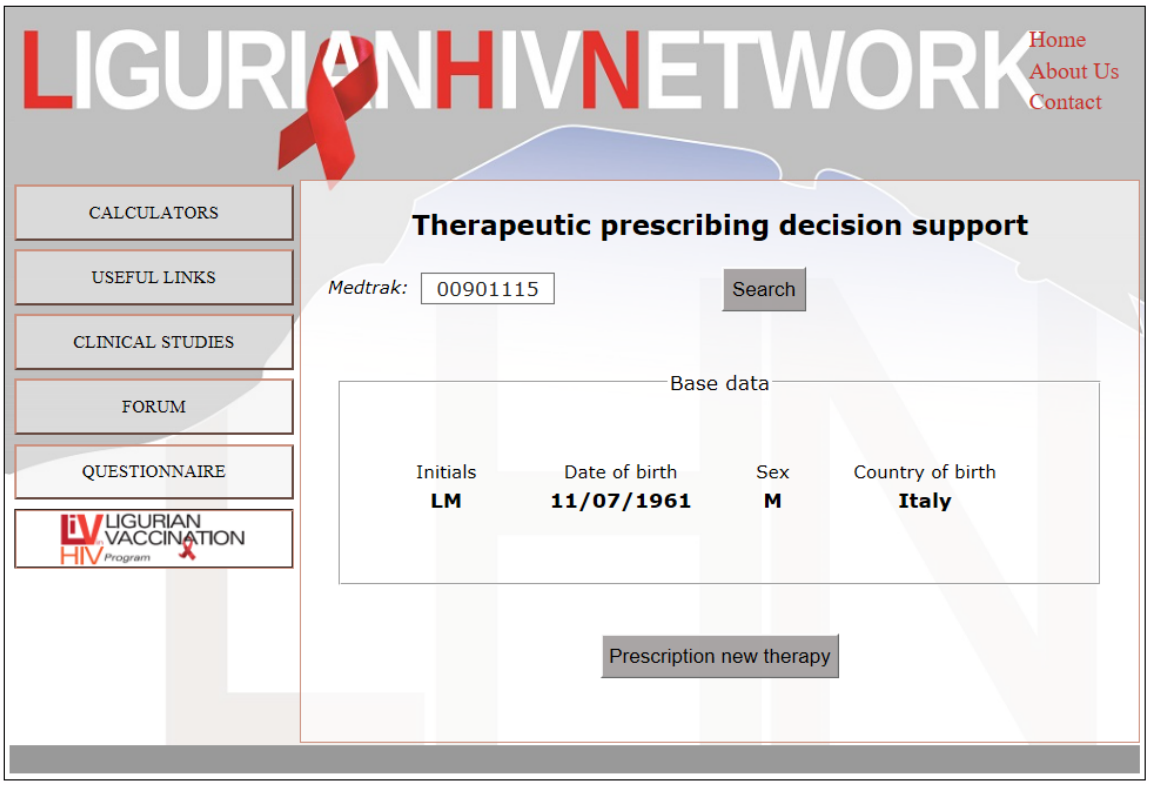


Figure 4.21: Ligurian HIV Network web interface that provides HAART prescription support for a specific patient. Patient selection and anagraphic data display

There is also the possibility to call the prescription support from inside a patient section. In both cases, the next screen provides the list of all NRTI active ingredients colored according to the prescription support. Figure 4.22 displays the interface with the color legend. Selecting two of the proposed NRTIs it is possible to access to the second evaluation, according to the second KM created, to evaluate the third agent (figure 4.23). The next page displays the remaining active ingredients divided per class, colored according to the DSS guidance. Selecting the third agent, a text shows a summarization of the therapy selected and a comment about the appropriateness according to the selected patient's data.

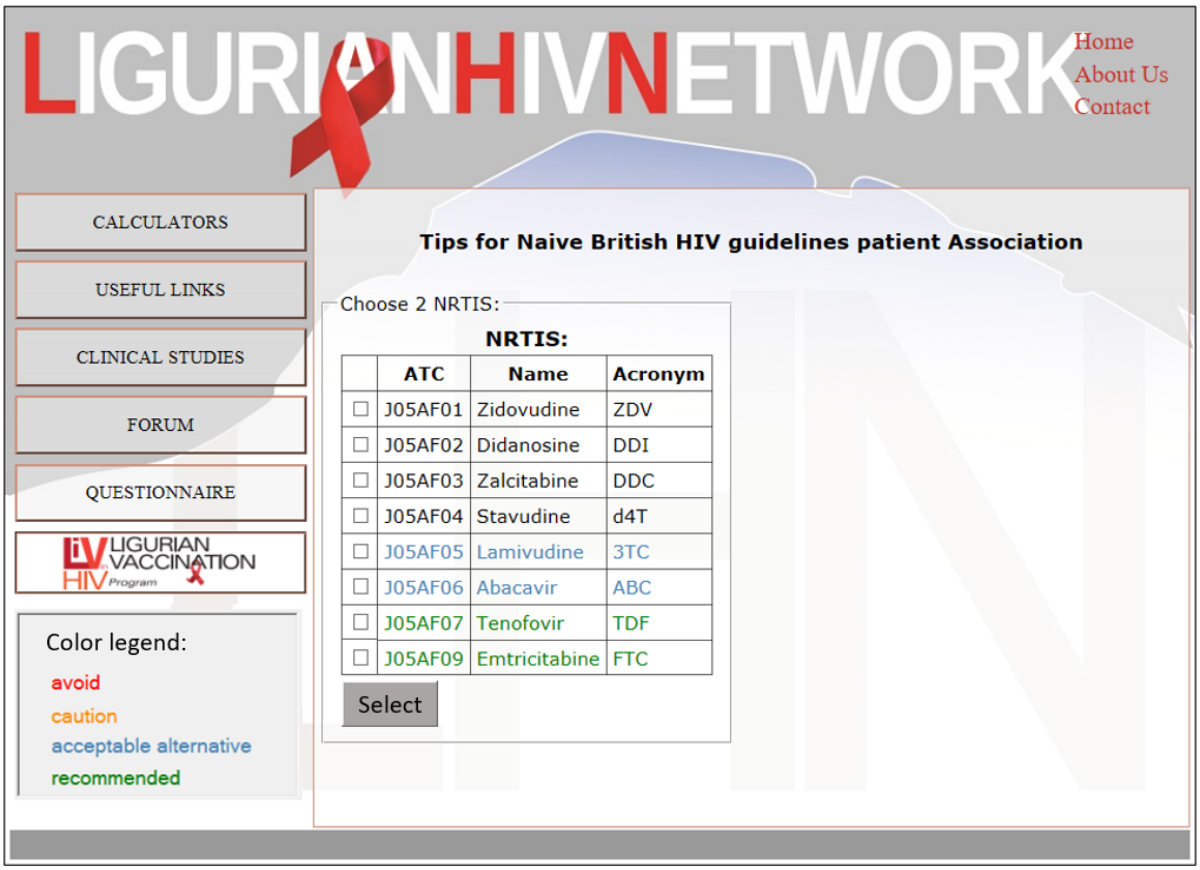


Figure 4.22: Ligurian HIV Network web interface that provides HAART prescription support for a specific patient. NRTIs choice with standard DSS guidance expressed with colors. The system provides an extremely user-friendly interface that conceals the complexity behind the system.

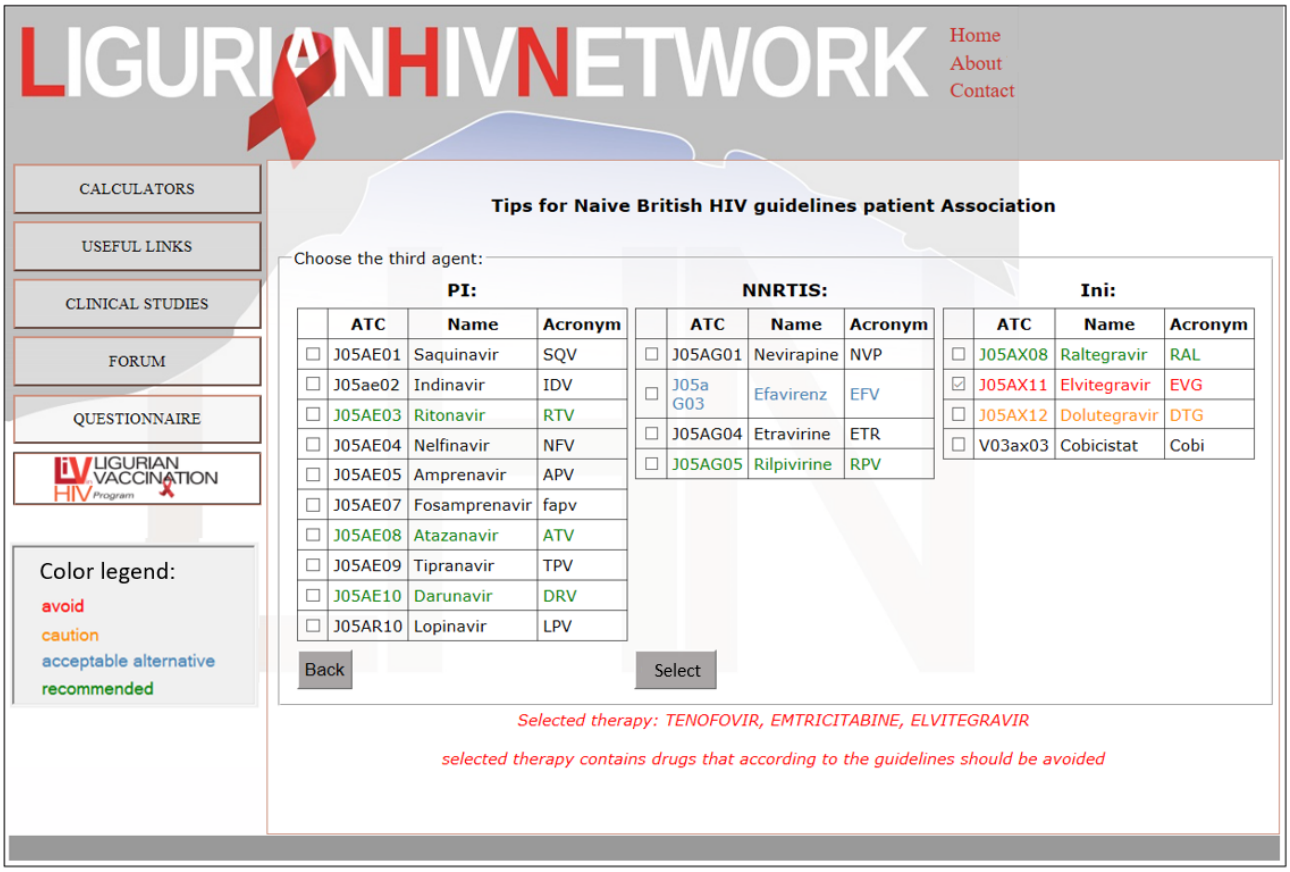


Figure 4.23: Ligurian HIV Network web interface that provides HAART prescription support for a specific patient. Third agent choice with standard DSS guidance expressed with colors. In the recap of the selected therapy, advices about the selected drugs are displayed.

The interface is very simple and user friendly and masks the complexity behind the system. The actors implied and the related list of calls among them is represented in the UML diagram in figure 4.24.

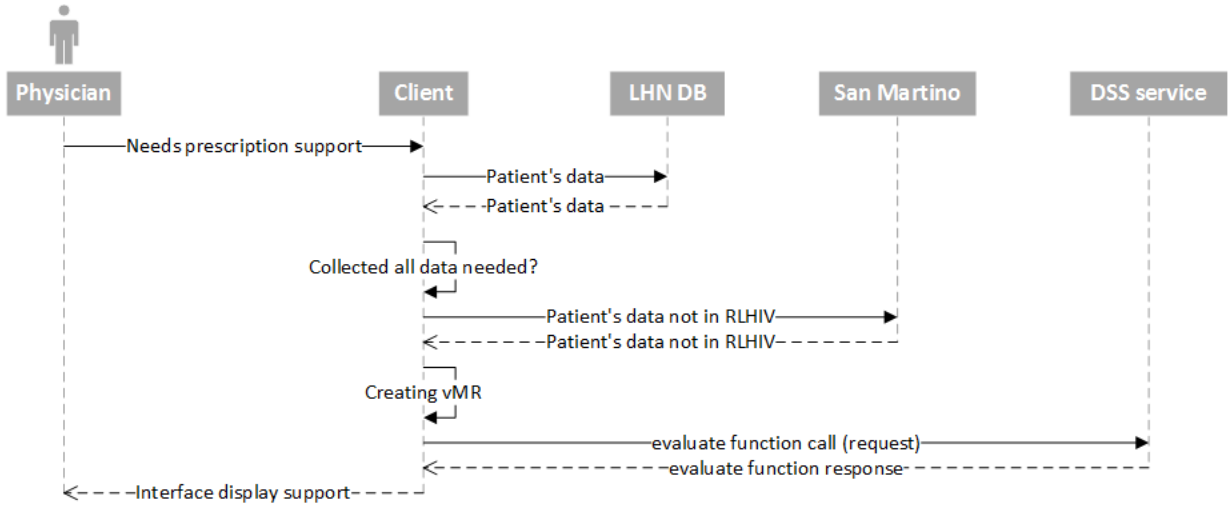


Figure 4.24: UML sequence diagram representing the data exchange among the users involved in the decision support process

The client is embedded into the Ligurian HIV Network web interface. The physician addresses the client to receive prescription support for a specific patient. The client asks for patient's data to the Ligurian HIV Network database. Then, the client checks if all the patient's data needed by the knowledge module has been provided by the LHN database, and if the answer is negative, another call to the San Martino hospital database is performed to retrieve all data. With this data, the client can create the vMR document that will be encapsulated into the evaluate object together with the KM to be used; this will be used as the input when calling the evaluate service function. The service elaborates the information received, evaluates it and returns an evaluationResponse object with the decision support information, which is the list of drug active ingredients suggested and the related weights. In order to codify the guidance on the most appropriate list of drug active ingredients, the response vMR extends the attribute element for the entity ClinicalStatement as SubstanceAdministrationProposal using the template vMR Extended Type according to "HL7 Virtual Medical Record for Clinical Decision Support (vMR-CDS) Templates, Release 1". The template code identifier has root 2.16.840.1.113883.3.1829.11.14.8.7 and name "attribute". The complete parameters are listed in table 4.4, with the possible values used to represent the list of drug active ingredients considered and the related weights in table 4.5.

