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EXPLOITING HEALTHCARE STANDARDS TO BUILD A MODULAR DECISION SUPPORT SYSTEM INTEGRATED IN A REAL-WORLD REHABILITATION SETTING

PhD Thesis by

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"Computers are incredibly fast,
accurate and stupid;
humans are incredibly slow,
inaccurate and brilliant;
together they are powerful beyond
imagination."

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Abstract (Italiano)

La misura dell'aspettativa di vita è uno degli indicatori più comuni per valutare lo stato di salute di una popolazione in termini quantitativi. Negli ultimi cinque anni questo score è cresciuto costantemente a livello italiano ed europeo. L'aspettativa di vita in buona salute alla nascita, invece, è sostanzialmente inferiore (66,8 anni nel 2018).

La riflessione che possiamo trarre da queste statistiche è che, sul totale di anni vissuti, potremmo spendere il 20% del tempo affetti da qualche forma di malattia. Per questo motivo a livello globale, l'importanza di migliorare l'aspettativa di vita in buona salute è considerata strategica, tanto da occupare un intero obiettivo di sviluppo sostenibile (numero tre).

Numerosi articoli di ricerca suggeriscono che dedicarsi all'attività fisica promuove un impatto positivo sulla salute e sul benessere in età avanzata. Molti autori concordano sul fatto che esercizi fisici sistematici siano in grado di apportare un impatto positivo sull'invecchiamento attivo, attenuando il degrado della salute, esercitando effetti cognitivi e psicologici positivi, oltre che fisici. Gli interventi di riabilitazione sono ugualmente importanti sia per i soggetti senza patologie che vogliono invecchiare in modo sano, che per i pazienti cronicamente malati, al fine di migliorare l'aspettativa di vita in buona salute.

Ad aggravare ulteriormente l'assenza di miglioramento dell'aspettativa di vita in buona salute, secondo Eurostat, è la costante crescita dell'indice di dipendenza degli anziani, un punteggio che valuta quanto la popolazione delle persone dipendenti "faccia pressione" sulle persone indipendenti.

Si deduce da queste misure che in un prossimo futuro sarà sempre più complicato per la popolazione in età lavorativa sostenere autonomamente la domanda di assistenza delle persone di età pari o superiore a 65 anni, anche nei bisogni quotidiani di base come raggiungere le strutture attrezzate per l'attività fisica.

Il passaggio al regime domiciliare è noto in letteratura per essere un momento di elevata discontinuità nell'assistenza a causa della scarsa aderenza e motivazione del paziente, scarsa comprensione dei benefici delle cure riabilitative, scarsa predisposizione al cambiamento nello stile di vita.

Efficaci interventi di riabilitazione implementati in uno scenario domiciliare possono fornire una terapia efficace per la popolazione anziana, portando di conseguenza a miglioramenti del sistema tra cui una riduzione dei costi e un uso più appropriato delle risorse.

In questo senso, negli ultimi anni la telemedicina è stata utilizzata per personalizzare l'applicazione delle terapie domiciliari per trasferire la gestione del paziente dall'ospedale a casa.

Le attività svolte a casa si sono dimostrate una valida alternativa ai corsi convenzionali e l'utilizzo del coaching virtuale ha aumentato l'aderenza ai programmi proposti.

Sebbene promettente, la gestione della cronicità con tecnologie innovative dell'informazione e della comunicazione (ICT) non ha ancora raggiunto un livello sufficiente di specializzazione, qualità e robustezza. Inoltre, le soluzioni ICT sono spesso viste come "elementi isolati" nella gestione del paziente piuttosto che essere principalmente interventi di supporto al cambiamento, nell'organizzazione e nei paradigmi di cura.

Il progetto regionale in cui è inserito il dottorato ha l'obiettivo di separare il divario tra soluzioni dell'Information Technology e della riabilitazione domestica. La soluzione proposta intende rispondere a questa esigenza creando una piattaforma integrata che coinvolga pazienti, operatori sanitari, caregiver e tecnologie ICT, per pianificare ed eseguire trattamenti domiciliari individualizzati e controllati da remoto.

L'obiettivo del lavoro presentato in questa dissertazione è la progettazione tecnica e implementazione di un sistema di supporto decisionale (DSS) interoperabile in grado di supportare il medico nel processo di prescrizione di un trattamento riabilitativo domiciliare a un paziente anziano.

L'obiettivo che si prefigge il lavoro è di presentare al medico raccomandazioni personalizzate basate sui dati del paziente al fine di costruire una prescrizione "su misura" in base alle condizioni attuali del paziente e ai risultati desiderati.

La raccomandazione fornita dal DSS deve essere basata sulle evidenze scientifiche più recenti disponibili, completamente interpretabile dalla macchina per supportare l'analisi automatica dei dati del paziente, eliminando così qualsiasi inserimento manuale ripetitivo di dati da parte del medico. Inoltre, l'architettura implementata deve essere progettata per essere una soluzione completamente funzionante e non un prototipo o una prova di concetto. Nella fase di sperimentazione del progetto regionale nel quale è inserito il dottorato di ricerca (sperimentazione prevista nel 2021), il DSS deve potersi integrare con i sistemi informativi reali di ICS Maugeri. L'obiettivo è stato raggiunto attraverso diverse fasi propedeutiche. In primis è stata effettuata un'analisi approfondita della letteratura, per identificare lo stato dell'arte a diversi livelli: il problema clinico della prescrizione di un regime riabilitativo domiciliare, il flusso di informazioni disponibili di ICS Maugeri nella prescrizione di un regime di assistenza domiciliare e metodi per aderire alle leggi e regolamenti (GDPR, leggi regionali). L'analisi della letteratura ha mostrato che il dominio clinico della riabilitazione domiciliare supportata dalle soluzioni ICT è ricca di articoli, incentrati principalmente sulle tecnologie che monitorano il paziente durante il trattamento domiciliare o sugli esiti clinici che tale intervento fornisce.

Mancano tuttavia le prove su quale processo di ragionamento spinga il medico a prescrivere un intervento rispetto a un altro, diverso dalla sua esperienza personale, o preferenze personali, o esigenze di disegno sperimentale. La tesi presenta i diversi approcci che un ricercatore potrebbe seguire nella costruzione di tali sistemi con un'analisi comparativa dei lati positivi e negativi di ogni approccio.

Inoltre, vengono brevemente analizzate le leggi e i regolamenti che devono essere seguiti per prendere in carico un paziente sfruttando soluzioni ICT. L'attività di ricerca prosegue individuando requisiti funzionali originati dall'analisi dello stato dell'arte, e requisiti provenienti dai medici di ICS Maugeri, gli utenti finali del DSS. Particolare attenzione è riservata alla scelta di aderire ai più recenti e stabili standard disponibili in sanità a diversi livelli:

- livello di modellazione dei dati: HL7 FHIR R4;
- paradigma di comunicazione: CDS Hooks versione 1.0.0;
- formalizzazione knowledge base: HL7 CQL versione 1.3, linee guida cliniche FHIR.

La dissertazione presenta in dettaglio il progetto tecnico che ha guidato lo sviluppo del DSS, sottolineando l'importanza di aderire agli standard internazionali, con un focus specifico su come costruire un sistema interoperabile che possa essere facilmente integrato in un contesto reale.

Vengono offerti i punti chiave dell'implementazione del DSS che rappresentano il contributo originale di questo lavoro e, quando possibile, viene fornito un riferimento ad un repository open source o a una porzione di codice sorgente. Inoltre, viene descritto un plug-in che arricchisce la navigazione del testo libero di una linea guida utilizzando il concetto di knowledge graph. Viene infine presentata la metodologia con la quale si intende validare il DSS nella fase sperimentale del progetto. Viene sottolineata la validazione interna del DSS dal punto di vista tecnico, funzionale e di usabilità.

Gli sviluppi futuri di questo lavoro includono lo sviluppo di un servizio per sollecitare automaticamente la revisione di un trattamento domiciliare analizzando i dati provenienti da sensori di monitoraggio remoto. Un altro interessante sviluppo futuro risiede nell’eseguire sull'architettura proposta alcuni degli artefatti di supporto decisionale standard disponibili su un archivio pubblico americano (Agency for Healthcare Research and Quality) per testare la robustezza dell'architettura in un altro dominio clinico.

L'ultimo sviluppo futuro riguarda la possibilità di fornire le raccomandazioni che emergono dal DSS non come semplice ma come un collegamento a un’applicazione SMART, per migliorare l'esperienza dell'utente nel beneficiare dell’output del DSS.

Abstract (English)

Life expectancy measure is one of the most common indicators to assess the state of health of a population in quantitative terms. In the last 5 years this score has been steadily growing over an Italian and European level. Healthy life expectancy at birth, on the other hand, is substantially lower (66.8 years in 2018).

The reflection that ensues from these statistics is that, of the total years we could live, we could spend 20% with some form of illness. For this reason, at a global level, importance of improving healthy life expectancy is mandated and supported with an entire sustainable development goal dedicated to it (number three).

Numerous Research paper suggests that being physically active promotes a positive impact of on health and wellbeing in older age. Plentiful of authors agree that systematic physical exercises are capable of positively impact healthy ageing, attenuating declines in health, exerting positive cognitive and psychological effects, on the top of physical ones.

Rehabilitation interventions are equally important for healthy subjects who want to age in a healthy manner and chronically ill patients, to improve healthy life expectancy.

Further aggravating the absence of improvement of healthy life expectancy, according to Eurostat, the old-age dependency ratio, a score which assess how much the population of dependent people "weighs" on independent people is increasing rapidly.

The operative implication of these numbers is that in the near future it will be more and more complicated for the working age population to independently support the demand for care of people aged 65 and over, even in day to day basic needs like reaching the gyms. The transition from hospital to home-care is known to be a time of high discontinuity in assistance due to poor adherence and patient motivation, poor understanding of benefits of rehabilitation care, poor predisposition to change in lifestyle.

Effective Rehabilitation interventions deployed in a home-based scenario could provide effective therapy for elderly population, consequently leading to system improvements including decreased costs, more appropriate resource use, and avoidance of institutional placements.

To this extent, telemedicine has been used to personalize the application of home therapies to relocate patient management from hospital to home.

The activities carried out at home have been proved to be a valid alternative to conventional courses and the use of virtual coaching increased adherence to the proposed programs.

Although promising, the management of chronicity with innovative information and communication technologies (ICT) has not yet reached a sufficient level of specialization, quality, and robustness. Furthermore, ICT solutions are often seen as "isolated elements" in patient management rather than being primarily supportive interventions change, in the organization and in the paradigms of care.

The regional project in which the PhD is inserted, has the aim to connect the bridge of ICT and home rehabilitation.

The project intends to respond to this need by creating an integrated platform involving patients, healthcare professionals, caregivers, and ICT technologies, to plan and carry out individualized and remotely controlled home treatments. The goal of the work presented in this dissertation is to design and implement an interoperable, Decision Support System (DSS) that can support the physician in the process of prescribing an elder patient a home-care rehabilitation treatment.

The desired outcome requires the system to present personalized recommendations based on patients' data to make a tailored prescription on patient current condition and desired outcomes.

The recommendation delivered by the DSS must be coming from the most recent Evidence Based Medicine and needs to be fully machine-interpretable in order to support automatic analysis of patient data, thus eliminating any repetitive manual data entry to the DSS by the physician.

In addition, the implemented architecture needs to be designed to be a full working solution and not a prototype or a proof of concept.

In the experimentation phase of the regional project the PhD is inserted (scheduled for 2021), the DSS must be able to integrate with the real ICS Maugeri information systems. The goal has been achieved by different propaedeutic phases. A thorough literature analysis, to identify the state of the art at different levels: the clinical problem of prescribing a home-care rehabilitation regimen, the available ICS Maugeri information flow when prescribing a home-care regimen and methods to adhere to the applicable laws and regulations (GDPR, regional laws).

The literature analysis showed that the clinical domain of home-care rehabilitation supported by ICT flourishes with articles, mainly focused on the technologies that monitor the patient during home-care treatment or the clinical outcomes that such an intervention provides. There is a lack however on evidence on what reasoning process motivates the physician to prescribe an intervention over another, other than his personal experience, or preference, or experimental design needs. The state of the art in constructing a decision support system is then reviewed. The dissertation presents the different approaches a researcher could follow to build such systems with a comparative analysis of positive and negative sides of each approach.

In addition, the laws and regulations that need to be followed to treat a patient with ICT solutions are briefly analyzed. The research activity

progress by identifying functional requirements that originated from the state of the art analysis, and requirements coming from the physicians of ICS Maugeri, the end users of the DSS. Special attention is paid to the choice of adhering to the most recent but stable healthcare standards at different levels:

- data modeling level: HL7 FHIR R4;
- communication paradigm: CDS Hooks Version 1.0.0;
- knowledge base formalization: HL7 CQL Version 1.3, FHIR clinical guidelines.

Thorough detailing of the technical design that guided the development of the DSS, stressing importance of adhering to international standard drives the discussion, with a specific focus on how to build an interoperable system that can be easily integrated in a real setting.

Key points of the implementation of the DSS that represent the original contribution of this work are provided and, when possible, a reference to an open source repository code or a code snippet is supplied. In addition, a plugin is outlined, which enhances navigation of the free text of a guideline using knowledge graphs. Finally, the discussion presents the validation methodology that will be applied in the experimental phase. The validation is presented from different points of view: technical, functional and usability. Future developments of this work may include a service to automatic solicit the revision of a home-care treatment by analyzing the data coming from remote monitoring sensors.

Another interesting future development could be to deploy on the proposed architecture some of the standard decision support artifacts available on an American public repository (Agency for Healthcare Research and Quality outside the rehabilitation setting) to test the architecture robustness in another clinical domain. The last noteworthy future development would be to deliver the recommendations that emerge from the DSS not as plain text but as a link to a SMART App, to enhance user experience in benefiting from the recommendations.

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List of Abbreviations

6 MWT	6 Minute Walking Test
ADL	Activities of daily living
AHRQ	Agency for Healthcare Research and Quality
AI	Artificial Intelligence
API	Application Programming Interface
APP	Application Programming Interface
ATS	American Thoracic Society
CDA2	Clinical Document Architecture Version 2
CDS	Clinical Decision Support
CDSS	Clinical Decision Support system
CHD	coronary heart disease
CMET	Common Message Element Type
COPD	Chronic Obstructive Pulmonary Disease
COVID	Corona Virus Disease
CPG	Clinical Practice Guideline
CQL	Clinical Quality Language
CREMA	Cardio-Respiratory Exercise Maugeri Algorithm
cTAKES	clinical Text Analysis and Knowledge Extraction System
CUI	Concept Unique Identifier
CWA	closed-world assumption
DB	Database
DGR	Decision of the Regional Council
DPCM	Prime Ministerial Decree
DSS	Decision Support System
EBM	Evidence Based Medicine
EHR	Electronic Health Record
ERDF	European Regional Development Fund
ERS	European Respiratory Society
FHIR	Fast Healthcare Interoperability Resources
FSE	Electronic Health Record
GDPR	General data protection regulation
GP	General Practitioner
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HIMSS	Information and Management Systems Society
HL7	Health Level 7
HSPC	Healthcare Services Platform Consortium
HTTP	HyperText Transfer Protocol
ICD	International Classification of Disease
ICD9-CM	ICD 9 - Clinical Modification
ICF	International Classification of Functioning, Disability and Health

ICS	Clinical Institute
IHE	Integrating the Healthcare Enterprise
IRCCS	Institutes of Hospitalization and Scientific Care
ISO	International Organization for Standardization
JSON	JavaScript Object Notation
JWE	JSON Web Encryption
JWS	JSON Web Signature
JWT	JSON Web Token
KB	Knowledge Base
KG	Knowledge Graph
LOINC	Logical Observation Identifiers Names and Codes
MAC	Message Authentication Code
MCID	minimum clinically important difference
MEP	Maximal expiratory pressures
MeSH	Medical Subject Headings
MIP	Maximal inspiratory pressure
ML	Maschine Learning
NLM	National Library of Medicine
NLP	Natural Language Processing
OLTP	Online transaction processing
OWA	open-world assumption
OWL	Web Ontology Language
PAI	Individualized Care Plan
PDTA	Diagnostic Therapeutic Assistance Plans
PHR	personal health records
POR	Regional Operational Program
PRI	Individualized Rehabilitative Project
pri	Individualized Rehabilitative Program
RCT	randomised controlled trial
RDF	Resource Description Framework
REST	Representational State Transfer
RPE	Rate of Perceived Exertion
SMART	Substitutable Medical Applications, Reusable Technologies
SNOMED CT	Systematized Nomenclature of Medicine, Clinical Terms
SOAP	Simple Object Access Protocol
SQL	Structured Query Language
SSN	National Health Service
TLS	Transport Layer Security
TUI	Type Unique Identifier
UML	Unified Modeling Language
URL	Uniform Resource Locator
VSAC	Value Set Authority Center
WHO	World Health Organization
XML	eXtensible Markup Language

Chapter 1:

Introduction

Measures on life expectancy, infant mortality and the causes of death used to be an adequate basis for assessing population health status and determining public health priorities.

However, as the rate of mortality declines and life expectancy increases, scientists are beginning to doubt if longer lives are correlated with better lives. As a result, Europe now includes life expectancy rate free from disability among the main structural indicators for the verification of its strategic objectives.

In this context, rehabilitation interventions are equally important for healthy subjects who want to age in a healthy manner and chronically ill patient. Numerous research papers suggest that physical activity promotes a positive impact of on health and wellbeing in older age, the literature agrees that systematic physical exercises can exert positive cognitive and psychological effects, on the top of physical ones.

A downside of an ageing population is that the old-age dependency ratio is increasing rapidly. Old-age dependency ratio is the ratio of the number of over 65 (who are generally economical active) against the number of people of working age. The operative implication of these numbers is that in the near future it will be more and more complicated for the working age population to independently support the demand for care of people aged 65 and over, even in day to day basic needs like reaching the gyms.

This scenario calls for a reorganization of how long-term care gets delivered, by making significant use of both tools and technological innovation to share information and data between the patient and other professionals involved in the care process. Telemedicine is a key factor in this reorganization process and represents a modality for the provision of health care services using innovative technologies, in particular to Information and Communication Technologies (ICT). One of the most

popular interventions to support behavior change and healthy aging in older people is the provision of interactive games, since the entertainment and engagement aspects are shown to have positive outcomes.

Although these technological solutions are largely used in the new generations, their potential application to address healthy aging in older people is greatly underdeveloped.

Having seen this clinical scenario, the goal of the work presented in this dissertation is to design and implement an interoperable Decision Support System that is able to assist a physician in the process of prescribing an elder patient a home-care physical rehabilitation treatment.

The desired outcome is to deliver personalized recommendation based on patient's data and medical evidence coming from national guidelines, to make a tailored prescription on patient current condition and desired outcomes. The PhD is incorporated in a Lombardy regional project. The goal of the project is to develop and validate innovative rehabilitative treatment and assistance strategies for the chronic patient. The project runs in the frame the European funds Regional Operational Program (POR) European Regional Development Fund (ERDF) 2014-2020 [1].

Chapter 2 describes an overview of the clinical problem of prescribing a home-care rehabilitation regimen. To this end in the chapter are presented the following themes: the clinical problem, the information flow currently followed to prescribe a rehabilitation treatment, the laws that historically defined the provision of rehabilitation interventions both at Italian and regional level.

Chapter 3 analyses the state of the art in constructing a decision support system. In this section the different approaches to build such systems are described with a comparative analysis of positive and negative sides of each approach. In addition, the laws and regulations that need to be followed to treat a patient with ICT solutions are briefly analyzed. The end of the chapter provides the motivation for the chosen methodology.

Chapter 4 focuses on the functional requirements that originated from the state of the art analysis, and requirements coming from the physicians of ICS Maugeri, the end users of the DSS. At this stage, a list of use cases better describes the requirements.

Chapter 5 provides an exhaustive detailing of the technical design that guided the development of the DSS. The importance of adhering to international standard drives the discussion, with a specific focus on how to build an interoperable system that can be easily integrated in a real setting.

Chapter 6: describes the key points of the implementation of the DSS that represent the original contribution of this work. When possible, a reference to an open source repository code or a code snippet is provided. In addition, the chapter discusses a prototype of a plugin to provide

enhanced navigation of the free-text of a guideline using knowledge graphs.

Chapter 7: draws the conclusions of this work, presenting challenges and possible future implementations.

Chapter 2

Background: The Clinical Problem

Life expectancy is one of the most common indicators to assess the state of health of a population in quantitative terms. The indicator expresses an estimate of the average number of years of life expected for an individual at newborn age, and it is computed the basis of the mortality rates of the reference year. In 2015, the average life span in Italy reached 80.47 years for males and 85 for females, values higher than Europe of 2.2 and 1.3 respectively [2]. In 2018, life expectancy at birth reaches a peak of 81.13 years for men and 85.4 years for women [2].

Healthy life expectancy at birth, on the other hand, is substantially lower with values of 62.6 in 2015 and 66.8 years in 2018 respectively [3]. The measure of "Healthy life expectancy" belongs to a group of measures developed to discover if an increase of life span is enchained to an increase in the years lived in good health (the compression of morbidity scenario) or in bad health (expansion of morbidity).

These statistics, available in full in the attached Appendix A, clearly show that, of the total years we could live, we could spend 20% with some form of illness. At a European level, life expectancy free from disability figures among the main structural indicators for the verification of strategic objectives of the European Union [4]. At a global scale wellbeing promotion is addressed in Sustainable Development Goal 3 and articulates the importance of improving healthy life expectancy [5]. Rehabilitation is considered a crucial intervention in optimizing life expectancy, so it is essential that health systems provide rehabilitation services to meet both European and Global goals.

Rehabilitation interventions are equally important for healthy subjects who want to age in a healthy manner and chronically ill patients. Numerous research papers suggest that physical activity promotes a positive impact of health and wellbeing in older age, by investigating the associations between physical activity and heterogeneous trajectories of healthy ageing [6] [7]

[8] [9] [10] [11] [12] [13] [14] [15]. In particular, a study by Darío Moreno-Agostino et al. investigates how physical activity can influence healthy ageing trajectories using a harmonized dataset of eight ageing cohorts across the world (Australia, USA, Mexico, Japan, South Korea, and Europe) [16]. The result of the study suggests a positive impact of physical activity on healthy ageing, by lowering health decline. The study defines three latent classes of healthy ageing trajectories:

- stable trajectory with high starting point;
- stable trajectory with low starting point;
- high starting point associated with a fast decline over time.

Engagement in any level of physical activity seems to be associated with lower odds of being in the low stable and fast decline trajectories groups compared to the high stable trajectory group.

In addition, numerous authors agree that systematic physical exercise exerts positive cognitive and psychological effects, on the top of physical ones [17].

Even though the clinical evidence on this topic is clear and demonstrated the implementation of rehabilitation intervention on a large scale poses some difficulties.

Firstly, access to rehabilitation facilities or the possibility to practice physical activities may be difficult if one lives in a high disconnected environment rural and semi-rural areas [18] or has limited income. In addition the patient can be hesitant to benefit from the changing rooms, as they would like not to share intimacy with people they know too little, especially if they suffer from embarrassing, even when not invalidating, physical problems. At the same time, the primary and comprehensible wish of elderly persons is to remain in their homes if possible, despite a possible need for professional care.

Further aggravating such scenario, according to Eurostat, the old-age dependency ratio is increasing rapidly. Old-age dependency ratio is the ratio of the number of elderly people at an age when they are generally economically inactive (i.e. aged 65 and over), compared to the number of people of working age (i.e. 15-64 years old). A generally increasing trend can be observed for the EU-27's old-age. The old-age dependency ratio increased by 5.4 percentage points during the past decade (from 26.0 % in 2009 to 31.4 % in 2019) [19]. The operative implication of these number is that in the near future it will be more and more complicated for the working age population to independently support the demand for care of people aged 65 and over, even in day to day basic needs like reaching the gyms.

Despite compelling evidence from numerous studies of the benefits of training, treating physical exercise as though it was a pharmaceutical prescription is still underutilized by health systems around the world.

Compared to drug therapy, exercise can be cheaper and sometimes more effective treatment for several age-related health conditions, including diabetes, cancer, arthritis, and cardio-respiratory diseases.

The efficiency of exercise interventions versus or in collaboration with drug interventions on mortality risks has been recently compared in a meta-epidemiological study which included 305 randomized controlled trials involving almost 0.5 million participants [20]. The findings reported either better effectiveness or no difference for exercise interventions compared with drug treatments in three out of four outcomes, which included secondary prevention of coronary heart disease, rehabilitation of stroke, treatment of heart failure, and prevention of diabetes.

The study concludes that recommending physical activity as a preventative therapy for all ages is essential, on low-risk and especially on high-risk older populations [20].

Narrowing the search focus on Italy, the rehabilitation process has historically been regarded as the third component of the health management pathway, the first component as prevention while the second is treatment.

However, to optimize the health potential of an individual, a more modern and comprehensive approach is one that integrates all three components. Such an approach would maximize the potential benefits derived from physical, cognitive and motivational rehabilitation activities.

Furthermore, an integration of these activities with an aim to facilitate a return to independence, should be promptly initiated during the acute phase of disablement. This social framework has been deeply analyzed by the authors of " a periodical review published by the Italian Ministry of Health to inform and update the public on healthcare issues.

According to National Institute of Statistics historical data, in Italy more than 2.8 million people suffered in 2005 from a disability [21] [22] [23].

This scenario has prompted the Italian Ministry of Health to review the Guidelines for rehabilitation activities issued in 1998 [24]. The aim of the review was to improve rehabilitation by establishing a strategy that would encompass patient care, patient assessment, the design of a rehabilitation project and the implementation of a specific program focused on the individual.

While the 1998 Guidelines provided a reference for the guiding principles and the philosophy behind rehabilitation, it was recognized that the document lacked some key concepts:

- outcome identification and evaluation;
- criteria for intervention suitability.

To fill this shortcoming a working Group was established for a revision of the contents of the Guideline. The output of this revision, "*The Piano di Indirizzo per la Riabilitazione*" (plan for rehabilitation guidelines) was presented on 7th October 2010, and was approved by the "*Conferenza Stato Regioni*" (Programmatic panel between Central government and regional authorities) on February 10th, 2011. The document evaluated the considerable progress achieved in rehabilitation from scientific, clinical, and organizational perspectives, as well as in terms of interdisciplinary activity. The goal was to implement these advances and to make them

seamlessly integrate within the Italian healthcare and welfare services, in the interest of people with any type of disability or health impairment. All these breakthroughs in patient care have been then adopted by the health facilities of all Italian region. Among all the regions that diligently harmonized national recommendations into local guidelines, I chose to analyze the case of Lombardy as it shows efforts have been consistent and numerous in time and extent. This is motivated by a demographic justification.

According to Censis, the most important Italian socio-economic research institute, in Lombardy, the population aged over 65 constitutes 22.4% of the total and 49.7% of the population is affected by chronic diseases of which those cardiorespiratory, cerebrovascular, osteoarticular and neurodegenerative determine the greatest social and welfare impact, due to long-term disability and worsening of the quality of life of the caregiver, resulting in an increase in stress-related diseases [25].

In response to this socio-economic scenario, the Lombardy Regional System has redefined the healthcare model of assistance. The most important steps in the last 20 years are reviewed in the following timeline:

- **1998 - Implementation of "Guidelines of the Minister of Health for rehabilitation activities"** Official Gazette May 30th, 1998, described in the preceding paragraph. The implementation regarded the definition of individual rehabilitation project like
    - needs;
    - desired outcomes;
    - objectives;
    - times:
    - actions of the rehabilitation program:
        - methods of taking charge;
        - specific interventions;
        - element of verification for the rehabilitation project.

2011 - State Regions Agreement 2011 - Guidance plan for Rehabilitation, phases of treatment are formally defined**:**

- intensive rehabilitation;
- intensive rehabilitation with high specialization;
- extensive rehabilitation;
- outpatient rehabilitation;
- home care rehabilitation;
- outpatient rehabilitation;
- rehabilitation in an elderly focused structure.

In the same document healthcare regimens are formally defined

- day Hospital;
- day Service;

- out-of-hospital assistance of a continuous-cycle residential nature;
- outpatient assistance;
- house assistance;

focusing on a global and integrated care of the individual. Figure 1 summarizes the normative context of rehabilitation in Italy:

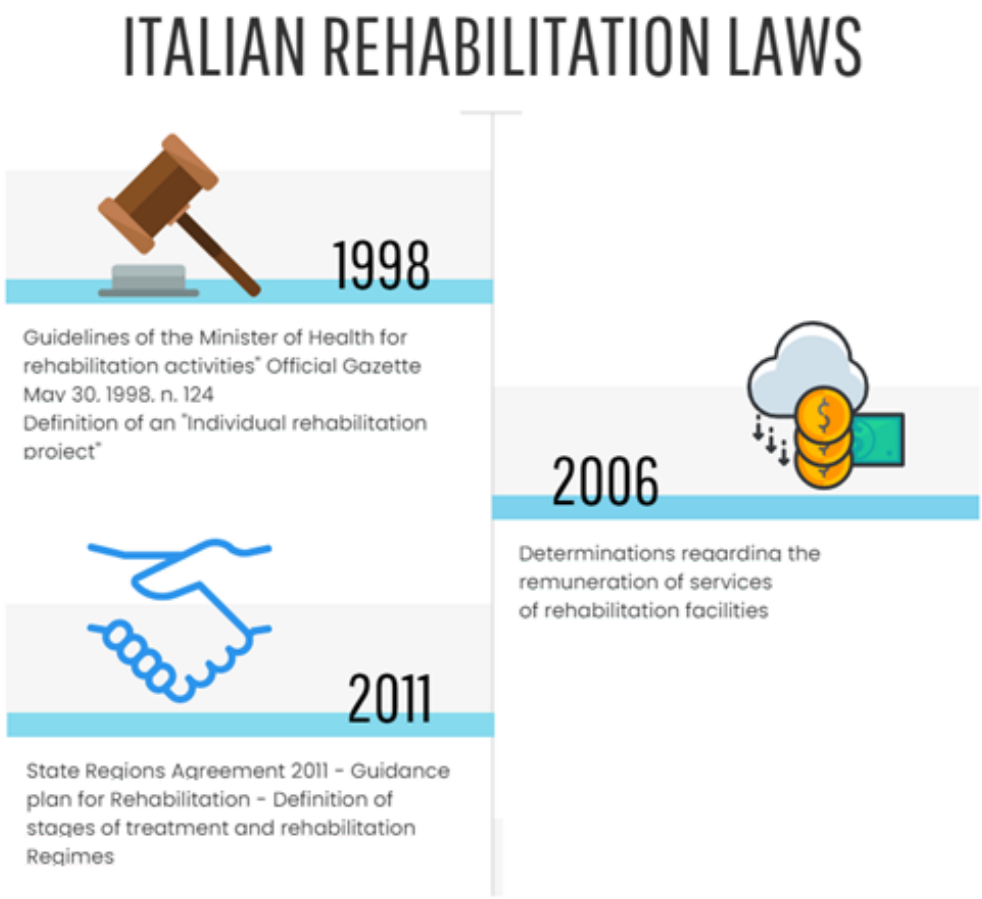


Figure 1: Italian Rehabilitation laws

2.1. **Home-Care rehabilitation Regimen**

The improvement of survival for numerous acute diseases with a high risk of disability, the increase in chronic disabling diseases, the constant increase in the average age of the population represent an important challenge for the health and social system, especially for those services dedicated to rehabilitation treatment.

The rehabilitation intervention aims to "gain health", in a perspective that sees the person with disabilities and limitations no longer as "sick",or “incapable” but as a "person with rights" [26].

Therefore the objective of a rehabilitation project is to carry out the health and social interventions necessary to obtain the maximum level of recovery of the function in relation to the clinical condition of the person, his level of participation and his abilities, the context in which he is inserted, taking into account the availability of resources.

In this perspective, "Integrated care pathway" is a crucial concept, characterized by a close interaction between the health professionals and caregivers, to obtain a multidisciplinar and multi-professional charge of the patient. In this context evidence-based medicine (EBM) and the introduction of the Guidelines as a tool for rationalizing clinical-organizational behavior to govern demand and guide health planning. children and adolescents gain major relevance.

In recent years, rehabilitation has increasingly focused on treating the person with his or her possibilities and potentials of participation, rather than the impairment causing the limitation. Regardless of the disability cause, the rehabilitation objective is to identify appropriate interventions in distinct and specific settings; the presence of comorbidities is also a contributing factor in the decision process. The following paragraphs will analyze in – depth how the Lombardy region currently delivers an individualized rehabilitation intervention in an inpatient or outpatient setting.

2.1.1. The PRI

This concept of “taking on the individual” and delivering an intervention based on a personalized rehabilitation program, has been defined and constructed in a cohesive framework: the so called “*Progetto Riabilitativo Individuale*” (PRI written in capital, individual rehabilitation project, as opposed to the “pri” that will be described later in this document).

The PRI defines the prognosis, the expectations, the priorities of the patient and his or her family. The parameters considered in the definition of the PRI include impairment, activity limitation and social participation restriction as listed by the International Classification of Functioning, Disability and Health (ICF).

The PRI aims to define the characteristics of suitability and appropriateness of the various interventions, as well as the termination of the patient management according to the results achieved and in cooperation with the patient, the family, and the caregivers.

In the decision process, the rehabilitation specialist (the clinician responsible for the patient must consider, according to the PRI, the functional prognosis, the extent to which the disabled state can be modified, the degree of the patient’s clinical stability and compliance to the program.

The rehabilitation specialist also ensures, through the involvement of a team of professionals, a constant flow of information to all people involved

in the activities of the PRI including the patient, the family, the caregivers and the general practitioners.

Given the complexity of the rehabilitation pathways and their need to be cohesively articulated in various settings (e.g. hospital, outpatient, geographical, healthcare, welfare), it is not only desirable but essential that all the Italian regions have a departmental organization of the rehabilitation activities.

The rehabilitation department guarantees the implementation of an adequate pathway of rehabilitation for all the patient who need it and constitutes the true interconnection point of Clinical Governance.

It is necessary to develop greater attention to the accompaniment of the patient, considering the domicile as a setting for rehabilitation, in order to give back the patient his everyday life as soon as possible. In this sense, home rehabilitation treatments can constitute a continuation of what carried out in the previous phases and in a inpatient setting within the PRI.

2.1.2. The PAI

The Individualized Care Plan (PAI), is the summary document that collects and describes in a multidisciplinary perspective the information relating to subjects in need, with the aim of formulating and implementing a care and assistance project that can favor the best health condition and well-being for the patient.

The PAI can be developed both during the patient's hospitalization and in the later stages. The differences with the Diagnostic Therapeutic Assistance Plans (PDTA) are the following: While in the PDTA an attempt is made to standardize and standardize the treatment approaches to certain categories of patients, through the PAI the aim is to individualize and therefore maximize the personalization of care.

Within the PAI there are elements of clinical, welfare, social, psychological and linguistic-communicative evaluation, all integrated and shared with the family unit and/or with the patient's caregivers, in order to ensure empowerment as much as possible.

The PAI is applied for a pre-established period, which however can undergo variations and it is developed in four phases:

1. observation;
2. planning;
3. delivery of the intervention;
4. verification of results.

The objectives in the PAI are subject to periodic verification and adjustment and for this reason the choice of measurable and quantifiable indicators that can guarantee constant monitoring of the interventions that have been implemented is of fundamental importance.

The planning of care activities is essentially based on an initial assessment of the patient by a multidisciplinary team and the drafting of the Individual Care Plan (PAI) or the Individual Rehabilitation Project (PRI) depending on the care setting in which the patient is inserted. The evaluation is conducted on different levels:

- Evaluation of clinical-health aspects of medical competence;
- Assessment of nursing care needs and the OSS;
- Assessment of the reactivation needs of the physiotherapist;
- Assessment of personal, relationship and socialization needs within the competence of the social worker (the educator, the social worker, the psychologist);
- Assessment of communication problems or dysphagia problems within the competence of the speech therapist.

In the PAI, the person as a whole is taken into consideration: each document must specify the reasons why the patient came to need an assistance intervention. Secondly the first draft of the document must specify the objectives of the intervention, that must be concrete, measurable and congruent with the global evaluation of the patient.

The structure's working method is that of the multidisciplinary team, where each professional figure makes their own contribution, to achieve the goals of care and assistance set for the real well-being of users.

This translates operationally into work by projects, in continuous verification, which allows an effective personalization of assistance.

The multidisciplinary team is usually made up of these kinds of figures:

- doctor;
- psychologist;
- nurse;
- physiotherapist;
- occupational therapist;
- speech therapist;
- social worker;
- socio-health worker.

This team whose composition in number may vary, works in an integrated way to achieve the best possible well-being of the person; elaborates general departmental projects and programs and plans assistance activities for each user; it meets periodically for the verification of the results and the reshaping of the objectives.

When a final version of the PAI is ready it is communicated in an understandable and appropriate way to the patient and his family or guardians. This approach allows the team to share open problems and existing resources by communicating, possibly, with the help of professionals, which expectations expressed by family members are difficult to achieve.