NRTI active drugs are evaluated in couples (combination of two). To represent this concept, the relatedEntity of the substance entity is used.

The response vMR is re-elaborated by the client to provide user friendly support to the physician.

The sample scenario created to support HAART prescription was set up at the end of 2016, and it was thoroughly tested in the following months. After about a year of usage, this system should have positively affected the antiretroviral prescriptions to Ligurian HIV+ naïve patients in 2017. To evaluate its real impact on clinical care, it was necessary to find a way to measure the improvements in the quality of life, in the prescription appropriateness and in therapy adherence.

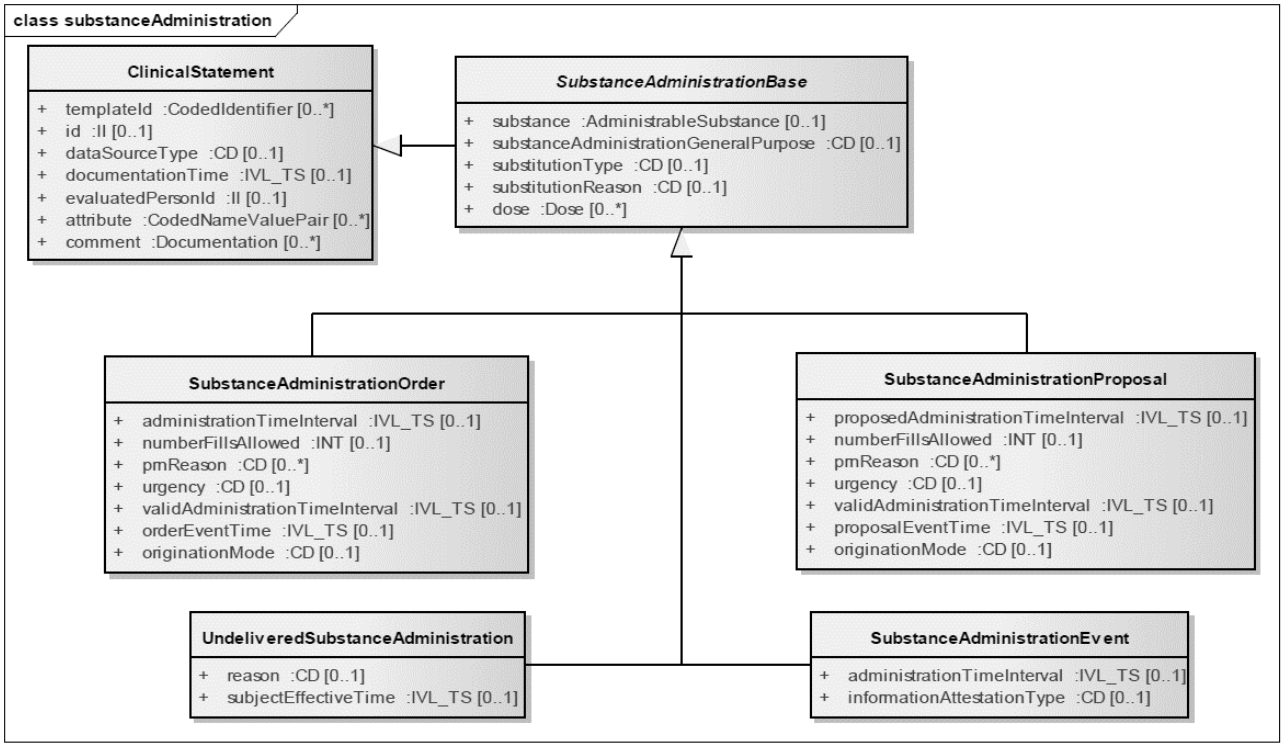


Figure 4.25: substanceAdministration class diagram

Data Element Name	vMR Data Element	Cardinality	Mandatory	Conformance	Fixed Value	vMR Data Type	Constraints
Template ID	templateId	1..1	Y	R	Y	CodedIdentifier	root SHALL be 2.16.840.1.113883.3.1829.11.14.8.7 identifier name SHALL be "Attribute"
Name of Concept	name	1..1	Y	R		ST	This token represents the name of the extension attribute
Concept Semantic Code	semanticCode	0..1	N			CD	The code SHALL represent a concept from a managed terminology
Value of Concept	value	1..1	Y	R		ExtendedVmrTypeBase	The value SHALL be expressed using either a datatype that extends ANY, or using any ExtendedVmrType

Table 4.4: Schema of the vMR Extended Type template defined into HL7 Virtual Medical Record for Clinical Decision Support (vMR-CDS) Templates, Release 1

Name	Value
-2	Avoid
-1	Caution
1	Acceptable alternative
2	Recommended

Table 4.5: List of all the possible values used to recommend or avoid the drug active ingredients considered and the related weights

4.3.4.1 Quality of life improvement

To give an objective measurement of the quality of life, I referred to the last results evidenced in IANUA study [78]. According to this study, the values of Lymphocytes T CD4 and viral load (HIVRNA) parameters can be optimal predictors of the quality of life of HIV infected patients. Lymphocytes T CD4 are positively correlated with quality of life, while HIVRNA is inversely correlated. Appendix A1 shows two tables with CD4 and HIVRNA values in the last three years for patients that started antiretroviral therapy from 2015 to 2017. To assess if the quality of life of the patients considered had increased after the setup of the HAART prescription support tool, values of the two-year period 2016/2017 were considered, in order to evaluate if significant differences were registered between 2016 and 2017. Moreover, if the results highlighted a significant improvement from 2016 to 2017, I thought it would be interesting to prove that no significant improvement is registered in the period before 2016, to demonstrate that the improvement has to be attributed to the system developed.

Data registered reveal that from 2015 to 2016 there is no significant improvement both in HIVRNA and CD4 values, as we considered an interval of confidence of 99%. From 2016 to 2017 there is a highly significant drop of HIVRNA values ($p=4.2 \cdot 10^{-4}$) and a significant increase of CD4 values ($p=5.8 \cdot 10^{-3}$).

4.3.4.2 HAART prescription appropriateness improvement

Prescription appropriateness on such a large sample of patients can be assessed through a score system based on the Italian guidelines. Specifically, the system attributes to each HAART regimen a score that combines the recommendation suggested by the Italian guidelines and the relative monthly costs. The most appropriate and cheaper therapeutic regimens get a maximum score of 1.00, while the other regimens are assigned a decrementing score based on the two parameters above (range: 0.001-1). The score system was used in VELA study and it demonstrated to be an effective tool for monitoring the correlation of treatment appropriateness, drug expense and clinical outcomes [85]. Overall appropriateness score was calculated for therapy prescribed in 2015 and in 2016 to naïve patients and its results were respectively 0.60 and 0.75. The Student's T test reveals that the prescription appropriateness improvement that was registered was statistically significant ($p=1.7 \cdot 10^{-4}$). Monthly therapy mean cost in 2015 was € 919.60 ± 247.19. In

2016 the average monthly cost was significantly decreased to € 816.18 ± 150.42 ($p=1.4 \cdot 10^{-4}$). Complete data are reported in appendix A3.

4.3.4.3 Therapy adherence improvement

Therapy adherence monitoring is assisted by a system that is currently under refinement, which automatically retrieves data from San Martino hospital's therapy dispense system. This system deals with both ambulatory delivery and unit dose management (the robotized system of drug administration to hospitalized patients). Adherence is calculated according to the formula below (1):

$$Adherence = \frac{1}{\#recurrence} \frac{\#delivered\ doses + \#remaining\ doses}{\Delta days} \quad (1)$$

where:

- #recurrence is the number of doses that the patient has to take daily
- #delivered doses is the number of doses that the pharmacy delivered to the patient
- #remaining doses is the number of remaining doses if the drug was, as desirable, retired before the end of the cycle.
- Δdays is the number of days between the date of delivery of the drug and the expected date of the end of the therapeutic cycle.

Adherence calculated in this way can range from 0 to 1. The values of adherence were calculated on patients undergoing new therapy in the period 2015-2017. The table containing all the values is reported in appendix A2. A significant improvement was registered in therapy adherence from 2016 to 2017 ($p=1.7 \cdot 10^{-5}$), while no significant difference is registered from 2015 to 2016.

4.3.4.4 Timings monitoring

Speed is a focal point in a system that provides decision support and it is highly recognized the importance of velocity optimization [86]. Timings have been accurately monitored during the testing phase of the HAART prescription support system developed. Timings of the two evaluation phases were measured. In the evaluation phase, the actions in table 4.6 were considered:

Actor	Action
Client	Patient's data retrieve from the electronic data source (hospital EHR or CDMS)
Client	vMR construction with patient's data and KMs
Client	vMR dispatch to the web service
Web Service	vMR validation
Web Service	Evaluation of the KMs according to the data contained into the vMR
Web Service	Response vMR construction with the evaluation results
Web Service	Response vMR dispatch to the client
Client	vMR validation
Client	Display of the evaluation results

Table 4.6: List of all actions carried out by the client and the web service in the evaluation phase

The client, the DSS service and the data sources are all on the same network, even if not on the same server machine. Therefore, the timing measured could be misrepresented. To assess the real capabilities of the system and to evaluate its actual efficiency, a proof of evidence with an external client was developed. This client with its fake patients' data source were installed on a server within the university network, to simulate a call to the standard DSS web service by an external entity. The related timings were measured.

In both cases, the timings were measured through the "Page load time" Google web extension, which measures page load time and displays it in the toolbar (figure 4.26).

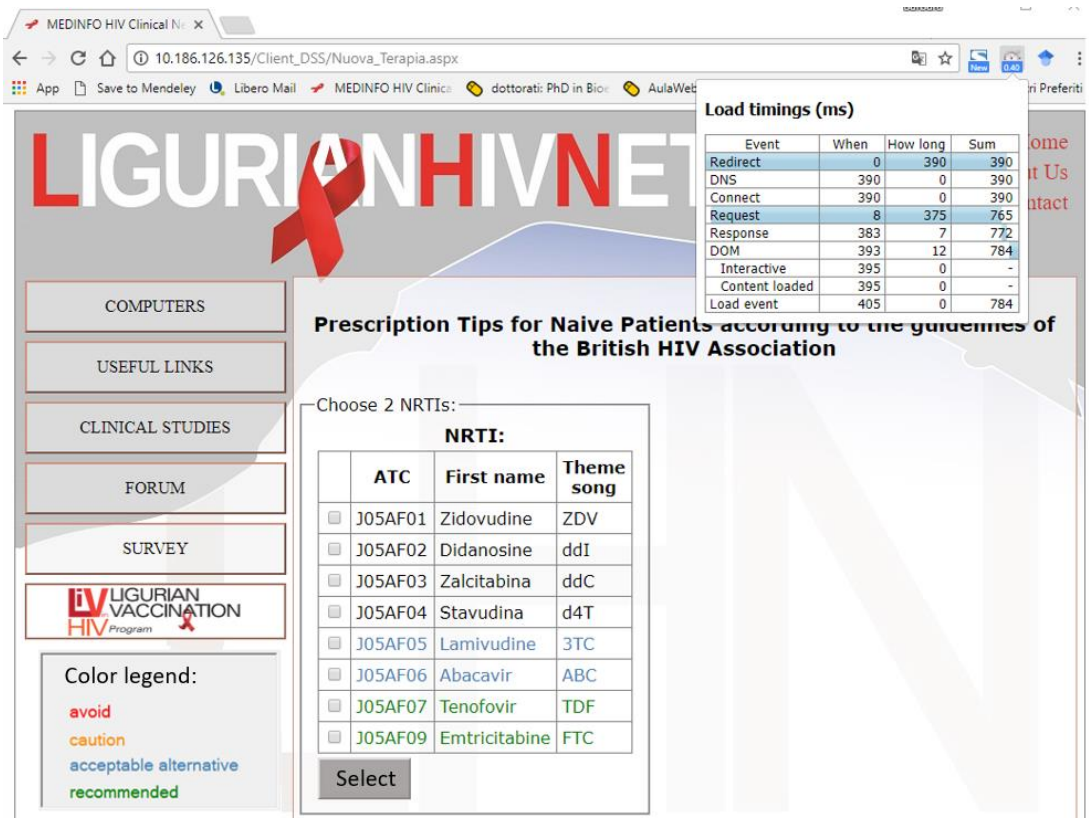


Figure 4.26: Timings measuring through the "Page load time" web extension of Google

The results of the timings measured are displayed in table 4.7.

	Client in hospital server		External client	
	Hospital network		University network-hospital network	
	First DSS evaluation response time (s)	Second DSS evaluation response time (s)	First DSS evaluation response time (s)	Second DSS evaluation response time (s)
09:00	0.33	0.44	0.48	0.53
09:30	0.41	0.39	0.64	0.47
10:00	0.38	0.37	0.61	0.45
10:30	0.35	0.40	0.73	1.20
11:00	0.37	0.41	0.68	0.45
11:30	0.43	0.38	0.69	0.52
12:00	0.35	0.41	0.78	0.47
12:30	0.35	0.36	0.58	0.45
14:30	0.36	0.41	0.64	0.46
15:00	0.35	0.45	1.30	0.47
15:30	0.36	0.49	0.73	0.51
16:00	0.41	0.37	1.15	0.46
16:30	0.35	0.40	0.52	0.50
17:00	0.40	0.38	0.69	0.49
17:30	0.35	0.41	0.48	0.47
18:00	0.37	0.40	0.74	0.47
Average	0.37	0.40	0.72	0.52
Std dev	0.03	0.03	0.22	0.18

Table 4.7: Timings measured in executing the list of all actions carried out by the client and the web service in the evaluation phase (crf table 4.6). The timings were measured in both the architecture configurations developed: for the client inside the hospital server (that is the case of the Ligurian HIV Network embedded HAART prescription support) and for an external client (that is the proof configuration created on the university server). Timings were monitored during all the day at different time intervals.