The multidisciplinary team considers the information collected and defines the possible specific objectives, bearing in mind however that the expected output is the best possible well-being of the person, despite illness and disability. In Figure 2 and Figure 3 are reported some real examples of PAI used by different health structures in Italy:

Diagnosi d'ingresso:

PROVENIENZA PAZIENTE

Patologia prevalente (codice ICD9-CM) _____

Patologie concomitante (codice ICD9-CM) _____

❒ Domicilio
❒ Struttura: (specificare)
_____

Problemi attuali:

Tipologia di non autosufficienza/fragilità

- ❑ Paziente in dimissione protetta
- ❑ Paziente con gravi artopatie
- ❑ Paziente con incidenti vascolari acuti
- ❑ Paziente con patologie temporaneamente invalidanti
- ❑ Demente grave
- ❑ Anziano con pluripatologie invalidanti
- ❑ Malato oncologico non autosufficiente
- ❑ Altro_____

Obiettivi di salute

O Miglioramento della qualità di vita
O Miglioramento/controllo delle condizioni cliniche
O Prevenzione delle cadute
O Miglioramento/mantenimento dell'attività motoria
O Recupero funzionalità articolare
O Recupero/mantenimento mobilità-trasferimenti
O Miglioramento stato cognitivo-percettivo
O Miglioramento orientamento nella realtà
O Miglioramento/mantenimento dello stato funzionale globale
O Prevenzione/trattamento delle lesioni da decubito
O Prevenzione della sindrome da immobilizzazione
O Recupero tono-forza-trofismo muscolare
O Recupero postura seduta e/o eretta
O Recupero/mantenimento deambulazione
O Miglioramento/contenzione disturbi psichici e comportamentali
O Miglioramento capacità relazionali e contatto socio-ambientale
O Altro_____

PAI – Cure Domiciliari 1

Figure 2: Example of PAI, first section

Interventi

Equipe domiciliare		Prestazioni		Frequenza g/sett	Frequenza g/mese	Durata	Struttura erogante
• MMG							
• PLS							
• Medico cont. assisteniale							
Specialista	○ Oncologo						
	○ Cardiologo						
	○ Pneumologo						
	○ Neurologo						
	○ Fisiatra						
	○ Chirurgo						
	○ Urologo						
	○ Ginecologo						
	○ Nefrologo						
	○ Gastroenterologo						
	○ Ortopedico						
	○ Dermatologo						
	○ Oculista						
	○ Geriatra						
	○ Altro						
• Medico esperto cure palliative							
• Controlli specialistici strumentali programmati in struttura specialistica		○ Rx ○ TAC ○ Risonanza magnetica ○ Ecocardiogramma ○ Altro					
• Infermiere			**Farmaci/ausili e mod somm.**				
		○ Parametri funzionali					
		○ Terapia farmacologica					
		○ Terapia infusionale					
		○ Nutrizione					
		○ Catetere vescicale					
		○ Medicazione					
		○ Controllo drenaggi					
		○ Gestione lesioni da decupito					
		○ Gestione Peg					
		○ Gestione tracheotomia					
		○ Altro.....					

PAI – Cure Domiciliari 2

Figure 3: Example of PAI, second section

The emergence of the PAI is the result of numerous elements:

- philosophy based on values and beliefs;
- regulatory reference framework;
- knowledge baggage composed of data, observations, analysis;
- procedures, strategies, and activities;
- objectives and expected results.

This enables the evaluation of the patient on a multiperspective point of view. The planning for a treatment includes:

- the description of the objectives identified for the different areas of intervention;
- the definition of interventions and implementation methods (how? with what intensity? where is it? how long?);
- identification of the team or operators involved;
- the declination of the monitoring activities of the objectives and expected times;
- evidence of any suspension or interruption of interventions and related reasons;
- verification of the achievement of the objectives identified.

The intervention model is structured according to Italian law DGR 2569/2014 annex 1 [27]. The section relating to the user's path in the offer unit, provides evidence of the design, planning and implementation of interventions, care protocols and procedures adopted in the various areas concerned and identified above..

2.1.3. Lombardy Hl7 – CDA2 Compliant -PAI

The Lombardy Region, in application of the National Chronicity Plan, has defined new ways of taking care of chronic and/or frail patients.

From January 2018, in implementation of DGR n. X/6551, [28] the Government has stratified the entire Lombardy regional population based on the clinical characteristics and consumption of health services.

About 3.5 million people affected by chronic diseases were identified as a population that involves the health and social health system with different care needs and assistance. This population has been offered an opportunity to of individual care that puts the person at the center, by assigning each patient to a dedicated hospital whose task is to deal with emergencies and high specialization.

The system allows citizens to be personally followed by a Manager, who can be identified in the figure of a General Practitioner (GP)/Free Choice Pediatrician or in an accredited public or private health/social health facility. Patients identified as chronic are sent a personal letter in which it the general aspects of the management plan and the references of their doctor, manager or regional Contact Center is illustrated. By contacting these figures, the citizen can express the will to join the path by indicating the chosen Manager.

After assessing the eligibility of the patient, the Manager proceeds by signing the Pact of Care (which explains the manager's commitments and the patient's willingness to engage) which is followed by the preparation of the PAI (Individual Care Plan). The PAI is drawn up annually.

The computational format of the PAI document is described in Article 24 - Data coding system - of DPCM 178/2015 [29] . The technical specifications identify the Clinical Document Architecture Version 2 (CDA-2) format and the Logical Observation Identifiers Names and Codes (LOINC) coding system, for univocal identification of clinical and laboratory observations [30] [31].

In detail, the specifications state that developers must structure the document following the national standard XML-CDA2_RefertoMedicinaLab of HL7 Italy [32] and the use of LOINC Coding for the interpretation of the results.

Once validated according to the national reference standards for health documentation (HL7 - CDA2), the PAI can be published in the Electronic Health Record (FSE) [33] of the citizen, thus facilitating the sharing and exchange of data between doctors and operators of different structures , subject to the consent of the interested party. Both the Manager and the

patient have the possibility to consult the PAI by directly accessing the reference portal. The structure of the CDA2 is described in more depth in the technical chapter 5.2.

2.1.4. The capital case PRI and the lower case pri

As mentioned in the preceding paragraph the Individual Rehabilitation Project (capital PRI) indicates interventions, times, modalities to achieve healthcare objectives, by applying a multidimensional and continual assessment of the specific characteristics of the patient, taking in consideration health conditions, residual and recoverable skills, needs, preferences, family situation and environmental and personal factors. When the document reaches a final version, it is shared with the patient, family and caregivers.

The expected global outcome of the PRI is in different areas:

- increased levels of independence;
- increased level of participation;
- minimizing the need for hospitalization;
- increase and use of residual skills to improve the quality of life.

Within the PRI, the individual program rehabilitation **program** (lowercase pri) defines:

- the specific intervention areas;
- the short-term goals;
- timing and arrangements;
- provision of interventions, the operators involved;
- verification of interventions.

The pri is a structured **program** with the operative interventions the patient must undergo to reach the rehabilitation objectives defined by the **project.** The operative interventions are the following:

- identification of the desired timing to achieve the objective defined in the project, it can be a short-term objective or a medium-term objective
- identification of the health care intervention that need to be implemented to achieve the objective in the following areas:
    - basic vital functions;
    - sensory - motor functions;
    - mobility and transfers;
    - competence;
    - communicative – relational;
    - cognitive areas;

    - behavioral;
    - autonomy;
    - rehabilitation;
    - social reintegration;
    - emotional – affective.
- definition of the appropriate outcome measures for the evaluation of the interventions;
- identification of the healthcare operators involved in the interventions and their commitment.

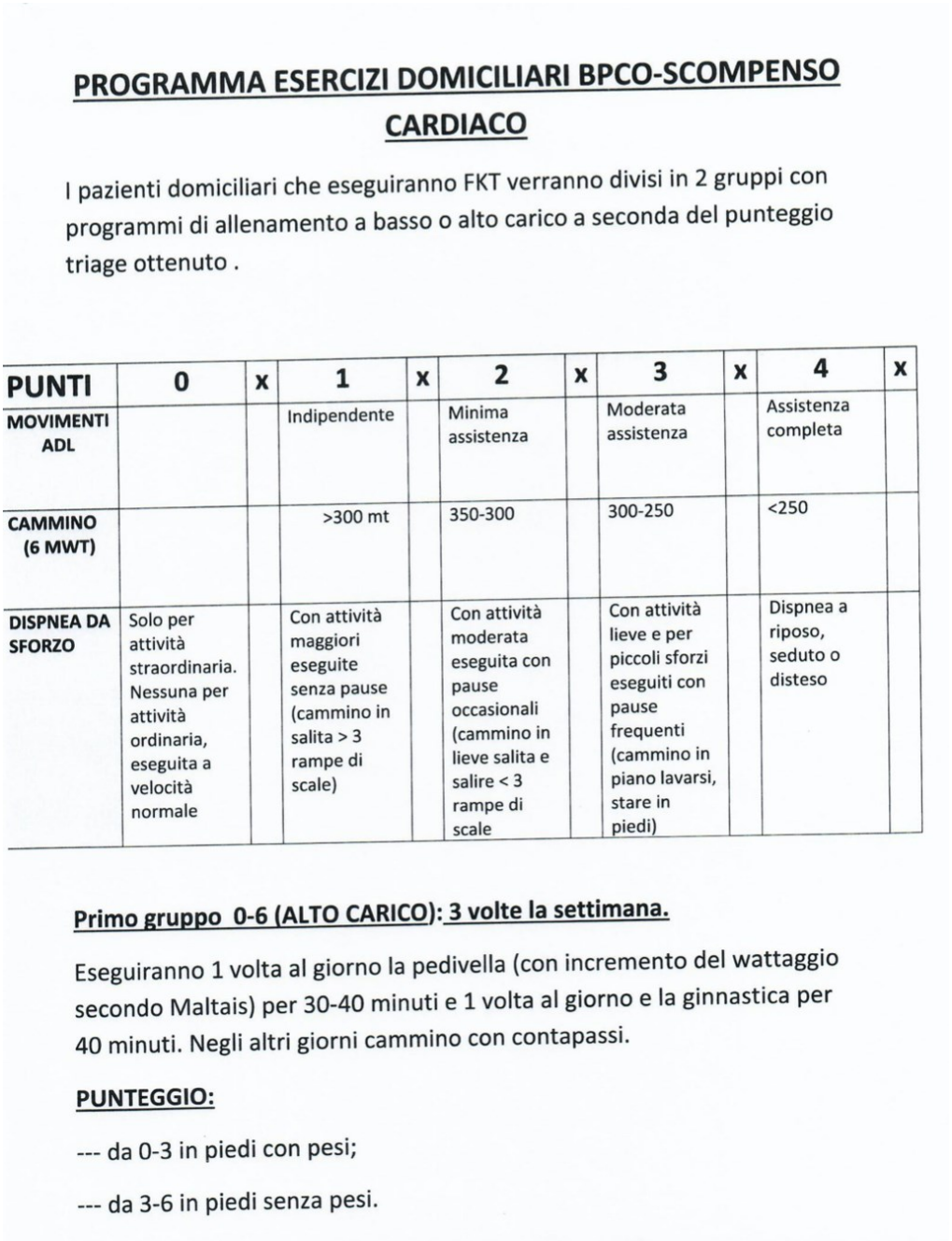
In the following, an example is reported of a pri delivered at discharge to patients with chronic obstructive pulmonary disease (COPD) or heart failure (provided by ICS Maugeri headquarters in Lumezzane). The exercises are the content of the Rehabilitation section of the pri.

The document contains the list of exercises to be performed, a brief guide for their execution, and the dosage which includes the intensity and frequency for each exercise (speed, time, weight, repetitions, series, times a day, times a week, break, etc.).

In addition, the document reports the indicators that determine the overall *load* of the program. In this case, indicators are scores that consider the following dimensions to which different weights are applied:

- level of autonomy (ADL movements);
- walking (6 Minute Walking Distance/Time);
- Exertional dyspnea.

In this way, the difficulty level of the rehabilitation program is customized according to the patient's ability. The following figures 4 and 5 show the traditional paper-based homecare regimen prescribed to the patient:



PROGRAMMA ESERCIZI DOMICILIARI BPCO-SCOMPENSO CARDIACO

I pazienti domiciliari che eseguiranno FKT verranno divisi in 2 gruppi con programmi di allenamento a basso o alto carico a seconda del punteggio triage ottenuto .

PUNTI	0	x	1	x	2	x	3	x	4	x
MOVIMENTI ADL			Indipendente		Minima assistenza		Moderata assistenza		Assistenza completa	
CAMMINO (6 MWT)			>300 mt		350-300		300-250		<250	
DISPNEA DA SFORZO	Solo per attività straordinaria. Nessuna per attività ordinaria, eseguita a velocità normale		Con attività maggiori eseguite senza pause (cammino in salita > 3 rampe di scale)		Con attività moderata eseguita con pause occasionali (cammino in lieve salita e salire < 3 rampe di scale		Con attività lieve e per piccoli sforzi eseguiti con pause frequenti (cammino in piano lavarsi, stare in piedi)		Dispnea a riposo, seduto o disteso	

Primo gruppo 0-6 (ALTO CARICO): 3 volte la settimana.

Eseguiranno 1 volta al giorno la pedivella (con incremento del wattaggio secondo Maltais) per 30-40 minuti e 1 volta al giorno e la ginnastica per 40 minuti. Negli altri giorni cammino con contapassi.

PUNTEGGIO:

--- da 0-3 in piedi con pesi;

--- da 3-6 in piedi senza pesi.

Figure 4: Traditional paper-based pri

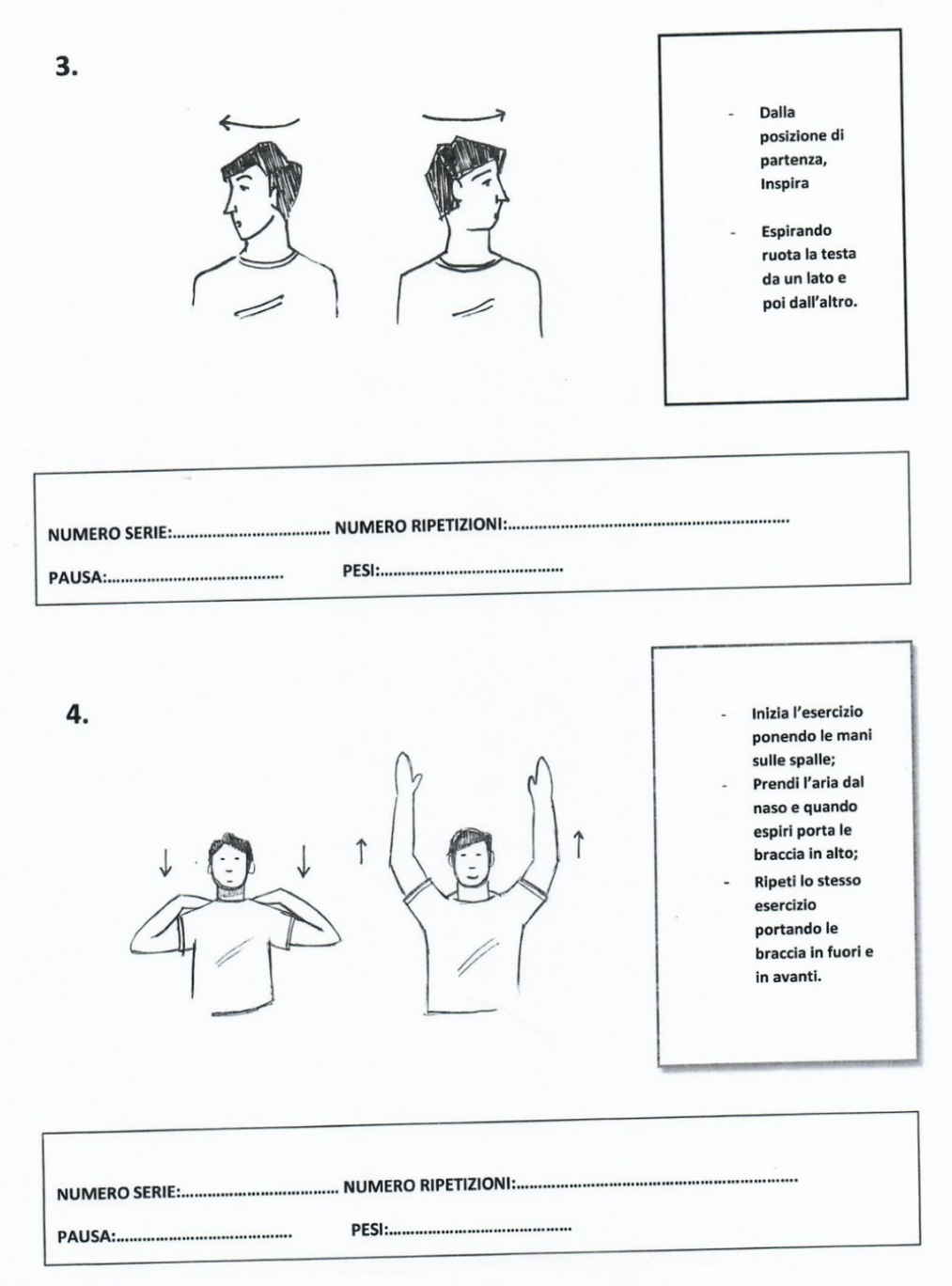


Figure 5: Home-based exercises

2.2. **Innovative models of aged care:**

After the (usually) short rehabilitation periods that hospitals can guarantee just after the acute phase of a disease, the transition to home is known to lead to high discontinuity in rehabilitation activities. This may be due to poor adherence and patient motivation, poor understanding of benefits of rehabilitation care, poor predisposition to change in lifestyle.

Effective rehabilitation interventions deployed in a home-based scenario could provide effective therapy for elderly population thus leading to better and focused care while containing costs, more appropriate resource use, and avoidance of institutional placements. [34] [35]. Despite these well-established benefits, providing service to this fragile population poses some difficulties.

This clinical background marks the urgency to validate models of assistance that can combine technological solutions with health needs to ensure continuity and quality of care for patients.

To this extent, telemedicine has been used to counteract the increase of non-self-sufficient chronic patients, and to personalize the application of home therapies. This helps relocating patient management from hospital to home. The activities carried out at home have been proved to be a valid alternative to conventional courses and the use of virtual coaching increased adherence to the proposed programs [36].

Technology to support aged care traditionally can provide additional capabilities to those available to professionals and caregivers. According to The Royal Commission into Aged Care Quality and Safety [37], these types of technologies can be conceptualized into four main areas of usage:

- assistive and supportive technologies;
- monitoring devices and systems;
- communications and connection technologies;
- intelligent health information systems.

Providing remote options for elderly to manage their health can be useful because it enables automation of care, self-monitoring of progression, delivery of feedback, and possibilities for tailoring to suit individuals' preferences.

These technologies act as coach/facilitator/counsellor for a variety of health education and behavior management purposes [38] such as health risk factor modification [39] and medication compliance. They are also commonly used for health behavior change, including in areas of physical activity, [40] obesity arthritis and pain management [41].

Figure 6 summarizes the main innovative technological approaches to aged care:

Area of technology usage	Key features	Examples
Assistive and supportive technologies	Provide physical or cognitive aids to activities undertaken by a care recipient as an adjunct component of the activity.	Balance enhancement in walking frames Assistive Robots
Monitoring devices and systems	Measure and analyse personal health characteristics of a care recipient.	Wearables Telecare stations Ambient assistive environments Health smart homes for ageing
Communications and connection technologies	Allow care recipients to interact with health carers remotely.	Health management websites Conversational agents for health care assistance
Intelligent health information systems	Empower care recipients to access information and exercise informed control on their health circumstances.	Health portals and support sites Care coordination

Figure 6: Innovative models of Aged Care

Some technology-based models of care that have been shown to be viable internationally but have not seen successful adoption at scale for the ageing population include:

- **Televisit** technologies that enable the provision of remote medical services like follow up visits for older people less able to travel, including those living in residential aged care, at home without accessible transport options and in rural and remote regions.
- **Telemonitoring** of independently living elders' vital parameters. This population is in fact is susceptible to incidents, such as falling, or to isolation from physical and social activities. Telemonitoring is delivered through ambient assistive environments (health smart homes) providing decision support and alerting services.

A pitfall has been lack of cost-effective models for reimbursement or service delivery funding to cover the quite extensive underlying business support services ecosystem.

To this end it must be considered a "*Roadmap to technology aged care*" in order to develop smoothly a solution.

The result of a systematic search on the literature portraits telemedicine as very effective in managing chronic health conditions, improving functional status, general health, and wellbeing. The systematic review by Khosravi and Ghapanchi [42] concludes for example that among all the technologies studied for their effectiveness, telemedicine was the only one applied to assist older people living with a chronic health condition to show

"significant changes" that ranged from improvement in condition to reduced hospital readmission.

Positive findings about the effectiveness and impact of Information and Communication Technologies (ICTs) on five major chronic diseases were identified in a scoping review undertaken by Wildevuur & Simonse [43] This investigated the extent, range, and nature of ICT based interventions (primarily telemedicine) in the management of diabetes mellitus, cardiovascular disease, chronic respiratory disease, cancer, and stroke by analysing findings from 350 studies published between 1989 and 2013. The highest impacts were found to involve increased consumer empowerment (15.4% of studies), improved clinical outcomes (11.7% of studies), and decreased hospitalisation rates (12.3% of studies). Most of these findings agree with the conclusions of another review that identified positive impacts on clinical processes and consumer health outcomes, as well as positive clinician and consumer satisfaction. [44]. Most of the studies analyzed had involved the care of people with chronic illness. There was a trend across these studies for different ICT applications in home care to be received positively by people living with chronic illnesses and by health care professionals.

Most studies showed that communication between health care professionals and patients living at home was improved by the use of ICTs, which were also regarded useful in home patients' follow-up [45].

2.2.1. Telerehabilitation

A well agreed-on definition of Telemedicine is the secure transmission of information and data of a medical nature in the form of texts, sounds, images or other formats, necessary for the prevention, diagnosis, treatment and monitoring of patients.

The services of Telemedicine are assimilated to other diagnostic/therapeutic health services and the service provided in Telemedicine does not replace health services traditionally provided in the direct personal doctor-patient relationship, but integrates it to potentially improve its effectiveness, efficiency and appropriateness.

Several Telemedicine initiatives and projects have been conducted or are active at national and regional level, with an inhomogeneous diffusion of health services provided. Long-distance communication can now in fact be easily achieved by synchronous communications such as videoconference, email, and text messages. The intersection of an ageing population with technological progress has produced the term Gerontechnology [46] which emerged in the early 1990s to describe a new interdisciplinary academic and professional field combining gerontology and technology. Rehabilitation is an old branch of medicine, but in the last few years, new technologies have influenced the practice all over the world. These approaches are defined as telerehabilitation, which should be considered as

a telemedicine subcategory consisting of a system to control rehabilitation at a distance [47] [48] [49].

Telehealth services can offer a technology-based mechanism for supporting person-centered care and enabling new models of care [50]. In fact, it involves delivery of care by remote clinicians through teleconsultations and tele procedures.

The ability to deliver remotely to the home, to residential aged care settings, to people with limited access to transport and those living in rural and remote locations is a major strength [51].

In the UK, it has been suggested that expansion of telehealth [52] services may provide a favourable environment for achieving integrated care delivery, but also state that acceptance of home telehealth largely depends on the sensitivity and support given to the end users. To have a shared governance model, on February 2014 the State-Regions Conference sanctioned the Agreement on the "*National guidelines on Telemedicine*" [53]. The guidelines are aimed at harmonizing the application models of Telemedicine, as a prerequisite for interoperability of Telemedicine services and as a requirement for the transition from experimental logic to a structured logic of widespread use of the services themselves. .Lombardy is one of the Italian regions that has invested most in innovative care models at the level home, in some cases with the support of Telemedicine tools. Since the early 2000s, there is a long experience of research projects aimed at integrated management of patients with chronic diseases with the support of Telemedicine for home care, with taking charge by the specialist center hospital [54].

2.2.2. Remote monitoring sensors

Wearable monitoring devices provide ageing support by collecting data and providing measurement and feedback on someone's health circumstances [55]. The information collected may include aspects of healthy lifestyle habits, physiological status, and preventive practices to help people manage and maintain their condition [56]. Some example of remote monitoring sensors used for rehabilitation are accelerometry-based devices can measure limb movement as an indicator of physical activity and mobility Other devices allow for prediction or detection of adverse circumstances by combining measurement of movement with physiological measures such as falling [57] or cardiac situations. More comprehensive data collection can be used for the tracking of performance of daily living activities [58] or the remote observation of individuals by health service providers [59] For example, sensors may be able to trigger an alarm in cases of significant deviations from normal activities [60]. Increasingly, these types of devices have 'smart' inbuilt control and data processing logic, which promotes efficiency and reliability and may allow individual customization [61].

2.2.3. Gamification in rehabilitation

A popular approach to support behavior change and healthy aging in older people is the provision of interactive games [62] since the entertainment and engagement aspects may have positive influences [63].

This has been shown as an effective approach in a number of health areas particularly in promoting physical activity using ‘exergames [64]. Another important issue that can benefit from gamification social isolation [65]. In fact engagement in social networking sites and an increase in online activity has proven to lower loneliness and isolation in older people [66]. Whilst these technological approaches are no longer considered innovative in the general population, their potential application to address social isolation in older people is greatly underdeveloped.

2.2.4. Computer interpretable guidelines

Evidence-based medicine led to the introduction of the guidelines as a tool to rationalize the clinical-organizational behavior to govern demand and orient health planning. The Institute of Medicine (IOM) defines clinical practice guidelines (CPG) as:

> *“Statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [67]*

CPGs are used in clinical setting to establish standards of care backed by strong scientific evidence. Historically, CPG were disseminated in paper format. In recent years however, CPGs have been started to be encoded in a computer-interpretable format (CIG). This enables the development of CIG-driven decision support systems, which automatically match patient data to the guideline in order to deliver tailored recommendations. A detailed discussion on how CIG have been formalized in literature is available in paragraph 3.

2.2.5. Home-care innovative prescription and monitoring: the PAIR

As shown in the preceding paragraphs, the management of chronicity with innovative information and communication technologies (ICT) has not yet reached a sufficient level of specialization, availability and solidity, other than research such as to guarantee individualized and controlled treatments at home and encourage patient involvement and adherence to the rehabilitation program. Furthermore, ICT solutions are often seen as "isolated elements" in patient management rather than being primarily supportive interventions change, in the organization and in the paradigms

of care. The aim of the project in which the PhD was inserted intends to respond to these needs by creating an integrated platform involving patients, healthcare professionals, caregivers, and ICT technologies, to plan and carry out individualized and remotely controlled home treatments. The ICT technology platform will present enabling innovations:

- Development of devices, systems, with ICT, methods based on Artificial Intelligence for personalized cognitive and motor rehabilitation.
- Innovative models for monitoring, evaluation and support to the rehabilitation program through personalized virtual coaching activities for the patient and caregiver.
- Investigation on the use of techniques like the psychology of persuasion to facilitate adherence to rehabilitation plan.
- Development of new instrumental methods and evaluation of rehabilitation procedures using wearable sensors that make use of Artificial Intelligence systems capable of recognizing specific motor and cognitive patterns.
- Development of videogames and exergames aimed at the exercise of cognitive skills and motor.
- Creation and experimentation of a holistic rehabilitation approach, in which the patient is central and proactive both in terms of therapies and quality of his life.
- Creation of a network between Institutes of Hospitalization and Scientific Care (IRCCS) of ICS Maugeri (Pavia-Lumezzane-Milan) for the remote evaluation of patient, inclusive model.

The "home-care prescription", called PAIR in the project (*Piano Assistenziale Individualizzato di Riabilitazione*), is a structured and computer-interpretable document. The PAIR is sent to a "home-care rehabilitation kit" composed by exergames administered through a virtual coaching app, a chatbot and a set of remote monitoring sensors. An Example of PAIR is available in the attached Appendix B. The PAIR is structured according to the format envisaged for the PAI of the Lombardy Region, and contains the following sections:

- Information on the multidisciplinary team that contributes to patient care:
  - general practitioner;
  - physiotherapist;
  - dietician;
  - …
- patient demographic information;
- past medical history;
- current medical history;
- rehabilitation Objective;

- rehabilitation plan provided for the patient.

The document is structured as a HL7 – Compliant Clinical Document Architecture Version 2 (CDA2) and is automatically processed by the home-care rehabilitation kit. The document uniquely identifies the patient inside the hospital so that the result of the rehabilitation can be reimbursed by the information systems in the same way as the services provided in the assistance and outpatient regime. An in-depth discussion of the solution is discussed in the functional (4) and technical (5) chapters.

2.3. Addendum: The importance of remote patient care in a post-pandemic society

The debate on connected health is increasingly important. According to World Health Organization (WHO) at least 3 billion people are currently trying to practice social distancing to different extents in order to temper the 2020 Coronavirus pandemic. Social networks, online eHealth platforms, exercise training mobile applications, and youtube workouts videos have never been so used and appreciated.

The actual health situation and the massive use of mobile technologies and internet connection during pandemic has become an important help for rehabilitation. General purpose health trackers and connected tools like smart scale or intelligent wearables allow regular and individualized remote monitoring by physiotherapists, health practitioners, and patient to promote healthy behavior.

Within the health crisis of COVID-19, some countries use smartphones on a large scale to compel individuals to communicate their temperature, identify the movements of infected patients, identify their contacts, etc. The modernization of clinical care services with digital tools allows better promotion of telerehabilitation programs. Australian GP Justin Beilby states:

> *To secure telehealth's success into the future it is crucial that telehealth platforms are easy to use, enable the delivery of high-quality care and support a positive experience for patients and health providers. Older Australians have told us that telehealth is generally working well for them. Almost two-thirds of respondents feel confident to use telehealth and are willing to use telehealth into the future [65].*

In fact, an Australian study the Global Centre for Modern Ageing has reached out to Australians as part of an expansive study to understand their evolving experience during the pandemic. While there are many elements people hope will return to "normal", there are also changes they see value in retaining, Telehealth is one. During the pandemic, australians have used

telehealth for a range of general practitioner and specialist appointments. The study focuses on the following points:

- Most older Australians found their telehealth experience to be similar to or better than a face-to-face consultation.
- For phone and online consultations, 85% of older Australians said the quality of care/treatment provided was the same or better than normal.
- For phone and online consultations, 88% of older Australians said the value for money was the same or better than they usually experienced.

The study concludes that the pandemic created a disruption but telehealth could use this moment to leap forward [65].

ICT strategies to remotely take care of slightly healthy and chronically ill patient are more than ever important. This global situation has also shown us that there is an urgent need to validate these technological tools to personalize prevention care, help patients in their recovery, and prevent recurrent events. To date mostly clinical research experiences have been implemented, and no long-term follow-up is available.

2.4. Care pathways assisted by telemedicine - The regulatory framework in Italy

The process of taking charge of chronic and/or frail patients, outlined by Italian law, is a work in progress, as regards the patient enrollment procedure, and the purpose of achieving an overall management of the chronic and/or fragile patient.

The Italian Ministry of health has tried to define all the possible services that can delivered by remote, in the document "Telemedicine National guidelines" [53]. The document tries to analyze the ongoing evolution of demographic dynamics, and the consequent modification of health of the population that motivates the need to redesign of the service network especially focusing on territorial scope of assistance. To this end technological innovation can contribute to a reorganization of health care, in in particular by supporting the shift of the focus of health care from the hospital to the local area, through innovative citizen-centered care models and facilitating access to services on the national territory.

The document classifies smart remote monitoring of elderly patient under the umbrella-term "*Remote Health*". It concerns the systems and services that connect patients, especially chronic ones, with physicians for assist in the diagnosis, monitoring, management, accountability of the same.

It allows a doctor (often a general practitioner in collaboration with a specialist) to remotely interpret the data necessary for the Telemonitoring of a patient, and taking charge of the patient himself.

The data collection and data share can be automatized or recorded by the patient himself or a healthcare professional. Telehealth provides an active role of the doctor (taking charge of the patient) and an active role of the patient (self-care), mainly patients with chronic diseases. Telehealth includes Telemonitoring, but the exchange of data (vital parameters) between the patient (at home, in the pharmacy, in dedicated care facilities, ...) and one monitoring station is not only done for data interpretation, but also to support therapy management programs and to improve information and training (knowledge and behavior) of the patient.

The relationship between Telemonitoring in Telemedicine and in Telehealth is schematized in the following Figure:

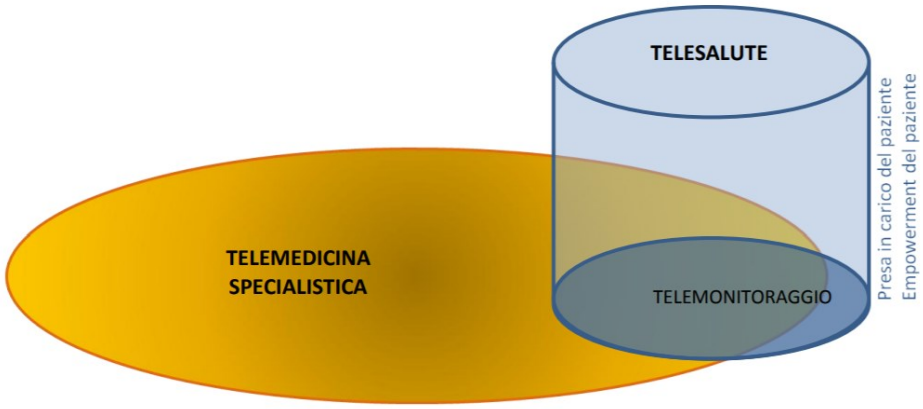


Figure 7: Schematic representation of the relationships between Telemonitoring, Telemedicine and Telehealth [53]

The active role of the Patient (Empowerment) and the Doctor is highlighted (taking charge) in the case of Telehealth, which expands the concept of care in the direction of individual care (own-initiative medicine).

The Regional Law n. 23 of 2015 affirms the orientation to treat person as a whole, in compliance with free choice, and promotes operational and managerial integration between health service providers, health and social care (art. 2, art. 3) [68]. In particular, in terms of chronicity, it Article 9 mandates to activate procedures what enable innovative management of chronic and fragile patients, even through the use of Telemedicine, developing organizational models that ensure the integration and connection between all the professional skills involved, hospital and territorial, through health care and social and health care networks [68].

The techniques of telemedicine and remote monitoring of clinical parameters can help reduce hospitalizations, because they create continuity

of care between patient, hospital and general practitioner (GP), promote self-control of the disease and compliance with drug treatment.

2.4.1. Treatment of Personal and Clinical data with electronic tools

The operations on the citizen's personal and health data necessary for the provision of Telemedicine services are among the normative section "*processing of sensitive data carried out by electronic means*", which are governed by the provisions of Legislative Decree 196/2003 [69]. The methods and solutions needed for ensure confidentiality, integrity and availability of data must, therefore, in any case be adopted in accordance with the security measures expressly provided for in Legislative Decree number. 196/2003 and in related Annex B (Technical Regulations on minimum security measures) [70].

In terms of obligations towards patients, the following aspects assume particular relevance:

- **Information on treatments** (examination, remote transmission, use, etc.) **and the processing of personal data Information**: as well as information on purposes as well as, in the case of specific therapeutic diagnostic paths, on protocols. It is necessary to develop precise information templates that are as uniform as possible at a national level, as remote services can also be carried out in different Regions.
- **Patient Informed consent:** it is necessary to let the patient know all the necessary information to provide thoughtful choices regarding his health. In the particular case of remote services, it is necessary to evaluate the need or not to repeat the consent for each performance, and the opportunity to make explicit specifically the risks involved (such as the risks associated with the lack of physical contact and of the doctor's clinical gaze, the impossibility of a complete visit and intervention immediate in case of urgency).
- **Rights of the client over their personal data:** it is necessary to develop increasingly clear and simple ways of respecting and guaranteeing rights over personal data, even more so in the context of Telemedicine which by its nature has on the one hand higher levels of technological complexity and, on the other hand, the possible interaction of multiple subjects who process the data.

The analysis and design of processes in the legal field on health processes is particularly important because it allows to define precisely responsibilities, and identify suitable organizational solutions and

technologies that make it possible to maintain the responsibility and availability of information only from those who are entitled to use them.

Chapter 3:

State of the Art: Decision Support Systems to prescribe and monitor a home-care rehabilitation regimen

The preceding chapter highlighted how in the recent years the demand for care has shift focus from the point of care towards remote-provided services. This demographic change has triggered an intensive interest towards remote monitoring devices and telehealth. While many advanced technologies are already available on the topic of remote monitoring sensors and telehealth technologies, the literature highlights a lack of decision support systems (DSS) for the prescription of a rigorous home-care rehabilitation regimen and the interpretation of data coming from remote monitoring devices.

The aim of the chapter is to analyze the state of the art of Decision Support Systems, to compare the features of the systems known in literature, and finally to collect some useful requirements for a successful DSS implementation.

A clinical decision support system (CDSS) is traditionally defined as any software that can enhance medical decisions by delivering precise, accurate, up to date and timely medical knowledge.

Traditionally the characteristics of an individual patient are matched against clinical knowledge that has been transformed in a computer-interpretable form. The results of the computation are delivered to the clinician in the form of recommendations or general-purpose information on a given clinical topic. The recommendations should be patient-specific and should be used by the clinician to provide a better response in care delivery.

Regardless of the definition choice, the clinical decision support system field of research is currently subjected to an exponential advance, which is,

for the most part, badly or not at all regulated. If the recommendation provided by the system is inadequate or wrong it could potentially harm, while on the other hand, if the system is well designed and adequately evaluated it has a huge potential to improve quality of care and patient outcomes.

Computer-based CDSSs are an interesting research topic since 1970s. In these 5 decades, giving clinical support in different domains, CDSS have proven to favorably influence quality and patient safety [71], promote prevention interventions and optimal treatment [72], reduce medical errors [73] [74] and improve clinical outcomes [75] [76] [77]. In the first decade of research they were especially developed in research laboratories, they usually lacked any kind of integration with the hospital information system and they required huge manual effort to impute all the needed data. Also, in those years, the legislation was not mature enough to provide regulation from ethical and legal point of view for the use of computers towards medical practice.

Presently, CDSS are often distributed in the form of zero-footprint solutions (software that is available on the internet, and does not require any installation). They may be integrated with electronic health records (EHR) or personal health records (PHR) and reached rom desktop, tablet, smartphone, but also from remote monitoring devices.

The topic of interest of the PhD work has been the support on the prescription and monitoring of a home-based rehabilitation treatment, following clinical practice guidelines. Numerous studies agree that the implementation of automatic decision support intervention improve the adherence to clinical practice guidelines [78]. This implication is relevant because it is a known fact that medical practice still fails to adhere to clinical guidelines and care pathways [79] [80].

The contribution of the CDSS to the clinical care resides in explicitly encoding in a computer interpretable format the rules implicitly encoded in guidelines. The CDSSs that is being developed in the project can also inform clinicians to contact patients who have not followed the prescribed regimen, or the prescribed regimen has expired, or even include or exclude patients from regimens based on different inclusion/exclusion.

CDSSs have been historically classified and subdivided into numerous conceptual axes, from intervention timing, or whether they provide active or passive delivery. One of the most known classifications is the type of knowledge model adopted by the CDSS: knowledge-based or non-knowledge based. In knowledge-based systems, rules (IF-THEN statements) are produced by one or more technical experts called knowledge engineers, and some domain experts, usually one or more physicians. The CDSS retrieves data to evaluate the created rule and produces an action or output. Rules are usually build using literature-based, practice-based, or patient-directed evidence.

CDSS that are not built using a rule-based approach still need a data source, but the decision itself is computed with statistical pattern

recognition taking advantage of Artificial intelligence techniques (AI) and machine learning (ML) techniques. The main difference between rule-based and non-rule-base systems is that the former needs to be explicitly programmed to follow expert medical knowledge while the latter induces the decision using a model learnt on data. Non-knowledge based CDSS, although a rapidly growing use case for AI in medicine, pose drawbacks and challenges.

The most evident is the current lack of understanding of the logic that the algorithm uses to produce recommendations (black boxes), making them not a difficult road to deploy a solution in a real healthcare scenario for the time being. Regardless of the application domain the conceptual underlying model of the CDSS is one of the three categories analyzed in depth in the following sub-paragraphs.

3.1. **Rule-based decision support systems**

As mentioned in the introduction of the chapter, rule-based decision support systems were and are the most used and appreciated branch of decision support systems. Ever since the seminar "*To Err Is Human*" [81] was published in 2000, CDSSs were chosen to be an effective method to evaluate and improve clinical practice. Early systems tightly decided on the intervention by superimposing user input data and receiving an input on the necessary actions to implement. The first known CDSS, developed in the 1970s were "Caduceus"," MYCIN" and "Iliad". Alle three were defined as "Expert System":

> *A computer system that, when well-crafted, gives decision support in the form of accurate diagnostic information or, less commonly, suggests treatment or prognosis [82].*

Expert systems present some features which separate them from any other "traditional" medical software. One of these features is that the program is often developed to replicate the reasoning process of the clinicians. In fact, medical practice must deal with uncertainty, so expert systems may have to consider the output of the computation as a probability.

Caduceus, mostly known as "the Internist", was developed in the 1970s and its original aim was to create a general "hypothetico-deductive" model to medical practice. The main feature consisted in probabilistic method for ranking diagnoses. It analyzed patient symptoms and then retrieved in a knowledge base the most likely disease, based on a statistic of patients in the KB presenting the same symptoms. Unfortunately, Caduceus' diagnostic accuracy was exceptionally low outside the research setting, especially in a real clinical scenario. Caduceus was in fact unable to match

the diagnostic accuracy of a real expert. For this reason, by 2001 Caduceus was abandoned in favor of more accurate CDSSs.

The second most historically known CDSS was MYCIN, a program developed in the 1970s with the goal of detecting infectious diseases and recommending antibiotics for treatment. MYCIN was described by the contemporary literature of that period as an Artificial Intelligence software, ant it contained over two hundred decision rules in the knowledge base. An example of a MYCIN production rule is visible in Figure 8:

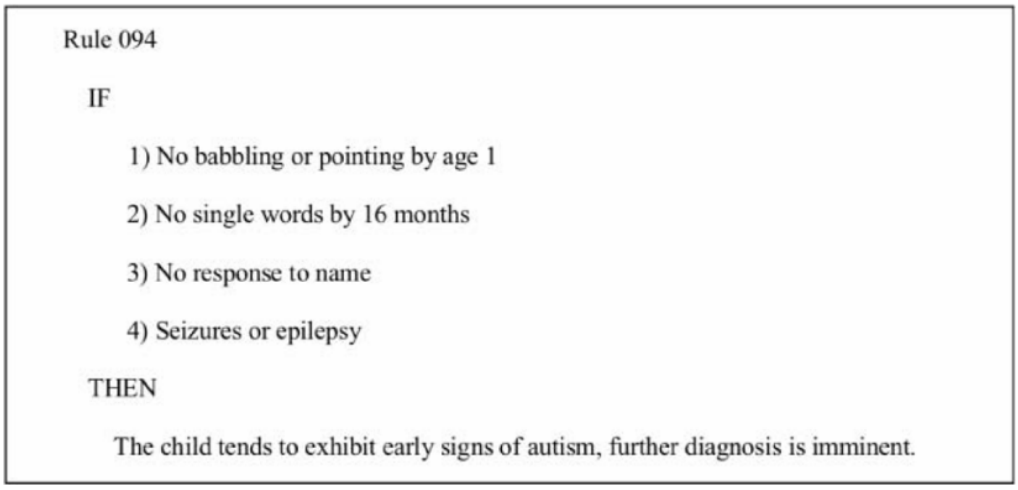


Figure 8: Example of a rule of MYCIN system.

The rule-based system allowed clinicians to either modify existing rules or adding new ones as they saw fit, making MYCIN robust to change in medical trends and discoveries. For these reasons MYCIN was classified as an AI component, because the reasoning process was similar with the one provided by a real expert. In this case the downfall was the computation time: MYCIN required 30 minutes to reach a decision, making it unusable in real clinical setting. Another issue presented at the time was the accountability of the system and the doubt of who was to be held responsible of a possible error made by the machine.

Finally, the intrinsic problem of MYCIN was that it was simply too ahead of its time. In fact, the software was built before the explosion of the Internet and desktop computing, so the computing power was not sufficient to reach the goal. The importance of MYCIN, however, is to have shown a conceptual model for making a CDSS that influences the development of solutions to this day.

Analyzing historical papers lets us reflect on how the fundamental doubts and issues raised more than five decades ago are still truly relevant.

For example, the issue of accountability is still an open topic of discussion at decision-making tables in clinical practice. Numerous other CDSSs appeared after in literature and the rule-based model for reasoning was accepted as the gold standard approach.

In general, a rule based CDSS is comprised of three main components:

- knowledge base;
- inference engine;
- human-computer interface.

The knowledge base is fundamentally an ensemble of computer interpretable clinical information written in the form of "production rules" as "IF-THEN" propositions. The rules contained in the knowledge base are retrieved by the inference engine which analyzes which production rule must be triggered and at what time. The combination of patient data and production rules enables the inference engine to build a patient-specific and effective output [77].

An important aspect of the components is that in theory the inference engine and the knowledge base should be conceptually and operationally separated. CDSSs are in fact very time consuming to build and even harder to maintain so the reusability is a key point on projecting these kinds of intervention. Regrettably, most real-life systems known in literature are developed with a specific goal in mind (for example, detect drug-drug interaction, prescribe the most appropriate drug to a specific category of patient) and the knowledge base is tightly coupled to the inference architecture. Thus, it is either difficult or impossible to use them beyond their intended purpose.

3.2. Machine- Learning decision support systems

The literature counts numerous applications of machine learning systems in the area of home-care rehabilitation monitoring [83] [84] [85] [86] [87].

Little to no research however is available on the application of machine learning techniques in the prescription of a home-care rehabilitation regimen by following clinical practice guidelines on rehabilitation.

Some authors propose machine learning algorithms to prevent home risk (falling or unwanted events) by detecting anomalies in the usual activity pattern using data fed by remote monitoring sensors. These systems have been tested in real-life environments to respond to routine patterns with a high accuracy [83] but they don't provide any assistance to the doctor in detecting if a prescribed regimen has been followed by the patient.

If the system detects an activity which does not follow the usual pattern, it simply sends a "real-time" alert to the contacts configured on the system, without any human intervention.

The authors highlight that home-care rehabilitation has both positive and negative effects [88]. One of the significant barriers to adoption of these kind of clinical flux adjuvanted by ICT solutions is the amount of non-reimbursed time and effort required to incorporate new tools and strategies into existing clinical practice. This time loss gets unmanageable if the

amount of time spent to manage the patients' progression becomes more burdensome and time consuming than following the patient directly. The authors conclude that these solutions should not increase the amount of time required by the clinician between outpatient visits. The un-billable time could be spent in different "offline" activities, for example reviewing the patient's remote sensor data log, keeping up with the communications from the patient or caregiver, reviewing the prescribed level according to data coming from the sensors [88]. The real promise of a "smart" remote care intervention resides in the potential that it offers for autonomous or semi-autonomous management of the patient's progression between outpatient clinic visits [88].

The work is dated February 2020 so, although the project is promising, unfortunately results of the proposed method are not yet available. A general issue that afflicts machine-learning based CDSS and in general a "data-hungry" approach, is that these systems are only as strong as their knowledge base.

Besides the major side effect of low explanability, another issue is that problems are not easily solvable by adding data to the knowledge base. For example, a DSS could exploit remote monitoring sensors to adjust the air conditioning level according to the vital parameters of the user during the physical session. If the environment is detected to be too hot for the best performance, air conditioning should be turned on. But if the system is built using a data-hungry approach, it could reach for example the conclusion to open the fridge to lower the environment temperature. With approaches like Deep Learning or Machine Learning the answer this question implies an accurate analysis, but with a rule-based approach, the answer is straightforward: either a knowledge model constraint would prevent such behavior or a rule would prohibit the action. From this example we can conclude that a single approach is not the right approach for each problem, but different approaches better suit different problem categories.

3.3. **Ontology-based decision support systems**

Medical reasoning involves complex inferential processes to produce a decision. The difficulty in developing a sophisticated CDSS that can provide the right information at the right time lies in decoding what constitutes clinical reasoning. Many authors have proposed different approaches for utilizing a form of knowledge representation called Ontology to decrypt the underlying model of clinical reasoning [89] [90] [91] [92]. An ontology is defined as a formal representation of knowledge within a domain [93]. Typically, it is comprised by a set of unique terms known as concepts that are hierarchically arranged. The concepts are linked to their attributes and are linked with other concepts by semantic relationships.

Regardless of the thriving presence of ontologies in the literature at all decades [94] [95] [96] [97] [98] [99] [100] [101] [102] there isn't to this day a formal standard for healthcare ontologies like Health Level 7 o IHE, other than initiatives to suggest desirable design patterns to follow during implementation [103]. Almost all ontologies are generally being developed and studied in isolation, focusing on a specific disease process, workflow, or subspecialty. For this reason, each ontology tends to map only those concepts strictly required by the specific domain and relationships related those aspects. Thus, most ontologies represent only a little portion of all the clinical knowledge used by clinicians. Few clinical ontologies are really used as a base for clinical reasoning and inference used outside the scope of definition.

Biomedical ontologies are usually developed using the Web Ontology Language (OWL) [104], a language designed to model knowledge about things, groups of things, and relations between things by using description logic [105]. Many ontology-based analysis methods, including machine learning methods rely on generating some form of graph structures from the axioms in an ontology.

OWL has not taken a significant importance outside the construction of ontologies for academic purposes has different reasons.

- **Too "Open" - world Assumption:** OWL is built upon the idea of open-world assumption (OWA), as opposed to the closed-world assumption (CWA) which is an essential feature of relational database systems. In this case if the information is not present the reason process cannot conclude that the information is false. This approach fits web environment, where incompleteness of information is acceptable, this is not however true in standalone application, which require constraint validation offered by a traditional relational schema.
- **Expressiveness at the cost of complexity:** Healthcare require rich constraint patterns which are only available in the most complex OWL profiles. Usually developers only exploit basic profiles, degrading data quality.

In the last ten years application of ontology in other domains besides healthcare generated the concept of "Knowledge Graphs" (KG), in attempt to use ontologies outside formal data definition of complex domain data. Although a shared, unique definition is not yet available to this date, and KGs are still confused with knowledge bases, it can be argued that the first represents an evolution of the latter. KGs can integrate information from various sources and apply a reasoning method to generate new knowledge. In the recent years different researchers have tried to give a precise definition. In 2014 Ehrlinger and Wolfram described KGs as:

> *A knowledge graph acquires and integrates information into an ontology and applies a reasoner to derive new knowledge [106].*

In 2020 a paper tried to precisely define KGs as:

> *A graph of data intended to accumulate and convey knowledge of the real world, whose nodes represent entities of interest and whose edges represent relations between these entities. The graph of data (aka data graph) conforms to a graph-based data model, which may be a directed edge-labelled graph, a property graph [107].*

From a mathematical point of view, a KG is characterized as a multi-relational graph, directed edge-labelled graph, a property graph or a hyper graph, composed of entities as nodes and relations as different types of edges [108] [109].

An instance of edge is a triplet of fact *(entity, relation, entity),* which is denoted as *(h, r, t),* such a combination can be recognized as subject h is in relation *r* to object *t.* RDF-based representation captures entities, attributes, and relationships, as the nodes in the graph are entities, and it is labeled with attributes. The typed edges between two nodes correspond to a connection between the entities [110]. The funding idea of the "buzzword" knowledge graph is the idea to exploit the mathematical properties of graphs to manage data persistence in complex scenarios.

The most common scenario requires to integrate, manage and extract deductions using heterogeneous resources at a large scale [111]. The approach of using ontologies a database schema brings diverse benefits:

- Edges capture relations between objects (even potentially cyclical ones), the relation is more intuitive and manageable than a join on a table. The concept of cyclical relationship is relevant in healthcare because biological entities are inherently connected (For example genes with proteins, diseases, and symptoms).
- The management of incomplete knowledge is more manageable because of the absence of a rigid schema.
- The mathematics of graph is exploitable (measures of centrality, clustering, summarization, machine learning algorithms).

The most regularly accepted standard representation in medical KG metathesaurus are, for example, the Unified Medical Language System (UMLS) [112] , a repository of biomedical vocabularies developed by the US National Library of Medicine, which includes over 2 million vocabularies for 900 000 biomedical concepts as well as 12 million relations accompanying these concept, and International Classification of Diseases (ICD-10/11)[113].

A promising representation of ontologies into graph representation is the formal model proposed by Grakn [114]. Grakn is an open-source, distributed, hyper relational database which provides:

- **Knowledge schema**: The schema allows users to model type hierarchies, hyper-entities, hyper-relationships and rules [115]. The schema can be updated and extended regardless of the stage of development.
- **Logical Inference**: Grakn is distributed with an open-source query language called Graql. Graql performs logical inference through deductive reasoning. The goal of the inference can be of various kind:
    - To infer implicit facts: The inference process is performed on of entity types and relationships, The computation is performed at runtime associations and conclusions in real-time, during runtime of Online transaction processing (OLTP) queries. This allows the discovery of facts that would otherwise be too complex or implicit to find.
    - Abstraction of complex relationships into simpler conclusion.
    - Translation of higher level queries into the lower level and more complex data representation [115].

The main differences between Grakn and OWL are the following:

- **Fitness to the problem:** semantic web standards are built for the web while Grakn is though works for heterogeneous closed world systems with private data.
- **Simpleness while maintaining expressiveness:** the ontology language Graql provides a smaller set of constructs but can model all the core use cases of OWL. Graql is composed by:
    - [N-ary] hyper-relations;
    - hyper-objects.

  This is the main difference with OWL (data/object) property separately and then combining them into N-ary relation patterns using auxiliary class names and property restrictions [116]. As mentioned before, although OWL in theory offers higher expressivity, it comes at the cost of increased complexity.
- **Meta-knowledge and Higher-level modelling** OWL is unable to model nested relations, information about relations, hypernodes, which consequently leaves the developer the burden to map those concepts to object Types that OWL is aware of.

For the reasons forementioned I decided to use Grakn as one of the tools in the PhD work. An in-depth discussion on how Grakn has been used is available on the technical chapter (6.3).

3.4. The "Right of Explanation"

CDSSs based on recent data-driven techniques like Artificial Intelligence and Machine Learning represent promising new tools in the era of 'personalized' or 'precision' medicine. As the volume of scientific evidence grows and more kind of patient data are available for monitoring, CDSSs have enormous potential to help healthcare professionals improve diagnosis and clinical patient care.

However, the implementation of these tools in a real setting, and not only on synthetic data, raised legal challenges for healthcare providers and DSS-suppliers in Europe since the last 5 years.

The year 2016 marked in fact a notable change in the development of Clinical Decision Support Systems in Europe. In that year, European government has laid down General Data Protection Regulation (GDPR) [117] for data privacy and security, which had a major impact on the way health data was being collected, accessed, analyzed, stored, and shared in any healthcare ecosystem. The GDPR has influenced and still influences the current development on different planes.

A detailed presentation of the implications of AI and GDPR is outside the scope of this thesis, however, in the following paragraphs the discussion mentions the points to consider before deciding on what conceptual framework to adopt in the development. At full end there is not a "one size fits all" solution but the most appropriate choice to respond to a precise clinical problem.

The first article of interest is the Number 4, which defines profiling as:

> *"Any form of automated processing of personal data consisting of the use of personal data to evaluate certain personal aspects relating to a natural person, in particular to analyze or predict aspects concerning that natural person's performance at work, economic situation, health, personal preferences, interests, reliability, behavior, location or movements" [117].*

Recital n.71 of the GDPR also exposes the right of the data subject about automated decision-making, and provides examples of areas of application:

> *"The data subject should have the right not to be subject to a decision, which may include a measure, evaluating personal aspects relating to him or her which is based solely on automated processing and which produces legal effects concerning him or her or similarly significantly affects him or*

> *her", adding that such processing would include 'profiling' [117].*

This means that everyone that is treated with a system that performs automatic decision-making processes has the right to be informed.
Finally, Article 29 provides further guidance as to the interpretation of automated individual decision-making tasks explaining it as:

> *"the ability to make decisions by technological means **without human involvement** (...) based on any type of data, for example: - data provided directly by the individuals concerned (such as responses to a questionnaire); - data observed about the individuals (such as location data collected via an application); - derived or inferred data such as a profile of the individual that has already been created (e.g. a credit score)"[118].*

According to the regulation, data processing can significantly affect someone if the decision has the potential to:

> *"Significantly affect the circumstances, behavior or choices of the individuals concerned; - have prolonged or permanent impact on the data subject; or - at its most extreme, lead to the exclusion or discrimination."*

Numerous discussions have been made on this topic, Floridi et al. argument that a right to explanation of automated decision-making does not exist in the GDPR [119]. They critique legal existence and the feasibility of such a right. In fact, according to the authors, the ambiguity and limited scope of the "*right not to be subject to automated decision-making*" contained in Article 22 (from which the alleged right to explanation discussion is sparked) raises questions over the protection actually afforded to data subjects. These problems show that the GDPR currently lacks precise language as well as explicit and well-defined rights and safeguards against automated decision-making [119].

In turn in the 2020 the European parliament published a document explaining the implication between AI and GDPR [120]. The document seems to align with the previous authors assertions. If fact, it states that GDPR does not notably argue about AI, but the GDPR is relevant to AI, and some are indeed challenged by the new ways of processing personal data that are enabled by AI. The document concludes:

> *A number of AI-related data-protection issues do not have an explicit answer in the GDPR. This may lead to uncertainties and costs, and may needlessly hamper the development of AI applications [120].*

With regard to the last paragraph, the reasons why I followed a rule-based were different: first of all, it was not possible to exploit data driven algorithm because no previous data lake nor data aggregation was available for the project making all the "data hungry" methods unavailable to use. The second reason is that GDPR mandates that automatic decisions should be "explainable", but today's regulations are not yet clear on the extent of the explanation one system must give [120].

3.5. The pitfall of transportability and interoperability

Regardless of the conceptual method used to implement a CDSS, according to Sutton et al., one of the main downfalls of CDSSs widespread adoption is the general absence of interoperability and transportability of Clinical Decision support artifacts [121].

Although the interest towards CDSSs first started in the 1970s, CDSSs and EHRs suffer from interoperability issues. Most healthcare solutions are deployed as unmanageable monoliths or exist in an environment that cannot communicate effectively with other systems. The authors reflect on the reasons why the transportability so difficult to achieve. The response relies in the intrinsic difficulties that are needed for the development, the diversity of clinical data sources, and the complexity of building a program whose aim is to model such a complex domain as clinical reasoning [121]. Interoperability examines the ways in which software systems exchange information with each other.

The formal definition of interoperability, according to Healthcare Information and Management Systems Society (HIMSS) is the following:

> *Interoperability is the ability of different information systems, devices and applications (systems) to access, exchange, integrate and cooperatively use data in a coordinated manner, within and across organizational, regional and national boundaries, to provide timely and seamless portability of information and optimize the health of individuals and populations globally. Health data exchange architectures, application interfaces and standards enable data to be accessed and shared appropriately and securely across the complete spectrum of care, within all applicable settings and with relevant stakeholders, including the individual [122].*

HIMMS defines four levels of interoperability:

- **Foundational (Level 1):** establishes the functional connection requirements to secure data exchange.

- **Structural/Syntactic (Level 2):** defines data format, syntax and organization exchange.
- **Semantic (Level 3):** gives common data model and codification in standardized vocabularies.
- **Organizational (Level 4):** includes governance, policy, social, legal, and organizational considerations to facilitate data exchange.

Current systems usually lack two kinds of interoperability: syntactic interoperability and semantic interoperability. The first allows exchanging data between different systems while the second enables different systems to interpret meaningfully and accurately exchanged data. The desirable outcome of a useful clinical decision support is a semantic interoperable system which can work together with EHR to achieve better patient outcomes and virtuous healthcare.

3.5.1. How can interoperability be achieved

The communication and interaction between healthcare software systems has been always considered a big deal breaker in implementing CDSSs. For these systems to communicate seamlessly, the adoption of standards is crucial.

A single set of standards would be the most appropriate solution to effectively share information. However, the difficult reality of health information systems has generated a growing emergence of specific standards for each field of application. This obscurity in interpretation and complexity favors the non-acceptance and non-use of existing healthcare standards.

To ease the adoption of healthcare standards, two international organization are joining efforts to align and unify interoperability criteria: Health Level Seven International (HL7) and Healthcare Services Platform Consortium (HSPC). The technical chapter (5.4) discusses in depth how the following standards have been used inside this work.

3.5.1.1. Clinical Document Architecture

Clinical Document Architecture is a HL7 standard that defines the structure of digital clinical documents, such as discharge letters, referrals, consultation notes and image or laboratory reports. CDA specifies the markup of XML documents and standardizes the document structure required to create clinical documents. The level of terminology and section coding is a crucial to a CDA: the more the developer invests in codifying the information contained in the data, the better the reusability (and semantic understanding) of the data is provided, allowing, for example,

better CDSS applications. Clinical Document Architecture was chosen as the standard to adopt in this work to formally model the rehabilitation plan.

3.5.1.2. Fast Healthcare Interoperability Resource (FHIR)

FHIR enables developers to create EHR-based applications exploiting the same data the HER provides. The standard provides a common data modelling, rich enough to capture the complex attributes needed by healthcare domain. This standard will be discussed more in depth in the technical chapter (5.4.3).

3.5.1.3. SMART on FHIR

Boston Children's Hospital and Harvard Bioinformatics joint efforts created an open source standard-based healthcare application platform called "Substitutable Medical Applications, Reusable Technology" (SMART) [123]. The original aim of the project was to enable any IT company or single developer to create a health care application that followed the paradigm "write once, run everywhere" regardless of the EHR and the health organization.

SMART on FHIR applications are launched from EHR and enable users to connect directly to applications in their workflow to more easily visualize, interact and transmit health data.

3.5.1.4. CDS Hooks

Clinical Decision Support (CDS) Hooks is a specification for vendor-agnostic, workflow-integrated, clinical decision support communication

The idea behind CDS hooks is to run decision support services automatically, presenting to the physician a recommendation only when it matters. The result of the computation is displayed in the form of a card inside the EHR. This standard will be discussed more in depth in the technical chapter (5.4.3).

3.6. Implementation choice: a standard, rule-based Decision Support System

One of the challenges encountered in the analysis of the state of the art was that the word "telerehabilitation" is used as an umbrella term for varied rehabilitation methods delivered via ICT solutions. All the paper that were analyzed used some form of technology as a common feature to provide

remote patient care but there was a great deal of heterogeneity in terms of how the technology was exploited [124].

While some studies used professional technical equipment to deliver remote care, other studies used commonly available tools (Like mobile phones, Teams, Zoom and FitBit). Similarly, the clinical parameters that were monitored through sensors also varied significantly.

In all of the papers analyzed in this chapter there were no explicit or evidence-based justifications regarding the decision-making process on what and how the technology was used, which indicates that the design of the project was probably driven by contextual (availability of resources) and health professional (knowledge, skills and competence in technology use) reasons.

The knowledge model adopted in this work is a rule-based approach. To the best my knowledge, this is one of the first work which can guide homecare rehabilitation prescription and monitoring by integrating both with health information system and a home-care rehabilitation kit, connecting the line between clinical care at the "point-of-care" to "the bedside" and back to the "point-of-care".

In fact the literature presents studies illustrating the development and evaluation outcomes of a technical infrastructure dedicated to computerized decision support in other domains [125] [126] or in the domain of physical rehabilitation but focusing on a very small patient population affected by only one disease [127]. The goal of the project instead is to be able to support patients with one, two or even more comorbidities, that however do not undermine the ability to perform exercise but they just require particular precautions.

One example is the systems described by and Song et al. [128] which focuses on chronic obstructive pulmonary disease and recommends in real time the adjustments to be made in a single rehabilitation session. The study however does not consider the process of rehabilitation prescription and monitoring but only delivers recommendation on a single session of training and on a single population of patients. Another example is the one by Reid et al. [126] in which an internet-based system was distributed to in patients with coronary heart disease (CHD) in order to promote physical activity when the patient were not participating in cardiac rehabilitation.

The study design provided two patient groups. One was assigned to be monitored through the system, while the second category followed usual care. The study states that the group followed by the system received a personally tailored physical-activity plan upon discharge from the hospital. The study however does not explain if the "*personally tailored physical-activity plan*" was built according only to the physician opinion or if the construction was aided by the system and to what extent, nor does the study cite the materials of evidence used to build the system (Guidelines, consensus reference, common practice flow charts..). In addition, the patients were:

> *Provided with an access to a secure website for activity planning and tracking. They completed five online tutorials over a 6-month period and were in email contact with an exercise specialist. Usual care consisted of physical activity guidance from an attending cardiologist. Physical activity was measured by pedometer and self-reported over a 7-day period, 6 and 12 months after randomization [126].*

From the study description it's understandable that the only remote monitoring that was performed was manual (email contact) and did not involve any kind on processing on remotely collected data in order to upgrade the rehabilitation prescription. Another study however did manage to exploit CDSS to prescribe a remote rehabilitation regimen by exploiting a Decision support system. In 2018, Andreas Triantafyllidis et al. published a paper whose aim was to provide:

> *"Decision support for beneficial home-based exercise rehabilitation in patients with cardiovascular disease"[129].*

The CDSS was a rule-based system, built using international guidelines and expert knowledge and recommending the categories of exercises that were to be included or excluded from the rehabilitation treatment for cardiovascular disease. The CDSS did not act on the prescription of the home-care regimen but was able to recommend if a regimen needed to be changed by using information coming from a wristband device which monitored just the hearth rate.

Although the system exploits guidelines and medical evidence, it exploits just a Fitbit and only the measure of hearth rate and a motion camera to provide recommendations to change the prescribed treatment. These kinds of devices, although economical and more or less generally available to the public are afflicted with some problems like low accuracy [130].

In addition, the *if-then rules* are written as Python scripts and not in a standard format, making them not transparent to a non-technical user, prone to error in the building portion of the system, and difficult if not impossible to maintain, both in term of technological advancement (the newer version of a particular language may require a complete rewrite of the codebase) and the clinical advancement.

After a period one rule may not reflect clinical evidence anymore, if production rules are tightly coupled and embedded in the code base, the project is poorly robust to change.

The aim of this work is giving support in the act of prescription and building of the remote-care regimen, by:

- Identifying the criteria of inclusion and exclusion for a patient to be considered in the project, considering the common features

across morbidities that prevent a patient from executing some kind, or all physical exercise.
- Identify inclusion and exclusion criteria from a particular category of exercises available in the rehabilitation catalogue and vital parameters to be monitored during exercise sessions.

To this end, the system is original in the sense that it supports the prescription of rehabilitation regimen by providing a set of features that can be found in literature by themselves but unlikely all together:

- Unique patient identification inside the hospital system.
- Clinical decision support in the prescription of a home-care rehabilitation regimen using computer interpretable clinical practice guidelines.
- Automatic distribution of the prescription to all software agents that are registered for retrieving the remote plan of care.
- Exploitation the most recent and stable healthcare standards to make the CDSS software infrastructure reusable and interoperable.

Chapter 4:

Functional requirements of the proposed solution

The analysis of the state of the art provides valuable "desiderata" for building a clinical decision support system that can be seamlessly integrated with real hospital information systems.

The first operative task of this work consisted in collecting all the functional requirements of the solution using a standard and replicable methodology.

Each functional requirement described in the following paragraphs has been analyzed with a technical perspective and then partially or completely implemented. Every requirement was analyzed on various conceptual axis:

- **Cluster:** identifies the conceptual area of belonging of the requirement. The identified clusters are the following:
  - patient demographic;
  - knowledge base rules;
  - Inference Engine;
  - integration;
  - software Architecture;
  - security.
- **Milestone:** identifies in which step of the entire project the requirement is involved. The belonging to a milestone classifies the requirements in order of urgency of development. The three macro milestones of the project are the following:
  - support in the "First Prescription of a home-care rehabilitation regimen;
  - remote monitoring of the patient by data coming from sensors;

    - support in the early solicitation for a home-care prescription revision.
- **Unique Identifier:** an incremental counter which uniquely identifies the functional requirement across all phases of the development (Functional and technical design, implementation, and testing). This is necessary to keep track of the global effort certain function needed.
- **Brief description of the function need:** a synthetic description of the functional requirement that needs to be developed.
- **Functional requirement state:** a representation of the progression of the development of the functionality. It can be one of the following states:
    - **Deprecated:** the requirement has been developed and then substituted with a more appropriate or more detailed requirement. Especially in the first phases of the project the functional requirements change rapidly so it is a good design choice to keep the old requirements in the basket of function needs with a deprecated state.
    - **To Be Defined:** the requirement has been collected but it needs to be further analyzed to be taken into consideration for technical design.
    - **Defined:** the functional requirement has been analyzed and shared with all the interested actors and it is ready to be technically designed and implemented. At this stage, the requirement is ready to be taken into consideration for operative work, but it has not yet taken into development.
    - **Transferred:** the functional requirement is being actively developed.
    - **Deployed:** the requirement has been designed, developed, tested, and deployed in production.
- **Effort:** describes the amount of time estimated for each functionality to be delivered. The estimation of the effort is the amount of work performed by the average worker in one hour. The effort label has been indicated with the methodology of "Expert estimation" as the literature shows that up to this day it is the dominant strategy when estimating software development effort [131]. The following levels have been chosen:
    - **negligible** (Up to 1 man-day);
    - **low** (Up to 1 man-week);
    - **moderate** (Up to 2 man-week);
    - **high** (Up to 1 man-month);
    - **high+** (Unpredictable, more than 1 man-month).

From a functional point of view there is no interest in keeping track of the phases of the development, but just to know is a particular function is being used by those who asked for it. In addition to the global analysis of

the requirements, CDSS was categorized in the following conceptual axes [132]:

- by model:
  - **knowledge based CDSS;**
  - non knowledge CDSS.
- by delivery method:
  - **cloud-based;**
  - on-premise.
- by component:
  - hardware;
  - software;
  - **services.**
- by product:
  - **integrated system;**
  - stand-alone system;
  - **standard-based;**
  - service model-based;
  - other products.
- by application:
  - medical diagnosis;
  - **alerts and reminders;**
  - **prescription decision support;**
  - information retrieval;
  - image recognition and interpretation;
  - **therapy critiquing and planning;**
  - other applications.

In the following paragraph the requirements defined for each milestone will be described with more detail.

4.1. First Prescription of a home - care rehabilitation regimen

This section describes the use case for the first milestone of the project, aiding in identifying the most appropriate home-care rehabilitation regimen. All the use case have been analyzed using Unified Modeling Language (UML) Standard [133]. Here down below are the functional requirements implied in the described milestones:

4.1.1. Guideline modelling

This macro functional requirement is a frame for different minor requirements:

- reconciliation of clinical practice guidelines relating to rehabilitation, provided by ICS Maugeri;
- automatic identification of inclusion or exclusion criteria to participate in the project;
- automatic identification of inclusion or exclusion criteria to carry out particular exercises;
- identification of the most appropriate rehabilitation prescription, by following clinical practice guidelines and a clinical algorithm published by Institute Maugeri [134];
- suggestions about physiological parameters to be monitored during delivery;
- suggestions on the proposed frequency of activity for home rehabilitation.

To develop this functional requirement a thorough analysis of the guidelines was performed. The guideline that has being used as a knowledge base is the "*LINEE GUIDA ED EVIDENZE SCIENTIFICHE IN MEDICINA FISICA E RIABILITATIVA*" curated by Walter Santilli (October 2017 revision). The guideline that was provided in free text form has been transformed into a formal representation that has been be used as a basis for building a computerized decision support system. For this process, a set of techniques synthesized by an analysis of the state of the art is used as a reference [135] [136] [137]. Following the gold standard analysis methodology the following conceptual steps were performed.

4.1.1.1. Classification of the text portions of the guideline according to "Axes of interest"

The Possible axes of interest of a guideline are the following:

- **categorization by type of text:**
  - informative text;
  - recommendation;
  - recommendation including criteria relating to the individual patient (pathology, demographic data ...);
  - recommendation including the type and degree of evidence.
- **time-based categorization:**
  - the recommendation or information note refers to the moment preceding the prescription of the treatment;
  - the recommendation or information note refers to when prescribing the treatment;
  - the recommendation or information note refers to the follow up.

- **categorization based on the actor receiving the recommendation** (it is necessary to identify the actors of the domain):
  - patient;
  - doctor;
  - compilation operator;
  - others interested;

4.1.1.2. "Formal translation", Draft of the recommendations

Each portion of the text has been further analyzed and an attempt has been made to rewrite the information content of the recommendation in a "formal" logic, by trying to make explicit all implicit knowledge that might be "hidden" within the text.

In this phase, it has been an invaluable asset having a constant dialogue with the clinical counterpart, who had useful suggestions to explain the knowledge contained within the portion of the text. For the translation into a more formal language the “Population, Suggestion, and Outcome” model [135] has been adopted. This model starts from the reflection according to which a recommendation is written to give a series of suggestions (Suggestion) for a particular population (Population) to reach a certain goal that benefits the patient (Outcome). Figure 9 shows a general description taken from the analysis by Ravi P Garg et al. [135].

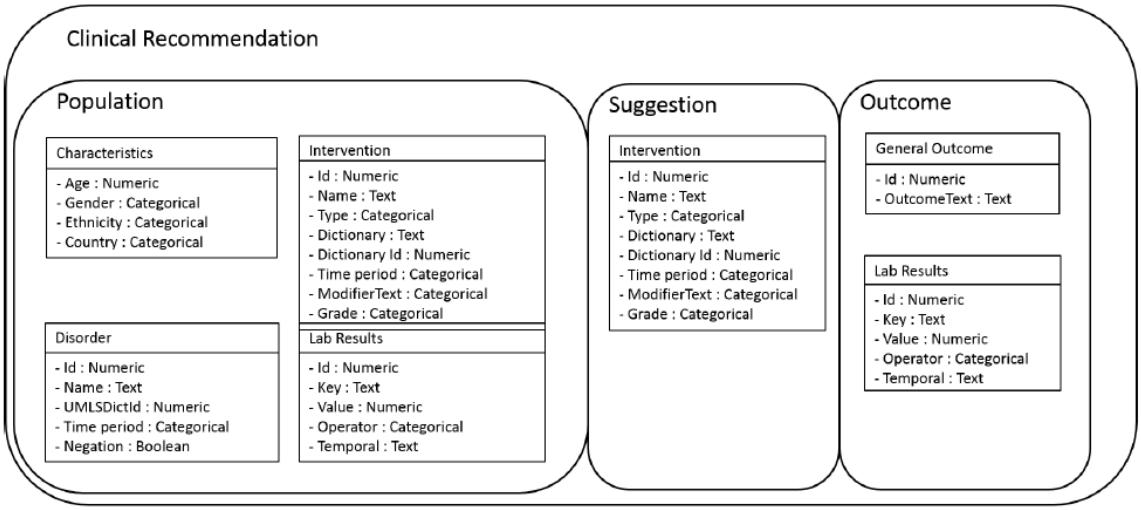


Figure 9: A visual representation of Population, Suggestion, Outcome model

4.1.1.3. Identification of a "MINIMUM" dataset necessary for the formalization of the Guideline

All the data required for each recommendation has been collected and divided into two types:

1. **Primitive data** that can be collected directly from patient measures like heart rate, weight, height etc.
2. **Derived data** that can be inferred starting from primitive data or derived by estimation: For example VO2max is the metric that represents the maximum volume of oxygen consumed per minute (in milliliters) per kilogram of weight and define the cardiorespiratory level and personal aerobic, this data is not easily detectable with instrumentation and therefore is computed with estimation algorithms.

4.1.1.4. Implementation of the guideline in a "Computer Interpretable" format

This step will be further discussed in paragraph 5.4.2 but in in general, each pseudo-rule candidate for the development has been transformed in a portion of knowledge artifact of Hl7 Clinical Quality Language, a standard syntax to represent clinical decision support artifacts.

The result of the analysis is available in the attached Appendix B. A total of 54 rules of interest have been extracted and formally modelled.

4.1.2. Semantic Integration with “Nomenclatore Maugeri”

The DSS should be able to integrate with the so called “*Nomenclatore Maugeri*” (a coded dictionary of medical services available for ICS Maugeri).