The measuring were conducted in different moments of the day with scheduled intervals, in order to consider the variability within daytime. No significant difference was noticed among the intervals considered or between the two DSS evaluations (related to the two different KMs). A significant difference between the means of the two different architectural samples is registered with T Student Test (p value = $2.6 \cdot 10^{-6}$). In both cases, timings are very short with a mean value of 0.385 ± 0.035 seconds when all the architecture is inside the hospital server and 0.620 ± 0.221 seconds when an external client calls the DSS web service.

5 Discussion and conclusion

The platform developed is an example of Learning Health System applied to chronical infectious disease field. Knowledge is generated from the data flowing from routine care, and it is fed back into the healthcare system to improve outcomes, through the decision support service implemented. The use of EHRs in both patient care and clinical research is a key element of the LHS vision and the standardization is necessary to inter-institutions data exchange.

The already existing platform was enforced and widened, in order to make it the data base for the learning health system. User-free daily collection of clinical data from LIS was fine-tuned. Three hospitals are actually involved in automatic data extraction: San Martino, Galliera and Sanremo hospitals. The automatic and daily updated flow of data have been enriched with microbiologic tests, antibiotic resistance tests to bacteria, serology data, immunization administration and therapy withdraws. After these extensions of the platform, the "Ligurian Vaccination in HIV Project" was developed in collaboration with the Department of Health Sciences (DiSSal) for the monitoring of vaccination coverage in HIV population [74].

A project about clinical data re-use applied to tuberculosis management has also been developed, to consider a different approach to infectious diseases [76]. Indeed, tuberculosis is not chronical but could have relapses if not properly treated. The platform allows TB patients' surveillance by tracking their transfers to other hospitals or outpatient departments: a complete surveillance could be reached with a total adherence of hospitals to the network [75].

Continuous and close cooperation with physicians working in Ligurian infectious diseases wards was necessary to the development of the platform, since coordination and collaboration are essential features to achieve improvements in healthcare. Several meetings with the participation of other professional figures like psychologists and economists have periodically been organized, with the aim to create a multidisciplinary working group. Many clinical studies have been carried on within this team exploiting the developed platform; initially data entry was manually executed, but the last clinical trials performed benefit from the automatic data sharing. Appreciating the low effort in

participating in these clinical trials, physicians of connected centers requested an extension of this mechanism to facilitate the participation to external trials too. In chronical infectious diseases field, there are many research databases that collect data at national level [50] [51] [52]. Solutions to fulfill this request have been set up for ARCA and CISAI databases. A semi-automatic solution has been set to enable physicians to connect from CISAI web site to the network, asking for the data of interest, in a specific time interval. This solution is not fully automatable, due to intrinsic complications in the trial structure that requires human supervision. The connection with ARCA database enables a complete automatic and bidirectional data exchange between the two platforms, but on a limited number of parameters. In both cases, the first step was an initial matching of the anonymous codes used by the two systems to identify patients. The second step consisted in a manual matching of the clinical parameters involved in both sites and their translation into standard LOINC codes according to their meaning, measurement units and properties. To feed ICONA database without data manual copy, Excel files containing the interest information of patients involved are presently downloaded from the network and reloaded into ICONA database by their technicians. A fully automated system for this research database will be set up when bureaucratic constraints will permit it.

Generally, clinical trials generate data on safety and efficacy of a medication or device. This knowledge used together with existing clinical guidelines, could form the basis for a decision support system. To express clinical guidelines in computable format, different standards exist. GLIF 3 (GuideLine Interchange Format) is a language for the structured representation of clinical guidelines. The GLIFeditor developed by Medical Objects has been used to draw the logical flux that describes the "BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015" of the British HIV Association. This guideline, together with the national "Linee guida italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnostic-clinica delle persone con infezione da HIV1" has been used in VELA project. VELA (Valore Esiti Liguri per l'Appropriatezza della terapie HIV) is one of the regional studies conducted on the platform, whose main objective is the evaluation of the appropriateness of HIV therapy prescribed in the Ligurian centers of infectious diseases during 2015 and 2016 according to guidelines. Using GLIF editor, patients' states, decisions, actions and the related links were descripted in a computer interpretable way. To embed automatic decision steps, scripts in GELLO language was

integrated, to query archetype data or data from vMR (virtual medical record). After representing the acquired knowledge using GLIF, in order to use this knowledge as the basis of the decision support system, I developed a database structure suitable to store it and to make it available to a computer program. The database has a flexible structure, thanks to normalization, in order to manage knowledge maintenance and versioning. This database is able to reproduce the GLIF flux diagram logic, assuming that each knowledge module (KM) should have an ordered collection of criteria that has to be evaluated according to a specific comparison operator. The decision support service was developed according to the HSSP standard Decision Support Service (DSS) Release 1. The decision support service utilizes patients' data for the execution of the evaluation logic that is contained into the knowledge modules. The DSS service is called by a client, which specifies the knowledge modules to be used in the evaluation phase and provides patient's data. The primary functionality of a DSS service is to receive patient's data as input and to return patient specific conclusions as output. For both input and output, the HeD group suggests the use of the HL7 Virtual Medical Record (vMR). The normative specifications defined in the implementation guide consist of two functional profiles: the HSSP Simple Evaluation DSS Functional Profile and the HSSP Complete DSS Functional Profile. The service developed grants conformance with the HSSP Simple Evaluation DSS Functional Profile version 1.0. The evaluate operation evaluates one or more knowledge modules using the data provided and returns the results of the evaluation. To describe the service interface, a common language exists: the Web Service Definition Language (WSDL). WSDL documents have an associated XSD (XML Schema Definition) file that describes the static structure of the complex data types being exchanged by the service methods. A WSDL document and the associated XSD files are provided by HL7 with the specification of the DSS. I developed the WCF web service starting from the WSDL (the schema-based contract-first design approach) using WSCF.blue tool. To test the web service functionalities, I developed a web client application that creates a vMR document to wrap patient's clinical data needed by the DSS service. The web service (WCF service) and the web client were realized using.NET framework 4.5 in Visual Basic language. To test these programs in a real scenario, with real data collected by the Ligurian HIV Network, I developed a HAART prescription support service for naïve patients exploiting the GLIF representation of the BHIVA guidelines on HAART prescription. The structure of the system developed is generic and highly reusable for different purposes, so further additions

are very easily manageable. It is not necessary for the service to be modified, thanks to the use of standard interfaces and standard format for both input and output. The database structure remains unchanged too. To add a new knowledge module, it only takes to add new lines to specific tables of the database. The client application is the only piece that changes, because it is the conjunction ring between the standard service and the custom hospital database. The flexible and standardized structure makes the network suitable to future extensions and the decision support system ready to new scenarios.

The sample scenario created to support HAART prescription was thoroughly tested and the positive impact on clinical care was measured in terms of quality of life, prescription appropriateness and therapy adherence improvements. The benefits expected from the employment of the system developed were verified. Student's T test was used to establish if significant differences were registered between the data collected before and after the introduction of the system developed. The results were extremely acceptable with the minimum p value in the order of 10^{-5} and the maximum in the order of 10^{-3}. We can reasonably affirm that the improvements registered in the three analysis considered are ascribable to the system developed and not to other factors, because no significant differences were found in the period before its release.

Speed is a focal point in a system that provides decision support and the importance of velocity optimization is highly recognized [86] [45]. Timings were monitored to evaluate the responsiveness of the system developed. We obtained extremely acceptable results, with the waiting times of the order of 10^{-1} seconds.

The importance of the network developed has been widely recognized by the medical staff involved, as it is also assessed by a questionnaire they compiled to evaluate their level of satisfaction. From the questionnaires, a great level of satisfaction concerning the developed system arose. In particular, all the first scenario users agreed on the indisputable benefits that the adoption of the automatic system could provide on the workload. That condition is confirmed by the high grades given by the users belonging to the second scenario.

During the implementation of this project, several difficulties were found and addressed. The high level of standardization allows the system to involve other healthcare facilities. The initial aim was to include all the infectious disease departments of Liguria region into the project, but we encountered bureaucratic difficulties. One persistent obstacle to the

transformation of existing systems into a linked LHS is the friction that may arise between researchers, healthcare providers, and health systems. Many health systems and individual hospitals are primarily configured to support the efficient provision of patient care, but are less accommodating to the presence of research activities within the same space. Thus, we encountered several difficulties in persuading hospitals' HIS administrators and external clinical trials administrators to give us access to data, even with the ethical committee approval. Once tackled these challenges, bureaucratic timing slowed down the implementation phase.

The system developed has few limitations that could be arranged in future developments. The CDSS client is only able to fill vMR documents with structured data, covering diagnosis, laboratory results and medication orders. Currently free text information cannot be processed. To overcome this limitation, natural language processing tools could be employed. Another limitation of the system developed is that the LHS cycle is not fully automated: a manual passage is required to insert the GLIF coded guidelines into the knowledge database. In future developments a tool that automatically validates GLIF code and embeds it into the knowledge database structure could be implemented, to bypass the manual insertion of a new knowledge module inside the platform. Few difficulties were identified in this process: a GELLO compiler is necessary to completely interpret the XML file with the GLIF guidelines. The GELLO code could be embedded into the XML file into a string type field, to describe the decision options. Another problem is that the "display_name" attribute of the "Decision_Option" tag is a free text field; it should be forced to a coded value to maintain the meaning of the objects within different institutions. Furthermore, the "Medical_Task" in the action tasks is a coded value, but the code system is not associated to an OID that univocally identifies it. Knowledge Artifact standard should be considered in the process of GLIF code integration into the knowledge database structure.

Another future development should be the implementation of the HSSP Complete DSS Functional Profile, instead of the HSSP Simple Evaluation DSS Functional Profile to include the extended functionalities discussed in the "HSSP HL7 Decision Support Service (DSS)" paragraph.

Bibliography

[1] M.-P. Gagnon, M. Desmartis, M. Labrecque, J. Car, C. Pagliari, P. Pluye, P. Frémont, J. Gagnon, N. Tremblay, and F. Légaré, "Systematic review of factors influencing the adoption of information and communication technologies by healthcare professionals," *J. Med. Syst.*, vol. 36, no. 1, pp. 241–277, 2012.

[2] S. S. Jones, R. S. Rudin, T. Perry, and P. G. Shekelle, "Health information technology: an updated systematic review with a focus on meaningful use," *Ann. Intern. Med.*, vol. 160, no. 1, pp. 48–54, 2014.

[3] J. Mantas, "Electronic health record.," *Stud. Health Technol. Inform.*, vol. 65, pp. 250–257, 2002.

[4] Agenzia per l'Italia Digitale, "Fascicolo Sanitario Elettronico." [Online]. Available: https://www.fascicolosanitario.gov.it/. [Accessed: 24-Nov-2017].

[5] C. Grossmann, B. Powers, and J. M. McGinnis, "Digital Infrastructure for the Learning Health System," 2011.

[6] T. P. Giordano, A. L. Gifford, A. C. White, M. E. S. Almazor, L. Rabeneck, C. Hartman, L. I. Backus, L. A. Mole, and R. O. Morgan, "Retention in care: a challenge to survival with HIV infection," *Clin. Infect. Dis.*, vol. 44, no. 11, pp. 1493–1499, 2007.

[7] C. Grossman and J. M. McGinnis, *Digital infrastructure for the learning health system: the foundation for continuous improvement in health and health care: workshop series summary*. National Academies Press, 2011.

[8] C. P. Friedman, A. K. Wong, and D. Blumenthal, "Achieving a nationwide learning health system," *Sci. Transl. Med.*, vol. 2, no. 57, p. 57cm29-57cm29, 2010.

[9] A. Geissbuhler, C. Safran, I. Buchan, R. Bellazzi, S. Labkoff, K. Eilenberg, A. Leese, C. Richardson, J. Mantas, P. Murray, and G. De Moor, "Trustworthy reuse of health data: A transnational perspective," *Int. J. Med. Inform.*, 2013.

[10] C. Friedman and M. Rigby, "Conceptualising and creating a global learning health system," *Int. J. Med. Inform.*, vol. 82, no. 4, pp. e63–e71, 2013.

[11] P. P. Yu, "Knowledge Bases, Clinical Decision Support Systems, and Rapid Learning in Oncology," *J. Oncol. Pract.*, p. JOP-2014, 2015.

[12] I. Sim, P. Gorman, R. A. Greenes, R. B. Haynes, B. Kaplan, H. Lehmann, and P. C. Tang, "Clinical decision support systems for the practice of evidence-based medicine," *J. Am. Med. Informatics Assoc.*, vol. 8, no. 6, pp. 527–534, 2001.

[13] J. V Selby and S. H. Lipstein, "PCORI at 3 years—progress, lessons, and plans," *N. Engl. J. Med.*, vol. 370, no. 7, pp. 592–595, 2014.

[14] L. J. F. Rutten, A. Alexander, P. J. Embi, G. Flores, C. Friedman, I. V Haller, P. Haug, D. Jensen, S. Khosla, and G. Runger, "Patient-Centered Network of Learning Health Systems: Developing a resource for clinical translational research," *J. Clin. Transl. Sci.*, vol. 1, no. 1, pp. 40–44, 2017.

[15] C. B. Forrest, P. A. Margolis, L. C. Bailey, K. Marsolo, M. A. Del Beccaro, J. A. Finkelstein, D. E. Milov, V. J. Vieland, B. A. Wolf, and F. B. Yu, "PEDSnet: a national pediatric learning health system," *J. Am. Med. Informatics Assoc.*, vol. 21, no. 4, pp. 602–

606, 2014.

[16] S. N. Murphy, G. Weber, M. Mendis, V. Gainer, H. C. Chueh, S. Churchill, and I. Kohane, “Serving the enterprise and beyond with informatics for integrating biology and the bedside (i2b2),” *J. Am. Med. Informatics Assoc.*, vol. 17, no. 2, pp. 124–130, 2010.