The DSS should provide more generally the possibility of reasoning using standard dictionaries (Snomed, LOINC) and local coding (For example the Nomenclatore Maugeri).

4.1.3. Interoperability “by design” at the Data Model Level

The DSS is required to be able to interface with different medical records (EHR) or data sources using the Health Level Seven (HL7) International Fast Healthcare Interoperability Resources standard (FHIR). This is necessary because the DSS could be connected not only to the platform that

generates the rehabilitation prescription platform but could receive data from various external sources.

4.1.4. Interoperability “by design” at the communication paradigm level

The communication between the platform that produces the rehabilitation prescription and the DSS is required to be agnostic with respect to the actors, therefore it is required to adopt the emerging standard of HL7 called CDS Hooks [138]. This is necessary to distribute the same DSS to each system that adopts this communication standard. The communication interface is available in the attached Appendix B. The Appendix provides the API definition according to OpenAPI specification, a description format for REST APIs [139].

4.1.5. Interoperability “by design” at the knowledge base formalization and distribution

Numerous authors agree that to build a robust CDSS the software architecture must be separated from inference engine and the Clinical rules. The rules should be developed using Hl7 standard “Clinical Quality Language” (CQL) [140] so they can be developed, maintained, and documented separated from the inference engine and the software architecture. Any tight coupling between the concept forementioned bust be discouraged.

4.2. Remote monitoring of the patient by data coming from sensors

This section describes the use case for the second milestone of the project: automatic analysis of patient data coming from sensors. The project states in fact that when entering the project, the patient is given a “rehabilitation kit”, comprising a tablet with exergames and a set of remote monitoring sensors that record the patient’s vital parameters during the rehabilitation sessions.

The second milestone of the project in large base depends on the data available from the remote sensors that monitor the patient during home-care physical exercise sessions. However, real data coming from sensors is unavailable because the experimental phase is due in the following steps of this project, so the functional requirements will be subject to revision right after. Independently from the specific data that could flow into the DSS the scenario would be the one presented in this next section.

4.2.1. "FITT-PRESCRIPTION" automatic review and Early Solicitation for a home prescription revision

A background automatic software worker must cyclically review the Frequency, Intensity, Time, Type of exercises prescribed to each patient and monitor if the session indicators coming from the rehabilitation kit align with the prescription. The DSS, according to the configured rules, must return a particular value that has deviated too much from the normal range, and must therefore return corrective actions. An example of a Monitoring Event would be the following:

During the "FITT prescription" phase (Frequency of sessions per week, Intensity Time or duration per Session, Type of exercise: Aerobic/Muscle strengthening, balance) it is decided that the patient John Smith must sustain 3 sessions of Aerobic exercise, each lasting one hour.

Cyclically the client sends the DSS a request for a *FITT-prescription-review*, transmitting the time range to be analyzed, the identification of the patient being analyzed. This process runs in the background during the night, so that the operator has the current situation in the morning.

The DSS retrieves the patient's current FITT prescription and uses this to perform the analysis:

- Counts the number of records that have been received in session terms.
- Computes the duration of each session.
- Reads the data collected by the Rehabilitation kit during the FITT Session.

The DSS compares the FITT prescription with what is found in the patient's data and returns a CARD containing the inconsistencies, which can be consumed by the client. The CARD must also contain a configurable Alert Level, for example:

- 1 standard deviation from the nominal value = Yellow Alert.
- 2 standard deviations from the nominal value = Orange Alert.
- 3 standard deviations from the nominal value = Red Alert.

At the end of the *FITT prescription-review* process the client shows if a patent needs to be called in for a prescription review.

4.2.2. Explanability of recommendations received

During the delivery of a specific recommendation, the DSS is required to be able to "explain" to the operator the criteria that led to the plan revision alert. The criteria can be shown in various ways:

- time progression graphs;

- synthetic indicators agreed with clinicians and related thresholds;
- possibility of interaction with the knowledge base portion that produced a given recommendation;

The explanation of the recommendations received can be conveyed with a link to "SMART APP" compliant with the HL7 standard called "CDS Hooks" [138].

Chapter 5:

Technical specification and architecture of the proposed solution

This chapter describes the technical design adopted in the development of the DSS architecture to support the physician in prescribing a home-care rehabilitation regimen.

The overall architecture has been designed by following the functional requirements defined in the previous chapter and described using the standard specification of Unified Modeling Language Class Diagrams [141]. In this diagram classes are depicted as boxes with two sections, the top one indicates the name of the class, the bottom one lists the attributes of the class. The following paragraph discusses at a high level the regional project and the position of the DSS inside the project. The other subchapters will describe in depth the architecture of the DSS.

5.1. RE-Hub-ILITY: the overall project

RE-Hub-ILITY is a project funded by the Italian Lombardy region whose goal is to develop and validate innovative rehabilitative treatment and assistance strategies for the chronic patient. The project is inserted within the European framework POR-FESR 2014-2020 (Regional Operational Program-European Regional Development Fund [1]. The project started in December 2019 and will end on in May 2022.

The intervention is exploiting an innovative ICT infrastructure for the provision of personalized home rehabilitation services for chronic patients. In particular, it envisages these components (in this paragraph the DSS' scope inside the project is highlighted in bold character):

- a virtual coaching system in the form of a conversational agent based on artificial intelligence built using techniques deriving from the psychology of persuasion, personalized interaction with the patient through an app that detects provides indications and promotes adherence to the rehabilitation program.
- exercise kits, consisting of:
    - Exergames aimed at exercising motor and cognitive skills.
    - Wearable sensors to support and evaluate devices to guide and monitor patients during the execution of the exercises remotely.
- **in cloud Decision Support System (DSS)** capable of interacting with hospital information systems, for the management of the rehabilitation plan by therapists. This point is the focus of the PhD research activity. A platform called PAIR Platform has the responsibility to produce a home-care prescription with the help of a DSS. The DSS analyzes patients' data, to allow an individualized prescription of rehabilitation programs thus maximizing the effectiveness of each program.

The operational objectives that the project aims to achieve are:

- Improve the psychosocial impact and the degree of satisfaction obtained with the rehabilitation program administered with the ICT platform.
- Improve patient adherence and motivation to the personalized rehabilitation program carried out at home, through the technological platform.
- Evaluate the effectiveness of the personalized home rehabilitation program, on motor function, cognitive-behavioral profile, quality of life.

- Creation a library of motor exercises and cognitive tasks to be implemented in the integrated system for the home rehabilitation of chronic subjects with remote supervision.
- **Evaluation of the adequacy of the DSS in terms of interoperability and usability** in the network between different ICS Maugeri Institutes for the sharing and integration of rehabilitation paths in taking care of the chronic patient from discharge to home.

Figure 10 describes on a high level the relations between the different components:

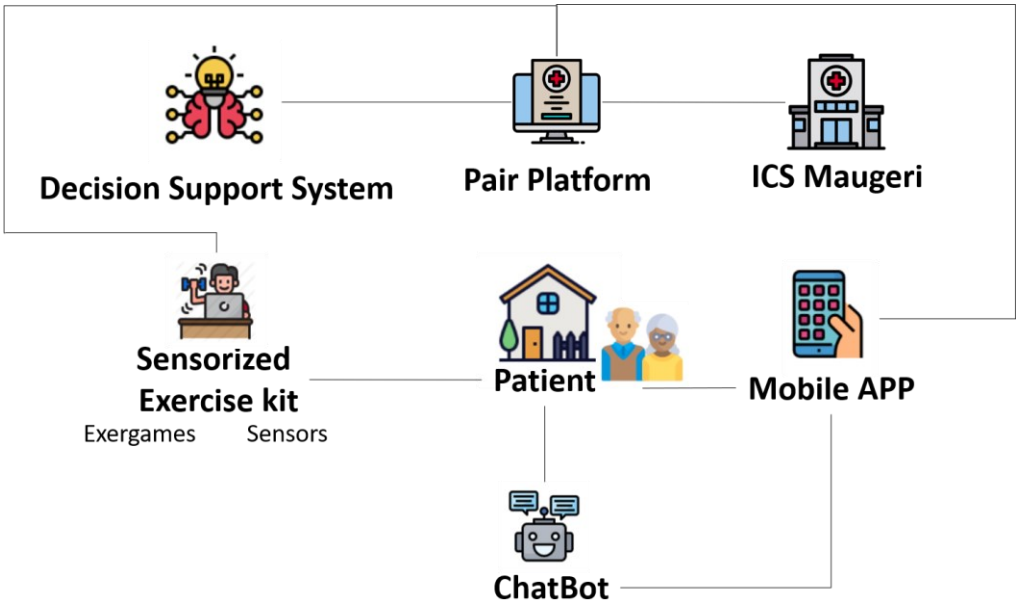


Figure 10: High level Architecture of RE-Hub-ILITY

As mentioned, Figure 10 shows the system architecture, highlighting the various components and the logical interfaces between the different modules. The components or modules of the system are:

- **PAIR platform:** represents the main point of interaction between the system and the doctor, therapist or healthcare professional. The platform connects with the existing hospital information systems in terms of demographic registry and clinical history of the patient. The platform is also connected with the different system modules and with the DSS. It allows the user to collect and organize patient's data and make them available to the DSS (and all the modules that need them) to update and modify the rehabilitation plan.
- **Clinical Decision Support System (CDSS):** supports the clinician in creating and updating the personalized rehabilitation

plan, considering the data available at the beginning of the rehabilitation process and during its execution at home (pathology, guidelines,scales and evaluation tests, adherence, performance, etc.).

- **Mobile app:** represents the patient's main interface with the system, allows him to receive the therapeutic and rehabilitation plan, supporting him in the scheduling and programming of activities (medicines, exercises, visits, questionnaires, etc.). In addition, through the app, the patient can provide data regarding the execution of the planned activities. By taking advantage of the app, the system can deduce information on adherence to the therapeutic and rehabilitation plan. Furthermore, through the app, the patient can monitor the therapeutic path and the performance obtained and interact with the ChatBot.
- **ChatBot:** represents a virtual assistant to which the patient can ask questions in natural language regarding different aspects of the treatment and rehabilitation plan, from more general aspects such as the recommended diet and the best times of the day to perform the exercises to more detailed information on positioning the sensors and the correct execution of the exercises. The ChatBot can intervene proactively, giving suggestions and alerts to the patient based on data provided by the various modules of the system and interacting with human and non-human elements (e.g. mobile app).
- **Sensorized exercise kit:** consists of a set of exergame and sensors/devices that support the patient in performing the exercises prescribed to the patient. The exergames are video games aimed at the execution of particular movements and cognitive and motor tasks in the form of a game, the sensors and devices allow the correct execution of the exercises, monitoring the performance remotely on the one hand and correcting incorrect executions on the other.

As stated in the previous chapters, the main objective of this dissertation is to support the physician in the definition of the rehabilitation treatment at home. The Individualized Care Plan for Rehabilitation (PAIR) is the home-care regimen term coined for the RE-Hub-ILITY project, and it is shown in Figure 11.

Figure 11: PAIR Definition

The PAIR is the collection of pri and PAI, described in the clinical background chapter (2.2.5).

- **PAI: Individualized Care Plan** is the summary document that collects and describes the information relating to patients in a multidisciplinary perspective.
- **PRI: Individual Rehabilitation Project**, which in turn is divided into:
    - Capital PRI: defines the objectives to be achieved (in the **Project**).
    - Lower case pri: (Individual Rehabilitation **Program**) identifies the type of exercise, frequency, dosage, etc. the patient must adhere to for reaching the objectives described in the PRI.

The data flow follows these steps:

- The PAIR Platform produces/revises a document called PAIR which defines the Individualized Rehabilitation Care Plan, structured according to the format provided for the PAI of the Lombardy Region (CDA2); the PAIR extends the PAI by adding a section which contains the rehabilitation plan provided for the patient.
- Following the production/review of a PAIR, the PAIR Platform notifies the event to all those who have expressed their intention to receive these types of notifications.
- The Applications participating in the project access the PAIR document of interest and use the data to organize the rehabilitation activities of competence; In particular, the rehabilitation kit receives the prescription of the exercises, in terms of number of sessions, type of exercise and difficulty proposed.
- The Applications participating in the project produce a summary document, which contains the data relating to the activity carried out, and send it to the PAIR-DSS Platform.

- Following the receipt of the summary document, the PAIR Platform notifies the event to all subjects who have expressed their intention to receive these types of notifications.

The Clinical Decision Support System has the goal of supporting the clinician in drafting the first version of the PAIR and any update versions, indicating the need to modify parameters by following the monitoring of the data received from the various modules. From the received data the DSS must deduce information on the execution by of the patient, achievement of objectives and performance.

To this end the Pair Platform, adjuvanted by the DSS must integrate with the different modules and components of the system for different reasons:

- Send the PAIR and subsequent update versions that the various modules will use as input.
- Receive information, data, and documents from:
    - Maugeri Information Systems, to create the first version of the PAIR.
    - Other modules of the system, to monitor the execution and progress of the PAIR and be able to update it, which constitute the power supply of the DSS.

The output of the DSS/PAIR platform is a Hl7-compliant CDA2 and contains the home-care regimen whose technical details are discussed in the following chapter.

5.2. DSS Client: The PAIR Platform

Currently at the ICS Maugeri structures, the patient in the discharge phase is given the drug therapy and the program of exercises to be performed at home. Pharmacological therapy is part of the PAI and contains the list of drugs to be taken, with the relative dosage, which includes frequency, daily intakes, and times. Therapy may also include checks and visits to be carried out during the reference period, with the relative dates, if defined, and/or frequency.

The exercise program section contains the list of exercises to be performed, a brief description that guides the execution of the exercise, and the dosage which includes the intensity and frequency with which to perform each exercise (speed, time, weight, repetitions, series , times a day, times a week, breaks, etc.).

Furthermore, the traditional paper-based document can also report the indicators used to determine the overall load level of the program based on the patient's capabilities, the objectives and the monitoring indices to be used to verify the achievement of these objectives. These requirements

have been translated in the hl7 CDA2 document structure [142]. The final structure of the PAIR is still however matter of modification.

An in-depth analysis of the structure of the PAIR is outside the scope of this final work, however a brief description of the inner structure of the CDA is hereby presented.

The Clinical Document Architecture (CDA) is a markup standard used for the exchange of clinical documents between software architectures developed by the international association Health Level 7 (HL7). The purpose of HL7 CDA is the standardization of the structure of clinical content into digital documents to ensure interoperability of medical data.

Version 2 of the CDA has been adopted as the ISO/HL7 standard 27932: 2009 [143]. In Italy, as in many other countries, HL7 CDA 2 represents the reference standard for structuring of clinical documents stored in health information systems.

For each exercise, the PAIR contains the following information:

- name of the exercise;
- sequence ID: unique identifier of the exercise;
- exercise difficulty level;
- category: classification of the exercise (for example power, muscle strength);
- division macro area of intervention (for example cardiorespiratory rehabilitation);
- exercise description: brief description in free text of the exercise;
- target: group of muscles that will benefit from the exercise;
- assistance;
- devices;
- monitoring indices (for example monitor after each session the BORG scale).

In compliance with the structure of an XML-CDA2 document, the PAIR is structured in two parts: Header and Body.

The Header structure contains information about the document (for example: the type of document; the unique identifier and the version of the document) and on the subjects that have a role in the process of generating the document itself (the subject - the patient - to which the document relates; the author; the signer, a possible set of relations with previous versions of the document).

The Body contains the information about the content of the document; It is structured in a sequence of "sections", each of which is composed of two sections, one intended to contain the narrative parts of the document (visible by the end user) and one computer-interpretable dedicated to devices and applications; the latter consists of one or more "entries", which encode the content presented in the narrative block of the same section and make these machine-processable information.

The Body of a PAIR contains the XML structure required for a normal PAI produced in the management activities of a Patient promoted by the Lombardy Region [30]. A rehabilitation section is added to the standard PAI to provide specific information contained in the rehabilitation plan.

The plan defined in the PAIR must be built with the support of the DSS. The PAIR Platform acts as a Client for the DSS and shows the final user the recommendations provided by the server. The trigger point of execution of the DSS logic is the digital signature of the PAIR document by the user on the PAIR platform.

Preliminary to the digital signature the Exercise portion of the PAIR document, Patient Demographic data and clinical information are sent to the DSS for validation. A high-level description of the interaction Is detailed in Figure 12.

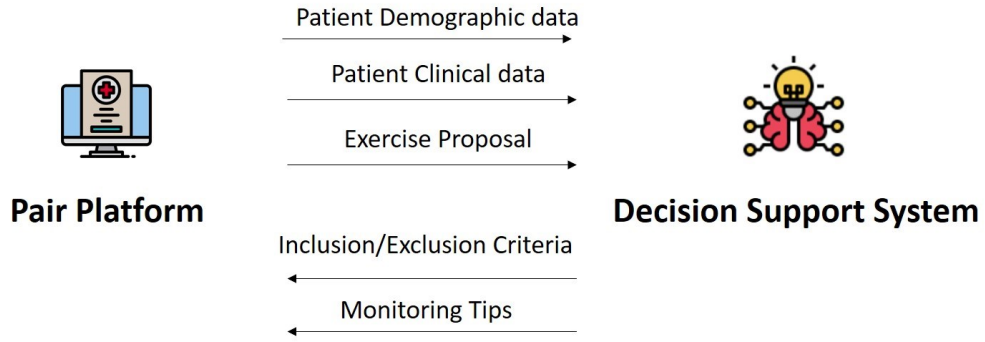


Figure 12: High level description of DSS-Pair platform interaction

5.3. DSS Client - Server communication:

One of the challenges of healthcare solutions which are connected to a EHR is that the user needs actively to decide that an app is useful for a particular context and he needs to take action to launch the application.

Doctors therefore need to know which application will be useful at what point in their workflow. For example, if the physician wants to run an app that is going to help him verify if a drug has some drug-drug interaction he might have to invoke that app while making a prescription.

This information flow opens the possibility for ignored clinical decision support or time loss in invoking the service each time a prescription is made. The idea behind CDS hooks is to run those kinds of services automatically, presenting to the physician a recommendation only when it matters.

As the physician is using the system, the EHR may fire a notification towards an external clinical decision support service. When writing the prescription, the external service learns that the clinician is in the process of prescribing a drug it computes proprietary logic, optionally exploiting a FHIR server. The result of the computation (for example drug-drug interaction present/absent) is displayed in the form of a card inside the EHR.

In the project, the standardization of communication flow is between the PAIR Platform which acts as the client and the DSS which acts as a server with decision support capabilities [144].

The positive effect in complying with CDS hooks specification is the separation of concerns that CDS Hooks provides. In fact, the provision of complex functionality like CDS services is conceptually and operatively separated from their consumption.

By standardizing the interface between the two, a CDS client can connect to any the service that meets their needs, with a communication interface that has been modeled using a standard approach.

The supplier of the DSS server on the other hand can seamlessly connect to any other DSS client that supports CDS Hooks, which makes it simpler to provide services and reduces the proliferation of custom-developed interfaces.

The communication pattern is based on the concept of "hooks", which are predefined connections in the clinical workflow that can initiate the request for decision support. CDS Hooks defines:

- Methods the developer needs to implement to register for the services offered by a decision support system.
- Communication specifications for invoking decision support services.
- Modeling the response from the decision support system. The output of the DSS execution is in the form of informational cards contextualized in the clinical workflow.

The design of the communication flow between the PAIR Platform and the DSS follows the specifications of the first stable version of CDS Hooks, 1.0, published by HL7 [144].

To be compliant with the CDS Hooks HL7 specification the following components must be defined:

- **CDS Service:** One or more services that provide decision support, accepting requests from outside that contain patient data and executing proprietary logic to provide the caller with an answer. Four services are being developed and are described in detail in the Implementation chapter (6.1):
  - discovery service;
  - patient enrollment service;
  - exercise prescribe service;
  - exercise monitor prescribe service.
- **CDS Client:** software component with the role of client with respect to DSS services. The client forwards the request for decision support and consumes the result of the DSS execution. If required by the information flow, it must provide the data of the patient who is the subject of the call, in the form of an FHIR resource and a service authentication token. The PAIR platform in the context of communication based on CDS Hooks plays the role of CDS Client.
- **Hook:** defined point in the CDS Client workflow that acts as a trigger for the creation of the decision support request. In the first phase of development, the Hook is the moment that precedes the digital signature of the PAIR.
- **Card:** result conveyed in the form of a JSON object by the DSS. A card represents a suggestion or recommendation of a defined length. The card is shown to the end user by the PAIR module.

Figure 13 visually explains the communication between a DSS Client and a DSS Server.

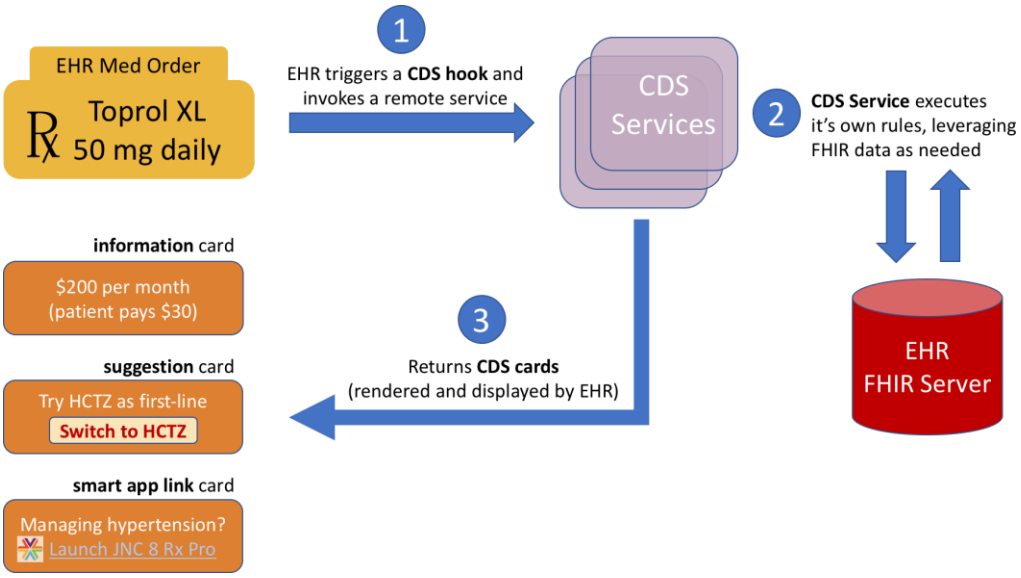


Figure 13: CDS Hooks Specification

5.3.1. Authorization Layer

Implementing a secure communication between client and the server when exchanging clinical data is a crucial point. The CDS Hooks specification describes how to set up a secure communication between the CDS client and the CDS server. It is expected that the organization using the client is protected before engaging in any connection towards CDS server.

5.3.2. Ensure Trust in CDS Services

When the client triggers a CDS Service, it is responsible for ensuring trust with the CDS Services it intends to call.

This trust is ensuref via a Transport Layer Security (TLS) connection to the CDS Service. Thus, all CDS Service endpoints must be exposed to a TLS protected URL (https).

In addition, DSS clients should use accepted authenticity and trust standards for TLS connections. Two common examples are rfc5280 [145] and rfc6125 [146].

5.3.3. Ensure Trust in CDS Clients

Since the CDS Service is invoked by the CDS Client, the CDS Service does not have the same mechanism as the CDS Client to establish trust of the caller. To establish trust of the EHR, JSON web tokens (JWT) are used.

JSON Web Token (JWT) is a compact, URL-safe means of representing claims to be transferred between two parties. The claims in a JWT are encoded as a JSON object that is used as the payload of a JSON Web Signature (JWS) structure or as the plaintext of a JSON Web Encryption (JWE) structure, enabling the claims to be digitally signed or integrity protected with a Message Authentication Code (MAC) and/or encrypted [147].

When the physician is ready to digitally sign the PAIR and has decided the possible home – care prescription a request to the CDS Service is sent. Inside the request payload the CDS Client, sends an Authorization header where the value is Bearer <token>, where <token> must be substituted with the actual JWT. An example of the JWT represented is the following code box:

```
{
  "iss": "https://pair-
platform/",
  "sub": "mariorossi",
  "aud": "44b16507-8a59-4369-
96f9-1e9b1f9a0ace",
  "exp": 1422568860,
  "iat": 1311280970
}
```

The JWT from the PAIR platform is signed with a private key and contains the following fields:

Table 1: JWT Attributes

Field	Value
iss	The base URL of the CDS Client's FHIR server. This must be the same URL as the fhirServer field in a CDS Service request.
sub	The unique identifer for the current user
aud	The OAuth 2 client id of the CDS Service
exp	Expiration time integer for this authentication JWT, expressed in seconds since the "Epoch" (1970-01-01T00:00:00Z UTC).
iat	The time at which this JWT was issued, expressed in seconds since the "Epoch" (1970-01-01T00:00:00Z UTC).

Using the above JWT payload, the complete JWT as passed in the Authorization HTTP header is described in decoded form in Figure 14 and in encoded form in Figure 15:

Figure 14: Decoded JWT Token

eyJhbGciOiJIUzI1NiIsInR5cCI6IkpXVCJ9.ey
Jpc3MiOiJodHRwczovL3BhaXItcGxhdGZvcm0vI
iwic3ViIjoibWFyaW9yb3NzaSIsImF1ZCI6IjQ0
YjE2NTA3LThhNTktNDM2OS05NmY5LTFlOWIxZjl
hMGFjZSIsImV4cCI6MTQyMjU2ODg2MCwiaWF0Ij
oxMzExMjgwOTcwfQ.pgrHgSu2lWwKfbiBpoL6Po
Yjh1SWbMYN-sCLmOx9--s

Figure 15: Encoded JWT Token

5.4. DSS Server

5.4.1. The Knowledge Base

The volume "*GUIDELINES AND SCIENTIFIC EVIDENCES IN PHYSICAL AND REHABILITATION MEDICINE*" (hereinafter referred to as "The Santilli" for brevity sake) was the subject of a preliminary analysis

by the doctoral students of the Maugeri Institute, assisted by Prof. Nardone. In addition, ICS Maugeri shared a paper to use as an additional source for the construction of rules: "*Therapist Driven Rehabilitation Protocol for Patients with Chronic Heart and Lung Diseases: A Real-Life Study*". The analysis of these materials led to the drafting of a document containing a set of paragraphs of clinical interest for the project.

The preliminary analysis, the Santilli volume, and the paper were used to draw up a technical analysis, from which emerged 54 rules written in pseudocode for implementation. The entire set of the rules is available in the attached Appendix B. Each detected rule has been subject to a joint evaluation and validation between clinicians and implementers, to make the domain knowledge implicit in each recommendation explicit. The following pathologies were included in the analysis:

- stroke;
- Parkinson's disease;
- scoliosis;
- rheumatoid arthritis;
- neuropathies;
- multiple sclerosis;
- neck pain;
- pneumological rehabilitation (chronic respiratory failure);
- cardiological rehabilitation (cardiovascular rehabilitation);
- post-prosthesis rehabilitation (hip and knee prosthesis).

Pathologies excluded from the preliminary analysis were excluded from the technical analysis, due to their irrelevance to the project:

- infantile cerebral palsy;
- myelolesions;
- spasticity;
- low back pain;
- osteoarthritis;
- osteoporosis;
- arthropathies;
- tendinopathies;
- amputee patient;
- post intervention;
- breast cancer;
- dysfunctions of the temporomandibular joint;
- unconventional medicine.

For the sake of the discussion a rule extracted from the candidate rules basket available in the attached Appendix B has been be considered for the

analysis as a reference template. All the other rules must undergo the same analysis process.

The chosen rule is based on a paper written by ICS Maugeri Physicians "*Therapist Driven Rehabilitation Protocol for Patients with Chronic Heart and Lung Diseases: A Real-Life Study*" [134].

This has been chosen for a first implementation to help the physicians embrace the task of formalizing medical knowledge by putting them at their ease with algorithms that they use every day in medical practice.

An internal ICS Maugeri audit elaborated the Cardio-Respiratory Exercise Maugeri Algorithm (CREMA) based on:

- standardized baseline assessments;
- decision-making pathways;
- frequency/intensity/time/type (FITT) of prescription for each exercise.

In this case a portion of the CREMA algorithm is used an example for each step for the sake of discussion. CREMA is a therapist driven protocol: a consensus of medical knowledge and professional opinions based on an operative flow chart. The flow chart must be built according to objective measurable variables with the goal to reduce operator anarchy in prescription [148].

These kinds of algorithms are used as practical decision support tools when the reference guidelines are too complex to operatively be followed because sometimes these documents are not specifically designed for healthcare professionals prescribing exercise-based [149] [150]. In this case the therapist- driven algorithms are used in addition to guidelines to better guide professional in the operative task of prescribing for example a rehabilitation regimen.

In particular, the rules extracted from the CREMA algorithm belong to the same basket of rules extracted from the Santilli volume but the strength of the recommendation that they produce is lower than recommendations extracted from the Santilli volume. Figure 16 shows the entire CREMA algorithm.

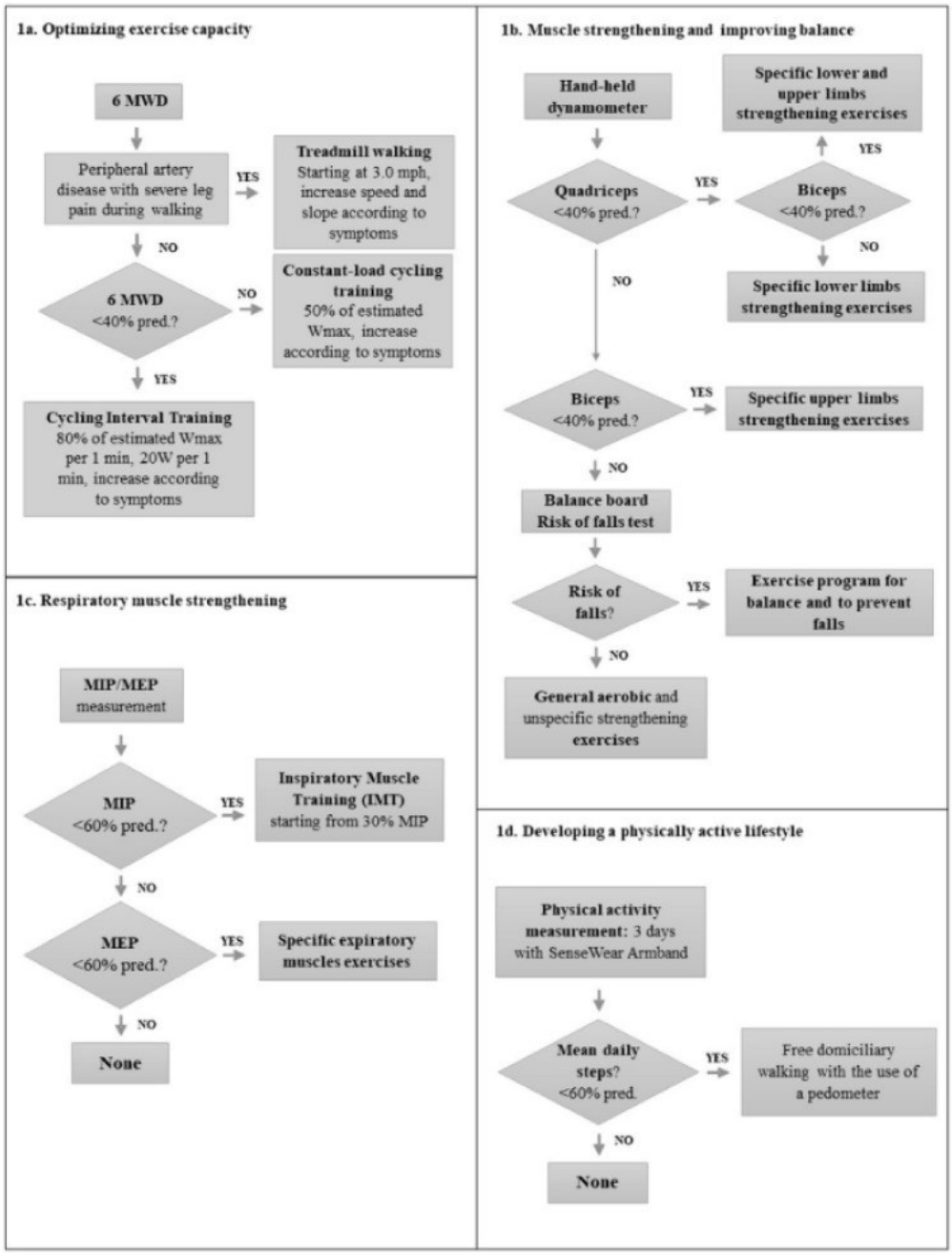


Figure 16: CREMA Algorithm

The algorithm was built by considering each impairment in performing an intervention (e.g. exercise intolerance) for a specific exercise-based goal (e.g. improve exercise tolerance).

In addition, the authors defined a set of measures to quantify each specific limitation (e.g. six-minute walking test). Then they defined training program pathways (in terms of modalities, volume, and intensity) for reaching a specific goal and overcome the limitation defined (e.g. continuous or interval cycling training).

The identified objectives were the following:

- optimizing exercise capacity;
- respiratory muscle strengthening;
- muscle strengthening and improving balance;
- developing a physically active lifestyle.

The proposed measurements were:

- **6 min walking distance (6MWD):** A test which measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface, chosen in accordance to the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines [151], using the predicted values by Chetta et al. [152] (593 +/- 57 meters, considered the minimum possible value). The minimum clinically important difference (MCID) according to the study for 6MWD is 30.5 m [153].
- **Maximal voluntary contraction (MVC)** of biceps and quadriceps muscles through hand-held dynamometry using the predicted values by Andrews et al. [154]. The MCID for quadriceps and biceps strength is 0.76 kg. [155] Muscle weakness was defined as MVC < 60% of the predicted values.
- **Maximal inspiratory (MIP) and expiratory pressures (MEP),** Are global measures of maximal strength of respiratory muscles and they are respectively the greater pressure which may be generated during maximal inspiration and expiration against an occluded airway [156]. Values are considered according to the ATS/ERS guidelines [157] the predicted values were those by Black and Hyatt [158].
- **Stability index and risk of fall index:** The patients were categorized into one of two groups, "Fallers" and "Non-fallers". The subjects who had reported the experience of having fallen unexpectedly at least once in the past year was assigned into the group "Fallers", if no fall history occurred in the past year the category was "Non-fallers" [159].
- **Domiciliary physical activity assessing daily steps** [160]. The MCID is an increase of 1100 steps/day [161] [162].

The proposed programs were:

- aerobic training (moderate–high intensity continuous or interval cycle training, treadmill walking, arm ergometer) [151] [163];
- calisthenics [151] [163] [164] [165] [166];
- lower and/or upper limb selective muscle strengthening [151] [163];
- balance training including core stability training, standing on unstable surfaces, balance boards, walking on tips and heels [167];
- inspiratory muscle training [168] [169] [170] [171];

- domiciliary walking with pedometer [172] [173].

5.4.1.1. Population category

Each rule derived from the literature provided by ICS Maugeri always has a population precondition. The precondition is the pathology of the subject under analysis or a subpopulation (for example, patients with mild or moderate stroke).

5.4.1.2. Suggestion category

Each recommendation was evaluated with respect to the type of suggestion:

- **TIP:** Low information content, concerns general advice to be given to a specific patient population;
- **INTERVENTION:** High informative content, it could concern more levels of intervention:
  - positive inclusion intervention: Inclusion in the home-care treatment;
  - negative inclusion intervention: exclusion from home treatment;
  - positive exercise intervention: Recommend a particular category of exercises (for example aerobic, endurance, task oriented ...);
  - negative exercise intervention: It is recommended to exclude a particular category of exercises (for example aerobic, endurance, task oriented).
- **INTERVENTION MONITORING:** Recommend one or more sets of parameters or scales useful for monitoring the patient from a distance (For example Fc, Vo2MAX ...).

5.4.1.3. Strength of the recommendation category

Each recommendation analyzed is accompanied by an indicator specifying the so-called "*Strength of the recommendation*". If indicated, the Grading of Recommendations Assessment, Development and Evaluation (short GRADE) level of the recommendation is traced [174] [175] [176].

The GRADE system is a common approach to grading quality (or certainty) of evidence and strength of recommendations and a reference tool to describe the reliability of scientific evidence and for formulating evidence-based clinical recommendations.

GRADE has four levels of evidence, also known as certainty in evidence or quality of evidence: very low, low, moderate, and high. Figure 17 explains the meaning of the different levels:

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

Figure 17: GRADE Levels

Usually randomized controlled trials starts at high quality while evidence that includes observational data starts at low quality. The analyzed recommendations have the following categories:

- informative text;
- generic Recommendation (no degree of strength is indicated);
- very low, low grade of evidence recommendation (GRADE method);
- moderate recommendation against or in favor (GRADE method);
- high recommendation against or in favor (GRADE method).

5.4.1.4. Recipient of the recommendation category

The Santilli indicates 2 main recipients of its recommendations:

- doctor;
- patient.

5.4.1.5. Timing of the recommendation category

Two time points have been identified in which to deliver recommendations based on the Guidelines:

- while filling out the PAIR (by the Doctor);
- during the delivery of the PAIR (by the Patient).

5.4.2. Rule formalization with Hl7 Clinical Quality Language syntax

Each rule extracted from the literature provided by ICS Maugeri and translated into pseudo code must be written into a computer interpretable form.

In this work, Clinical Quality Language (CQL) [140] is adopted as a formalization language. CQL is a HL7 standard for the formal representation of logical expressions, like the clinical algorithm CREMA described in the preceding paragraph, or the rules extracted from the Santilli Guideline. CQL is in fact high-level, domain-specific language focused on modeling in a computer interpretable format the clinical logic that a domain expert would use when taking a clinical decision.

CQL development effort is based on the separation of responsibilities within a decision support artifact into metadata, clinical information, and expression logic.