[17] A. S. of C. Oncology, “CancerLinQ.” 2014.

[18] A. Shah, A. K. Stewart, A. Kolacevski, D. Michels, and R. Miller, “Building a rapid learning health care system for oncology: why CancerLinQ collects identifiable health information to achieve its vision,” *J. Clin. Oncol.*, p. JCO650598, 2016.

[19] G. M. Weber, S. N. Murphy, A. J. McMurry, D. MacFadden, D. J. Nigrin, S. Churchill, and I. S. Kohane, “The Shared Health Research Information Network (SHRINE): a prototype federated query tool for clinical data repositories,” *J. Am. Med. Informatics Assoc.*, vol. 16, no. 5, pp. 624–630, 2009.

[20] M. D. Natter, J. Quan, D. M. Ortiz, A. Bousvaros, N. T. Ilowite, C. J. Inman, K. Marsolo, A. J. McMurry, C. I. Sandborg, and L. E. Schanberg, “An i2b2-based, generalizable, open source, self-scaling chronic disease registry,” *J. Am. Med. Informatics Assoc.*, vol. 20, no. 1, pp. 172–179, 2013.

[21] K. Marsolo, P. A. Margolis, C. B. Forrest, R. B. Colletti, and J. J. Hutton, “A Digital Architecture for a Network-Based Learning Health System: Integrating Chronic Care Management, Quality Improvement, and Research,” *eGEMs*, vol. 3, no. 1, 2015.

[22] “Standards & Interoperability (S&I) Framework - Health eDecisions Homepage.” [Online]. Available: http://wiki.siframework.org/Health+eDecisions+Homepage.

[23] K. Kawamoto, T. Hongsermeier, A. A. Boxwala, B. Rhodes, A. A. Morton, J. Parker, C. J. Nanjo, V. C. Lee, B. K. Minton, and D. Sottara, “Health eDecisions (HeD): a Public-Private Partnership to Develop and Validate Standards to Enable Clinical Decision Support at Scale.,” in *AMIA*, 2013.

[24] L. P. Lowes, G. H. Noritz, A. Newmeyer, P. J. Embi, H. Yin, and W. E. Smoyer, “‘Learn From Every Patient’: implementation and early results of a learning health system,” *Dev. Med. Child Neurol.*, vol. 59, no. 2, pp. 183–191, 2017.

[25] G. De Moor, M. Sundgren, D. Kalra, A. Schmidt, M. Dugas, B. Claerhout, T. Karakoyun, C. Ohmann, P.-Y. Lastic, and N. Ammour, “Using electronic health records for clinical research: the case of the EHR4CR project,” *J. Biomed. Inform.*, vol. 53, pp. 162–173, 2015.

[26] B. C. Delaney, V. Curcin, A. Andreasson, T. N. Arvanitis, H. Bastiaens, D. Corrigan, J.-F. Ethier, O. Kostopoulou, W. Kuchinke, and M. McGilchrist, “Translational medicine and patient safety in Europe: TRANSFoRm—architecture for the Learning Health System in Europe,” *Biomed Res. Int.*, vol. 2015, 2015.

[27] S. Saganowski, A. Misiaszek, P. Bródka, A. Andreasson, V. Curcin, B. Delaney, and K. Frączkowski, “TRANSFoRm eHealth solution for quality of life monitoring.,” *AMIA Summits Transl. Sci. Proc.*, vol. 2016, p. 231, 2016.

[28] B. Middleton, D. F. Sittig, and A. Wright, “Clinical decision support: a 25 year retrospective and a 25 year vision,” *IMIA Yearb.*, 2016.

[29] T. Oluoch, X. Santas, D. Kwaro, M. Were, P. Biondich, C. Bailey, A. Abu-Hanna, and N. de Keizer, “The effect of electronic medical record-based clinical decision support on HIV care in resource-constrained settings: A systematic review,” *Int. J. Med. Inform.*, vol. 81,

no. 10, pp. e83–e92, 2012.

[30] N. Delvaux, K. Van Thienen, A. Heselmans, S. Van de Velde, D. Ramaekers, and B. Aertgeerts, "The Effects of Computerized Clinical Decision Support Systems on Laboratory Test Ordering: A Systematic Review," *Arch. Pathol. Lab. Med.*, vol. 141, no. 4, pp. 585–595, 2017.

[31] N. Mackintosh, M. Terblanche, R. Maharaj, A. Xyrichis, K. Franklin, J. Keddie, E. Larkins, A. Maslen, J. Skinner, and S. Newman, "Telemedicine with clinical decision support for critical care: a systematic review," *Syst. Rev.*, vol. 5, no. 1, p. 176, 2016.

[32] P. Bennett and N. R. Hardiker, "The use of computerized clinical decision support systems in emergency care: a substantive review of the literature," *J. Am. Med. Informatics Assoc.*, vol. 24, no. 3, pp. 655–668, 2016.

[33] R. Koposov, S. Fossum, T. Frodl, Ø. Nytrø, B. Leventhal, A. Sourander, S. Quaglini, M. Molteni, M. de la Iglesia Vayá, and H.-U. Prokosch, "Clinical decision support systems in child and adolescent psychiatry: a systematic review," *Eur. Child Adolesc. Psychiatry*, pp. 1–9, 2017.

[34] Z. M. Borab, M. A. Lanni, M. G. Tecce, C. J. Pannucci, and J. P. Fischer, "Use of computerized clinical decision support systems to prevent venous thromboembolism in surgical patients: a systematic review and meta-analysis," *JAMA Surg.*, 2017.

[35] G. K. Robbins, W. Lester, K. L. Johnson, Y. Chang, G. Estey, D. Surrao, K. Zachary, S. M. Lammert, H. C. Chueh, and J. B. Meigs, "Efficacy of a Clinical Decision-Support System in an HIV PracticeA Randomized Trial," *Ann. Intern. Med.*, vol. 157, no. 11, pp. 757–766, 2012.

[36] S. M. Ali, R. Giordano, S. Lakhani, and D. M. Walker, "A review of randomized controlled trials of medical record powered clinical decision support system to improve quality of diabetes care," *Int. J. Med. Inform.*, vol. 87, pp. 91–100, 2016.

[37] E. Kilsdonk, L. W. Peute, and M. W. M. Jaspers, "Factors influencing implementation success of guideline-based clinical decision support systems: A systematic review and gaps analysis," *Int. J. Med. Inform.*, vol. 98, pp. 56–64, 2017.

[38] K. Kawamoto, G. Del Fiol, H. R. Strasberg, N. Hulse, C. Curtis, J. J. Cimino, B. H. Rocha, S. Maviglia, E. Fry, and H. J. Scherpbier, "Multi-national, multi-institutional analysis of clinical decision support data needs to inform development of the HL7 virtual medical record standard," in *AMIA annual symposium proceedings*, 2010, vol. 2010, p. 377.

[39] K. Kawamoto, G. Del Fiol, D. F. Lobach, and R. A. Jenders, "Standards for scalable clinical decision support: need, current and emerging standards, gaps, and proposal for progress," *Open Med. Inform. J.*, vol. 4, p. 235, 2010.

[40] L. Marco-Ruiz, A. Budrionis, K. Y. Y. Yigzaw, and J. G. Bellika, "Interoperability Mechanisms of Clinical Decision Support Systems: A Systematic Review," in *Proceedings from The 14th Scandinavian Conference on Health Informatics 2016, Gothenburg, Sweden, April 6-7 2016*, 2016, no. 122, pp. 13–21.

[41] S. R. Loya, K. Kawamoto, C. Chatwin, and V. Huser, "Service oriented architecture for clinical decision support: A systematic review and future directions," *J. Med. Syst.*, vol. 38, no. 12, pp. 1–22, 2014.

[42] K. Kawamoto, "OpenCDS: An open-source, standards-based, service-oriented framework for scalable CDS," in *SOA in Healthcare 2011 Conference*, 2011.

[43] B. M. Welch, S. Rodriguez-Loya, K. Eilbeck, and K. Kawamoto, “Clinical decision support for whole genome sequence information leveraging a service-oriented architecture: a prototype,” in *AMIA Annual Symposium Proceedings*, 2014, vol. 2014, p. 1188.

[44] Y.-F. Zhang, L. Gou, Y. Tian, T.-C. Li, M. Zhang, and J.-S. Li, “Design and Development of a Sharable Clinical Decision Support System Based on a Semantic Web Service Framework,” *J. Med. Syst.*, vol. 40, no. 5, p. 118, 2016.

[45] D. W. Bates, G. J. Kuperman, S. Wang, T. Gandhi, A. Kittler, L. Volk, C. Spurr, R. Khorasani, M. Tanasijevic, and B. Middleton, “Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality,” *J. Am. Med. Informatics Assoc.*, vol. 10, no. 6, pp. 523–530, 2003.

[46] P. Fraccaro and M. Giacomini, “A web-based tool for patients cohorts and clinical trials management,” *Stud Heal. Technol Inf.*, vol. 180, pp. 554–558, 2012.

[47] P. Fraccaro, C. Dentone, D. Fenoglio, and M. Giacomini, “Multicentre clinical trials’ data management: a hybrid solution to exploit the strengths of electronic data capture and electronic health records systems,” *Informatics Heal. Soc. Care*, vol. 38, no. 4, pp. 313–329, 2013.

[48] T. Fahey, S. Griffiths, and T. J. Peters, “Evidence based purchasing: understanding results of clinical trials and systematic reviews,” *Bmj*, vol. 311, no. 7012, pp. 1056–1059, 1995.

[49] O. of the Commissioner, “What Are the Different Types of Clinical Research?”

[50] “ARCA (Antiretroviral Resistance Cohort Analysis).” [Online]. Available: http://www.dbarca.net/.

[51] “Fondazione ICONA Italian Cohort Naive Antiretrovirals,” 2017. .

[52] “CISAI Coordinamento Italiano Studio Allergie e Infezioni da HIV,” 2017. .

[53] P. J. Lisboa and A. F. G. Taktak, “The use of artificial neural networks in decision support in cancer: a systematic review,” *Neural networks*, vol. 19, no. 4, pp. 408–415, 2006.

[54] M. Marcos, J. A. Maldonado, B. Martínez-Salvador, D. Boscá, and M. Robles, “Interoperability of clinical decision-support systems and electronic health records using archetypes: a case study in clinical trial eligibility,” *J. Biomed. Inform.*, vol. 46, no. 4, pp. 676–689, 2013.

[55] D. F. Sittig, A. Wright, J. A. Osheroff, B. Middleton, J. M. Teich, J. S. Ash, E. Campbell, and D. W. Bates, “Grand challenges in clinical decision support,” *J. Biomed. Inform.*, vol. 41, no. 2, pp. 387–392, 2008.

[56] K. Kawamoto, D. Shields, A. K. McIntyre, H. R. Strasberg, Z. Liu, Y. Bao, G. E. Healthcare, and I. L. Barrington, “Evaluation of HL7 Continuity of Care Document as the Foundation for an International Virtual Medical Record Standard for Clinical Decision Support.",” 2011.

[57] K. Koumaditis, M. Themistocleous, and P. Rupino Da Cunha, “SOA implementation critical success factors in healthcare,” *J. Enterp. Inf. Manag.*, vol. 26, no. 4, pp. 343–362, 2013.

[58] P. M. Nadkarni and R. A. Miller, “Service-oriented architecture in medical software: promises and perils.” BMJ Group BMA House, Tavistock Square, London, WC1H 9JR, 2007.

[59] D. Vito, G. Casagrande, C. Bianchi, and M. L. Costantino, “An interoperable common storage system for shared dialysis clinical data,” in *Student Conference (ISC), 2016 IEEE EMBS International*, 2016, pp. 1–4.

[60] K. Kawamoto, A. Honey, and K. Rubin, “The HL7-OMG healthcare services specification project: motivation, methodology, and deliverables for enabling a semantically interoperable service-oriented architecture for healthcare,” *J. Am. Med. Informatics Assoc.*, vol. 16, no. 6, pp. 874–881, 2009.

[61] K. N. Lohr and M. J. Field, *Guidelines for clinical practice: from development to use*. National Academies Press, 1992.

[62] S. W. Tu and M. A. Musen, “Representation formalisms and computational methods for modeling guideline-based patient care,” *Stud. Health Technol. Inform.*, pp. 115–132, 2001.

[63] G. Hripcsak, P. Ludemann, T. A. Pryor, O. B. Wigertz, and P. D. Clayton, “Rationale for the Arden syntax,” *Comput. Biomed. Res.*, vol. 27, no. 4, pp. 291–324, 1994.

[64] A. A. Boxwala, M. Peleg, S. Tu, O. Ogunyemi, Q. T. Zeng, D. Wang, V. L. Patel, R. A. Greenes, and E. H. Shortliffe, “GLIF3: a representation format for sharable computer-interpretable clinical practice guidelines,” *J. Biomed. Inform.*, vol. 37, no. 3, pp. 147–161, 2004.

[65] L. Ohno-Machado, J. H. Gennari, S. N. Murphy, N. L. Jain, S. W. Tu, D. E. Oliver, E. Pattison-Gordon, R. A. Greenes, E. H. Shortliffe, and G. O. Barnett, “The guideline interchange format: a model for representing guidelines,” *J. Am. Med. Informatics Assoc.*, vol. 5, no. 4, pp. 357–372, 1998.

[66] S. Miksch, Y. Shahar, and P. Johnson, “Asbru: a task-specific, intention-based, and time-oriented language for representing skeletal plans,” in *Proceedings of the 7th Workshop on Knowledge Engineering: Methods & Languages (KEML-97)*, 1997, pp. 9–19.

[67] M. Sordo, O. Ogunyemi, A. A. Boxwala, and R. A. Greenes, “GELLO: an object-oriented query and expression language for clinical decision support: AMIA 2003 Open Source Expo,” in *AMIA Annual Symposium Proceedings*, 2003, vol. 2003, p. 1012.

[68] M. Peleg, “Computer-interpretable clinical guidelines: a methodological review,” *J. Biomed. Inform.*, vol. 46, no. 4, pp. 744–763, 2013.