The hypothesis which motivates the use of an emergent but stable standard like CQL is that it enables the execution across data platforms with a one-time cost. That one-time cost is estimated as the development cost of writing a CQL script that can ben then deployed on any DSS that exposes a standard CQL execution engine [177].

Each rule or set of rules is transformed into a clinical decision support artifact written in CQL. Each rule contains a set of Metadata compliant to the standard FHIR Clinical Guidelines [178]. The metadata registered are the versioned according to Apache APR versioning scheme [179].

As depicted in Figure 18, CQL-based DSSs consist of four main components:

- **Data model** based on FHIR R4: represents the source on which reasoning is performed. Data is modeled as follows: (i) patient demographic information, (ii) observations (tests and measures performed on the patient), (iii) conditions (optional list of pathologies affecting the patient).
- Value set service and cache for retrieving coded clinical concepts from the National Library of Medicine (NLM) Value Set Authority Center **(VSAC)** [180]. VSAC provides downloadable access to codes and descriptions drawn from standard vocabularies such as LOINC, RxNorm and SNOMED CT, that are used to define clinical data elements used in CQL.
- **CQL libraries**: rules expressed in CQL syntax.
- **Execution engine**: a computer program which can interpret CQL, or a more machine-friendly version of CQL, and provide results according to CQL rules. At the current state only two open-source engines interpret CQL: A java-based engine [177] and a javascript-based CQL engine [181].

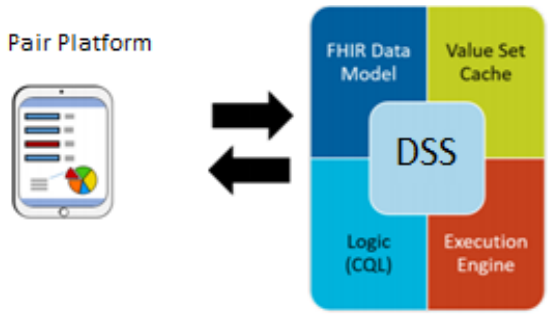


Figure 18: Integration using CQL

The specification enables the sharing of a decision support artifact by defining a high-level syntax suitable for authors, a logical-level representation suitable for language processing applications, and a mechanism for translation between them. Figure 19, available in the official specification [182] depicts the different levels:

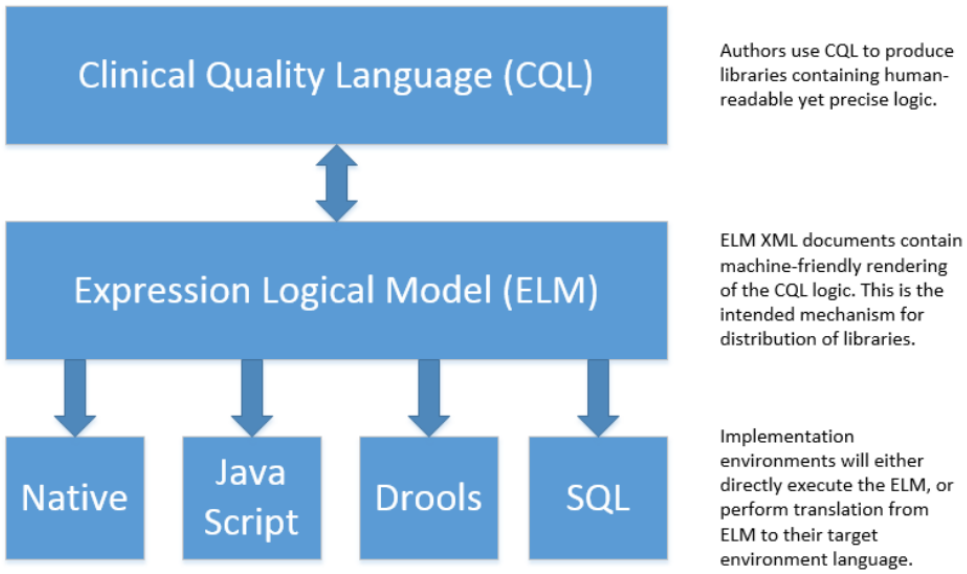


Figure 19: Machine Interpretable rule

The rules have been written using the CDS Authoring Tool Editor [183], a very recent editor that is part of the CDS Connect project [184], sponsored by the Agency for Healthcare Research and Quality (AHRQ) [185], and developed under contract with AHRQ by MITRE's alliance to modernize care [186].The rules are then translated into ELM format and added into the DSS, which includes the javascript engine mentioned before.

Taking for example the prescription of a “Cycling Interval Training” the inclusion and exclusion logic looks for the following:

- **Inclusion criteria:**

    - Goal Fitness is optimizing exercise capability.
    - 6 Minute walking test performed, the value assessed for the patient is less than 40% of the predicted value (593 minus 57 meters - minimum literature value) equals less than 214.4 meters.
- **Exclusion criteria:**
    - peripheral artery disease;
    - severe leg pain during walking.

If a patient meets the inclusion criteria and does not meet the exclusion criteria, the following interventions and suggested actions will be generated:

- **Intervention:** prescribe the patient Cycling Interval Training.
- **Suggested action:** the session should be the following: 80% of the estimated maximum workload (Wmax) for 1 minute, then 20W for 1 minute, and increase according to symptoms.
- **Outcome:** optimization of the exercise capability.

For the sake of discussion's fluidity, the complete resulting rule is available in the attached Appendix B. Figure 20 shows the inclusion criteria of the example rule inside the editor.

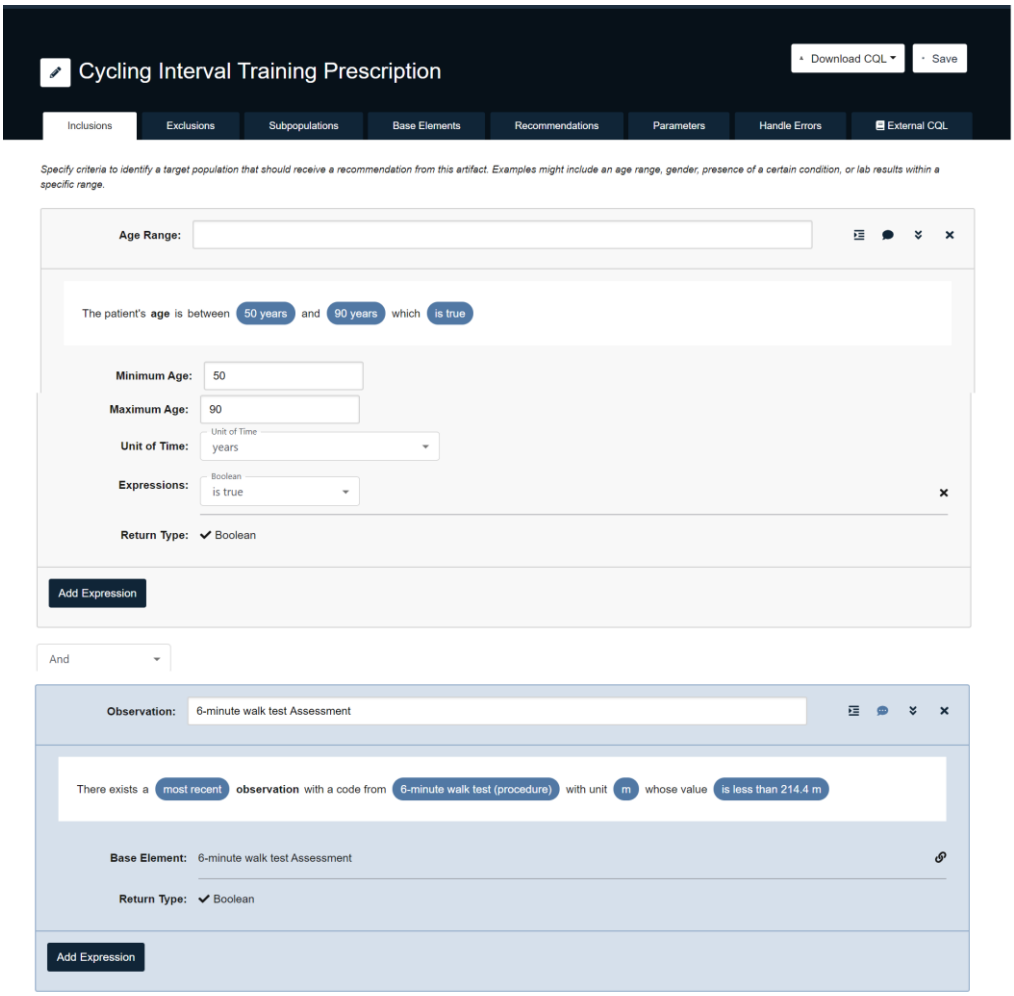


Figure 20: Example of inclusion criteria inside the editor

In particular, the definition of the concept **"6-minute walk test (procedure)"** has been defined in the Base Elements section of the editor, in this way, the same concept can be applied across different sections of the same rule. Figure 21 shows the concept definition:

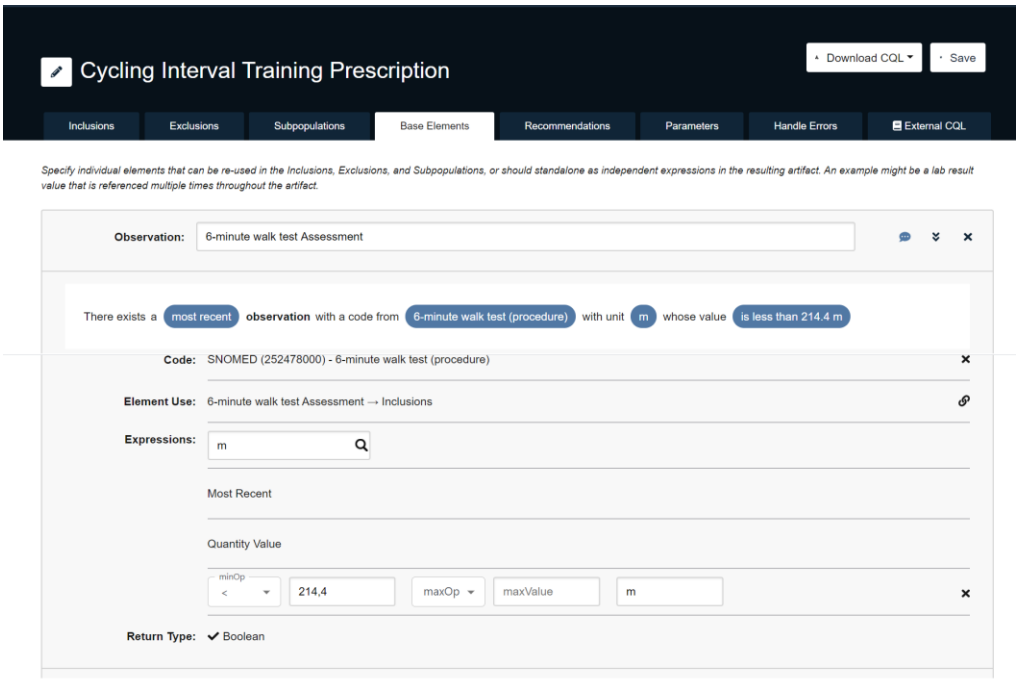


Figure 21: 6-minute walk test definition

5.4.3. Data Model

The data model underpinning the development of Clinical Quality Language rules is FHIR [176]. FHIR is a standard for health care data modeling and exchange, published by HL7. The major advantage in using FHIR as a data model is that it describes how clinical data should be formatted in a standard way. It also describes how to exchange this data over a network between two system that wish to interoperate. Each concept in FHIR is named "*Resource*".

A resource is the smallest unit of exchange that can be modeled in an interoperability problem, such as an observation, a patient, or a clinical condition.

The correspondence of the concept of a FHIR resource with other HL7 standards is the following:

- HL7 V2.x: Resource ~ Segment;
- HL7 V3: Resource ~ CMET.

The building blocks of all FHIR artifacts are a combination of a small set of most user FHIR resources.

A resource exposes the notion of identity, something that identifies a real-world object with its location, a Uniform Resource Identifier (URI), where it can be found. The location is expressed in terms of the unique id and the host where that resource is stored.

A resource is composed by elements, each element has a particular datatype (like String or CodeableConcept). A complete example of some of the FHIR resource that have been used in this work is available in the attached Appendix B. In general FHIR holds a list [187] of all the available Resources that can be extended by developers:

Name	Purpose	Examples
General	Resources that provide core clinical record keeping - focused on the content of the provider/patient encounter	AllergyIntolerance, Condition, Procedure
Medications	Support the medication & Immunization process	Medication, MedicationAdministration
Diagnostics	Provider support for diagnostic services - lab, pathology, imaging, etc	DiagnosticReport, Specimen, ImagingStudy
Device Interactions	Support for reading measurements made by devices	DeviceObservationReport
Attribution	Track individuals and organizations involved in the provision of healthcare	Patient, Practitioner
Entities	Track general support resources used when healthcare is provided	Device, Substance
Workflow Management	Support for the processes involved in healthcare	Encounter, Supply, Order
Support	Generally useful resources wherever resources are used	List, Media, Binary
Document Handling	Supporting Management	Composition, DocumentReference
Exchange	Used to support the process of exchanging data	MessageHeader, Query
Conformance	Make statements about how resources are used	Conformance, Profile, ValueSet

Figure 22: List of most common FHIR resources

Each resource is defined by three main components:

- **A narrative section:** a free text description of the resource which allows human interpretation of the resource content.
- **Core dataset:** a structured representation of the resource with its elements.
- **Extensions:** Custom additions to the standard resource. This is a bucket for all custom business requirement each organization may need.

A UML diagram of the used resources in this work is reported in Figure 23, Figure 24, and Figure 25.

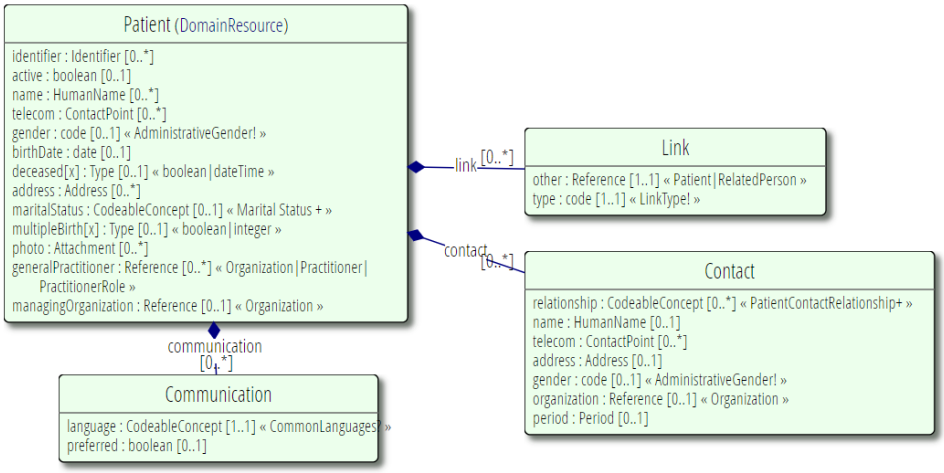


Figure 23: UML Patient resource

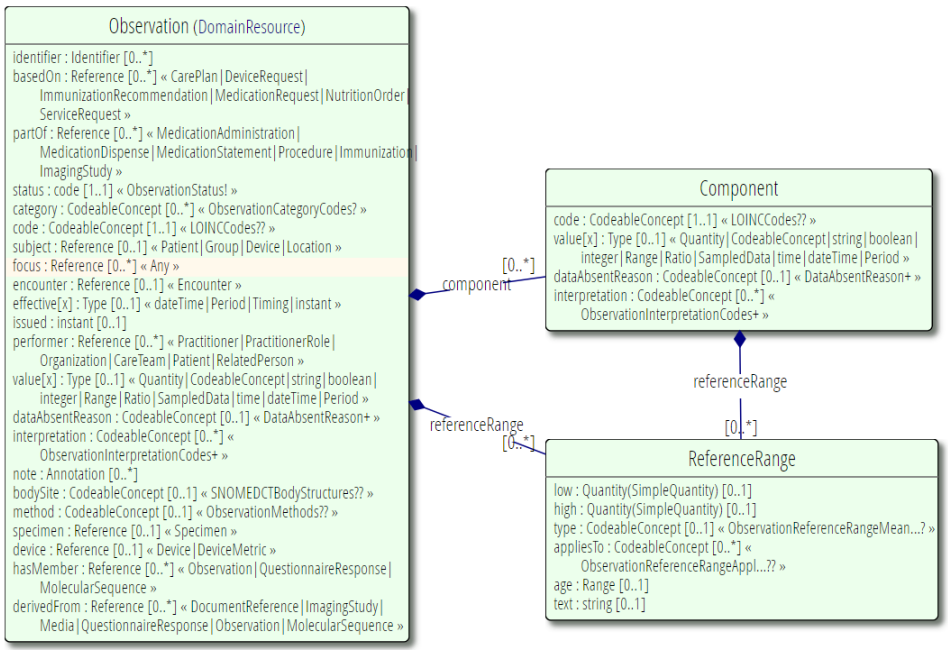


Figure 24: UML Observation resource

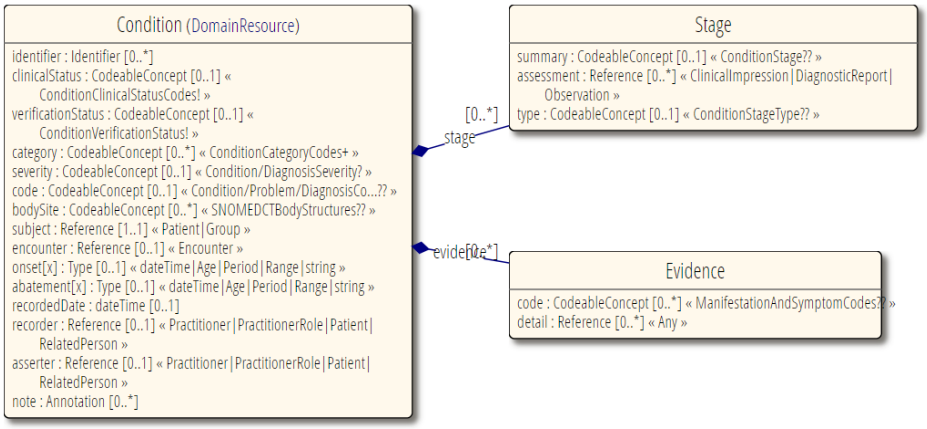


Figure 25: UML Condition resource

Any FHIR resource is then marshalled either as an XML document or as a JSON document to exchange it over the network.

5.4.4. Artifacts execution

To execute the rules, the clinical decision support artifacts written in CQL need to be translated in a computer interpretable format. As depicted in Figure 19 the machine-interpretable version of a CQL artifact is an Expression Logical Model ELM file. ELM is a JSON or XML CQL representation which provides the information needed to automatically retrieve data from an electronic health record. The ELM files are then executed on an open-source engine able to interpret those formats. The choice to exploit an existing open-source engine [188] and not developing the rules from scratch in Java, C#, or any other commercially supported language would not achieve the goal of sharing the logic in a platform independent way, nor would it serve as a vehicle for communicating the intent of the measures in the way that CQL/ELM does. CQL supports the required set of operations for expressing clinical measure logic, and traditional query languages, in addition to important aspects like terminology and interval-based timing. For the nature of the rules currently implemented on the DSS there is not any rule superimposition; the rules that are behind each service are independent and checked one at a time. The resulting recommendation is collected from the answers of the verified rules. It is worth mentioning however that the concept of a “rule” or “artifact” is the umbrella term for a set of subrules. To trigger a rule THE FHIR resource must:

- Meet inclusion criteria
- Do not meet exclusion criteria
- Optionally belong to a defined subpolulation

These steps are checked sequentially. To deduce the outcome the engine goes through all the Observation if a forward-chaining strategy.

5.4.5. Artifacts dissemination

CDS Connect Project [184] provides a repository of Clinical Decision Support artifacts written using the standard language CQL and a prototype infrastructure for sharing CDS across different health care settings and technologies. This repository is designed to promote the creation and use of CDS in everyday clinical settings, connecting high-quality CDS to the healthcare community. The artifacts developed in the PhD work are currently saved in a private repository on the CDS Authoring Tool, but they can be easily shared and benefited from the healthcare community.

On the other hand if the ICS Maugeri physicians find a Clinical Decision Support Artifact on the repository that they wish to deploy in their daily practice, since it is written in a standard format can be executed on the same engine with no development effort involved.

5.5. DSS Deployment and Delivery

The last phase of the implementation consisted in providing a distribution strategy for the DSS services. Two strategies have been considered:

- **Bare metal approach:** installing the compiled software on an application server "physically installed on a machine" that distributes the application. By choosing this strategy the developer must consider many implications: operating system of the machine, presence of a data persistence compatible with the machine, infrastructure (virtual, cloud), middleware (tomcat, apache httpd, jboss, ibm websphere …)
- **Docker containers** [189]: a virtualization-of-resources approach which isolates a single application and the external required libraries, both from the underlying operating system and from other containers.

An in-depth discussion of software deployment is beyond the scope of this dissertation but it is worth mentioning that Docker has been chosen as a deployment strategy to enable the distribution of DSS services on any OS-compatible host (Linux or Windows) that has the Docker runtime [190] installed.

Chapter 6:

Implementation

This chapter discusses the implementation strategies that guided the software development of my PhD work. UML activity diagram are used to support the discussion. These diagrams analyze the interactions of software agents and specify how operations are carried out; they also define the timeline of the interaction. They visually show the order of the interaction by using the vertical axis of the diagram to separate different agents and horizontal oriented arrows to describe the communication flow [133].

6.1. Structured Patient Data Flow

The DSS server receives a REST call from the PAIR Platform, which plays the role of the Client with respect to the client-server communication. The DSS:

- Evaluates the data that is transmitted in the call in the form of a FHIR Resources set (Patient, Encounters, Observations).
- Queries the rule base built using the clinical knowledge contained in the guidelines and written in CQL.
- Builds the response for the client, adding the appropriate recommendation retrieved from the database.

The first version of the DSS supports four services:

- **DiscoveryService:** allows the client to receive information about the services currently implemented on the DSS, their version, description, and preconditions for invocation.
- **Patient-enrollment:** returns information about the patient's eligibility or non-eligibility to participate in the home-care rehabilitation project.

- **Exercise-prescribe**: evaluates the appropriateness of the exercises prescribed to the patient when completing the PAIR.
- **Exercise-monitor-prescribe:** Evaluates whether a condition detected in the patient requires a particular vital signal to be monitored during the execution of the exercises.

Figure 26: Sequence diagram of the DSS ServerFigure 26 shows a Sequence Diagram of the DSS Server services:

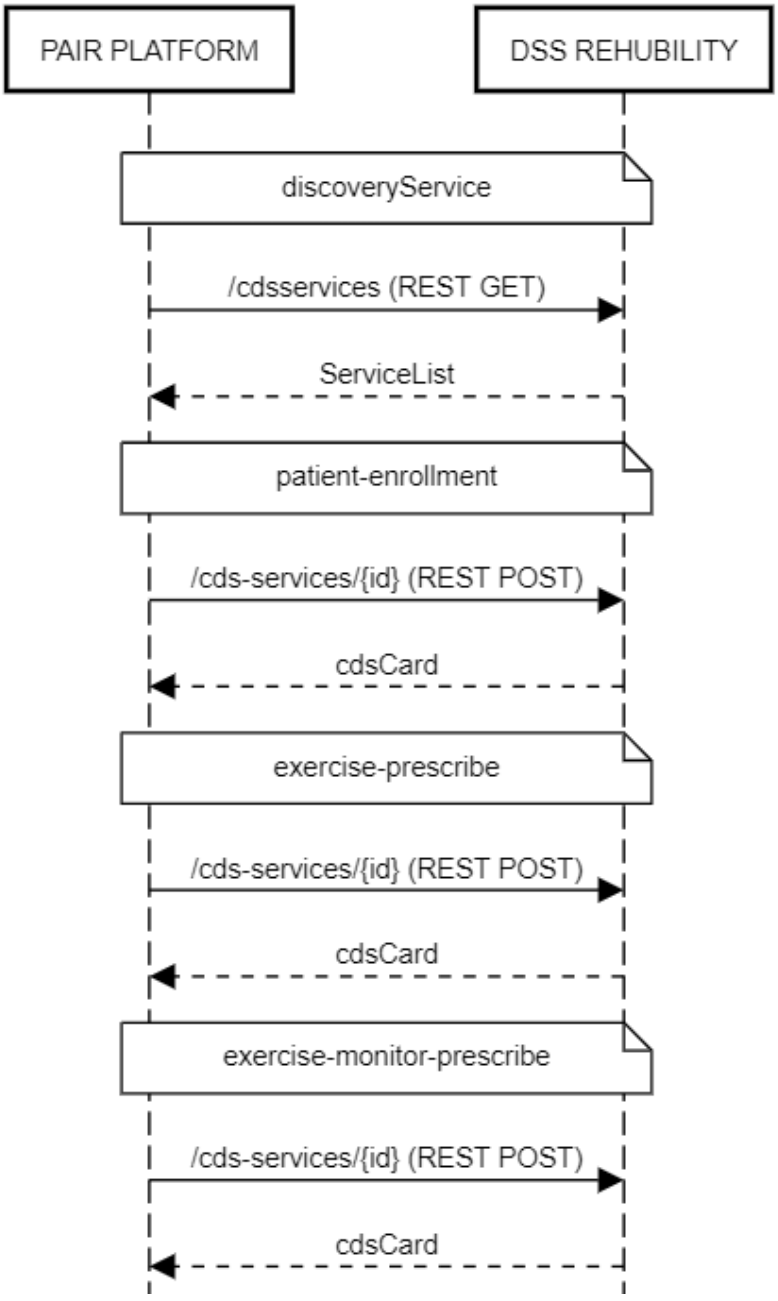


Figure 26: Sequence diagram of the DSS Server Services

6.1.1. Data persistence

As mentioned in the previous chapter, CQL rules get persisted on the DSS. In addition, the FHIR resources used for the analysis need to be persisted. FHIR standard describes how to model and exchange resources but does not impose constraints on how to store them. For this reason, a transformation from the DSS schema to FHIR and backward is needed.

Such transformation is trivial if the data model is isomorphic to FHIR. If, on the contrary, the model to translate is very different from the FHIR structure, the transformation layer could become unnecessarily complex and computationally intensive, as stated by the "*Object-Relational Impedance Mismatch"* problem [191]. For this reason, the data persistence for the resources, maps every FHIR attribute needed for the computation.

The Object which is responsible to collect the rules is called *cqlArtifact.* The attributes that define *cqlArtifact* are the following:

- ***metadata*** (Object): Each decision support artifact must be accompanied by additional information such as:
  - *id:* internal identifier;
  - *uniqueIdentifier*: unique identifier within the list of artifacts;
  - *version*: incremental counter that tracks changes to the artifact;
  - *description*: brief description in natural language of the artifact;
  - *authorList* (Set): indicates the committee who oversaw the development of the rule. The authors include the developer of the rule, the physicians who provided the clinical knowledge to translate the free text into the computer interpretable rule.
- ***supportingEvidence*** (List<Reference>): references (bibliographical and otherwise) that motivate the writing of the artifact;
- ***clinicalQualityInformation*** (String): structure and content of the clinical data involved in the artifact;
- ***ExpressionLogic*** (Object): representation of the artifact in machine language, this field is retrieved during computation.

The persistence is composed by other domain objects:

- ***ClinicalConditionDictionaryModeling*** (Object): a coding of pathologies based on several levels must be envisaged:

  - *wxternalDictionary*: for example, ICD9-CM or ICD10-CM, subject of a joint evaluation with clinicians and Maugeri information systems.
  - *localDictionary*: each concept supports the mapping in a local coding agreed with the partners (for example the "*Nomenclatore Maugeri*", a nomenclator for the procedures that are delivered inside the ICS Maugeri's facilities).
- ***exerciseList*** (List<Exercise>): The list of all exercises that can be prescribed in a home-care intervention and their description. Exercise modeling follows the definition by schema.org [192] for *exercisePlan* Object [193];
- ***actorIdentification*** (String): it must be possible to distinguish on the basis of the input parameters whether the request comes from a doctor role (or from the management system that the doctor uses) or from the patient (the devices in charge of the patient) or by other actors who decide to take advantage of the recommendations of the DSS;
- ***project*** (Object): indicates a thematic project for which a client wishes to receive support. The motivation behind this entity arises from the fact that a specific company (in this case a specific ICS Maugeri facility) may decide in future to activate different thematic projects on the same DSS (for example Drug-Drug Interaction analysis or home rehabilitation support). Each project is defined by the following attributes:
  - *id* (Long): internal identifier of the project;
  - *code* (String): unique identifier representing the decision support project (the code attribute must be shared between DSS client client and DSS server);
  - *displayName*: represents the name of the project;
  - *active* (Boolean): a flag which indicates if a specific project is currently in use;
  - *dateCreated* (Date): date of the first creation;
  - *lastUpdated* (Date): date of the last modification;
  - *startValidityDate* (Date): date of the start of the project;
  - *endValidityDate* (Date): date of the end of the project;
  - *cqlArtifactList* (List<cqlArtifact>): the list of clinical decision support artifacts that have been developed for each thematic project.
- ***recommendation*****:** this object models the output of the rule that is delivered to the DSS client:
  - *originalText* (String): contains the unstructured text of the complete recommendation;
  - *displayCard* (String): may contain Santilli's original unstructured text or summary, or a structured version of

the recommendation, depending on clinicians' preference (the information content must remain the same);

- *referenceList (*List <Reference>): contains the list of bibliographic references that have produced a specific recommendation;
- *rule:* (CQL Script) representation in machine readable format of the rule that must trigger the delivery of a recommendation;
- *smartLink* (String): optional interactive link to a resource adhering to the HL7 "SMART on FHIR" standard;
- *active* (boolean): by default, true. Based on the occurrence of certain conditions, the user can decide to deactivate a certain rule, in which case the *endValidityDate* and the *endValidityReasons* for deactivation are traced. From the moment of deactivation, the criteria for delivering that rule will not be tested, the associated recommendation will therefore no longer be delivered;
- *recommendationLevel* (Enumeration): an enumeration that indicates the alert level that needs to be displayed. The level represents the strength of the recommendation. DSS Clients may choose to suppress conditionally the delivery by filtering on this level. For example one hospital may choose to deliver only the recommendations associated with a GRADE score, or may choose to suppress all the informative recommendation to discourage alert fatigue, one of the main downside of using CDSSs in clinical practice [194] [195]. It can assume one of the following values:
  - *informative;*
  - *generic;*
  - *other;*
  - *veryLowInFavor;*
  - *lowInFavor;*
  - *moderateInFavor;*
  - *highInFavor;*
  - *veryLowAgainst;*
  - *lowAgainst;*
  - *moderateAgainst;*
  - *highAgainst;*
  - *A;*
  - *B;*
  - *C;*
  - *I.*
- *ruleType* (Enumeration): an enumeration that indicates the type of the recommendation. It can assume one of the following values:

        - *homeActivityInclusion;*
        - *homeActivityExclusion;*
        - *physicalExerciseDosing;*
        - *physicalExerciseInclusion;*
        - *physicalExerciseExclusion;*
        - *drugAllergy;*
        - *drugDrugInteraction*.
    - *dateCreated* (Date): date of the first creation;
    - *lastUpdated* (Date): date of the last modification;
    - *startValidityDate* (Date): start date of the recommendation's validity;
    - *endValidityDate* (Date): end date of the recommendation's validity;
    - *endValidityReasons* (String): in case of deactivation traces the reason why the rule is no longer used.
- ***reference:*** represents a bibliographic reference used within the Santilli or the additional materials provided by ICS Maugeri. The representative attributes are the following:
    - *sourceType* (Enumeration): type of Source, can assume one of the publication types included in MeSH Pubtypes [196]:
        - guideline;
        - observational study;
        - review;
        - meta-Analysis;
        - […].
    - *sourceTitle* (String): title of the reference;
    - *provenance* (String): indicates, if present, the research group that prepared the bibliographic reference;
    - *publishYear* (Integer): year of publication;
    - *language* (String): indicates the language of the document;
    - *grade* (boolean): indicates whether the recommendations contained in the bibliographic reference are evaluated with the GRADE method;
    - *multiprofessional* (boolean): indicates if the bibliographic reference was written by a multi-professional team;
    - *multidisciplinary* (boolean): indicates whether the bibliographic reference was written by a multidisciplinary team;
    - *dateCreated* (Date): date of the first creation;
    - *lastUpdated* (Date): date of the last modification.

The other objects that get persisted in the DSS are the patient, observation, conditions FHIR resources that CQL engine needs for the

evaluation. In this case the definition of the attributes is a subset derived from the standard documentation. As mentioned before, isomorphism with FHIR attributes is important to avoid Object-Relational Impedance Mismatch. Table 2 shows the implemented attributes for the Patient FHIR resource, while Table 3 and Table 4 show the implemented attributes for Condition and Observation resources.

Table 2: Patient FHIR Resource supported attributes [188]

Name	Cardinality	Type	Description and Constraints
Patient		DomainResource	Information about an individual or animal receiving health care services Elements defined in Ancestors: id, meta, implicitRules, l anguage, text, contained, extension, modifierExtension
identifier	0..*	Identifier	An identifier for this patient
active	0..1	boolean	Whether this patient's record is in active use
name	0..*	HumanName	A name associated with the patient
telecom	0..*	ContactPoint	A contact detail for the individual
gender	0..1	code	male | female | other | unknown AdministrativeGender (Required)
birthDate	0..1	date	The date of birth for the individual
name	0..1	HumanName	A name associated with the contact person

Table 3: Condition FHIR Resource supported attributes [197]

Name	Card.	Type	Description & Constraints

Condition		DomainResource	Detailed information about conditions, problems or diagnoses + Guideline: Condition.clinicalStatus SHALL be present if verificationStatus is not entered-in-error and category is problem-list-item + Rule: If condition is abated, then clinicalStatus must be either inactive, resolved, or remission + Rule: Condition.clinicalStatus SHALL NOT be present if verification Status is entered-in-error Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	0..*	Identifier	External Ids for this condition
clinicalStatus	0..1	CodeableConcept	active | recurrence | relapse | inactive | remission | resolved Condition Clinical Status Codes (Required)
verificationStatus	0..1	CodeableConcept	unconfirmed | provisional | differential | confirmed | refuted | entered-in-error ConditionVerificationStatus (Required)
category	0..*	CodeableConcept	problem-list-item | encounter-diagnosis Condition Category Codes (Extensible)
severity	0..1	CodeableConcept	Subjective severity of condition Condition/Diagnosis Severity (Preferred)
code	0..1	CodeableConcept	Identification of the condition, problem or diagnosis Condition/Problem/Diagnosis Codes (Example)
bodySite	0..*	CodeableConcept	Anatomical location, if relevant SNOMED CT Body Structures (Example)

subject	1..1	Reference(Patient | Group)	Who has the condition?
onset[x]	0..1		Estimated or actual date, date-time, or age
recordedDate	0..1	dateTime	Date record was first recorded
summary	0..1	CodeableConcept	Simple summary (disease specific) Condition Stage (Example)
assessment	0..*	Reference(ClinicalImpression | DiagnosticReport | Observation)	Formal record of assessment
type	0..1	CodeableConcept	Kind of staging Condition Stage Type (Example)
code	0..*	CodeableConcept	Manifestation/symptom Manifestation and Symptom Codes (Example)
note	0..*	Annotation	Additional information about the Condition

Table 4: Observation FHIR Resource implemented attributes [190]

Name	Card.	Type	Description & Constraints
Observation		DomainResource	Measurements and simple assertions + Rule: dataAbsentReason SHALL only be present if Observation.value[x] is not present + Rule: If Observation.code is the same as an Observation.component.code then the value element associated with the code

			SHALL NOT be present Elements defined in Ancestors: id, meta, implicitRules, language, text, contained, extension, modifierExtension
identifier	0..*	Identifier	Business Identifier for observation
status	1..1	code	registered | preliminary | final | amended + ObservationStatus (Required)
category	0..*	CodeableConcept	Classification of type of observation Observation Category Codes (Preferred)
code	1..1	CodeableConcept	Type of observation (code/type) LOINC Codes (Example)
encounter	0..1	Reference(Encounter)	Healthcare event during which this observation is made
effective[x]	0..1		Clinically relevant time/time-period for observation
issued	0..1	instant	Date/Time this version was made available
value[x]	0..1		Actual result
interpretation	0..*	CodeableConcept	High, low, normal, etc. Observation Interpretation Codes (Extensible)
note	0..*	Annotation	Comments about the observation
bodySite	0..1	CodeableConcept	Observed body part SNOMED CT Body Structures (Example)

method	0..1	CodeableConcept	How it was done Observation Methods (Example)
specimen	0..1	Reference(Specimen)	Specimen used for this observation
device	0..1	Reference(Device | DeviceMetric)	(Measurement) Device
derivedFrom	0..*	Reference(DocumentReference | ImagingStudy | Media | QuestionnaireResponse | Observation | MolecularSequence)	Related measurements the observation is made from
code	1..1	CodeableConcept	Type of component observation (code/type) LOINC Codes (Example)
value[x]	0..1		Actual component result
interpretation	0..*	CodeableConcept	High, low, normal, etc. Observation Interpretation Codes (Extensible)

Some of the attributes described in the forementioned table contain a rule in the description. These rules, also known in HL7 formalism as "invariants" detail constraints that must be applied to the attributes. For example, in the Observation resource the following rule is presented:

> *Rule: dataAbsentReason SHALL only be present if Observation.value[x] is not present.*

This constraint prescribes that, if an observation is present without a registered value, the transmitter can optionally populate the field *dataAbsentReason* describing why the value has not been registered. One common cause for missing data could be that the patient did not express his consent to share that data.
Another kind of rule can be expressed for coded elements. For example, the rule:

If Observation.code is the same as an Observation.component.code then the value element associated with the code SHALL NOT be present.

This rule asserts that a value must not be duplicated for the same resource in different structures which hold the same meaning.

In the invariants the word “SHALL”, or “MUST” indicate the severity of the rule. If the severity level is error (MUST keyword) it means that any resource which does not respect the rule will be marked by a FHIR validator as invalid and rejected by an application.

6.1.2. Discovery Service

The first service exposed by the DSS, in agreement with the CDS Hooks specifications, is the *Discovery service*. According to the specifications, the DSS must expose an address to which decision support services are available at any given time.

By invoking the endpoint

```
{baseUrl} / cdsservices
```

the client receives the list of services available on the DSS.

For each available service, the following information is returned:

- *description* (String): short description of the service;
- *timing* (String): description of when the service is supposed to be invoked;
- *prefetchData* (JSON): data that are necessary to invoke a certain service (for example patient demographics, drug treatment, encounter data, conditions ...).

6.1.3. Patient enrollment Service

Provides support in identifying eligibility/non-eligibility criteria to participate in the home rehabilitation program. According to the project experimental design the category of patients which should be included When the client invokes this service, it triggers the execution of all the rules which include/exclude a patient from the home-care regimen. See the following example:

Per pazienti affetti da Ictus [...] alcuni fattori come l’età avanzata, i deficit cognitivi, un basso livello funzionale e l’incontinenza urinaria sono predittivi della necessità di eseguire una riabilitazione in regime di ricovero

In this case there are four factors which indicate that the patient affected by a stroke should not follow a home-care regimen: advanced age, cognitive deficits, low functional level, and urinary incontinence.

The timing of the client trigger should occur during the first prescription of the PAIR.

The prefetch data that should be transmitted in the REST call are the following:

- patient demographics:
  - birth date;
  - list of clinical conditions;
  - severity of the clinical condition;
  - fitness goal.

6.1.4. Exercise prescribe Service

Provides support in identifying eligibility/non-eligibility criteria to perform a category of exercises. When the client invokes this service, it triggers the execution of all the rules which include/exclude a patient from a particular category of exercises. See the following example:

> *Se il Paziente è affetto da Sclerosi Multipla [..] dall'analisi di revisioni sistematiche della letteratura e meta-analisi sull'efficacia e la sicurezza dell'esercizio terapeutico nel trattamento della fatica in pazienti con SM, si evidenzia un effetto significativo in favore della fisioterapia ed esercizio terapeutico (con qualità di evidenza degli studi alta valutata col metodo GRADE sia aerobico che resistivo, in particolare per l'allenamento di endurance, con miglioramento della capacità aerobica, della forza muscolare e dei parametri cinematici della deambulazione*

In this case if the patient suffers from multiple sclerosis, he should follow a regimen of both aerobic and resistive, in particular endurance training. The timing of the client trigger should occur during the first prescription of the PAIR.

The prefetch data that should be transmitted in the REST call are the following:

- patient demographics:
  - birth date;
  - list of clinical conditions;
  - severity of the clinical condition;
  - fitness goal;
  - FITT prescription.

6.1.5. "Exercise monitor prescribe" Service

Provides support suggesting the physician a signal that the patient should report during the home-care rehabilitation sessions. When the client invokes this service, it triggers the execution of all the rules which goal is to suggest a particular signal that must be monitored. See the following example:

> *Se il paziente ha come obiettivo di fitness la riabilitazione pneumologica [...] l'intensità di esercizio deve essere adattata in base ai livelli di fatica muscolare percepita facendo lavorare il paziente tra i livelli 5-6 (fatica moderata) e 7-8 (fatica severa) della scala di Borg RPE.*

In this case the patient must report as a measure the Borg RPE scale periodically (Perceived Exertion scale) [198]. The measure should not be less than 5 and more than 8.

The timing of the client trigger should occur during the first prescription of the PAIR.

The prefetch data that should be transmitted in the REST call are the following:

- Patient demographics:
  - birth date;
  - list of clinical conditions;
  - severity of the clinical condition;
  - fitness goal;
  - FITT prescription.

6.2. Structured data flow example

Taking the example of the "Cyclic Interval Training" rule from the previous chapter, PAIR Platform invokes the DSS server requesting the *exercise-prescribe* service.

The DSS triggers all the rules contained in the knowledge base of type "*physicalExerciseInclusion*", "*physicalExerciseExclusion*", including the one depicted in Figure 29.

The rule engine transvers the data provided by the client, in search for an inclusion/exclusion critera possible match.

For example the rule section presented in Figure 27 searches inside the Observation Resource for a value less than 214.4 meters. The implementation of the rule is based on Clinical Quality Language.

```
library "Cycling-Interval-Training-Prescription" version '1.0.0'
using FHIR version '1.0.2'
include "FHIRHelpers" version '1.0.2' called FHIRHelpers
codesystem "SNOMED": 'http://snomed.info/sct'
codesystem "Other": 'https://uts.nlm.nih.gov/uts/umls'
code "6-minute walk test (procedure) code": '252478000' from "SNOMED" display '6-minute walk test (procedure)'
code "C2024890 code": 'C2024890' from "Other" display 'Other C2024890 Display'
code "Peripheral vascular disease (disorder) code": '400047006' from "SNOMED" display 'Peripheral vascular disease (d
code "Difficulty walking (finding) code": '719232003' from "SNOMED" display 'Difficulty walking (finding)'
context Patient

// o  6 Minute walking test performed, The value assessed for the patient is less than 40% of the predicted
// value ( 593-57 m, literature value) so less than 214.4
define "6-minute walk test Assessment":
  QuantityValue(MostRecent(WithUnit([Observation: "6-minute walk test (procedure) code"],  'm'))) < 214.4 'm'
```

Figure 27: 6MWT rule

The information flow of the entire communication is portrayed in Figure 28. The client transmits Patient, Condition, Observation FHIR resources of the patient that needs a home-care rehabilitation prescription. The DSS executes the rules contained in the *physicalExerciseInclusion* and *physicalExerciseExclusion* basket, leveraging FHIR Resources. The DSS returns CDS Cards containing recommendations that are shown by the PAIR Platform. Figure 29 describes a complete example of the rule used as example for the discussion in written in CQL.

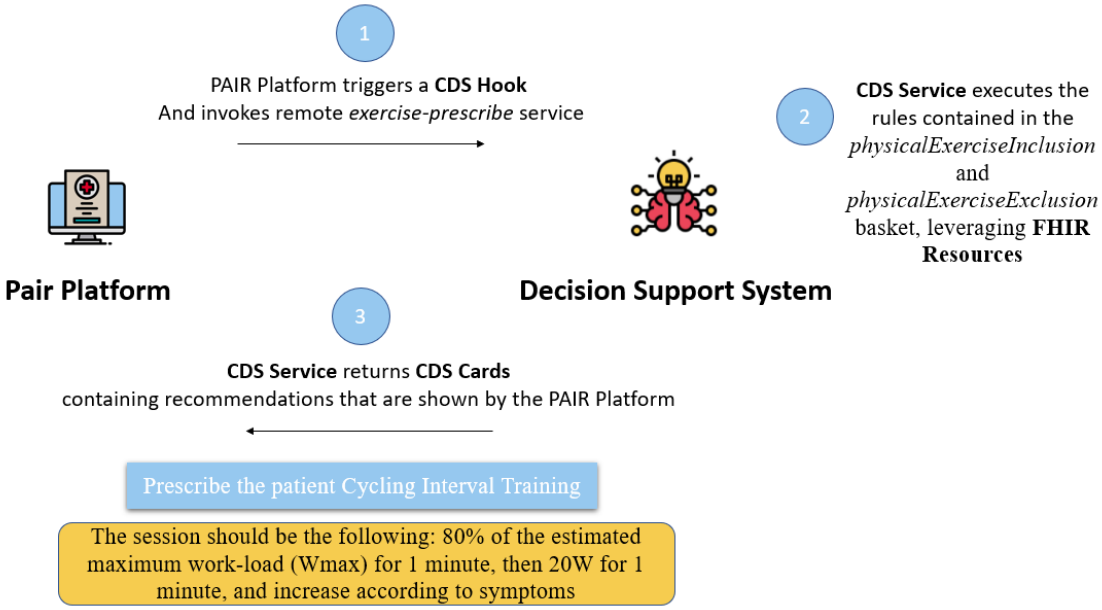
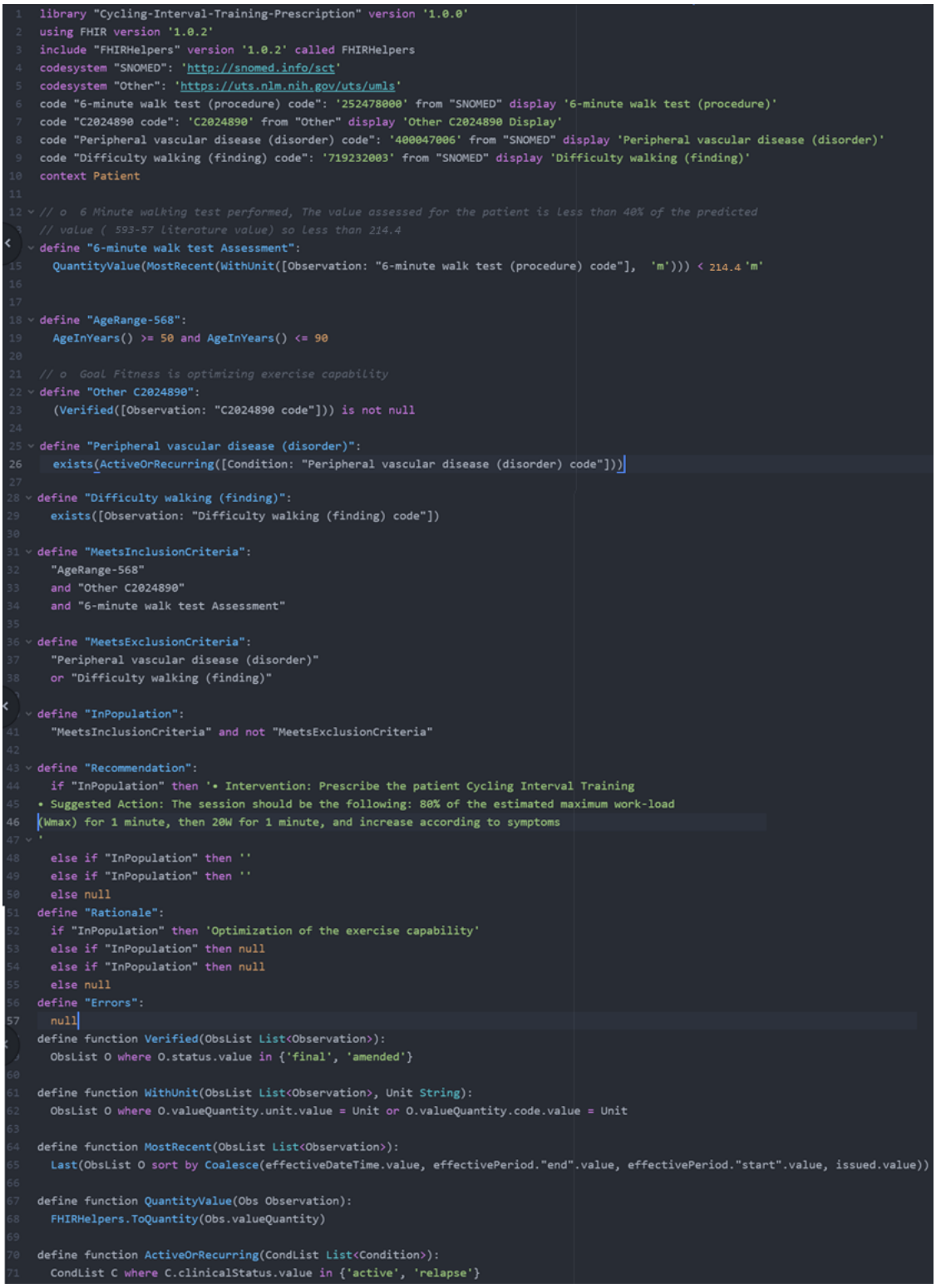


Figure 28: Structured Data flow example



```
library "Cycling-Interval-Training-Prescription" version '1.0.0'
using FHIR version '1.0.2'
include "FHIRHelpers" version '1.0.2' called FHIRHelpers
codesystem "SNOMED": 'http://snomed.info/sct'
codesystem "Other": 'https://uts.nlm.nih.gov/uts/umls'
code "6-minute walk test (procedure) code": '252478000' from "SNOMED" display '6-minute walk test (procedure)'
code "C2024890 code": 'C2024890' from "Other" display 'Other C2024890 Display'
code "Peripheral vascular disease (disorder) code": '400047006' from "SNOMED" display 'Peripheral vascular disease (disorder)'
code "Difficulty walking (finding) code": '719232003' from "SNOMED" display 'Difficulty walking (finding)'
context Patient

// o  6 Minute walking test performed, The value assessed for the patient is less than 40% of the predicted
// value ( 593-57 literature value) so Less than 214.4
define "6-minute walk test Assessment":
  QuantityValue(MostRecent(WithUnit([Observation: "6-minute walk test (procedure) code"],  'm'))) < 214.4 'm'


define "AgeRange-568":
  AgeInYears() >= 50 and AgeInYears() <= 90

// o  Goal Fitness is optimizing exercise capability
define "Other C2024890":
  (Verified([Observation: "C2024890 code"])) is not null

define "Peripheral vascular disease (disorder)":
  exists(ActiveOrRecurring([Condition: "Peripheral vascular disease (disorder) code"]))

define "Difficulty walking (finding)":
  exists([Observation: "Difficulty walking (finding) code"])

define "MeetsInclusionCriteria":
  "AgeRange-568"
  and "Other C2024890"
  and "6-minute walk test Assessment"

define "MeetsExclusionCriteria":
  "Peripheral vascular disease (disorder)"
  or "Difficulty walking (finding)"

define "InPopulation":
  "MeetsInclusionCriteria" and not "MeetsExclusionCriteria"

define "Recommendation":
  if "InPopulation" then '• Intervention: Prescribe the patient Cycling Interval Training
• Suggested Action: The session should be the following: 80% of the estimated maximum work-load
(Wmax) for 1 minute, then 20W for 1 minute, and increase according to symptoms
'
  else if "InPopulation" then ''
  else if "InPopulation" then ''
  else null
define "Rationale":
  if "InPopulation" then 'Optimization of the exercise capability'
  else if "InPopulation" then null
  else if "InPopulation" then null
  else null
define "Errors":
  null
define function Verified(ObsList List<Observation>):
  ObsList O where O.status.value in {'final', 'amended'}

define function WithUnit(ObsList List<Observation>, Unit String):
  ObsList O where O.valueQuantity.unit.value = Unit or O.valueQuantity.code.value = Unit

define function MostRecent(ObsList List<Observation>):
  Last(ObsList O sort by Coalesce(effectiveDateTime.value, effectivePeriod."end".value, effectivePeriod."start".value, issued.value))

define function QuantityValue(Obs Observation):
  FHIRHelpers.ToQuantity(Obs.valueQuantity)

define function ActiveOrRecurring(CondList List<Condition>):
  CondList C where C.clinicalStatus.value in {'active', 'relapse'}
```

Figure 29: Example of an implemented rule

As mentioned in the functional requirement chapter n.4, the implemented architecture must be able to model medical terms mapped both on local and international dictionaries. The “Nomenclatore Maugeri”

is only one of the many local dictionaries ought to be supported on a interoperable DSS. In the project context, this "Nomenclatore" is still subject to the sign of a non-disclosure agreement so local terms are not available at this time. All the local terms however can already be inserted in each rule by adding a "or" condition and a reference to a generical local dictionary, by providing a link to the dictionary definition.

Taking one practical example from the rule depicted in Figure 29, a local definition of the concept *"Peripheral vascular disease (disorder)"* could be available with a code *"PERARTDIS0001"*. In this case the rule, written in CQL, would be modified in the following points:

- In the code section, adding the *PERARTDIS0001* local code, as shown in Figure 30;

```
codesystem "CONDCLINSTATUS": 'http://terminology.hl7.org/CodeSystem/condition-clinical'
code "6-minute walk test (procedure) code": '252478000' from "SNOMED" display '6-minute walk test (procedure)'
code "C2024890 code": 'C2024890' from "Other" display 'Other C2024890 Display'
code "Peripheral vascular disease (disorder) code": '400047006' from "SNOMED" display 'Peripheral vascular disease (d
code "Difficulty walking (finding) code": '719232003' from "SNOMED" display 'Difficulty walking (finding)'
code "PERARTDIS0001 code": 'PERARTDIS0001' from "Other_1" display 'Other PERARTDIS0001 Display'
code "Condition Relapse code": 'relapse' from "CONDCLINSTATUS" display 'Relapse'
code "Condition Recurrence code": 'recurrence' from "CONDCLINSTATUS" display 'Recurrence'
code "Condition Active code": 'active' from "CONDCLINSTATUS" display 'Active'
concept "Condition Relapse": { "Condition Relapse code" } display 'Relapse'
```

Figure 30: Local dictionary in the code section

- In the recurrence definition of the condition, as shown in Figure 31;

```
define "Peripheral vascular disease (disorder)":
  exists(ActiveOrRecurring([Condition: "Peripheral vascular disease (disorder) code"]))

define "Difficulty walking (finding)":
  exists([Observation: "Difficulty walking (finding) code"])

// Peripheral vascular disease (disorder) in Nomenclatore Maugeri Dictionary
define "Other PERARTDIS0001":
  (ActiveOrRecurring([Condition: "PERARTDIS0001 code"])) is not null

define "MeetsInclusionCriteria":
```

Figure 31:Clinical condition recurrence definition

- In the exclusion criteria definition, where the two synonyms are defined in an "or" condition, as shown in Figure 32.

```
44  define "MeetsInclusionCriteria":
45    "AgeRange-568"
46    and "Other C2024890"
47    and "6-minute walk test Assessment"
48
49  define "MeetsExclusionCriteria":
50    "Peripheral vascular disease (disorder)"
51    or "Difficulty walking (finding)"
52    or "Other PERARTDIS0001"
53
```

Figure 32: Exclusion criteria definition with a local dictionary

6.3. DSS Validation

REHubILITY project is going to be the subject of an internal evaluation in the first trimester of 2021. A study protocol is then going to be presented to the Ethics Committee of ICS Maugeri after the first round of internal tests on the separate components of the project (Pair Platform, DSS, rehabilitation kit). A final version of the objectives that are going to be evaluated is not yet available at this stage of the project, as the pilot test on 30 patients is scheduled for the second trimester of 2021. The evaluation of the benefits arising by using the DSS is however worth a preparatory discussion. To this end, a proposal of evaluation for the DSS only, is going to be described in the following paragraphs.

6.3.1. Technical validation using Synthetic patients

The technical evaluation has been addressed by exploiting a synthetic patient generator service. Patient generation has been performed using Synthea [199], a synthetic patient population simulator. The Java-based open-source tool is able to output synthetic, realistic (but not real), patient data and associated health records in a variety of formats, for example FHIR data. Synthea generates a patient whose demographic information, signs and symptoms and conditions are generated according to JSON based configuration files called Modules. By adding to the project custom written modules [200], a patient or a cohort of patient is generated having those conditions. An example of a custom module to generate a patient with a 6-minute walking distance observation is available in Figure 33.

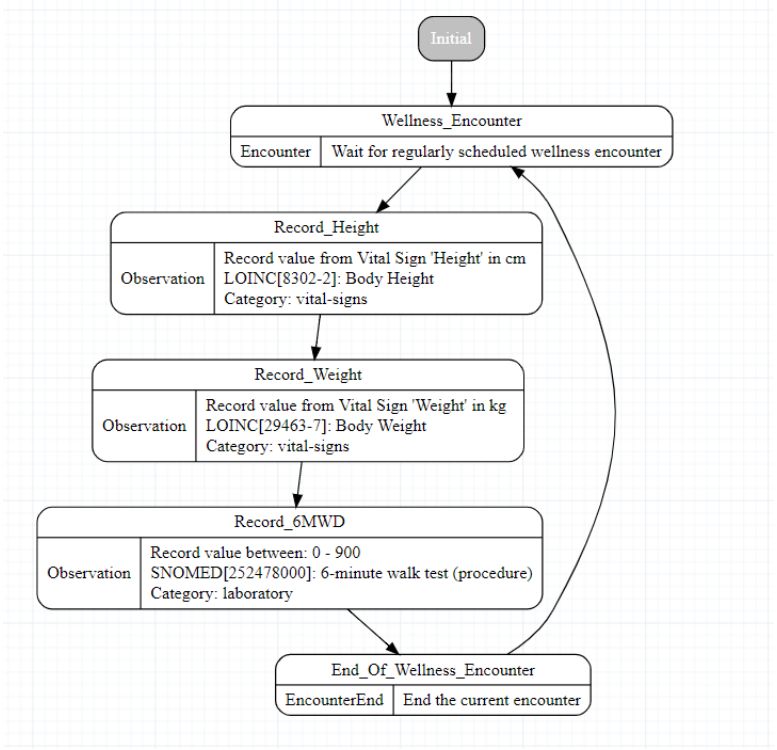


Figure 33: Module builder for a synthetic patient with a 6 minute walking distance observation

In particular, the section *"Record_6MWD"* instructs Synthea to generate a random value between 0 and 900 and marks the value as an Observation FHIR resource with code 252478000 in the SNOMED database. By adjusting the parameters in the module builder, it is possible to generate a list of patients complying to the different rules present on the DSS. An example of a patient generated with Synthea and candidate for rule evaluation is available in Figure 34:

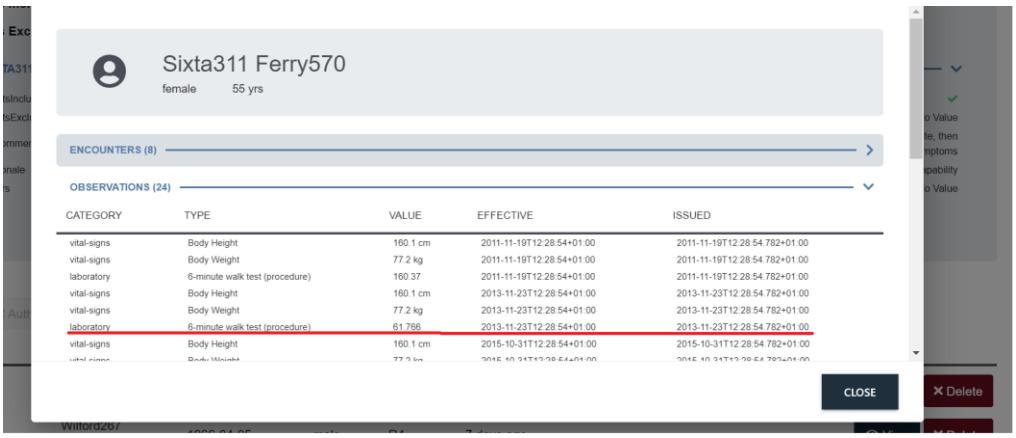


Figure 34: An example of a synthetic patient

Since the patient presents the most recent record for 6MWD with a value less than 214.4 (the threshold used to prescribe cycling interval training), the patient is eligible to receive the recommendation, as shown in Figure 35:

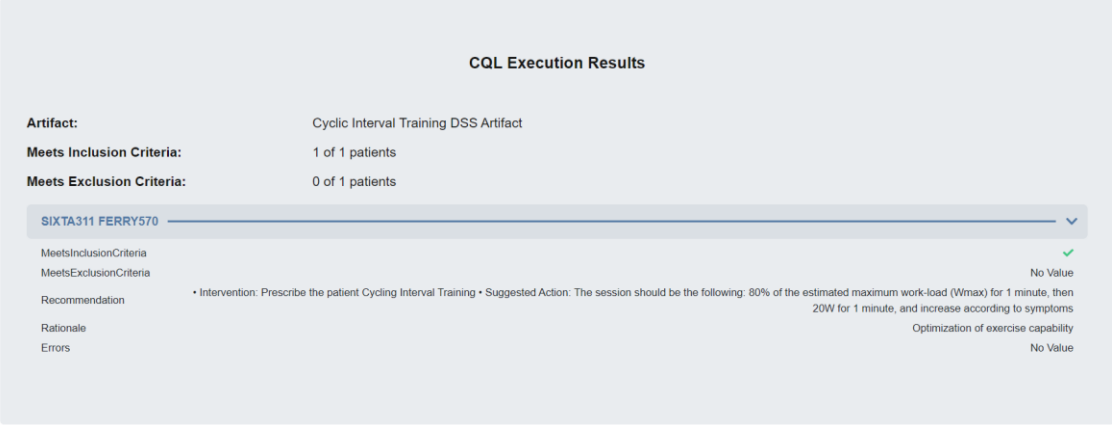


Figure 35: CQL execution results

6.3.2. Functional validation

A uniquely defined baseline to validate the functionalities a successful clinical decision support system is not available in literature, mainly due to the heterogeneous nature of systems that are described under the umbrella-term DSS. Usually, studies are mainly focused on the improvement process of care or patient outcomes, but few studies address the common features that define the decision support system quality.

The methodological approach considered in this discussion has been to evaluate previous studies which have highlighted pitfalls and difficulties [199] [121] [200] of the implemented DSSs and the attempt to answer the question:

"Does this DSS outperform some of the pitfalls and risks in CDSS design, implementation, evaluation, and maintenance?"

The following Table presents a list of the common pitfalls [121] known in literature for DSS development, and how each pitfall has been approached:

DSS Pitfall	Pitfall description	Approah
Fragmented workflows	"Many CDSS are designed as systems that required the provider to document or source information	EHR-DSS interaction is transparent for the doctor who interacts only with the Pair

	outside their typical workspace. Disrupted workflow can lead to increased cognitive effort, more time required to complete tasks, and less time face-to-face with patients."	platform and consumes in the Pair platform the DSS recommendations.
Alert fatigue and inappropriate alerts	"If physicians are presented with excessive/unimportant alerts, they can suffer from alert fatigue."	Recommendations are presented to the physician if the patient meets the inclusion criteria and does not meet the exclusion criteria. The response card contains an attribute called **"indicator"** which conveys the urgency/importance of the recommendation. Allowed values, in order of increasing urgency, are: **info, warning, critical.** The CDS Client may use this field to help make display decisions such as: sort order or suppress or coloring or trigger a notification to the doctor/patient.
Impact on user skill	"Over time a CDSS can exert a training effect, so that the CDSS itself may no longer be require or, on the other hand if the user relies only in the CDSS."	The Pair Platform is able to switch on and off the decision support services as the two components are independent.
CDSS may be dependent on computer literacy	"Some CDSS are found to be overly complex, relying too much on user skill. […]	Does not impact implementation, must be elicited from end users with specific

	Baseline evaluations of users' technological competence may be appropriate."	indicators. This point is detailed in 6.3.3.
System and content maintenance	"Maintenance of CDSS is an important but often neglected part of the CDSS life-cycle. This includes technical maintenance of systems, applications and databases that power the CDSS. Another challenge is the maintenance of knowledge-base and its rules, which must keep apace with the fast-changing nature of medical practice and clinical guidelines."	The rule repository is conceptually and operatively separated from the execution engine. It allows the versioning of the rules and the track of the rule development, thus facilitating the task to update the rule base.
Operational impact of poor data quality and incorrect content	"In poorly designed systems, users may develop workarounds that compromise data, such as entering generic or incorrect data. […] If data collection or input into the system is unstandardized, the data is effectively corrupted. The importance of using informational standards such as ICD, SNOMED, and others, cannot be understated."	Rule development uses informational standards such as SNOMED CT and LOINC.
Lack of transportability and interoperability	"Despite ongoing development for the better part of three decades, CDSS (and even EHRs in general) suffer from interoperability issues. Many CDSS exist as	Interoperability problem has been approached at a data model level, communication paradigm level, knowledge base formalization and

	cumbersome stand-alone systems, or exist in a system that cannot communicate effectively with other systems."	distribution.
Financial challenges	Outset costs to set up and integrate new systems can be substantial.	Not applicable

Table 5: DSS pitfalls

6.3.3. End-user perceived usefulness validation

The point "**CDSS may be dependent on computer literacy**", mentioned in the preceding paragraph, is worth a separate analysis. The correct use of the DSS and the perceived usefulness is an evaluation that should result from an analysis from the end user, in this case the doctor in charge of managing the home care rehabilitation treatment. Although a definite study design is not yet available, a proposition could be to administer a questionnaire to the doctors involved in the pilot. The literature offers numerous example of the measures that could be assessed, mainly based on the technology acceptance model (TAM) [201] and the Unified Theory of Acceptance and Use of Technology (UTAUT) model [202].

The questions administered to the doctors should record the following information:

- additional time needed to interact with the system, with respect to the traditional workflow;
- perceived reliability of the information displayed;
- degree of agreement/disagreement with the system;
- perceived loss/improved of productivity with the use of the DSS;
- perceived complexity in interacting with the system;
- user friendliness of the system;
- existence of unwanted or non pertinent alerts;
- reluctance to use system in front of patients.

6.4. Addendum: Adding free Text Analysis

All the data flows presented up to this point involve a manual translation of clinical practice guidelines into production rules executable by the computer.

This subchapter offers another point of view to approach the problem of formalizing a clinical practice guideline by safeguarding the original bibliographic source and build a “smart navigation” tool for the physician, whose goal is to deepen his knowledge of the guideline.

I present the results of applying the “Knowledge Graph” (KG) approach analyzed in chapter 3.3 to the free-text of an complete oncological guideline [203], but it can be argued that the methodological approach could be easily applied to the Santilli guideline, object of the regional project RE-Hub-ILITY, because the modelling focuses on the intrinsic components of a free text guideline and does not depend on the guideline clinical content. The only step needed to apply this approach to a new guideline would be to review the appropriateness of the dictionaries used to annotate the clinical concepts. The use case presented in this sub-chapter involves a guideline written in English text. If the text to be analyzed is available in another language (e.g. Italian), the default dictionaries [204] used to extract clinical concept should be substituted with the appropriate Italian-translated dictionaries [205]. The Dictionary Creator GUI requires a local installation of UMLS which can be downloaded as a compressed file [206]. The directory contains a utility called *MetamorphoSys* that allows the developer to choose which vocabularies from the UMLS need to be included in the installation. The architecture has been developed using Grakn [116], which has been discussed in the state of the art chapter (3.3).

The research project involved the design and development of a recommendation engine which allowed a clinician to relate the clinical data of a patient with a knowledge base composed by literature as heterogeneous as possible in the form of clinical practice guidelines in the oncology field.

The goal was to connect the prototype to *Pascal* [207], a medical oncology patient record distributed by Medas Srl [208] and deployed in a healthcare facility called “Centro Borgo Palazzo” (CBP) based in Bergamo [209]. The center is dedicated to the prevention and treatment of female pathologies, offering women a periodic monitoring and control service with visits and instrumental checks.

In this case the functional requirement was to be able to navigate the free text of the guideline highlighting the most relevant sections for the patient being treated. The final goal was to expand the knowledge, for example, of the trainees who served in the center. In this context the rule-based approach discussed in the preceding chapters seemed suboptimal, so I reviewed also process mining and knowledge-graph methodologies.

The initial approach focused on identifying tools that could be used for the purpose through an analysis of the state of the art. Commercial software such as Medilogy [210] and open-source products such as Drools [211], Activiti [212] and JBpm [213] were analyzed. MEDISS is a database of "medical rules" handled manually by doctors and operators that are

triggered based on patient data, while the open-source products mentioned above allow the developer to write processes and activate them with inferential engines, based on backward chaining and forward chaining. Overall, the in-depth analysis of the state of the art allowed me to conclude that to reach the objective of navigating the free text of the guideline in a more immediate way, the rule-based and process mining approaches were suboptimal. By contrast, experimentation with KGs it's still new in literature, especially in healthcare [214], but major vendors like LinkedIn [215] and Facebook [216] successfully used it to derive meaningful insights from voluminous data. For these reasons, the knowledge-graph method was chosen.

6.4.1. System's technical design

The goal of the research was to collect in a single formal structure the annotations resulting from the application of text mining processes to oncology reports produced by an electronic medical record. The same process of annotating and saving the output in the KG was also applied to the text of the oncological guidelines provided by CBP's hospital physicians. Once the knowledge base was built with the KG method, the goal was to apply inference processes to the KG, to correlate the entities belonging to the report with the entities belonging to the guideline.

In this particular scenario the choice of the KG seemed to me to be more appropriate than rule-based or process mining systems because it allows the developer to build a formal representation of clinical objects in a form that is at the same time easily understandable by humans who are able to navigate the free text of the guideline in a more precise way and easily interpreted by the machine. The KG is in fact "fed" with the output of the text-mining process (extraction of structured semantic information from unstructured text) and the reference to the original text of the guideline.

6.4.2. Lessons learned

The identification and analysis of the concepts extracted from the text is a complex operation, but an even harder challenge is posed by the transformation of NLP pipeline output into an insight capable of generating value for the healthcare worker.

The type of insight that would be desired from a decision support system could be the discovery of an apparently missing link between two entities or a hypothesis verification.

The difficulties found while approaching text mining algorithms for processing unstructured data included:

- **Collecting and integrating** complex networks resulting as output of NLP pipelines in a single database, the difficulty relies

especially in tracing relationships between different portions of text.

- **Contextualizing the concepts** extracted from a text with previous and universal knowledge, for example recognizing that the term “cancer” and “neoplasia” represent the same concept. This is especially true in a context in which the data sources are very heterogeneous (the linguistic register of a report written by a doctor is very different from the terms used in writing a guideline).
- **Translating the output** of an NLP pipeline into a form that can provide value to the end user.

In a later stage of the project functional requirements that could solve the aforementioned problems were identified:

- **Integrate the output** coming from the NLP pipeline into a single collection point, which must successfully tackle and solve the problem of the so-called "Semantic Integration" [217] to interpret as much as possible the meaning of data that comes from heterogeneous sources and been processed by heterogeneous tools.
- **Normalize all the data** entering the KG. On that account, it is necessary to write an ontology, a formal superstructure that has the dual task of contextualizing the concepts present within the database and at the same time describing in an exhaustive and explicit way the relationships between concepts. The ontology represents the data at a high level, categorizing the contents and consolidating their presence within the KG. Another responsibility of the ontology is to validate the data that becomes part of the KG with the migration process. The ontological data model acts as an aggregator and validator of incoming data and their relationships.
- **Writing a software layer** that, through automatic reasoning, can infer related or central concepts, "missing" relationships within the KG. The database alone only acts as a data aggregator, it is therefore necessary to provide a query mechanism for the constructed graph. The best-known databases, both relational and non, do not allow to operate in the "inferential mode" just described.

After having identified the limitations of the tools and approaches currently used both in literature and in production real healthcare contexts, and the desired requirements to interpret the free-text of the guideline, I identified the tool for developing the KG in Grakn [116] as optimal.

As mentioned in the state of the art chapter (3.3), Grakn is a NO-SQL database based on labelled, directed hypergraph that represents an

innovation from the point of view of data representation, presenting itself as a valid middle ground between relational and oriented graph models.

A further advantage is the existence of a database query language called Graql that allows the developer to retrieve data that has been explicitly saved in the database and implicit information that can be derived by browsing the data model. It is therefore possible to operate in the inferential mode.

6.4.3. Identification of Input Data

The first step to apply the KG approach to solve a data-integration and analysis problem was to define what kind of data I intended to migrate into the KG, in this case Grakn. The concept of "migrating" means writing custom software to perform data ingestion into the KG. For each entity that gets included into Grakn the developer must specify the attributes that define an entity and the relationship between the entities that are already inside the KG. The data can be structured and unstructured, and the source can be one of the following showed in Figure 36:

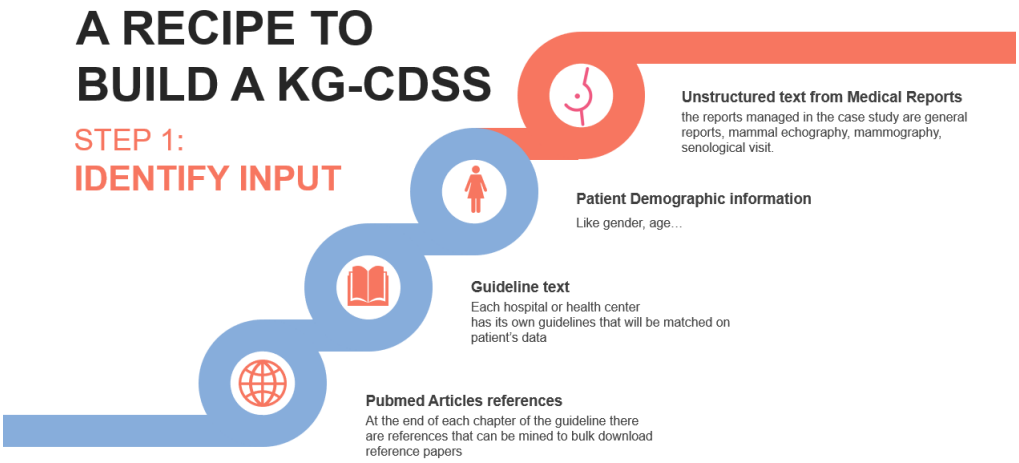


Figure 36: KG-CDSS Input Identification

- unstructured text from medical reports: the reports managed in the case study were general reports, thus the same methodology could be easily applied to free text portions of the PAIR document;
- patient demographic information such as age, gender, etc.;
- NLP output from medical guidelines text.

6.4.4. Identification of a text mining tool

The following step in the process was to assess the NLP tools available for the use case object of the problem. The activity involved the identification of one or more tools candidates for actual mining of the guideline text.

The general ideal approach I followed was to build the CDSS software as much "agnostic" as possible with respect to the choice of the mining tool. In case a new algorithm or tool for the NLP performs better than the one chosen, the CDSS implementation modification remains “confined” to rewriting the step of the NLP pipeline.