[69] V. Huser, S. P. Narus, and R. A. Rocha, “Evaluation of a flowchart-based EHR query system: A case study of RetroGuide,” *J. Biomed. Inform.*, vol. 43, no. 1, pp. 41–50, 2010.

[70] P. Kolesa, J. Spidlen, and J. Zvárová, “Obstacles to implementing an execution engine for clinical guidelines formalized in GLIF,” *Stud. Health Technol. Inform.*, vol. 116, p. 563, 2005.

[71] A. González-Ferrer, M. Peleg, E. Parimbelli, E. Shalom, C. Marcos, G. Klebanov, I. Martínez-Sarriegui, N. L. San Fung, and T. Broens, “Use of the virtual medical record data model for communication among components of a distributed decision-support system,” in *Biomedical and Health Informatics (BHI), 2014 IEEE-EMBS International Conference on*, 2014, pp. 526–530.

[72] HL7, “Implementation Guide: Decision Support Service, Release 1.” 2013.

[73] HL7, “Version 3 Standard: Virtual Medical Record for Clinical Decision Support (vMR-CDS) Templates, DSTU Release 1.” 2014.

[74] B. Giannini, R. Gazzarata, L. Sticchi, and M. Giacomini, “A SOA-Based Solution to Monitor Vaccination Coverage Among HIV-Infected Patients in Liguria,” *Heal. —*

Explor. Complex. an Interdiscip. Syst. approach HEC2016, pp. 0–4, 2016.

[75] N. Riccardi, B. Giannini, M. L. Borghesi, M. Giacomini, G. Cenderello, F. Toscanini, G. Cassola, C. Viscoli, and A. Di Biagio, "Time to change the single center approach in management of patients with tuberculosis. A novel network platform with automatic data import: one step toward to the eradication," *Int. J. Tuberc. Lung Dis. Submitt. Artic.*

[76] B. Giannini, N. Riccardi, A. Di Biagio, G. Cenderello, and M. Giacomini, "A web based tool to enhance monitoring and retention in care for tuberculosis affected patients," in *Studies in Health Technology and Informatics*, 2017, vol. 237, pp. 204–208.

[77] M. Ameri, G. Cassola, G. Cenderello, A. Di Biagio, M. Giacomini, B. Giannini, G. Mazzarello, C. Merlano, M. Montefiori, and P. Orcamo, "Quality of Life Among Hiv Patients: Results from the Ianua Clinical Trial.," *Value Heal. J. Int. Soc. Pharmacoeconomics Outcomes Res.*, vol. 18, no. 7, p. A592, 2015.

[78] B. Giannini, R. Gazzarata, P. Orcamo, C. Merlano, G. Cenderello, A. Venturini, A. Di Biagio, G. Mazzarello, M. Montefiori, and M. Ameri, "IANUA: a regional project for the determination of costs in HIV-infected patients," *Digit. Healthc. Empower. Eur. Proc. MIE2015*, vol. 210, p. 241, 2015.

[79] A. Venturini, B. Giannini, M. Montefiori, A. Di Biagio, G. Mazzarello, G. Cenderello, M. Giacomini, C. Merlano, P. Orcamo, and M. Setti, "Quality of life of people living with HIV, preliminary results from IANUA (Investigation on Antiretroviral Therapy) study," *J. Int. AIDS Soc.*, vol. 17, no. 4, 2014.

[80] V. Pupella, R. Gazzarata, M. Macrì, B. Giannini, I. Orlandi, E. Masi, P. Orcamo, G. Cenderello, A. Di Biagio, M. Montefiori, M. Setti, C. Viscoli, G. Cassola, and M. Giacomini, "A tool for the evaluation of the cost effectiveness of AIDS therapies," in *GNB*, 2014, p. 2.

[81] G. Cenderello, S. Artioli, D. Gaggero, A. Pasa, C. Dentone, C. Fraguglia, M. Giacomini, B. Giannini, G. Pastorino, and C. Viscoli, "Budget Impact Analysis of Sofosbuvir-Based Regimens for The Treatment of Hiv/Hcv Co-Infected Patients In Northern Italy: The Liguria Region Simulation.," *Value Heal. J. Int. Soc. Pharmacoeconomics Outcomes Res.*, vol. 18, no. 7, p. A579, 2015.

[82] A. Di Biagio, M. Ameri, D. Sirello, G. Cenderello, E. Di Bella, L. Taramasso, B. Giannini, M. Giacomini, C. Viscoli, and G. Cassola, "Is it still worthwhile to perform quarterly cd4+ t lymphocyte cell counts on hiv-1 infected stable patients?," *BMC Infect. Dis.*, vol. 17, no. 1, p. 127, 2017.

[83] D. Churchill, L. Waters, N. Ahmed, B. Angus, M. Boffito, M. Bower, D. Dunn, S. Edwards, C. Emerson, and S. Fidler, "BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015." 2015.

[84] M. Della Salute, "Linee guida italiane sull'utilizzo dei farmaci antiretrovirali e sulla gestione diagnositico-clinica delle persone con infezione da HIV-1. 2015." 2017.

[85] G. Cenderello, A. Di Biagio, F. Artom, C. Dentone, V. Bartolacci, P. De Leo, M. Anselmo, M. Guerra, B. Giannini, P. Orcamo, S. Artioli, G. Ferrea, G. Riccio, M. Giacomini, G. Cassola, and C. Viscoli, "Assessment of appropriateness of first-line combined antiretroviral treatment (cART): the preliminary results of Liguria experience V.E.L.A. study," in *ICAR*, 2017.

[86] Y. Anokwa, N. Ribeka, T. Parikh, G. Borriello, and M. C. Were, "Design of a phone-based clinical decision support system for resource-limited settings," in *Proceedings of the Fifth International Conference on Information and Communication Technologies and*

Development, 2012, pp. 13–24.

Appendix A: results tables

A1 Quality of life indicators

A1.1 HIVRNA

	Average HIVRNA value		
Patient ID	**2015**	**2016**	**2017**
106	972	471	0
107	630	0	0
136	64200		
152	45	48787	
285	49	36	
470		52	69
590	0	0	0
613		0	
644	0	0	
672		15	
688	0	0	0
707	0	0	0
750	14	2959	0
755	0	0	
847		79043	3120
918	0	0	0
935	0	32	0
1010	50	23	0
1014		0	
1039	65	63	
1054	0	0	0
1057	0	0	
1084	201	125	
1095	74020	194	
1218	6104	0	0
1256		5255	0
2021	0	0	0
2056	45	0	0
2058	31		64909
2225	15	12	4
2388	373	0	0
2410	323	486	0
2418	45	9	0
2433	0	0	0
2441	336	0	5

2461	10	0	0
2495	11	0	0
2496	0	295	0
2498	0	0	
2500	0	28	0
2509	34	0	0
2538	6094		
2539	27116	156	26433
2556	12	24	
2568	34700	0	0
2575	42200		
2594	17050	0	0
2595	42		0
2612	0	62500	0
2614	31	483	
2630		0	0
2645	14047	10	0
2652	29500	12	0
2653	2515	80	27
2654	20855	0	0
2655	76	0	0
2659	46	11	12
2661	1587	4962	0
2663	95033	0	0
2664	30841	19175	0
2665	14603	0	0
2668	138058	9080	
2670	10393	7622	0
2671	336	158	0
2672	106773	57000	57000
2673	54970	40	
2676	15753	0	0
2678	12352	2300	0
2682	10463	0	0
2684	5960	1595	0
2688	21075	78	0
2690	106379	27	
2691	71674	10	
2692	170597	55	
2693	353449	0	0
2695	123992	19	
2697	552767	20	14
2699	19	0	

2702	476	117	358
2705	6850	0	0
2706	13991	46	
2709	11100	1425	0
2710	2200	0	0
2715	2200	0	0
2749	9200	6903	4513
2751	13	0	0
2752	46809	5	0
2753	22568	9	0
2760	36709	17	0
2762	171573	8	0
2764	93472	0	0
2765	1695	0	
2771	103746	15	0
2773	1005	0	
2774	546469	20	
2775	100	0	0
2776	22008		
2778	70018	4	0
2779	34409		
2780	214546	0	0
2781	143600	0	20
2782	38917		0
2783	1009	8	1
2784	95170	10	1951
2785	10004	4	20
2787		34	12
2788	238	28	5
2790	12770	15	0
2791	6044	0	3
2793	97789	0	
2794	90422	33	
2795	32797	0	
2796	33162	0	
2797	77838	0	
2798	6787	0	
2799	140091	0	
2801	3677	0	
2802	37823	0	0
2805	1092	49219	0
2807	4525		
2808	61464	30	

2809	243159	152	37
2812	69186		
2815	24398	87	
2819	512100		
2825	9876	25	
2826	141671	13	7
2827	18761	11	0
2829	323055	12	
2837	11718	1495	0
2844	44500	170	
2846	18400	15900	
2847	4290	0	0
2848	215000	0	
2856	22486	0	
2859		18090	0
2860		83593	13
2861		12856	0
2862		165261	6
2863		89232	28
2865		37	0
2887		277002	0
2892		7578	18
2903		47040	0
2924	193	218	3
2925		75641	9
2926		538	0
2928	3500	1686	3
2929		350	0
2930		22426	0
2936	307643	28	8
2939		9219	17
2940	6874	261	
2943		276200	20
2945	1610	828	0
2946	72751	82	
2947	53824	0	0
2948	42775	0	
2952		3340	0
2953		7686	0
2956		23050	
2958		31	
2960		836	0
2961		7050	

2962	5450	1037	0
2964		6700	
2965		837419	24
2966		8598	0
2967	51200	46754	0
2976	16192	11	
2977	32840	16	
3260		8506	13
3364		69174	
3466		3050	9
3468		47530	8
3513	244618	28	0
3514	32906	20	
3515	12876	0	0
3549	64046	0	
3648		8926	12
3649		205672	
3650		28859	
3651	14533		
3675		169140	0
3677		1080	0
3678		37416	
3679		6250	0
3680		49190	0
3681		70280	0
3682		10459	
3683		60	0
3684		24428	0
3685		260487	
3686		8671	
3687	336723	20	0
3688	784548	122134	696
3689	5872	20	0
3690	30191	20	0
3691	379613	680	0
3692		27789	
3744	90878	56	
3769	5712	0	
3778	124388	34	
3847	795	0	
3848		367331	12
3869	51236	0	
3876	14551	19	

3877		45730	
3879	57745	14	
3880		9262	
3881		14925	
3882		15298	
3883		26014	
3884	4305	0	
3885	67735	0	
3910		54975	15
3924		45481	13
3963		1060327	419
3964	5840	4590	0
3965		0	0
4008		19	
4023		1759	25
4050		0	
4075		307	
4118		19	
4147		2200	5
4247		34400	84
4249		193000	
4251	20500	23444	0
4252		0	109
4255		37254	0
4256		45048	0
4257		12449	
4258		0	
4277		0	
4291		9028	
4292		2500047	
4293		43816	
4294		799	
4295		799056	
4297	44799	0	
4300		22890	0
4301		6708	
4309	74132	0	
4322	48605	0	
4329		19	
4330		0	
4331		0	
4332		0	
4333		37045	

4334		2188	
4335		25826	40
4336		16206	239
4337		3163	0
4338		881894	94
4348		6233	
4349		38171	0
4350		500066	0
4351		737538	
4352		900376	400
4353		576	
4354		83236	
4355		29161	29
Average	**57252**	**68231**	**1602**
Std Dev	**113849**	**210728**	**7267**
T TEST 2015-2016	0,595138798		
T TEST 2016-2017	0,000421452		

A1.2 CD4

	Average CD4 value		
Patient ID	**2015**	**2016**	**2017**
106	1097	924	1238
107	477	500	465
136	36		
152	316	246	220
285	940	792	810
470	727	704	891
590	587	495	637
613	1427	1408	
644	333	270	273
672		435	
688	742	829	748
707	687	656	903
750	826	812	678
755	1621	1809	1863
847		123	157
918	371	483	409
935	645	774	859
1010	425	499	478
1014	444	507	417
1039	1057	1116	1108

1054	453	531	578
1057	506	579	
1084	375	457	355
1095	541	744	
1218	425	666	650
1256		849	1264
1788		100	
2021	856	719	872
2056	309	369	465
2058	295		65
2225	217	202	290
2388	517	509	598
2410	815	734	816
2418	447	588	707
2433	805	945	1156
2441	495	625	676
2461	679	671	783
2495	256	461	557
2496	477	683	745
2498	141	202	308
2500	353	324	372
2509	753	808	964
2538	527		
2539	408	646	269
2556	605	727	681
2568	467	600	530
2575	150	185	
2594	630	708	913
2595	832	896	869
2612	511	491	598
2614	542	628	535
2630	720	724	863
2645	840	916	777
2652	725	641	634
2653	125	422	573
2654	819	1219	1020
2655	106	197	168
2659	283	318	365
2661	612	567	716
2663	358	619	434
2664	596	696	772
2665	588	975	999
2668	239	709	

2670	479	742	867
2671	795	789	821
2672	442	600	748
2673	438	785	867
2676	421	578	676
2678	730	902	1274
2682	514	722	573
2684	453	505	736
2688	494	703	836
2690	183	318	
2691	924	1282	
2692	73	154	
2693	412	579	530
2695	420	438	
2697	187	456	498
2699	624	1531	
2702	271	352	405
2705		318	
2706	927	1002	
2709	717	686	944
2710	507	659	716
2715	372	587	579
2749	733	542	474
2751	599	640	618
2752	326	518	526
2753	604	748	841
2760	266	506	476
2762	217	441	526
2764	177	370	385
2765	916	811	
2771	39	101	202
2773	444	501	
2774	573	797	
2775	281	313	420
2776	674		
2778	818	824	922
2779	557	953	895
2780	111	264	354
2781	121	500	310
2782	472	519	549
2783		1153	1124
2784	152	192	170
2785	598	835	952