An analysis of the state of the art was performed to compare the most known and used tools in literature for NLP Pipeline. Figure 37 shows a summary of the tools that have been experimented:

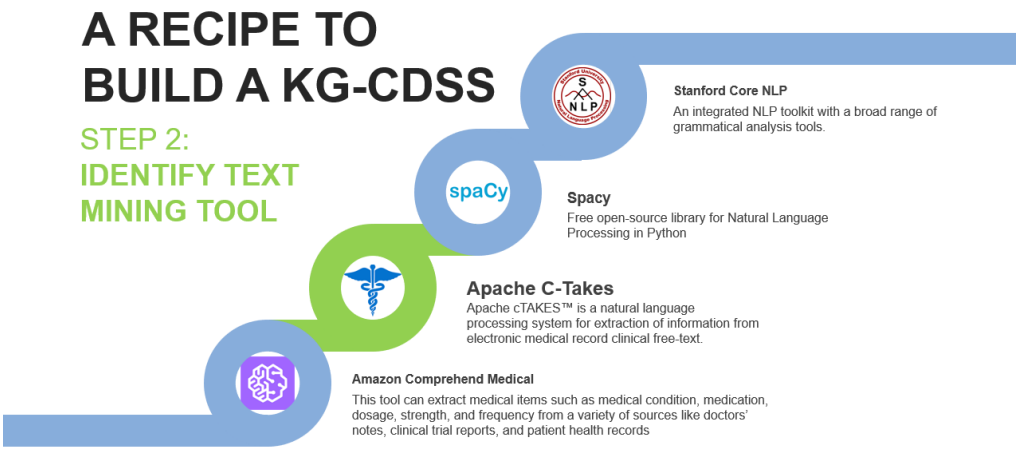


Figure 37: KG-CDSS NLP Pipeline

The results of the experimentation showed that tools like Stanford Core NLP [218] and Spacy [219] are useful for general domain use cases, but require intensive training to be used in healthcare domain. In fact, they require a custom named entity recognition model, which for the medical domain would involve a lot of work to make effective suggestions and although experimented the solution was not feasible for real use. The three other tools assessed for the use case were Apache cTAKES [220], MetaMap [221] and Amazon Comprehend Medical [222]. The latter exposes interesting functionalities but comes with a fee for the use of the service, while the first two are free for use.

Both Apache cTAKES and MetaMap are in fact an open-source systems widely used in the medical community. The training work that makes Core NLP and Spacy too resource-intensive to set up, is not required for both MetaMap and cTAKES systems, making them ideal solutions for the

medical and life sciences domains. Ultimately, I chose Apache cTAKES for the NLP work over MetaMap within the use case of the problem, because it was the best performer across multiple years [223] [224] [225].

MetaMap has shown to have an average of 0.88 in recall, 0.89 in precision, and 0.88 in F-score. With cTAKES, the average of recall, precision and F-score were 0.91, 0.89, and 0.89, respectively [224].

The tool can handle all the basic pipeline without any intervention in terms of configuration:

- **Boundary detection:** identification of the sentences inside of text [226].
- **Tokenisation:** extraction of single tokens from a sentence [227].
- **Stemming and Lemmatisation:** understanding derivationally related words with similar meanings [228].
- **Part-of-speech:** extraction of parts of speech within a sentence [229].
- **Shallow parsing:** the ability to take the parts described in the previous point and link them with higher order groups (noun groups or phrases, verb groups, etc.) [223].
- **Entity recognition:** extraction of named entities in unstructured text and classify them into defined categories. [224].

Although cTAKES has been identified as the best performer in terms of the quality of the annotations it has an operational problem: the only deployment option that cTAKES gives, is to run it as a desktop, standalone application.

Unlike Stanford Core, cTAKES does not expose APIs to easily communicate with the system but only distributes installation packages or source code.

This is a big limitation for the integration of the tool in a complex software architecture, so I decided to reflect on how to integrate cTAKES in a form usable by the CDSS to benefit from the quality of the annotations offered by the tool. A discussion on how I overcame cTAKES integration issues is detailed in paragraph 6.4.6.

6.4.5. Mine Text

The guideline free text has been annotated using cTAKES Default Clinical pipeline, visible in Figure 38 [230].

CTAKES can extract the following annotations:

- anatomical sites;
- signs/symptoms;
- procedures;
- diseases/disorders;

- medications;
- location;
- temporal events;
- history and subject;
- coreferences.

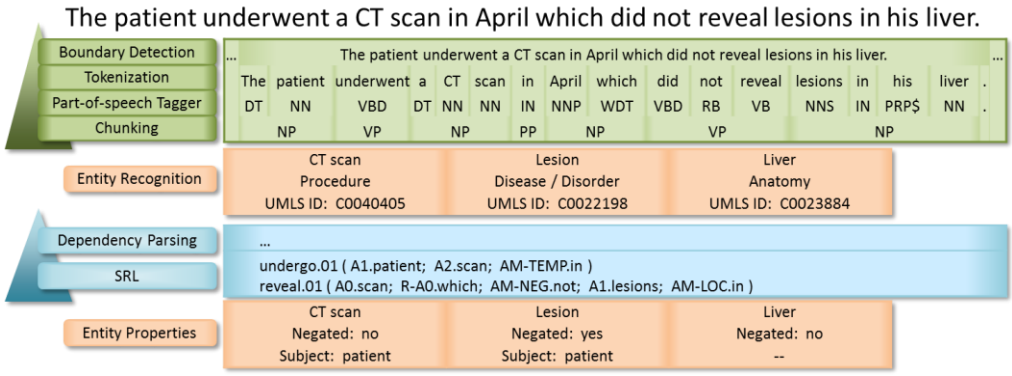


Figure 38: cTAKES Default Clinical Pipeline

For each recognized entity cTAKES provides the "*assertion annotators*", a mechanism for examining and documenting the real-world implications for annotations in text [231].

A practical example of the result of the assertion annotators could be performed on this piece of guideline: "*If blind sampling does not reveal endometrial hyperplasia or malignancy, further testing, such as hysteroscopy with dilation and curettage, is warranted in the evaluation of women with persistent or recurrent bleeding.*", one might assume that a mention of "*endometrial hyperplasia*" in text implies that further testing is required in case of bleeding.

Additionally, the subject of the statement may be someone other than the patient, this is particular relevant on the anamnesis section of every medical report (e.g. the patient has family history of breast cancer, the patient's mother suffered from triple-negative breast cancer cancer).

Each of these attributes illustrate how the "assertion" value of a named entity might be marked. The assertion provided by the Default pipeline are of three kind:

- **Uncertainty attribute annotator**: modifies an attribute on EntityMention and EventMention appending a score of 0 or 1, where 0 means that the concept is certain and 1 is uncertain.
- **History attribute annotator**: modifies an attribute on EntityMention and EventMention appending a score of 0 or 1, where 1 means that the concept is intended in the patient history health state, 0 otherwise.

- **Generic attribute annotator:** modifies an attribute on EntityMention and EventMention. The generic attribute is a boolean where true means that the entity is recognized inside a generic context, false otherwise.

6.4.6. cTAKES services exposed on the internet as a REST server

As mentioned in the previous paragraph a downside of the software cTAKES is that it lacks any Application Programming Interfaces to integrate it in a complex software.

I therefore decided to contribute to the work of an Open Source development team, called *GoTeamEpsilon* whose goal is to write a REST service to return the results of cTAKES annotations as a simple JSON file that can be easily integrated into a complex architecture [232].

The result of this activity was to rebuild the installation procedure for the service, install a web application server on a virtual machine generated on Google Cloud on which the developed software is running, and the source code is publicly accessible [233]. By querying the endpoint on which the service is exposed, it is possible to receive the annotations deriving from the text in JSON format.

6.4.7. Output of the implemented custom layer

The output of the custom software is a JSON file containing all the entities that have been found on each section of the guideline. The keys belong to the following list:

- AnatomicalSiteMention;
- MedicationMention;
- DrugChangeStatusAnnotation;
- StrengthAnnotation;
- FractionStrengthAnnotation;
- FrequencyUnitAnnotation;
- DiseaseDisorderMention;
- SignSymptomMention;
- RouteAnnotation;
- DateAnnotation;
- MeasurementAnnotation;
- ProcedureMention;
- TimeMention;
- StrengthUnitAnnotation.

Each key is an entity extracted by the named entity recognition of cTAKES [223]. Figure 39 and Figure 40 show an example of the

annotations that result from the custom software built upon cTAKES. In the attached Appendix C a complete example of a paragraph and the annotations extracted is available.


```
{
  "AnatomicalSiteMention": {
    "OVARY": [
      "start: 493",
      "end: 498",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 15497006, cui: C0029939, tui: T023]"
    ],
    "VAGINAL": [
      "start: 4474",
      "end: 4481",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 76784001, cui: C0042232, tui: T023]"
    ],
    "CERVICAL": [
      "start: 574",
      "end: 582",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 45048000, cui: C0027530, tui: T029]"
    ],
    "GLANDULAR": [
      "start: 544",
      "end: 553",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 362884007, cui: C1285092, tui: T023]"
    ],
    "ENDOMETRIUM": [
      "start: 138",
      "end: 149",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 2739003, cui: C0014180, tui: T023]"
    ],
    "UTERUS": [
```


Figure 39: NLP Pipeline Oputput 1


```
  },
  "MedicationMention": {
    "ESTROGEN": [
      "start: 435",
      "end: 443",
      "polarity: 1",
      "[codingScheme: SNOMEDCT_US, code: 41598000, cui: C0014939, tui: T121]",
      "[codingScheme: SNOMEDCT_US, code: 41598000, cui: C0014939, tui: T125]",
      "[codingScheme: SNOMEDCT_US, code: 41598000, cui: C0014939, tui: T109]",
      "[codingScheme: RXNORM, code: 4100, cui: C0014939, tui: T121]",
      "[codingScheme: RXNORM, code: 4100, cui: C0014939, tui: T125]",
      "[codingScheme: RXNORM, code: 4100, cui: C0014939, tui: T109]",
      "[codingScheme: SNOMEDCT_US, code: 61946003, cui: C0014939, tui: T121]",
      "[codingScheme: SNOMEDCT_US, code: 61946003, cui: C0014939, tui: T125]",
      "[codingScheme: SNOMEDCT_US, code: 61946003, cui: C0014939, tui: T109]"
    ]
  },
  "DrugChangeStatusAnnotation": {},
```


Figure 40: NLP Pipeline Oputput 2

6.4.8. Model Ontology

To build the KG that represents the entities involved in the Guideline text, it is necessary to build a representative ontology.

As mentioned in the last chapter, the ontology written using the Graql language has 4 conceptual building blocks:

- Entities
- relationships;
- roles;
- attributes.

Once the ontology has been written and the contents migrated within the KG, it is possible to query the database using the Graql language.

Using automatic reasoning Graql can extract explicit knowledge from the database and infer implicit knowledge. The power of querying the database through this language lies in the profound difference from querying the database in the traditional way of the Entity - Relationship model.

To collect information from different tables it would be necessary to join the interested tables, while in this case it is sufficient to recall the relationship between two concepts. In Figure 41 through Figure 44 I show an overview of the first implemented ontology from a high level to a detail of some interest entities. The ontology models the unstructured text with the annotations and the linguistic relationships that exist between the annotations.

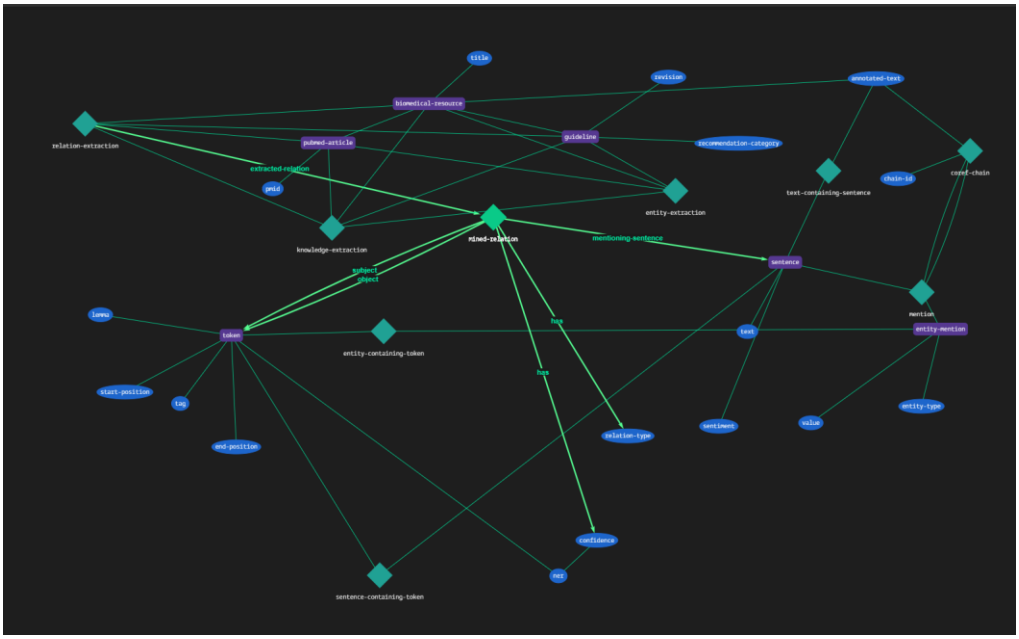


Figure 41: High-level representation of the modeled ontology

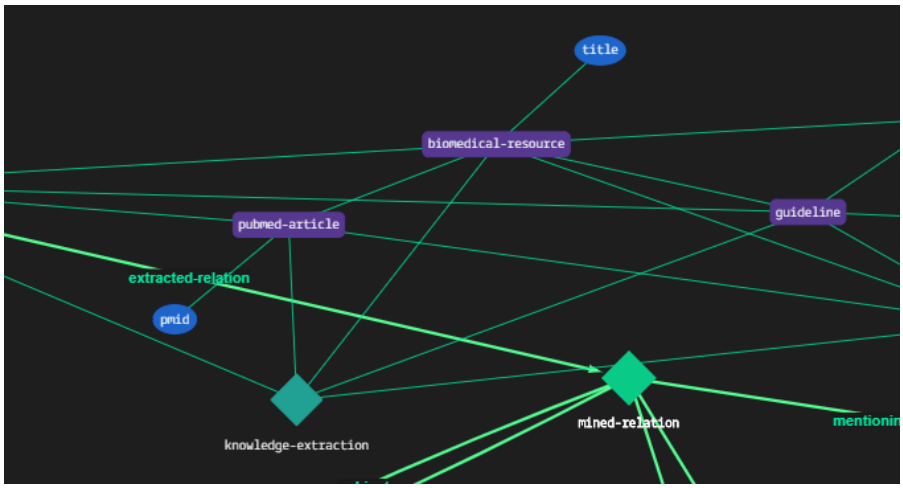


Figure 42: Biomedical resource

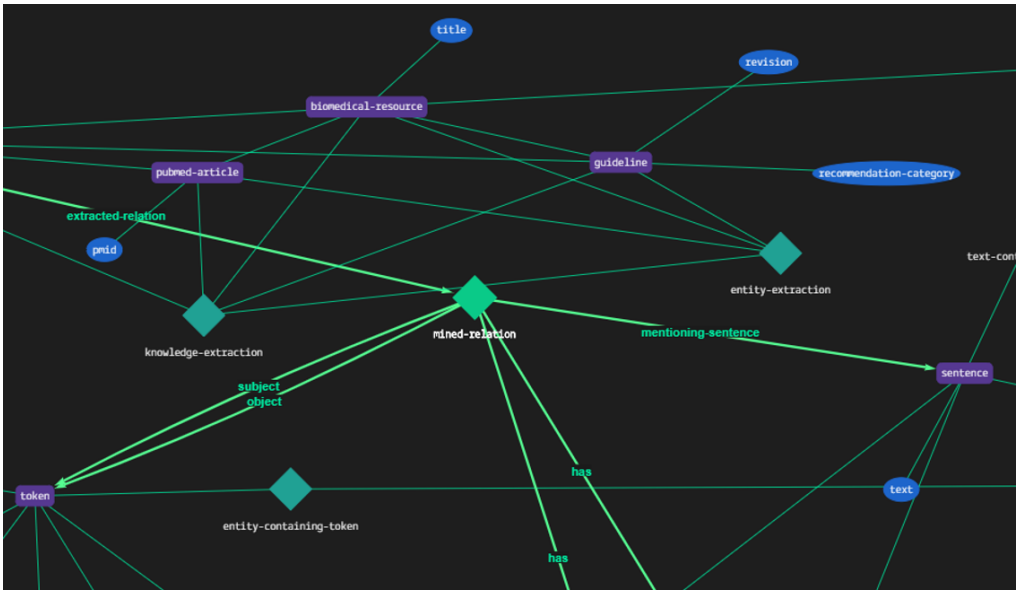


Figure 43: Detail of “mined-relation” relation

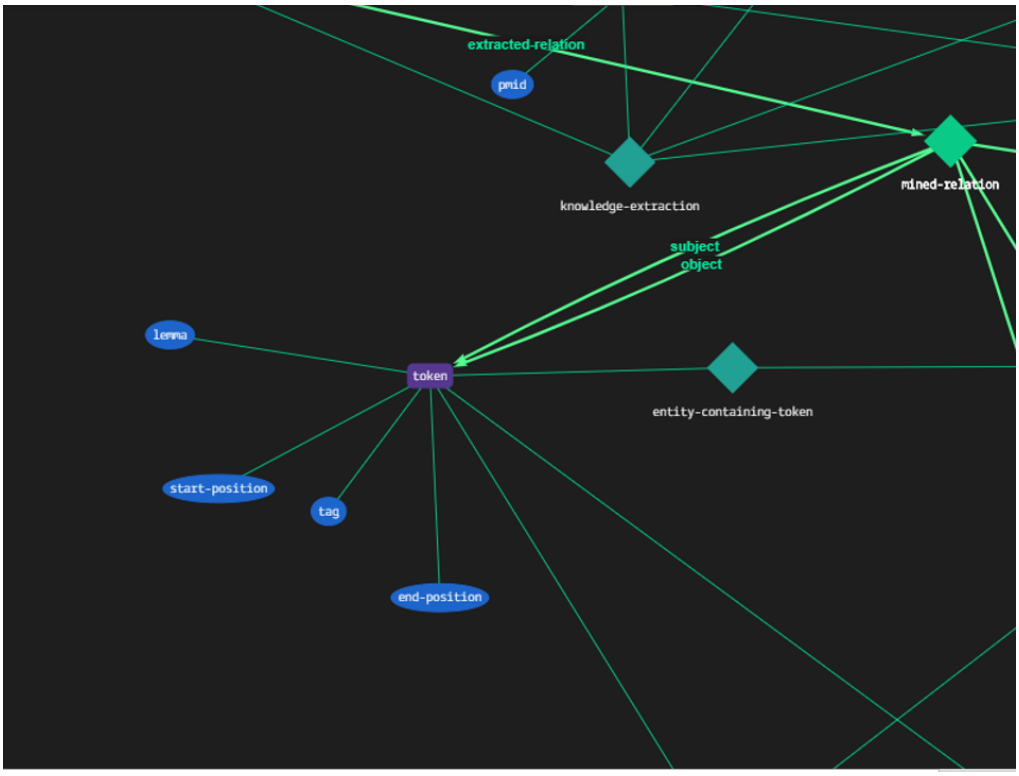


Figure 44: Detail of the "token" entity and its attributes of the first version of the ontology

In the image above we can see an entity, the *Guideline* entity, which has *thematic sections*, further broken down into sentences. After the development of a first version of the ontology, some refinements were added to further improve the model.

For example, a “super-attribute” called *rawText* was defined, which models the original free text of a bibliographic source of information. Each entity of the guideline has a raw text attribute which inherits the properties of the super set. With this improvement it is possible to easily recall all the original text of each portion of the guideline.

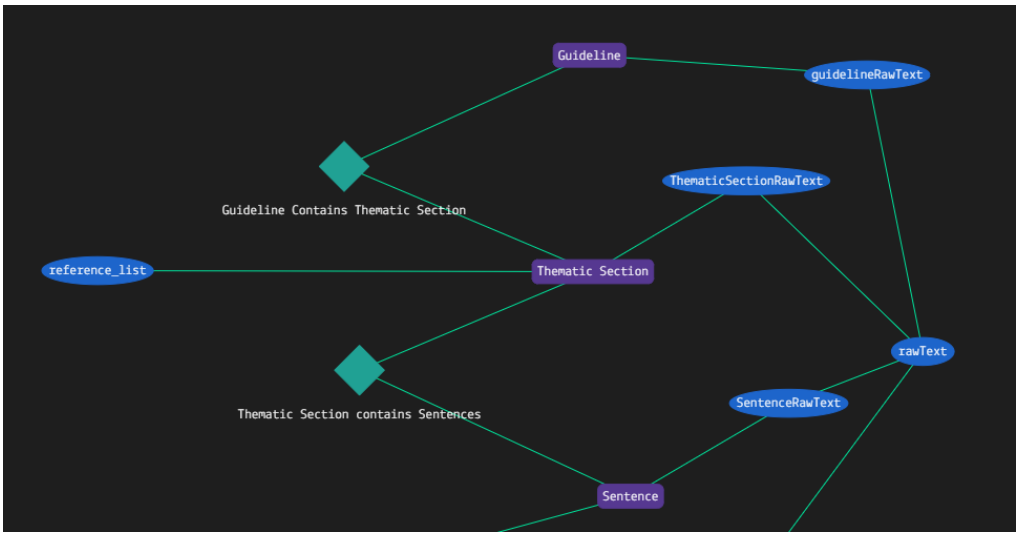


Figure 45: Detail of raw text attribute

The entities in Figure 45 are related to each other through a set of relations: *guideline-contains-thematic-section*, and *thematic-section-contains-sentences*.

The entity *sentence* is connected to a *token*. Another adjustment in respect of the first version of the ontology was made in this sense.

Each token has been further characterized with a relation that matches the cTAKES named entity recognition. The result of the NLP Pipeline on a token classifies the extracted token in one of the entities visible in Figure 46:

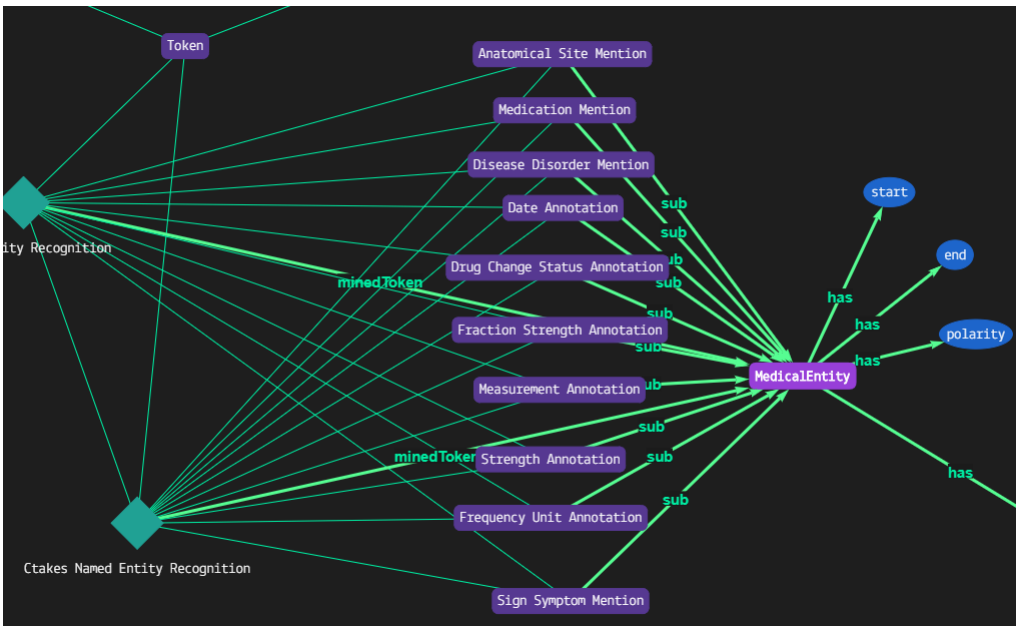


Figure 46: Migration of the cTAKES Named Entity Recognition

Each token that matches an entity recognized by Apache cTAKES in the NLP pipeline is linked via a relation with the sub types of the entity *medical-entity* where each entity plays the role of *mined-token*.

Grakn allows type inheritance, wherefore all sub types inherit the attributes assigned to the parent entity like start, end, polarity.

Polarity concept [234] is particularly relevant in Apache cTAKES. A polarity attribute appended on a recognized entity is the result of an algorithm of negation detection performed by cTAKES on each recognized entity.

An exhaustive discussion on *NegEx*, the regular-expression based algorithm that cTAKES uses to perform negation detection is outside the scope of the current work [235]. The meaning of the polarity score is however very straightforward: if an annotation presents a polarity equals to -1 then the context in which the token is mentioned intends the concept to be negated while if the polarity of the annotation equals +1 then the token is not negated.

Figure 47 shows a code box with a portion of the ontology written in Graql, the ontology syntax provided by Grakn, to model the free text of the Guideline:

```
define
medical-entity sub entity,
    has start,
    has end,
    has polarity,
    has [attribute-name],
    plays minded-token;
token sub entity,
    plays [role-name];
start sub attribute,
    value: string;
end sub attribute
    value string;
polarity sub attribute,
    value string;
ctakes-named-entity-recognition sub relation,
    relates mined-token,
    relates [role-name];
anatomical-site-mention sub medical-entity;
medication-mention sub medical-entity;
disease-disorder-mention sub medical-entity;
date-annotation sub medical-entity;
drug change status annotation sub medical-entity;
fraction-strength-annotation sub medical-entity;
measurement-annotation sub medical-entity;
strength-annotation sub medical-entity;
frequency-unit-annotation sub medical-entity;
sign-symptom-mention sub medical-entity;

```

Figure 47: A portion of ontology written in Graql

Another important concept that gets migrated into the ontology is the coded representation for each entity in one or more medical dictionaries. Each *medicalEntity* extracted from NLP Pipeline and migrated into Grakn has one or more attributes called *coding_scheme* and represents the name of the medical dictionary in which the term was found (e.g. SNOMED_CT, RxNorm). Figure 48 shows the detail of the ontology which represents this concept.

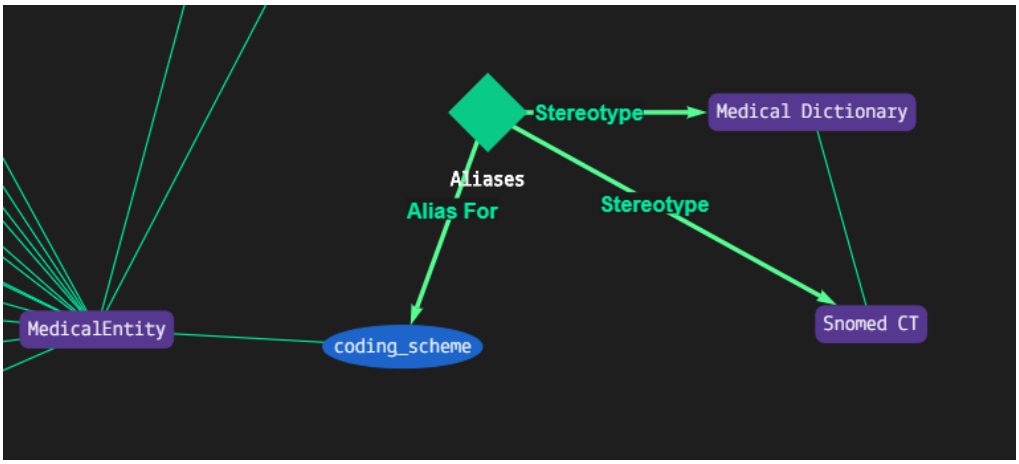


Figure 48: Modelization of Medical Dictionaries

Each attribute *coding_scheme* plays the role of *Alias for* in a relation with an entity called *Medical Dictionary* of which *Snomed CT* is a subtype.

This trick has been done to ensure that even if in the future I will add other ways to extract entities from free text, if the coding scheme is not the string "SNOMED_CT" in all capital letter but in another form like a code or a different text, I can always extend the same Medical Dictionary with another Alias to ensure the unique concept of the medical dictionary is always Snomed CT.

The attribute *coding_scheme* differs from attribute *coding_scheme_code* which represents the unique id of the token recognized as Medical Entity inside a Medical Dictionary. Figure 49 shows the attributes of each Medical Entity.

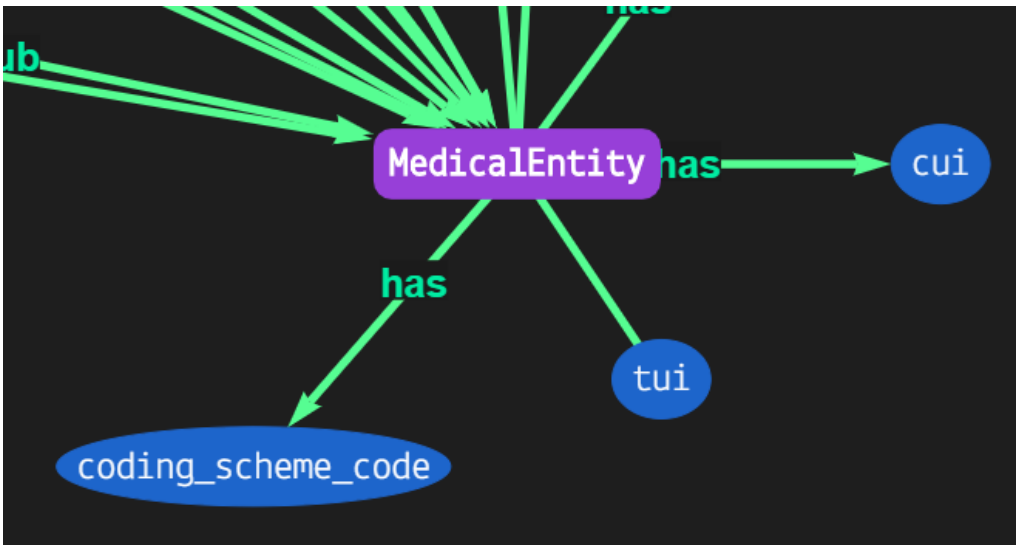


Figure 49: Medical entity attributes

The attributes match with the data fond in each annotation described in paragraph 6.4.5:

- **Concept Unique Identifier (CUI)** [236]: an 8-character identifier beginning with the letter "C" and followed by 7 digits provided by the Unified Medical Language System (UMLS). Each concept is assigned a CUI. The CUI has no intrinsic meaning but remains constant through time and across versions. Each concept is a meaning. A meaning can have many different names. A key goal the CUI is to understand the intended meaning of each name in each source vocabulary and to link all the names from all the source vocabularies that mean the same concept (the synonyms). Concept Unique Identifiers are often used as a tool for word sense disambiguation of biomedical text [237].
- **Type unique identifier (TUI)**: a unique code that belongs to an enumeration of all possible semantic types [238] [239] [240]. Some examples include:
  - anab|T190|Anatomical Abnormality;
  - dsyn|T047|Disease or Syndrome;
  - diap|T060|Diagnostic Procedure;

Figure 50 shows an example of the mined text and the detected CUI/TUI. Endometrial cancer, cancer of the endometrium, have the same code because they are the same pathology.

Malignancy has a different code but shares the same semantic type (neop|T191|Neoplastic Process).


```
],
"ENDOMETRIAL HYPERPLASIA": [
  "start: 1415",
  "end: 1438",
  "polarity: 1",
  "[codingScheme: SNOMEDCT_US, code: 237072009, cui: C0014173, tui: T047]"
],
"ENDOMETRIAL CANCER": [
  "start: 1940",
  "end: 1958",
  "polarity: 1",
  "[codingScheme: SNOMEDCT_US, code: 254878006, cui: C0476089, tui: T191]"
],
"CANCER OF THE ENDOMETRIUM": [
  "start: 124",
  "end: 149",
  "polarity: 1",
  "[codingScheme: SNOMEDCT_US, code: 254878006, cui: C0476089, tui: T191]"
],
"MALIGNANCY": [
  "start: 1442",
  "end: 1452",
  "polarity: -1",
  "[codingScheme: SNOMEDCT_US, code: 363346000, cui: C0006826, tui: T191]"
],
"OBESITY": [
  "start: 409"
```


Figure 50: Extracted CUI and TUI

Another example of the output of the pipeline is visible in Figure 51: obesity has been detected with two different SNOMED:CT codes [241] [242] but they share the same CUI [243]. The benefit is clear: by migrating all the available guideline text with the uniquely identified terms the free text of the Guideline can be navigated by analyzing the relationships between concepts, not terms.


```
    "[codingScheme: SNOMEDCT_US, code: 363346000, cui: C0006826, tui: T191]"
  ],
  "OBESITY": [
    "start: 409",
    "end: 416",
    "polarity: 1",
    "[codingScheme: SNOMEDCT_US, code: 414916001, cui: C0028754, tui: T047]",
    "[codingScheme: SNOMEDCT_US, code: 414915002, cui: C0028754, tui: T047]"
  ],
  "NEOPLASIA": [
    "start: 875",
    "end: 884",
    "polarity: 1",
    "[codingScheme: SNOMEDCT_US, code: 108369006, cui: C0027651, tui: T191]"
  ],
  "POLYCYSTIC OVARY": [
```


Figure 51: Obesity example TUI/CUI

As visible in Figure 47 through Figure 51 the modelling of the ontology and the migration into Grakn are performed on the intrinsic linguistic components that define a clinical practice guideline and do not depend at all on the clinical domain. The oncological domain is in fact used as a use case to drive the discussion.

From this we can deduce that this approach is feasible for every guideline, as long as it is divided in thematic sections, it is composed by free text, and contains concepts that can be mapped on a standard medical dictionary.

Because of it, the prototype could be added as an independent module to the DSS that is being developed for RE-Hub-ILITY project without any additional development effort to support an enhanced navigation of the guideline's free text. As mentioned in the beginning of the chapter, if the guideline text is written in another language, for example in Italian, the configurations to be changed are only confined in the NLP step of the entire pipeline. The original contribution in this intervention does not reside in inventing a new NLP pipeline to apply on free text. It resides instead in making available to an end user or another application the results of cTAKES, which is a known bottleneck for complex software architectures exploiting NLP pipelines.

Chapter 7:

Conclusions and future developments

The goal of the work presented in this dissertation was to design and implement a sustainable, interoperable, Decision Support System that could support the physician in the process of prescribing an elder patient a home-care rehabilitation treatment. The desired outcome was that the system presented personalized recommendation based on patient's data to make a tailored prescription on patient current condition and desired outcomes.

The recommendations needed to be based on the most recent Evidence Based Medicine and needed to be fully machine-interpretable in order to support automatic analysis of patient data, thus eliminating any repetitive manual data entry to the DSS by the physician.

In addition, the implemented architecture needed to be designed to be a full working solution and not a prototype or a proof of concept. In the experimentation phase of the regional project the PhD is inserted (scheduled for 2021), the DSS must be able to integrate with the real ICS Maugeri information systems. A study protocol to evaluate the entire project is therefore going to be submitted to the Ethics committee of ICS Maugeri involving approximately 30 patients.

The DSS goal has been achieved by these propaedeutics steps:

- A thorough **literature analysis**, to identify the state of the art in these domains:
    - the clinical problem of prescribing a home-care rehabilitation regimen;
    - ICS Maugeri information flow when prescribing a home-care regimen (paper-based);
    - methods to construct a modular decision support system;

- methods to adhere to the applicable laws and regulations (GDPR, regional laws).

The literature analysis showed that the clinical domain of home-care rehabilitation supported by ICT flourishes with articles, mainly focused on the technologies that monitor the patient during home-care treatment or the clinical outcomes that such an intervention provides. There is a lack however on evidence on what reasoning process motivates the physician to prescribe an intervention over another, other than his personal experience, or preference, or experimental design needs. The goal of this work is to fill this gap by providing evidence based, personalized recommendation through a DSS.

- A **functional requirement analysis**, a **technical design phase** and an **implementation phase** to deliver a first version of the DSS

The goal of making the Decision Support System interoperable has been reached by choosing to adhere to the most recent but stable healthcare standards at different levels:

- data Modeling Level: HL7 FHIR R4;
- communication paradigm: CDS Hooks Version 1.0.0;
- knowledge base formalization: HL7 CQL Version 1.3, FHIR clinical guidelines.

- A **"deployment and delivery" phase**, in which the first version of the DSS has been packaged as a Docker container [189] and has been installed on a virtual machine, that acts as a server for primary internal tests.

7.1. Original Contribution and generalization opportunities

As mentioned in the preceding paragraph, the literature analysis clearly shows that all the available interventions based on ICT solutions that prescribe a home-care rehabilitation regimen lack a decision support for the physician to recommend inclusion/exclusion criteria, optimal exercise prescription and parameters monitoring based on evidence based medicine.

That gap is being filled by providing the physician with an automatic decision support system, that can be integrated in a real information setting, based on recommendations extracted from the text of national guidelines and therapist driven algorithms to deliver both literature-based and practice-based evidence. The DSS is designed to be compliant with the existing regulations in term of data protection and exploits the most recent but stable healthcare standards. The architecture of the DSS is an original contribution as it does not exploit any existing commercial or open-source

software for the modelling of the guideline but only adheres to standard specifications.

In addition, the discussion presents a prototype plugin for an enhanced navigation of the guideline that is enough flexible to be adapted to every guideline for which a machine-readable free text is available.

The architecture to model the annotations resulting from cTAKES NLP pipeline and their migration into Grakn to perform inference is also an original contribution.

Although the dissertation is focused on the rehabilitation domain, it can be argued that the same approach, DSS architecture, and execution engine, can be deployed on other medical domains. The generalization on different domains could be addressed in different ways:

- **Decision support artifact present in the shared repository:** the main goal of the shared repository on which the artifacts are saved [244] is to share with the clinical community the results obtained in analyzing decision support interventions. If the clinicians are interested in exploiting a CQL artifact from the repository, the necessary steps to perform are the following: (i) identify if the client is sending all the data needed for the evaluation in the call, (ii) expose the artifact downloaded from the repository as a hook following CDS hooks specification at a given endpoint.
- **Decision support artifact not present in the shared repository:** in this case an additional effort is required to locate and formalize the guideline or the intervention into CQL language, the other steps are the following: (i) identify if the client is sending all the data needed for the evaluation in the call, (ii) expose the CQL artifact as a hook following CDS hooks specification at a given endpoint.

7.2. Challenges

Nevertheless, in this work I faced some challenges. The first challenge in the initial phase of this project was to track the application in a real healthcare setting of the solutions available in literature to guide me in inventing a feasible architecture.

Several approaches detected in literature based the guideline formalization and execution on commercial proprietary products, and this was not a viable choice for this work. Others exploited methods that were not replicable nor documented enough to be a starting point for a new technical proposal. Finally, all the Machine Learning approaches have been excluded because at the start of the project no data was available to perform analysis upon.

Another issue resides in the validation of the system. The first experimental phase on healthy subject of the project is scheduled for 2021

so at the current date is not possible to perform an extensive validation to evaluate the effect of introducing such system into the physician current workflow. On the far side, a common limitation in these kind of systems is the lack of connection between the DSS and the EHR, in this case the connection between the PAIR Platform and the DSS is not simulated and it is standard based.

7.3. Future Developments

The regional project RE-Hub-ILITY is an ongoing project. Future possible developments have been already analyzed in the functional requirement chapter (4.1) and need to be technically designed and implemented. An interesting near future development is embodied by the "*FITT-prescription*" automatic review and early solicitation for a home prescription revision. This service should collect the summary result for each session coming from the rehabilitation kit and detect if a revision of the PAIR document should be solicited to the physician taking care of the patient. The service should be added to the collection of services already available on the DSS.

Another interesting future development would be to deploy on the proposed architecture some of the CQL decision support artifacts available on the public repository shared by Agency for Healthcare Research and Quality outside the rehabilitation setting [244]. In case one or more artifact are useful for ICS Maugeri staff, the data persistence is designed to allow the activation of different decision support thematic projects for the same company.

The last noteworthy future development would be to deliver the recommendations that emerge from the DSS not as plain text but as a link to a SMART App [245]. When launched, the App could show the physician the recommendation, the original text of the guideline and the bibliographic reference that produced the specific recommendation or monitored signals' progression graphs.

APPENDIX A:

Life expectancy data according to WHO

Year In (2016,2017,2018,2019,2015)
WHO Region In (Europe)
Country In (Italy)

Indicator name	Life expectancy at birth
Data host	UN Population Division
Date of last update of database	11/17/2019
Export date	2020-11-06 10:53:29 (UTC+00:00)
Download	Downloaded from WHO MNCAH Data Portal, https://www.who.int/data/mncah

Table 1: Life expectancy at Birth (From 2015 to 2019)

Year	WHO Region	World Bank Income Group	Country ISO Code	Country	Sex	Value
2015	Europe	High income	ITA	Italy	Both sexes	82.828
2015	Europe	High income	ITA	Italy	Female	85.005
2015	Europe	High income	ITA	Italy	Male	80.474
2016	Europe	High income	ITA	Italy	Both sexes	83.008
2016	Europe	High income	ITA	Italy	Female	85.14
2016	Europe	High income	ITA	Italy	Male	80.702
2017	Europe	High income	ITA	Italy	Both sexes	83.184

2017	Europe	High income	ITA	Italy	Female	85.276
2017	Europe	High income	ITA	Italy	Male	80.922
2018	Europe	High income	ITA	Italy	Both sexes	83.352
2018	Europe	High income	ITA	Italy	Female	85.409
2018	Europe	High income	ITA	Italy	Male	81.13
2019	Europe	High income	ITA	Italy	Both sexes	83.512
2019	Europe	High income	ITA	Italy	Female	85.539
2019	Europe	High income	ITA	Italy	Male	81.325

Healthy life expectancy data according to Eurostat (WHO data are up until 2016)

Data extracted on 06/11/2020 12:49:53 from [ESTAT]

Dataset:	**Healthy life years by sex (from 2004 onwards) [HLTH_HLYE]**
Last updated:	15/05/2020 11:00

Time frequency	Annual
Unit of measure	Year
Sex	Total
Health indicator	Healthy life years in absolute value at birth

Tabella 2:Healty life Expectancy (From 2009 to 2018)

TIME	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
GEO (Labels)										
European Union - 28 countries	61,5	62,2	61,8	61,7	61,4	61,5	62,9	63,8	63,7	63,6
Italy	62,9	:	63	61,8	61,6	62,4	62,6	67,4	66,3	66,8

APPENDIX B:

CDS Hooks swagger API

```
swagger: '2.0'
info:
  version: '1.0'
  title: CDS Hooks REST API
host: cds-service-example.herokuapp.com
consumes:
  - application/json
produces:
  - application/json
paths:
  /cds-services:
    get:
      description: Get a description of all CDS services
      responses:
        200:
          description: Success (includes CDS service metadata)
          schema:
            $ref: '#/definitions/CDS%20Service%20Information'
  /cds-services/{id}:
    post:
      description: Invoke a CDS service offered by this CDS Provider
      parameters:
        - name: id
          in: path
          description: The id of this CDS service
          required: true
          type: string
        - name: request
          in: body
          description: Body of CDS service request
          required: true
          schema:
            $ref: '#/definitions/CDS%20Request'
      responses:
        200:
          description: Success (includes CDS Cards)
          schema:
            $ref: '#/definitions/CDS%20Response'
```

```
#############################################################################
#######
#                                  Definitions
#
#############################################################################
######
definitions:
  CDS Service Information:
    type: object
    properties:
      services:
        type: array
        items:
           $ref: '#/definitions/CDS%20Service'
  CDS Service:
    type: object
    required:
      - id
      - hook
      - description
    properties:
      id:
        type: string
        description: short id for this service, unique with the CDS
Provider (will be used in URL paths)
      hook:
        type: string
        description: The hook this service should be invoked on.
      title:
        type: string
        description: Human-readable name for the CDS Service (e.g. "CMS
Drug Pricing Service")
      description:
        type: string
        description: Longer-form description of what the service offers
      prefetch:
        $ref: '#/definitions/Prefetch'
  CDS Request:
    type: object
    required:
      - hook
      - hookInstance
      - context
    properties:
      hook:
        type: string
        description: The hook that triggered this CDS Service call.
      hookInstance:
        type: string
        format: uuid
      fhirServer:
        type: string
        format: url
      fhirAuthorization:
        $ref: '#/definitions/FHIR%20Authorization'
      context:
        type: object
      prefetch:
        type: object
```

```yaml
Card:
  type: object
  required:
    - summary
    - indicator
    - source
  properties:
    summary:
      type: string
    detail:
      type: string
    indicator:
      type: string
      enum:
        - info
        - warning
        - critical
    source:
      $ref: '#/definitions/Source'
    suggestions:
      type: array
      items:
        $ref: '#/definitions/Suggestion'
    selectionBehavior:
      type: string
      enum:
        - at-most-one
    links:
      type: array
      items:
        $ref: '#/definitions/Link'
Source:
  type: object
  required:
    - label
  properties:
    label:
      type: string
    url:
      type: string
      format: url
    icon:
      type: string
      format: url
Link:
  type: object
  properties:
    label:
      type: string
    url:
      type: string
      format: url
    type:
      type: string
    appContext:
      type: string
```

```
  Suggestion:
    type: object
    required:
      - label
    properties:
      label:
        type: string
      uuid:
        type: string
        format: uuid
      actions:
        type: array
        items:
          $ref: '#/definitions/Action'

  Action:
    type: object
    required:
      - type
      - description
    properties:
      type:
        type: string
        enum:
          - create
          - update
          - delete
      description:
        type: string
      resource:
        type: object

  Prefetch:
    type: object
    description: queries that the CDS Service would like the CDS Client
to execute before every call
    additionalProperties:
      type: string
```

Guideline Analysis (Integral)

Patologia	Regola	Population	Suggestion	Outcome	Parametri da misurare	Scale	Tipo di testo	Categoria temporale	Attore destinatario
Ictus	**IF** patologia = stroke and (grado_stroke = lieve or grado_stroke = moderato) **THEN** consiglia terapia di riabilitazione domiciliare	Pazienti affetti da stroke di grado lieve o moderato (Criteri di inclusione) Pazienti con stroke moderato/severo (Criteri di esclusione)	INTERVENTION: SUGGERIRE PROGRAMMA RIABILITATIVO DOMICILIARE	Promuovere il recupero precoce delle autonomie ed una riduzione dei costi.	Grado di Stroke	NIH Stroke Scale per la valutazione? Bartel Index (adl+iadl) er valutare post intervento il grado di recupero	Raccomandazione (AHA/ASA IIb,B [4], SPREAD forte favore [2]) **Classe IIb: Beneficio ≥ Rischio**	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** età_avanzata or deficit_congnitivo o basso_fit o incontinenza_urinaria **THEN** non raccomandare esercizi a casa	Pazienti con stroke e età_avanzata or deficit_congnitivo o basso_fit o incontinenza_urinaria	INTERVENTION: ESCLUDERE DAL TRATTAMENTO DOMICILIARE	Migliorare efficacia tratamento	Età Livello Cognitivo Livello FIT Incontinenza Urinaria		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** patologia = stroke **THEN** consiglia esercizi_aerobici and esercizi_resistenza	Pazienti con stoke	INTERVENTION ESERCIZI POSITIVO: Esercizi aerobici Esercizi di Resistenza	Migliorare la cognizione e i sottodomini dell'attenzione e della concentrazione, le funzioni visuospaziali ed esecutive			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** patologia = stroke **THEN** consiglia esercizi alta_frequenza e periodi_lunghi	Pazienti con stoke	INTERVENTION ESERCIZI POSITIVO: Esercizi Alta frequenza Esercizi per Periodi Lunghi	migliorare la sensibilità discriminativa			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** patologia = stroke and today - data_esordio_ictus < 3 mesi **THEN** consiglia inizio percorso domiciliare con esercizi task_oriented and rinforzo muscolare, di resistenza e cardiovascolari	Pazienti con Stroke	INTERVENTION ESERCIZI POSITIVO: Esercizi task oriented Esercizi di rinforzo muscolare Esercizi di resistenza Esercizi Cardio-vascolari	Migliorare le performances deambulatorie a lungo termine			Raccomandazione FORTE A FAVORE	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** patologia = stroke **THEN** raccomanda con forte favore il training con esercizi task specifici ripettivi a difficoltà progressiva, orientati ad un obiettivo	Pazienti con Stroke	INTERVENTION ESERCIZI POSITIVO: Esercizi ad obiettivo	Migliorare le performances			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Ictus	**IF** patologia=stroke and decondizionamento_normale **THEN** Monitorare Frequenza cardiaca (la frequenza cardiaca dovrebbe essere mantenuta al 40-70% della riserva o al 50-80% della frequenza massima) **IF** patologia=stroke and decondizionamento_grave **THEN** Monitorare Frequenza cardiaca (sessioni di 5 minuti di attività fisica ripetute durante il giorno, mantenendo la frequenza cardiaca al 30% della riserva)	Pazienti con Stroke e decondizionamento lieve o grave	TIP Parametri di Monitoraggio		Grado di decondizionamento	BORG	Raccomandazione	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla and obiettivo=Miglioramento umore **THEN** consiglia esercizi_resistivi and esercizi_endurance	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi resistivi and esercizi endurance	Migliorare il tono dell'umore	Patologia = sclerosi multipla		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla and obiettivo=Miglioramento_fatica **THEN** SCONSIGLIA allenamenti con intensita' elevata	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI NEGATIVO: Sconsiglia allenamenti ad alta intensità	Mantenimento capacità residua	Patologia = sclerosi multipla		Raccomandazione con grado di evidenza basso/molto basso	Durante COMPILAZIONE Pair	Medico

Sclerosi Multipla	**IF** patologia=Sclerosi_multipla and obiettivo=riduzione_fatica **THEN** consiglia allenamento_aerobico and allenamento_resistivo and allenamento_endurance	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI POSITIVO: Consiglia allenamento aerobico e resistivo e endurance	Miglioramento della capacità aerobica, della forza muscolare e dei parametri cinematici della deambulazione	Patologia = sclerosi multipla Obiettivo di cura			Raccomandazione Evidenza Alta a favore GRADE	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia=Sclerosi_multipla and obiettivo=riduzione_fatica **THEN** consiglia allenamento_aerobico and allenamento_resistivo and allenamento_endurance **CON SUPERVISIONE** (30 minuti 2/3 volte a settimana oppure tutti i giorni ad intensità moderata oppure 20 minuti 3 volte a settimana ad alta intensità)	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI POSITIVO: Consiglia posologia	Ottenere il massimo beneficio	Patologia = sclerosi multipla DISPONIBILITA' CAREGIVER	BORG PER L'AUTOMONITORAGGIO		NICE basato su studi di qualità di evidenza	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla **THEN** consiglia esercizi task_oriented	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI POSITIVO: Consiglia tipologia esercizio	Ottenere il massimo beneficio	Nessuno			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla and obiettivo = allenamento_forza **THEN** consiglia progressione (Set 1: 10/15 ripetizioni per ogni esercizio, Set 2 20/30 ripetizioni per ogni esercizio, riposo 1/2 minuti tra ogni set) **AND** consiglia lavoro su muscoli agonisti/antagonisti (cingolo scapolare, rachide, anche, estensori di ginocchio e muscoli dorsiflessori del piede)	Pazienti con sclerosi multipla and obiettivo = allenamento_forza	INTERVENTION ESERCIZI POSITIVO: Consiglia posologia esercizio	Ottenere il massimo beneficio	Obiettivo riabilitazione			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla and disabilità moderata/severa **THEN** consiglia teleriabilitazione e dispositivi robotici	Pazienti con sclerosi multipla and livello_disabilità moderato/severo	INTERVENTION ESERCIZI POSITIVO: Includi tra i pazienti candidati nonostante la patologia e il livello di disabilità	migliorare la funzione motoria e la coordinazione	Livello disabilità	Late-Life Function and Disability Index (LLFDI)		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Sclerosi Multipla	**IF** patologia = sclerosi_multipla **THEN** consiglia teleriabilitazione e dispositivi robotici	Pazienti con sclerosi multipla	INTERVENTION ESERCIZI POSITIVO: Consiglia riabilitazione degli arti superiori	migliorare la destrezza, la forza e la qualità della vita	Nessuno			qualità di evidenza degli studi bassa valutata col metodo GRADE	Durante COMPILAZIONE Pair	Medico
Malattia di Parkinson	**IF** patologia = malattia_di_parkinson **THEN** consiglia resistance_training and endurance_training	Pazienti con malattia di Parkinson	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi di endurance e training	Miglioramento forza muscolare e funzionalità del sistema ardio-respiratorio	Nessuno			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Malattia di Parkinson	Non esistono differenze significative nei vari approci riabilitativi	Pazienti con malattia di Parkinson						Testo informativo		
Malattia di Parkinson	**IF** patologia = malattia_di_parkinson **THEN** monitora intensita tra 61-90% della frequenza cardiaca massimale	Pazienti con malattia di Parkinson	INTERVENTION MONITORAGGIO: Monitora frequenza cardiaca massimale	Miglioramento forza muscolare e funzionalità del sistema ardio-respiratorio	Frequenza cardiaca			Raccomandazione	Durante EROGAZIONE Pair	Paziente
Malattia di Parkinson	IF patologia = malattia_di_parkinson THEN consiglia esercizi a casa	Pazienti con malattia di Parkinson	INTERVENTION INCLUSIONE POSITIVO: Includi tra i pazienti candidati nonostante la patologia e il livello di disabilità	Efficacia dello strumento riabilitativo	Nessuno			Raccomandazione	Durante COMPILAZIONE Pair	Medico

Cervicalgia	IF patologia = cervicalgia THEN consiglia esercizi recupero ROM, stretching, potenziamento	Pazienti con cervicalgia	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi recuper ROM, stretching, potenziamento	Efficacia dello strumento riabilitativo	Nessuno		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** iniziare il trattamento il prima possibile dopo l'evento acuto	Pazienti ai quali è destinata la riabilitazione pneumologica (BPCO)	INTERVENTION INCLUSIONE POSITIVO: Iniziare la riabilitazione nel momento della riacutizzazione o il prima possibile in seguito all'evento acuto	È inoltre ampiamente dimostrato che programmi di riabilitazione precoce dopo riacutizzazione, migliorano la tolleranza allo sforzo, la forza muscolare, gli indici di dispnea, la qualità di vita e riducono il numero di riacutizzazioni.			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica			TIP: Criteri di inclusione per la riabilitazione pneumologica	Definizione popolazione di pazienti a cui è destinata la riabilitazione pneumologica			Testo informativo	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica		Pazienti ai quali è destinata la riabilitazione pneumologica	TIP: Tipologie di esercizio indicate per pazienti in riabilitazione pneumologica	Definizione tipologie di allenamento			Testo informativo	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consiglia esercizio aerobico con intensità compresa tra il 30% e l'80% della capacità massima dell'individuo, con una frequenza di 3/5 volte a settimana, di durata minima di 30 minuti	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizio aerobico con intensità compresa tra il 30% e l'80% della capacità massima dell'individuo, con una frequenza di 3/5 volte a settimana, di durata minima di 30 minuti	Migliorare performance cardiorespiratoria	Intensità di allenamento massima (test da sforzo)		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consigliato esercizio fisico ad alta intensità (superiore al 60% della capacità massima dell'individuo), di durata compresa tra 20 e 60 minuti	Pazienti ai quali è destinata la riabilitazione pneumologica (che tollerano esercizio molto intenso)	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizio fisico ad alta intensità (superiore al 60% della capacità massima dell'individuo), di durata compresa tra 20 e 60 minuti	Migliorare performance cardiorespiratoria	Intensità di allenamento massima (test da sforzo)		Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consigliato esercizio aerobico mediante camminata in piano, treadmill o cyclette NOTA: treadmill escluso perché poco "safe"	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizio aerobico mediante camminata in piano, treadmill o cyclette NOTA: treadmill escluso perché poco "safe"	Migliorare efficacia trattamento			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** esercizio_aerobico **THEN** valutare intensità allenamento (scala di Borg o scala RPE) **IF** intensità_allenamento elevata (4-6 scala di Borg o 12-14 scala RPE) **THEN** ridurre allenamento **IF** intensità_allenamento bassa (soglie?) **THEN** aumentare allenamento	Pazienti ai quali è destinata la riabilitazione pneumologica che eseguono esercizi di tipo aerobico	INTERVENTION MONITORAGGIO: Valutare intensità allenamento mediante scala di Borg per la dispnea (4-6, da moderata a molto grave), o la scala RPE (12-14 di 20)	Valutazione intensità allenamento aerobico	Dispnea/Sensazione di fatica	Scala di Borg o scala RPE	Raccomandazione	Durante EROGAZIONE Pair	Paziente

Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica AND paziente_meno_FIT **THEN** consiglia "interval training"	Pazienti ai quali è destinata la riabilitazione pneumologica che non tollerano il "continuous training" a causa della elevata dispena	INTERVENTION ESERCIZI POSITIVO: Consiglia "interval training"						Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consiglia esercizi con una resistenza pari al 40% al 50% del massimo ottenuto nella prima ripetizione (1RM); l'utilizzo di gruppi di esercizi (da 1 a 4) da 10-15 ripetizioni per serie di esercizi da ripetere per 2 o più giorni a settimana. Alcuni pazienti possono essere in grado di incrementare l'allenamento aumentando le intensità al 60-70% della 1RM.	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi con una resistenza pari al 40% al 50% del massimo ottenuto nella prima ripetizione (1RM); l'utilizzo di gruppi di esercizi (da 1 a 4) da 10-15 ripetizioni per serie di esercizi da ripetere per 2 o più giorni a settimana. Alcuni pazienti possono essere in grado di incrementare l'allenamento aumentando le intensità al 60-70% della 1RM.	migliora la forza muscolare e la sintomatologia nelle ADL e migliora solo marginalmente la resistenza aerobica.				Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** esercizio_resistenza **THEN** valutare fatica muscolare percepita (scala di Borg RPE) **IF** fatica percepita superiore ai livelli 5-6 (fatica moderata) e 7-8 (fatica severa) della scala di Borg RPE **THEN** ridurre intensità allenamento **IF** fatica percepita inferiore ai livelli 5-6 (fatica moderata) e 7-8 (fatica severa) della scala di Borg RPE **THEN** aumentare intensità allenamento	Pazienti ai quali è destinata la riabilitazione pneumologica che eseguono esercizi di resistenza	INTERVENTION MONITORAGGIO: Mantenere il livello di fatica muscolare percepita dal paziente tra i livelli 5-6 (fatica moderata) e 7-8 (fatica severa) della scala di Borg RPE.	Valutazione intensità allenamento di resistenza			Raccomandazione	Durante EROGAZIONE Pair	Paziente
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consiglia esercizi di resistenza che includono l'uso di pesi (mano, caviglia), bande elastiche o utilizzando il proprio peso corporeo come salire le scale	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi di resistenza che includono l'uso di pesi (mano, caviglia), bande elastiche o utilizzando il proprio peso corporeo come salire le scale	Migliorare la forza muscolare			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** consiglia esercizi di allungamento degli arti superiori e inferiori eseguiti 2-3 volte a settimana, ogni esercizio di allungamento deve essere mantenuto per 30-60 secondi e ripetuto da 2 a 4 volte	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi di allungamento degli arti superiori e inferiori eseguiti 2-3 volte a settimana, ogni esercizio di allungamento deve essere mantenuto per 30-60 secondi e ripetuto da 2 a 4 volte	Migliorare capacità di eseguire gli esercizi e di eseguire le attività della vita quotidiana			Raccomandazione	Durante COMPILAZIONE Pair	Medico
Riabilitazione Pneumologica	**IF** riabilitazione_pneumologica **THEN** non raccomandato utilizzo della IMT Nota: IMT = Allenamento muscoli respiratori	Pazienti ai quali è destinata la riabilitazione pneumologica	INTERVENTION ESERCIZI NEGATIVO: Non raccomandato utilizzo della IMT				Raccomandazione	Durante COMPILAZIONE Pair	Medico

Riabilitazione Cardiologica		Pazienti ai quali è destinata la riabilitazione cardiologica	TIP: Tipologie di esercizio indicate per pazienti in riabilitazione cardiologica				Testo informativo			
Riabilitazione Cardiologica	**IF** riabilitazione_cardiologica **THEN** consiglia esercizi di resistenza insieme ad esercizi dinamici	Pazienti ai quali è destinata la riabilitazione cardiologica	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi di resistenza insieme ad esercizi dinamici	Aumenta la tolleranza al peso e la forza muscolare in maniera sicura ed efficace; migliora la funzione cardiaca e la gittata sistolica, modifica positivamente i fattori di rischio e aumenta il benessere psicologico del paziente con patologia coronarica stabile			Raccomandazione	Durante COMPILAZIONE Pair	Medico	
Riabilitazione Cardiologica	**IF** riabilitazione_cardiologica AND esercizi_di_resistenza **THEN** monitoraggio PA	Pazienti ai quali è destinata la riabilitazione cardiologica, in cui sono prescritti esercizi di resistenza	INTERVENTION MONITORAGGIO: monitoraggio PA		Pressione Arteriosa (PA)		Raccomandazione	Durante EROGAZIONE Pair	Medico	
Riabilitazione Cardiologica		Pazienti ai quali è destinata la riabilitazione cardiologica	TIP: Tipologie di esercizio indicate per pazienti in riabilitazione cardiologica				Testo informativo			
Artrite Reumatoide	**IF** patologia = artrite_reumatoide **THEN** sconsiglia sedentarietà	Pazienti affetti da artrite reumatoide (AR)	INTERVENTION: Sconsiglia sedentarietà	Evitare aumento di infiammazione			Raccomandazione	Durante COMPILAZIONE Pair	Medico	
Artrite Reumatoide	**IF** patologia = artrite_reumatoide AND AR_stabile **THEN** consiglia esercizi aerobici a moderata/alta intensità **IF** patologia = artrite_reumatoide AND (AR_attiva OR grave_compromissione_articolare) **THEN** consiglia riposo o esercizi aerobici a bassa intensità	Pazienti affetti da artrite reumatoide (AR)	INTERVENTION ESERCIZI POSITIVO: Consiglia esercizi aerobici a moderata/alta intensità nei pazienti con AR stabile. Consiglia riposo o esercizi aerobici a bassa intensità in pazienti con AR attiva o AR con grave compromissione articolare.	Migliorare capacità aerobica e forza muscolare	Fase malattia (AR stabile/attiva) Grado compromissione articolare	Rheumatoid Arthritis Seventy Scale ? https://academic.oup.com/rheumatology/article/41/1/38/1787947	Raccomandazione	Durante COMPILAZIONE/EROGAZIONE Pair	Medico	
Artrite Reumatoide	**IF** patologia = artrite_reumatoide **THEN** consiglia 30 minuti (o più) di attività fisica per almeno 5 volte a settimana	Pazienti affetti da artrite reumatoide (AR)	INTERVENTION ESERCIZI POSITIVO: Consiglia 30 minuti (o più) di attività fisica per almeno 5 volte a settimana	Migliorare capacità aerobica e forza muscolare			Raccomandazione	Durante COMPILAZIONE Pair	Medico	
Riabilitazione post-protesi	**IF** intervento di protesi anca o ginocchio **THEN** consiglia allenamento contro resistenza (allenamento RT)	Pazienti post intervento di protesi d'anca o ginocchio	INTERVENTION ESERCIZI POSITIVO: Consiglia allenamento contro resistenza (allenamento RT)	Aumentare la massa muscolare, per ridurre il rischio di atrofia postchirurgica. Aumentare la velocità di contrazione muscolare (aumento delle fibre veloci di tipo II), per rendere il paziente più responsivo alle perdite di equilibrio e quindi riducendo il rischio di cadute.			Raccomandazione	Durante COMPILAZIONE Pair	Medico	
Riabilitazione post-protesi	**IF** intervento di protesi anca o ginocchio **THEN** consigliata mobilitazione precoce (24/48 ore post operatorie)	Pazienti post intervento di protesi d'anca o ginocchio	INTERVENTION INCLUSIONE POSITIVO: Consiglia mobilitazione precoce (24/48 ore post operatorie)	Riduzione durata del ricovero			Raccomandazione (prove di evidenza moderate)	Durante COMPILAZIONE Pair	Medico	

CQL additional Outputs for each implemented Rule

```
   library "Cycling-Interval-Training-Prescription" version '1.0.0'
using FHIR version '1.0.2'
include "FHIRHelpers" version '1.0.2' called FHIRHelpers
codesystem "SNOMED": 'http://snomed.info/sct'
codesystem "Other": 'https://uts.nlm.nih.gov/uts/umls'
code "6-minute walk test (procedure) code": '252478000' from "SNOMED"
display '6-minute walk test (procedure)'
code "C2024890 code": 'C2024890' from "Other" display 'Other C2024890
Display'
code "Peripheral vascular disease (disorder) code": '400047006' from
"SNOMED" display 'Peripheral vascular disease (disorder)'
code "Difficulty walking (finding) code": '719232003' from "SNOMED"
display 'Difficulty walking (finding)'
context Patient

// o    6 Minute walking test performed, The value assessed for the
patient is less than 40% of the predicted
// value ( 30.5m, literature value) so less than 12.2
define "6-minute walk test Assessment":
  QuantityValue(MostRecent(WithUnit([Observation: "6-minute walk test
(procedure) code"],  'm'))) < 12.2 'm'


define "AgeRange-568":
  AgeInYears() >= 50 and AgeInYears() <= 90

// o    Goal Fitness is optimizing exercise capability
define "Other C2024890":
  (Verified([Observation: "C2024890 code"])) is not null

define "Peripheral vascular disease (disorder)":
  exists(ActiveOrRecurring([Condition: "Peripheral vascular disease
(disorder) code"]))

define "Difficulty walking (finding)":
  exists([Observation: "Difficulty walking (finding) code"])

define "MeetsInclusionCriteria":
  "AgeRange-568"
  and "Other C2024890"
  and "6-minute walk test Assessment"

define "MeetsExclusionCriteria":
  "Peripheral vascular disease (disorder)"
  or "Difficulty walking (finding)"

define "InPopulation":
  "MeetsInclusionCriteria" and not "MeetsExclusionCriteria"

))
```

```
define "Recommendation":
  if "InPopulation" then '•   Intervention: Prescribe the
patient Cycling Interval Training
•     Suggested Action: The session should be the following:
80% of the estimated maximum work-load (Wmax) for 1 minute,
then 20W for 1 minute, and increase according to symptoms
'
  else if "InPopulation" then ''
  else if "InPopulation" then ''
  else null


define "Rationale":
  if "InPopulation" then 'Optimization of the exercise
capability'
  else if "InPopulation" then null
  else if "InPopulation" then null
  else null

define "Errors":
  null


define function Verified(ObsList List<Observation>):
  ObsList O where O.status.value in {'final', 'amended'}

define function WithUnit(ObsList List<Observation>, Unit
String):
  ObsList O where O.valueQuantity.unit.value = Unit or
O.valueQuantity.code.value = Unit

define function MostRecent(ObsList List<Observation>):
  Last(ObsList O sort by Coalesce(effectiveDateTime.value,
effectivePeriod."end".value, effectivePeriod."start".value,
issued.value))

define function QuantityValue(Obs Observation):
  FHIRHelpers.ToQuantity(Obs.valueQuantity)

define function ActiveOrRecurring(CondList List<Condition>):
  CondList C where C.clinicalStatus.value in {'active',
'relapse'}
```

FHIR Helpers

```
   library FHIRHelpers version '1.0.2'

using FHIR version '1.0.2'

define function ToInterval(period FHIR.Period):
    if period is null then
        null
    else
        Interval[period."start".value, period."end".value]

define function ToQuantity(quantity FHIR.Quantity):
    if quantity is null then
        null
    else
        System.Quantity { value: quantity.value.value, unit:
quantity.unit.value }

define function ToInterval(range FHIR.Range):
    if range is null then
        null
    else
        Interval[ToQuantity(range.low), ToQuantity(range.high)]

define function ToCode(coding FHIR.Coding):
    if coding is null then
        null
    else
        System.Code {
          code: coding.code.value,
          system: coding.system.value,
          version: coding.version.value,
          display: coding.display.value
        }

define function ToConcept(concept FHIR.CodeableConcept):
    if concept is null then
        null
    else
        System.Concept {
            codes: concept.coding C return ToCode(C),
            display: concept.text.value
        }

define function ToString(value FHIR.uuid): value.value
define function ToString(value FHIR.ProvenanceEntityRole): value.value
  [...]
```

FHIR Clinical Guidelines Metatata [178]


```
{
  "resourceType": "Library",
  "type": {
    "coding": [
      {
        "system": "http://terminology.hl7.org/CodeSystem/library-
type",
        "code": "logic-library",
        "display": "Logic Library"
      }
    ]
  },
  "name": "Cycling_Interval_Training_Prescription",
  "title": "Cycling Interval Training Prescription",
  "date": "2020-11-24T23:42:40.459Z",
  "version": "1.0.0",
  "description": "Therapist Driven Rehabilitation Protocol for
Patients with Chronic Heart and Lung Diseases: A Real-Life Study",
  "url": "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7037983/",
  "status": "active",
  "publisher": "International Journal of Environmental Research and
Public Health",
  "useContext": [
    {
      "code": {
        "system": "http://terminology.hl7.org/CodeSystem/usage-
context-type",
        "code": "focus"
      },
      "valueCodeableConcept": {
        "coding": [
          {
            "system": "http://snomed.info/sct",
            "code": "454691000124100"
          }
        ]
      }
    }
  ],
  "purpose": "Optimal prescription of home-care rehabilitation
treatment",
  "approvalDate": "2020-10-31",
  "lastReviewDate": "2020-11-04",
  "topic": [
    {
      "coding": [
        {
          "system": "http://snomed.info/sct",
          "code": "454691000124100"
        }
      ]
    }
```

```
"author": [
    {
      "name": "Carla Simonelli"
    },
    {
      "name": "Michele Vitacca"
    },
    {
      "name": "Nicolino Ambrosino"
    },
    {
      "name": "Simonetta Scalvini"
    },
    {
      "name": "Francesca Rivadossi"
    },
    {
      "name": "Manuela Saleri"
    },
    {
      "name": "Aubin G Fokom"
    },
    {
      "name": "Ilaria Speltoni"
    },
    {
      "name": "Riccardo Ghirardi"
    },
    {
      "name": "Mara Paneroni"
    }
  ],
  "reviewer": [
    {
      "name": "Int J Environ Res Public Health"
    }
  ],
  "content": [
    {
      "contentType": "application/cql",
      "data": "BASE64 OMITTED"
    }
  ]
}
```

Example FHIR Resources

Patient Resource


```
{
  "resourceType": "Patient",
  "id": "109",
  "meta": {
    "versionId": "9",
    "lastUpdated": "2020-08-05T19:14:09.389+00:00"
  },
  "text": {
    "status": "generated",
  },
  "name": [
    {
      "use": "official",
      "family": "Babineau",
      "given": [
        "Musk"
      ]
    }
  ],
  "telecom": [
    {
      "system": "phone",
      "value": "613-555-5555"
    }
  ],
  "gender": "female",
  "birthDate": "1968-03-01"
    "text": "M"
  }
}
```

Observation Resource


```
{
  "resourceType": "Observation",
  "id": "138",
  "meta": {
    "versionId": "1",
    "lastUpdated": "2019-02-01T14:52:20.535+00:00"
  },
  "status": "final",
  "category": [
    {
      "coding": [
        {
          "system": "http://terminology.hl7.org/CodeSystem/observation-category",
          "code": "laboratory",
          "display": "laboratory"}]}],
  "code": {
    "coding": [
      {
        "system": "http://loinc.org",
        "code": "2093-3",
        "display": "Total Cholesterol"}],
    "text": "Total Cholesterol"},
  "subject": {
    "reference": "Patient/109"},
  "encounter": {
    "reference": "Encounter/132"},
  "effectiveDateTime": "2018-10-17T14:20:04-07:00",
  "issued": "2018-10-17T14:20:04.424-07:00",
  "valueQuantity": {
    "value": 195.43485010713596,
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Condition Resource


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APPENDIX C:

Example of the annotation output on an oncological guideline free text portion

Cancer of the endometrium is the most common type of gynecologic cancer in the United States. Vaginal bleeding is the presenting sign in more than 90% of postmenopausal women with endometrial carcinoma. Clinical risk factors for endometrial cancer, including but not limited to age, obesity, use of unopposed estrogen, specific medical comorbidities (eg, polycystic ovary syndrome, type 2 diabetes mellitus, atypical glandular cells on screening cervical cytology), and family history of gynecologic malignancy also should be considered when evaluating postmenopausal bleeding. The clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose endometrial carcinoma and endometrial intraepithelial neoplasia.

Transvaginal ultrasonography is a reasonable alternative to endometrial sampling as a first approach in evaluating a postmenopausal woman with an initial episode of bleeding. If blind sampling does not reveal endometrial hyperplasia or malignancy, further testing, such as hysteroscopy with dilation and curettage, is warranted in the evaluation of women with persistent or recurrent bleeding. An endometrial measurement greater than 4 mm that is incidentally discovered in a postmenopausal patient without bleeding need not routinely trigger evaluation, although an individualized assessment based on patient characteristics and risk factors is appropriate. Transvaginal ultrasonography is not an appropriate screening tool for endometrial cancer in postmenopausal women without bleeding. Recommendations and The American College of Obstetricians and Gynecologists makes the following recommendations and conclusions: The clinical approach to postmenopausal bleeding requires prompt and efficient evaluation to exclude or diagnose endometrial carcinoma and endometrial intraepithelial neoplasia. […] Transvaginal ultrasonography is a reasonable alternative to endometrial sampling as a first approach in evaluating a postmenopausal woman with an initial episode of bleeding. Transvaginal ultrasonography can be useful in the triage of women in whom office endometrial sampling was performed but tissue was insufficient for diagnosis. Failure to adequately identify a thin, distinct endometrial echo in a postmenopausal woman with bleeding should trigger sonohysterography, office hysteroscopy, or endometrial sampling. If blind sampling does not reveal endometrial hyperplasia or malignancy, further testing, such as hysteroscopy with dilation and curettage, is warranted in the evaluation of women with persistent or recurrent bleeding. An axial uterus, obesity, coexisting myomas, adenomyosis, or previous uterine surgery can contribute to difficulty in obtaining reliable transvaginal ultrasound assessment of endometrial thickness and texture. Because rare cases of endometrial carcinoma (particularly type II) can present with an endometrial thickness of less than 3 mm, persistent or recurrent uterine bleeding should prompt a histologic evaluation of the endometrium regardless of endometrial thickness. An endometrial measurement greater than 4 mm that is incidentally discovered in a postmenopausal patient without bleeding need not routinely trigger evaluation, although an individualized assessment based on patient characteristics and risk factors is appropriate.

Extracted Annotations from the custom software


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Contributions and Awards:

- Participation to the first international Grakn conference “Grakn Cosmos” with the discussion: “Developing a Clinical Decision Support System with Grakn” in London, February 6th -7th 2020.
- Winner of the HL7 scholarship announced by the board of HL7 Italy for a doctoral student whose research topic concerned the medical informatics sector. Participation in all modules of the HL7 Fundamentals course.
- E. Salvi, E. Parimbelli, A. Basadonne, N.Viani, A. Cavallini, G. Micieli, S. Quaglini, L. Sacchi - Exploring IBM Watson to extract meaningful information from the list of references of a clinical practice guideline (2017), Proceed AIME 2017, Lecture Notes in Computer Science, 10259 LNAI, pp. 193-197.