2787		556	602
2788		230	212
2790	167	289	348
2791	248	433	385
2793	101	121	
2794	273	687	
2795	216	397	
2796	568	514	
2797	299	364	
2798	714	816	
2799	386	528	
2801	395	343	
2802	987	1147	1370
2805	867	869	1164
2807	591		
2808	688	1131	1212
2809	88	275	392
2812	89		
2815	362	942	805
2819	261		
2825	391	710	
2826	214	355	366
2827	304	421	427
2829	102	122	
2837	438	529	548
2844	600	603	
2846	485	508	
2847	420	712	606
2848	122	324	456
2856	835	818	
2859		211	403
2860		47	207
2861		431	495
2862		767	902
2863		250	273
2865		413	450
2887		698	864
2892		79	136
2903		971	1481
2924	1093	841	981
2925		184	477
2926		700	448
2928	758	678	813

2929		795	745
2930		440	577
2936	80	231	216
2939		285	461
2940	361	362	
2943		600	954
2945	447	457	562
2946	114	266	326
2947	131	278	356
2948	96	168	
2952		814	940
2953		372	385
2956		139	337
2958		584	
2960		267	370
2961		321	
2962	368	585	617
2964		579	652
2965		7	39
2966		449	558
2967	561	444	651
2976	205	363	
2977	809	888	
3260		724	614
3364		41	
3466		103	159
3468		553	896
3513	0	100	
3514	280	690	
3515	300		
3549	474	448	
3648		688	772
3649		282	
3650		593	
3651	400		
3675		142	278
3677		259	369
3678		491	708
3679		533	584
3680		1313	1329
3681		1076	1352
3682		132	215
3683		273	428

3684		207	327
3685		135	
3686		490	
3687	550	940	
3688	0	110	
3689	130	230	
3690	340	350	
3691	330	720	
3744	159	230	
3769	48	108	
3778	107	361	
3847	483	946	
3848		68	198
3869	681	996	
3876	499	644	
3877		234	
3879	207	246	
3880		730	
3882		641	
3883		475	
3884	667	487	
3885	12	3	
3910		484	1160
3924		168	473
3963		165	131
3964	531	493	561
3965		802	1000
4008		263	
4023		495	531
4050		605	
4075		374	
4118		553	
4147		467	732
4247		498	
4249		2	
4251	918	791	1192
4252		248	380
4255		478	823
4256		425	734
4257		303	432
4258		932	955
4277		321	
4291		864	

4292		939	
4293		37	
4294		569	
4295		48	
4297	383	549	
4300		655	255
4301		732	
4309	565	625	
4322	902	937	
4329		1494	
4330		1203	
4331		1412	
4332		1449	
4333		164	
4334		755	
4335		730	730
4336		450	
4337		780	
4338		80	
4348		355	
4349		510	
4350		35	
4351		130	
4352		50	
4353		370	
4354		220	
4355		70	
Average	**489**	**548**	**637**
Std Dev	**282**	**318**	**317**
T TEST 2015-2016	0,014904603		
T TEST 2016-2017	0,005814978	p<0,01	

A2 Therapy adherence

Patient ID	2015	2016	2017
14544		0,2	0,5
14647		0,3	
15176			1,0
15393		1,0	
15404		0,4	0,5
15574		0,2	
15581		0,2	
16239		0,3	
16281		0,7	0,5
16447		0,2	1
51867		0,1	
53070		0,6	0,5
53225		0,7	
55708		0,2	
55977		0,4	1
56812		1,0	1,0
59127		0,2	0,5
59178		0,7	0,3
60853		1	1
61947		1,0	0,8
62972		0,7	1
65757			0,3
67587			1,0
70896	0,7		
71311			0,5
71734		0,4	
72547			0,3
72730	1	1,0	1,0
73434	0,5	0,4	1,0
73648			1,0
74753			0,3
75461		0,2	0,5
75798			0,5
76121		0,7	1
77198		1	1
79503		0,2	
80264			0,8
81129		0,8	1,0
83563		0,2	0,3
83790		0,7	0,5
84443		0,7	1

86640		0,8	0,8
87731		0,1	
87985		0,3	1
89520	1	1	1,0
89656			0,5
89885	1	0,9	1
90260	0,7	1	1,0
90396	1,0	1,0	1,0
90853		0,9	1
91329	0,9	1,0	1,0
91383	0,9	1,0	1,0
91606		0,7	1,0
91993	0,7	1,0	1,0
92075	0,7	1	1,0
92232	0,6	1,0	1
92573	0,6	0,9	0,8
93672	0,7	1	0,5
93699	0,2	1,0	0,8
93806	0,5	1,0	1,0
93849	0,3		
94220		1	1,0
94309	0,1		
94414	0,6	1	1,0
94610		0,9	1
94793	0,5	0,9	1,0
95313	0,5	0,9	1,0
95395	0,2	1	1,0
95560	0,3	1,0	1
95574	0,3	1,0	1
95585		0,7	1,0
95683		0,5	
96619		0,1	
96817	0,2	1,0	1,0
97033	0,2	1,0	1,0
97166	0,2	1,0	0,8
98029		0,7	0,5
98164		1	0,8
98183		0,1	
98192		0,6	1,0
98246		0,5	
98487		1,0	1,0
98580		1	1,0
98889		0,5	1

99115		1,0	1,0
99518		1	1
99657		0,8	1
100235		0,8	0,5
100589		0,8	1
100783		0,1	
100957		0,8	1,0
101327		0,7	1,0
101357		0,8	1,0
101395		0,2	
101417		0,8	
101419		0,2	1,0
101494		0,4	0,3
101744		0,8	1
101963		0,7	1,0
102030		0,2	
102122			1
102211		0,7	1
102250		0,2	
102389		0,6	1
102640		0,7	1,0
103049		0,7	0,3
103111		0,1	
103145		0,5	1,0
103289		0,7	0,5
103320		0,6	1
103492		0,6	1,0
103529		0,7	1,0
103828		0,6	0,5
104107		0,5	1,0
104189		0,5	1,0
104269	0,4	0,9	1
104359		0,3	1
104427		0,4	0,8
104584		0,4	1,0
104641		0,1	
104665		0,3	1
104729		0,5	0,8
104816		0,2	1
105009		0,3	1
105089		0,4	0,8
105171		0,2	0,5
105256		0,3	1,0

105311		0,1	
105862		0,4	1,0
106041		0,2	1,0
106201		0,1	
106461		0,2	0,3
106529		0,1	
106701			1
107163		0,2	1,0
107193		0,1	
107529			1
108409			0,3
108433			0,3
108444			1
109049			1
109364			0,8
110123			0,5
110173			0,5
110508			0,3
110577			0,3
2995			0,3
3727			0,3
Average	**0,5**	**0,6**	**0,7**
Std Dev	**0,3**	**0,3**	**0,3**

T TEST 2015-2016 0,342590479
T TEST 2016-2017 1,72004E-05

A3 HAART prescription appropriateness

Patient ID	Prescription date	Active drugs	Score	Price
2851	01/01/2015	TDF/FTC+RAL	0,69	960,39
2980	01/01/2015	MVC	0,033	903,16
2978	01/01/2015	3TC+MVC	0,027	964,21
2989	01/01/2015	r+MVC+DRV	0,001	1250,94
2979	01/01/2015	DRV+r+MVC	0,001	1250,94
2986	01/01/2015	MVC+ABC/3TC	0,001	1301,35
2984	01/01/2015	3TC+r+MVC+DRV	0,001	1311,99
2991	01/01/2015	MVC+TDF+FTC+EVG+COBI	0,001	1341,62
2990	01/01/2015	TDF/FTC+MVC	0,001	1342,02
2981	01/01/2015	RAL+MVC	0,001	1424,69
2987	01/01/2015	3TC+MVC+DTG	0,001	1510,01
2985	01/01/2015	r+MVC+DRV+TDF	0,001	1527,92
2982	01/01/2015	MVC+RPV+DTG	0,001	1679,72
2988	01/01/2015	RAL+DRV+r+MVC	0,001	1772,47
2983	01/01/2015	MVC+DTG+ATV	0,001	1781,93
2822	02/01/2015	TDF/FTC+RAL	0,69	960,39
2388	09/01/2015	TDF+FTC+RPV	1	669,22
2441	13/01/2015	TDF/FTC+DRV+r	0,88	786,64
2418	20/01/2015	DTG+ABC/3TC	0,71	943,99
2805	21/01/2015	DRV+RAL+RTV	0,106	894,28
2490	26/01/2015	TDF+FTC+RPV	1	669,22
1310	27/01/2015	DTG+ABC/3TC	0,71	943,99
1419	03/02/2015	TDF+FTC+RPV	1	669,22
2969	03/02/2015	RAL+DRV+r+ABC/3TC	0,001	1267,5
2793	03/02/2015	DRV+RAL+ABC/3TC	0,001	1267,5
2654	10/02/2015	TDF+FTC+RPV	1	669,22
2676	20/02/2015	TDF+FTC+RPV	1	669,22
2808	20/02/2015	TDF+FTC+EVG+COBI	0,41	904,56
2975	23/02/2015	RAL+MVC+ABC/3TC	0,001	1822,88
2794	26/02/2015	3TC+DRV+r+RAL	0,033	930,36
2795	27/02/2015	DTG+ABC/3TC	0,71	943,99
2645	12/03/2015	TDF+FTC+RPV	1	669,22
2784	19/03/2015	TDF/FTC+DRV+r	0,88	786,64
2655	19/03/2015	TDF/FTC+RTV+ATV	0,122	796,8
107	20/03/2015	TDF+FTC+RPV	1	669,22
2947	24/03/2015	TDF/FTC+RTV+ATV	0,122	796,8
2946	24/03/2015	DRV+RTV+DTG+ETR	0,001	1314,55
2691	30/03/2015	TDF+FTC+EVG+COBI	0,41	904,56
4297	02/04/2015	TDF/FTC/EVG/COBI	0,75	904,56
2692	08/04/2015	TDF/FTC+r+DRV	0,88	786,64
2791	10/04/2015	TDF/FTC+DTG	0,6	1038,86

2693	13/04/2015	TDF/FTC+DTG	0,6	1038,86
2767	14/04/2015	TDF+FTC+EVG+COBI	0,41	904,56
2690	16/04/2015	TDF/FTC+RTV+ATV	0,122	796,8
1218	21/04/2015	TDF+FTC+RPV	1	669,22
2663	22/04/2015	DTG+ABC/3TC	0,71	943,99
2976	27/04/2015	TDF+FTC+EVG+COBI	0,41	904,56
2755	27/04/2015	TDF/FTC+RAL	0,69	960,39
2665	04/05/2015	TDF+FTC+RPV	1	669,22
2770	04/05/2015	TDF+FTC+EVG+COBI	0,41	904,56
2766	04/05/2015	TDF/FTC+DTG	0,6	1038,86
2779	05/05/2015	TDF+FTC+EVG+COBI	0,41	904,56
2695	11/05/2015	TDF/FTC+r+DRV	0,88	786,64
2697	13/05/2015	TDF/FTC+DTG	0,6	1038,86
2764	18/05/2015	TDF/FTC+DRV+r	0,88	786,64
2790	22/05/2015	TDF/FTC+r+DRV	0,88	786,64
2797	27/05/2015	TDF/FTC+DTG	0,6	1038,86
2056	29/05/2015	TDF+FTC+RPV	1	669,22
2796	29/05/2015	TDF/FTC+DTG	0,6	1038,86
2949	18/06/2015	RAL+r+fAPV	0,033	837,82
2699	22/06/2015	DTG+ABC/3TC	0,71	943,99
2705	28/06/2015	TDF+FTC+EVG+COBI	0,41	904,56
2706	29/06/2015	TDF+FTC+EVG+COBI	0,41	904,56
3847	29/06/2015	DTG+ABC/3TC	0,71	943,99
2776	01/07/2015	TDF+FTC+RPV	1	669,22
2780	01/07/2015	TDF/FTC+DTG	0,6	1038,86
2948	02/07/2015	TDF/FTC+RAL	0,69	960,39
2785	07/07/2015	TDF/FTC+DTG	0,6	1038,86
2829	09/07/2015	TDF/FTC+RAL	0,69	960,39
183	10/07/2015	TDF+FTC+RPV	1	669,22
2771	15/07/2015	TDF/FTC+DTG	0,6	1038,86
2640	17/07/2015	TDF+FTC+RPV	1	669,22
2689	20/07/2015	TDF+FTC+RPV	1	669,22
2812	24/07/2015	DTG+ABC/3TC	0,71	943,99
2826	27/07/2015	TDF/FTC+DTG	0,6	1038,86
2710	28/07/2015	TDF+FTC+EVG+COBI	0,41	904,56
2650	29/07/2015	ABC+3TC+RAL	0,425	807,16
4309	03/08/2015	TDF+FTC+RPV	1	669,22
2798	03/08/2015	TDF+FTC+EVG+COBI	0,41	904,56
2807	04/08/2015	TDF+FTC+RPV	1	669,22
3885	05/08/2015	TDF/FTC+r+DRV	0,88	786,64
3688	05/08/2015	TDF/FTC+r+DRV	0,88	786,64
2815	06/08/2015	TDF+FTC+RPV	1	669,22
2781	10/08/2015	TDF/FTC+DRV+RTV	0,119	811,61

3549	11/08/2015	TDF+FTC+RPV	1	669,22
2664	12/08/2015	TDF+FTC+RPV	1	669,22
3687	14/08/2015	TDF+FTC+EVG+COBI	0,41	904,56
2752	18/08/2015	TDF/FTC+DTG	0,6	1038,86
2963	25/08/2015	TDF/FTC+r+DRV	0,88	786,64
3690	26/08/2015	TDF+FTC+RPV	1	669,22
2782	31/08/2015	TDF+FTC+EVG+COBI	0,41	904,56
2715	01/09/2015	DTG+ABC/3TC	0,71	943,99
2760	01/09/2015	TDF/FTC+DTG	0,6	1038,86
3689	04/09/2015	TDF+FTC+EVG+COBI	0,41	904,56
3513	09/09/2015	TDF/FTC+r+DRV	0,88	786,64
2708	11/09/2015	TDF/FTC+DTG	0,6	1038,86
3515	15/09/2015	TDF+FTC+RPV	1	669,22
3769	15/09/2015	DTG+ABC/3TC	0,71	943,99
2765	21/09/2015	DTG+ABC/3TC	0,71	943,99
2799	22/09/2015	DTG+ABC/3TC	0,71	943,99
2768	22/09/2015	TDF/FTC+RAL	0,69	960,39
2809	22/09/2015	TDF/FTC+DTG	0,6	1038,86
2773	23/09/2015	DTG+ABC/3TC	0,71	943,99
2774	29/09/2015	TDF/FTC+DTG	0,6	1038,86
2682	01/10/2015	TDF+FTC+RPV	1	669,22
2673	01/10/2015	TDF+FTC+EVG+COBI	0,41	904,56
3879	07/10/2015	TDF/FTC+DTG	0,6	1038,86
3691	08/10/2015	TDF/FTC+r+DRV	0,88	786,64
2668	08/10/2015	TDF/FTC+DRV+RAL+RTV	0,001	1308,17
2778	09/10/2015	TDF+FTC+EVG+COBI	0,41	904,56
2801	15/10/2015	TDF+FTC+RPV	1	669,22
3744	28/10/2015	TDF/FTC+r+DRV	0,88	786,64
2678	29/10/2015	TDF+FTC+RPV	1	669,22
3846	29/10/2015	TDF/FTC+RPV	1	669,62
2827	30/10/2015	TDF+FTC+RPV	1	669,22
2802	09/11/2015	TDF+FTC+RPV	1	669,22
2783	11/11/2015	TDF+FTC+RPV	1	669,22
2847	12/11/2015	TDF+FTC+RPV	1	669,22
3514	12/11/2015	DTG+ABC/3TC	0,71	943,99
2856	18/11/2015	TDF+FTC+RPV	1	669,22
3876	23/11/2015	TDF+FTC+RPV	1	669,22
2788	23/11/2015	TDF/FTC+RAL	0,69	960,39
4322	24/11/2015	TDF/FTC/RPV	1	650,86
4322	24/11/2015	TDF+FTC+RPV	1	669,22
2672	24/11/2015	TDF+FTC+EVG+COBI	0,41	904,56
2789	24/11/2015	DRV+r+ABC/3TC	0,874	745,97
2848	26/11/2015	RTV+DRV+ABC/3TC	0,125	770,94

2819	26/11/2015	TDF+FTC+EVG+COBI	0,41	904,56
3778	30/11/2015	TDF/FTC+r+DRV	0,88	786,64
2950	11/12/2015	r+ABC/3TC+ATV	0,94	731,16
2852	22/12/2015	r+DTG+DRV	0,033	893,58
2787	29/12/2015	TDF/FTC+DTG	0,6	1038,86
2940	11/01/2016	TDF/FTC/RPV	1	650,86
2844	12/01/2016	TDF/FTC/RPV	1	650,86
2684	18/01/2016	TDF/FTC/RPV	1	650,86
2977	26/01/2016	TDF/FTC/EVG/COBI	0,75	904,56
2837	28/01/2016	TDF/FTC/EVG/COBI	0,75	904,56
2956	28/01/2016	TDF/FTC/EVG/COBI	0,75	904,56
2945	09/02/2016	TDF/FTC/RPV	1	650,86
2962	15/02/2016	ABC/3TC+DRV+r	0,372	745,97
2958	18/02/2016	TDF/FTC/EVG/COBI	0,75	904,56
2863	25/02/2016	TDF/FTC+DTG	0,6	1038,86
2952	02/03/2016	ABC/3TC+DRV+r	0,372	745,97
2887	03/03/2016	TDF/FTC+DTG	0,6	1038,86
3685	05/03/2016	TDF/FTC/EVG/COBI	0,75	904,56
3877	09/03/2016	TDF/FTC+DRV+r	0,44	786,64
2749	11/03/2016	TDF/FTC/RPV	1	650,86
2862	11/03/2016	TDF/FTC+EFV	0,4	653,49
2709	15/03/2016	TDF/FTC/RPV	1	650,86
2865	17/03/2016	TDF/FTC/EVG/COBI	0,75	904,56
2964	22/03/2016	TDF/FTC/EVG/COBI	0,75	904,56
3880	30/03/2016	TDF/FTC+DTG	0,6	1038,86
2670	04/04/2016	TDF/FTC/RPV	1	650,86
2953	11/04/2016	TDF/FTC/EVG/COBI	0,75	904,56
4337	12/04/2016	TDF/FTC/RPV	1	650,86
2892	14/04/2016	3TC+TDF+RAL	0,28	860,55
2702	15/04/2016	TDF/FTC/RPV	1	650,86
106	18/04/2016	TDF/FTC/RPV	1	650,86
2960	19/04/2016	TDF/FTC/RPV	1	650,86
3686	19/04/2016	ABC/3TC/DTG	0,65	998,19
2961	20/04/2016	TDF/FTC/EVG/COBI	0,75	904,56
4338	21/04/2016	DRV+r+RAL	0,316	869,31
4334	26/04/2016	TDF/FTC/RPV	1	650,86
2943	26/04/2016	TDF/FTC/EVG/COBI	0,75	904,56
3965	12/05/2016	TDF/FTC/EFV	0,4	653,32
4294	17/05/2016	TDF/FTC/RPV	1	650,86
3649	19/05/2016	ABC/3TC+DTG	0,65	998,19
2661	24/05/2016	ABC/3TC/DTG	0,65	998,19
3964	24/05/2016	TDF/FTC+DTG	0,6	1038,86
2926	01/06/2016	TDF/FTC/RPV	1	650,86

2967	01/06/2016	TDF/FTC/RPV	1	650,86
2930	13/06/2016	TDF/FTC/RPV	1	650,86
2929	13/06/2016	TDF/FTC/EVG/COBI	0,75	904,56
3675	16/06/2016	TDF/FTC/EVG/COBI	0,75	904,56
2928	21/06/2016	TDF/FTC/RPV	1	650,86
3650	28/06/2016	TDF/FTC/RPV	1	650,86
4291	29/06/2016	TDF/FTC/RPV	1	650,86
2671	01/07/2016	TDF/FTC/RPV	1	650,86
4252	01/07/2016	TDF/FTC/EFV	0,4	653,32
2410	14/07/2016	TDF/FTC/RPV	1	650,86
3882	18/07/2016	TDF/FTC/RPV	1	650,86
3679	18/07/2016	TDF/FTC/EVG/COBI	0,75	904,56
4301	19/07/2016	ABC/3TC+DTG	0,65	998,19
4354	19/07/2016	TDF/FTC+DRV+r	0,44	786,64
3677	22/07/2016	TDF/FTC+RAL	0,69	960,39
4257	28/07/2016	TDF/FTC+DRV/COBI	0,44	786,64
3883	01/08/2016	TDF/FTC/RPV	1	650,86
3466	03/08/2016	TDF/FTC+DTG	0,6	1038,86
3681	05/08/2016	TDF/FTC/RPV	1	650,86
3468	05/08/2016	DRV/COBI+DTG	0,028	947,78
3881	09/08/2016	TDF/FTC/RPV	1	650,86
3678	11/08/2016	TDF/FTC/EVG/COBI	0,75	904,56
3682	12/08/2016	TDF/FTC/EVG/COBI	0,75	904,56
3364	14/08/2016	TDF/FTC+DTG	0,6	1038,86
3683	01/09/2016	TDF/FTC+DTG	0,6	1038,86
4258	07/09/2016	TDF/FTC/RPV	1	650,86
4293	13/09/2016	TDF/FTC+r+DRV	0,44	786,64
1256	14/09/2016	TDF/FTC/RPV	1	650,86
3648	16/09/2016	TDF/FTC/EVG/COBI	0,75	904,56
4256	20/09/2016	TDF/FTC+DTG	0,6	1038,86
4251	27/09/2016	TDF/FTC/RPV	1	650,86
3684	28/09/2016	TDF/FTC/RPV	1	650,86
4249	28/09/2016	TDF/FTC/EVG/COBI	0,75	904,56
4353	29/09/2016	TDF/FTC/RPV	1	650,86
4300	08/10/2016	DRV/COBI+DTG	0,028	947,78
4293	10/10/2016	TDF/FTC+r+DRV	0,44	786,64
4349	12/10/2016	TDF/FTC/EVG/COBI	0,75	904,56
4147	13/10/2016	TDF/FTC+DTG	0,6	1038,86
4336	17/10/2016	TDF/FTC/RPV	1	650,86
3848	20/10/2016	TDF/FTC+DTG	0,6	1038,86
4255	21/10/2016	TDF/FTC/EVG/COBI	0,75	904,56
3680	21/10/2016	ABC/3TC/DTG	0,65	998,19
4350	25/10/2016	TDF/FTC+DTG	0,6	1038,86

3910	28/10/2016	TDF/FTC/EVG/COBI	0,75	904,56
3924	08/11/2016	TDF/FTC/EVG/COBI	0,75	904,56
4351	14/11/2016	TDF/FTC/EVG/COBI	0,75	904,56
4355	28/11/2016	ABC/3TC/DTG	0,65	998,19
4247	30/11/2016	TDF/FTC/RPV	1	650,86
4023	14/12/2016	TDF/FTC/RPV	1	650,86
4295	19/12/2016	TDF/FTC+DRV+r	0,44	786,64
4335	22/12/2016	ABC/3TC/DTG	0,65	998,19
4352	13/01/2017	TDF/FTC/EVG/COBI	0,75	904,56

Average score 2015:	0,60
Average score 2016:	0,75
Student's T test	0,0001674
Average price 2015:	919,60
Average price 2016:	816,18
Student's T test	0,0001441

Appendix B: SOAP messages

B1 KM1 Naive NRTI

B1.1 Request


```
<s:Envelope xmlns:s="http://schemas.xmlsoap.org/soap/envelope/">
  <s:Header>
    <To s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://localhost:27956/SimpleEvaluation.svc</To>
    <Action s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://www.omg.org/spec/CDSS/201012/dssWsdl/ISimpleEvaluation/Evaluate</Action>
  </s:Header>
  <s:Body xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xmlns:xsd="http://www.w3.org/2001/XMLSchema">
    <evaluate xmlns="http://www.omg.org/spec/CDSS/201012/dss">
      <interactionId scopingEntityId="it.hsanmartino.cds" interactionId="979aa143ff8a4cb294b56afb988f2d32"
submissionTime="2017-04-07T10:05:18.4763818Z" xmlns=""></interactionId>
      <evaluationRequest clientLanguage="it-IT" clientTimeZoneOffset="+01:00" xmlns="">
        <kmEvaluationRequest>
          <kmId scopingEntityId="it.medinfo.km" businessId="NAIVESceltaNRTI" version="1.0"></kmId>
        </kmEvaluationRequest>
        <dataRequirementItemData>
          <driId itemId="RequiredDataId"></driId>
          <data>
            <informationModelSSId scopingEntityId="org.hl7.cds" businessId="cdsinput:r2:CDSInput"
version="2.0"></informationModelSSId>
            <base64EncodedPayload>
              <patient xmlns="urn:hl7-org:vmr:r2">
                <id root="2.16.840.1.113883.2.9.3.17.3.2.1.4" extension="00901115"></id>
                <gender code="M" codeSystem="2.16.840.1.113883.5.1"
codeSystemName="AdministrativeGender"></gender>
                <birthTime value="19610711"></birthTime>
                <age value="56" unit="years"></age>
                <clinicalStatement xsi:type="ObservationResult">
                  <id root="00901115.201704070000.50956-2"></id>
                  <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
                  <observationFocus code="50956-2" codeSystem="2.16.840.1.113883.6.1"
codeSystemName="LOINC"></observationFocus>
                  <observationValue>
                    <value xsi:type="q1:PQ" value="1" unit="" xmlns:q1="urn:hl7-org:cdsdt:r2"></value>
                  </observationValue>
                </clinicalStatement>
                <clinicalStatement xsi:type="DeniedProblem">
                  <id root="00901115.201704070000.4292"></id>
                  <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
                  <conditionCode code="4292" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
                </clinicalStatement>
                <clinicalStatement xsi:type="Problem">
```

```
            <id root="00901115.201704070000.7330"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <conditionCode code="7330" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
            <conditionEffectiveTime lowClosed="true">
              <low value="20120207" xmlns="urn:hl7-org:cdsdt:r2"></low>
            </conditionEffectiveTime>
          </clinicalStatement>
          <clinicalStatement xsi:type="DeniedProblem">
            <id root="00901115.201704070000.0703"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <conditionCode code="0703" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
          </clinicalStatement>
          <clinicalStatement xsi:type="ObservationResult">
            <id root="00901115.201704070000.20447-9"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <observationFocus code="20447-9" codeSystem="2.16.840.1.113883.6.1"
codeSystemName="LOINC"></observationFocus>
            <observationValue>
              <value xsi:type="q2:PQ" value="33" unit="Copie/ml" xmlns:q2="urn:hl7-org:cdsdt:r2"></value>
            </observationValue>
          </clinicalStatement>
          <clinicalStatement xsi:type="ObservationResult">
            <id root="00901115.201704070000.30525-0"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <observationFocus code="30525-0" codeSystem="2.16.840.1.113883.6.1"
codeSystemName="LOINC"></observationFocus>
            <observationValue>
              <value xsi:type="q3:PQ" value="56" unit="Years" xmlns:q3="urn:hl7-org:cdsdt:r2"></value>
            </observationValue>
          </clinicalStatement>
          <clinicalStatement xsi:type="DeniedProblem">
            <id root="00901115.201704070000.011"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <conditionCode code="011" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
          </clinicalStatement>
        </patient>
      </base64EncodedPayload>
    </data>
  </dataRequirementItemData>
 </evaluationRequest>
</evaluate>
</s:Body>
</s:Envelope>
```


B1.2 Response


```
<s:Envelope xmlns:s="http://schemas.xmlsoap.org/soap/envelope/">
 <s:Header>
  <Action s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://www.omg.org/spec/CDSS/201012/ds
sWsdl/ISimpleEvaluation/EvaluateResponse</Action>
 </s:Header>
 <s:Body xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xmlns:xsd="http://www.w3.org/2001/XMLSchema">
```

```
<evaluateResponse xmlns="http://www.omg.org/spec/CDSS/201012/dss">
 <evaluationResponse xmlns="">
  <finalKMEvaluationResponse>
   <kmId scopingEntityId="it.medinfo.km" businessId="NAIVESceltaNRTI" version="1.0"></kmId>
   <kmEvaluationResultData>
    <evaluationResultId itemId="76bb25b9-476b-47a0-9b54-2e9148e5e38b"></evaluationResultId>
    <data>
     <informationModelSSId scopingEntityId="org.hl7.cds" businessId="cdsoutput:r2:CDSOutputAsVMR"
version="2.0"></informationModelSSId>
      <base64EncodedPayload>
       <templateId root="2.16.840.1.113883.3.1829.11.1.3.5" identifierName="CDSOutputAsVMR"
xmlns="urn:hl7-org:vmr:r2"></templateId>
        <patient xmlns="urn:hl7-org:vmr:r2">
         <id root="2.16.840.1.113883.2.9.3.17.3.2.1.4" extension="00901115"></id>
         <gender code="M" codeSystem="2.16.840.1.113883.5.1"
codeSystemName="AdministrativeGender"></gender>
         <birthTime value="19610711"></birthTime>
         <age value="56" unit="years"></age>
         <clinicalStatement xsi:type="SubstanceAdministrationProposal">
          <id root="00901115.201704070000.J05AF07J05AF09"></id>
          <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
          <attribute>
           <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
           <name value="Recommended"></name>
           <value xsi:type="Value">
            <value xmlns:q1="urn:hl7-org:cdsdt:r2" xsi:type="q1:INT" value="2"></value>
           </value>
          </attribute>
          <substance>
           <relatedEntity>
            <entity xsi:type="AdministrableSubstance">
             <substanceCode code="J05AF09" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
            </entity>
           </relatedEntity>
           <substanceCode code="J05AF07" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
          </substance>
         </clinicalStatement>
         <clinicalStatement xsi:type="SubstanceAdministrationProposal">
          <id root="00901115.201704070000.J05AF06J05AF05"></id>
          <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
          <attribute>
           <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
           <name value="Acceptable alternative"></name>
           <value xsi:type="Value">
            <value xmlns:q2="urn:hl7-org:cdsdt:r2" xsi:type="q2:INT" value="1"></value>
           </value>
          </attribute>
          <substance>
           <relatedEntity>
            <entity xsi:type="AdministrableSubstance">
             <substanceCode code="J05AF05" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
            </entity>
           </relatedEntity>
           <substanceCode code="J05AF06" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
```

```
            </substance>
           </clinicalStatement>
          </patient>
         </base64EncodedPayload>
        </data>
       </kmEvaluationResultData>
      </finalKMEvaluationResponse>
     </evaluationResponse>
    </evaluateResponse>
  </s:Body>
</s:Envelope>
```


B2 KM2 Naive 3rd Agent

B2.1 Request


```
<s:Envelope xmlns:s="http://schemas.xmlsoap.org/soap/envelope/">
  <s:Header>
    <To s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://localhost:27956/SimpleEvaluation.svc</To>
    <Action s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://www.omg.org/spec/CDSS/201012/dssWsdl/ISimpleEvaluation/Evaluate</Action>
  </s:Header>
  <s:Body xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xmlns:xsd="http://www.w3.org/2001/XMLSchema">
    <evaluate xmlns="http://www.omg.org/spec/CDSS/201012/dss">
      <interactionId scopingEntityId="it.hsanmartino.cds" interactionId="0090d267d38f4d25bc8064530338b530"
submissionTime="2017-04-07T10:05:23.3713102Z" xmlns=""></interactionId>
      <evaluationRequest clientLanguage="it-IT" clientTimeZoneOffset="+01:00" xmlns="">
        <kmEvaluationRequest>
          <kmId scopingEntityId="it.medinfo.km" businessId="NAIVEScelta3Agente" version="1.0"></kmId>
        </kmEvaluationRequest>
        <dataRequirementItemData>
          <driId itemId="RequiredDataId"></driId>
          <data>
            <informationModelSSId scopingEntityId="org.hl7.cds" businessId="cdsinput:r2:CDSInput"
version="2.0"></informationModelSSId>
            <base64EncodedPayload>
              <patient xmlns="urn:hl7-org:vmr:r2">
                <id root="2.16.840.1.113883.2.9.3.17.3.2.1.4" extension="00901115"></id>
                <gender code="M" codeSystem="2.16.840.1.113883.5.1"
codeSystemName="AdministrativeGender"></gender>
                <birthTime value="19610711"></birthTime>
                <age value="56" unit="years"></age>
                <clinicalStatement xsi:type="DeniedProblem">
                  <id root="00901115.201704070000.4292"></id>
                  <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
                  <conditionCode code="4292" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
                </clinicalStatement>
                <clinicalStatement xsi:type="DeniedProblem">
                  <id root="00901115.201704070000.33183"></id>
                  <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
                  <conditionCode code="33183" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
                </clinicalStatement>
                <clinicalStatement xsi:type="ObservationResult">
```

<id root="00901115.201704070000.20447-9"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<observationFocus code="20447-9" codeSystem="2.16.840.1.113883.6.1"
codeSystemName="LOINC"></observationFocus>
<observationValue>
<value xsi:type="q1:PQ" value="33" unit="Copie/ml" xmlns:q1="urn:hl7-org:cdsdt:r2"></value>
</observationValue>
</clinicalStatement>
<clinicalStatement xsi:type="ObservationResult">
<id root="00901115.201704070000.35591-7"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<observationFocus code="35591-7" codeSystem="2.16.840.1.113883.6.1"
codeSystemName="LOINC"></observationFocus>
<observationValue>
<value xsi:type="q2:PQ" value="15.1" unit="" xmlns:q2="urn:hl7-org:cdsdt:r2"></value>
</observationValue>
</clinicalStatement>
<clinicalStatement xsi:type="DeniedProblem">
<id root="00901115.201704070000.011"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<conditionCode code="011" codeSystem="2.16.840.1.113883.6.103" codeSystemName="ICD-9-
CM"></conditionCode>
</clinicalStatement>
<clinicalStatement xsi:type="SubstanceAdministrationEvent">
<id root="00901115.201704070000.J04AB02"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<substance>
<substanceCode code="J04AB02" codeSystem="2.16.840.1.113883.2.9.6.1.23"
codeSystemName="Codice AIC Farmaco"></substanceCode>
</substance>
<administrationTimeInterval lowClosed="true">
<low value="00010101" xmlns="urn:hl7-org:cdsdt:r2"></low>
</administrationTimeInterval>
</clinicalStatement>
<clinicalStatement xsi:type="SubstanceAdministrationEvent">
<id root="00901115.201704070000.J05AF05"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<substance>
<substanceCode code="J05AF05" codeSystem="2.16.840.1.113883.2.9.6.1.23"
codeSystemName="Codice AIC Farmaco"></substanceCode>
</substance>
<administrationTimeInterval lowClosed="true">
<low value="20170407" xmlns="urn:hl7-org:cdsdt:r2"></low>
</administrationTimeInterval>
</clinicalStatement>
<clinicalStatement xsi:type="SubstanceAdministrationEvent">
<id root="00901115.201704070000.J05AF06"></id>
<evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
<substance>
<substanceCode code="J05AF06" codeSystem="2.16.840.1.113883.2.9.6.1.23"
codeSystemName="Codice AIC Farmaco"></substanceCode>
</substance>
<administrationTimeInterval lowClosed="true">
<low value="20170407" xmlns="urn:hl7-org:cdsdt:r2"></low>
</administrationTimeInterval>
</clinicalStatement>

```
          </patient>
         </base64EncodedPayload>
        </data>
       </dataRequirementItemData>
     </evaluationRequest>
   </evaluate>
  </s:Body>
</s:Envelope>
```

B2.2 Response

```
<s:Envelope xmlns:s="http://schemas.xmlsoap.org/soap/envelope/">
  <s:Header>
    <Action s:mustUnderstand="1"
xmlns="http://schemas.microsoft.com/ws/2005/05/addressing/none">http://www.omg.org/spec/CDSS/201012/ds
sWsdl/ISimpleEvaluation/EvaluateResponse</Action>
  </s:Header>
  <s:Body xmlns:xsi="http://www.w3.org/2001/XMLSchema-instance"
xmlns:xsd="http://www.w3.org/2001/XMLSchema">
    <evaluateResponse xmlns="http://www.omg.org/spec/CDSS/201012/dss">
      <evaluationResponse xmlns="">
        <finalKMEvaluationResponse>
          <kmId scopingEntityId="it.medinfo.km" businessId="NAIVEScelta3Agente" version="1.0"></kmId>
          <kmEvaluationResultData>
            <evaluationResultId itemId="4e53ca45-bf97-4c09-bbc7-eddd872a72f5"></evaluationResultId>
            <data>
              <informationModelSSId scopingEntityId="org.hl7.cds" businessId="cdsoutput:r2:CDSOutputAsVMR"
version="2.0"></informationModelSSId>
              <base64EncodedPayload>
                <templateId root="2.16.840.1.113883.3.1829.11.1.3.5" identifierName="CDSOutputAsVMR"
xmlns="urn:hl7-org:vmr:r2"></templateId>
                <patient xmlns="urn:hl7-org:vmr:r2">
                  <id root="2.16.840.1.113883.2.9.3.17.3.2.1.4" extension="00901115"></id>
                  <gender code="M" codeSystem="2.16.840.1.113883.5.1"
codeSystemName="AdministrativeGender"></gender>
                  <birthTime value="19610711"></birthTime>
                  <age value="56" unit="years"></age>
                  <clinicalStatement xsi:type="SubstanceAdministrationProposal">
                    <id root="00901115.201704070000.J05AE08J05AE03"></id>
                    <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
                    <attribute>
                      <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
                      <name value="Recommended"></name>
                      <value xsi:type="Value">
                        <value xmlns:q1="urn:hl7-org:cdsdt:r2" xsi:type="q1:INT" value="2"></value>
                      </value>
                    </attribute>
                    <substance>
                      <relatedEntity>
                        <entity xsi:type="AdministrableSubstance">
                          <substanceCode code="J05AE03" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
                        </entity>
                      </relatedEntity>
                      <substanceCode code="J05AE08" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
                    </substance>
                  </clinicalStatement>
                  <clinicalStatement xsi:type="SubstanceAdministrationProposal">
                    <id root="00901115.201704070000.J05AE10J05AE03"></id>
```

```
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <attribute>
              <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
              <name value="Recommended"></name>
              <value xsi:type="Value">
                <value xmlns:q2="urn:hl7-org:cdsdt:r2" xsi:type="q2:INT" value="2"></value>
              </value>
            </attribute>
            <substance>
              <relatedEntity>
                <entity xsi:type="AdministrableSubstance">
                  <substanceCode code="J05AE03" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
                </entity>
              </relatedEntity>
              <substanceCode code="J05AE10" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
            </substance>
          </clinicalStatement>
          <clinicalStatement xsi:type="SubstanceAdministrationProposal">
            <id root="00901115.201704070000.J05AX12"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <attribute>
              <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
              <name value="Caution"></name>
              <value xsi:type="Value">
                <value xmlns:q3="urn:hl7-org:cdsdt:r2" xsi:type="q3:INT" value="-1"></value>
              </value>
            </attribute>
            <substance>
              <substanceCode code="J05AX12" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
            </substance>
          </clinicalStatement>
          <clinicalStatement xsi:type="SubstanceAdministrationProposal">
            <id root="00901115.201704070000.J05AX11"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <attribute>
              <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
              <name value="Avoid"></name>
              <value xsi:type="Value">
                <value xmlns:q4="urn:hl7-org:cdsdt:r2" xsi:type="q4:INT" value="-2"></value>
              </value>
            </attribute>
            <substance>
              <substanceCode code="J05AX11" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
            </substance>
          </clinicalStatement>
          <clinicalStatement xsi:type="SubstanceAdministrationProposal">
            <id root="00901115.201704070000.J05AX08"></id>
            <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
            <attribute>
              <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
```

```
                <name value="Recommended"></name>
                <value xsi:type="Value">
                  <value xmlns:q5="urn:hl7-org:cdsdt:r2" xsi:type="q5:INT" value="2"></value>
                </value>
              </attribute>
              <substance>
                <substanceCode code="J05AX08" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
              </substance>
            </clinicalStatement>
            <clinicalStatement xsi:type="SubstanceAdministrationProposal">
              <id root="00901115.201704070000.J05AG05"></id>
              <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
              <attribute>
                <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
                <name value="Recommended"></name>
                <value xsi:type="Value">
                  <value xmlns:q6="urn:hl7-org:cdsdt:r2" xsi:type="q6:INT" value="2"></value>
                </value>
              </attribute>
              <substance>
                <substanceCode code="J05AG05" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
              </substance>
            </clinicalStatement>
            <clinicalStatement xsi:type="SubstanceAdministrationProposal">
              <id root="00901115.201704070000.J05AG03"></id>
              <evaluatedPersonId root="2.16.840.1.113883.2.9.3.17.3.2.1.4"
extension="00901115"></evaluatedPersonId>
              <attribute>
                <templateId root="2.16.840.1.113883.3.1829.11.14.8.7"
identifierName="Attribute"></templateId>
                <name value="Acceptable alternative"></name>
                <value xsi:type="Value">
                  <value xmlns:q7="urn:hl7-org:cdsdt:r2" xsi:type="q7:INT" value="1"></value>
                </value>
              </attribute>
              <substance>
                <substanceCode code="J05AG03" codeSystem="2.16.840.1.113883.6.73"
codeSystemName="Anatomical Therapeutic Chemical Classification System"></substanceCode>
              </substance>
            </clinicalStatement>
          </patient>
        </base64EncodedPayload>
      </data>
    </kmEvaluationResultData>
  </finalKMEvaluationResponse>
 </evaluationResponse>
</evaluateResponse>
</s:Body>
</s:Envelope>
```