ONTOLOGY-BASED KNOWLEDGE MODEL FOR AN ACS MANAGEMENT CLINICAL GUIDELINE: HANDLING KNOWLEDGE UPDATES AND INSTITUTIONAL PRIORITIES

by

Mostafa Omaish

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The undersigned hereby certify that they have read and recommend to the Faculty of Graduate Studies for acceptance a thesis entitled "ONTOLOGY-BASED KNOWLEDGE MODEL FOR AN ACS MANAGEMENT CLINICAL GUIDELINE: HANDLING KNOWLEDGE UPDATES AND INSTITUTIONAL PRIORITIES" by Mostafa Omaish in partial fulfilment of the requirements for the degree of Master of Health Informatics.

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Supervisor: _____

Readers: _____

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Signature of Author

To:

Fatimah Omaish

&

Maha Shirah

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ABSTRACT

Management of Acute Coronary Syndrome (ACS) in an emergency department setting is challenging due to the complexity of the disease and the multi-disciplinary care environment, leading to the need for standardized protocols to ensure patient safety and care quality. Clinical Practice Guidelines (CPG) for ACS are prevalent but they are not directly applicable in the ED setting due to their complex narrative nature.

In this thesis we present a knowledge modeling solution, using semantic web technologies, to computerize the ACS CPG published by the American Heart Association. Our knowledge modeling approach provides a modular characterization of the CPG knowledge and offers unique mechanisms to (a) update the knowledge model in response to periodic CPG updates; and (b) streamline the ACS management clinical pathway in response to resource constraints at an institution. The computerized CPG will serve as an ACS management decision support system, targeting tertiary hospitals in Saudi Arabia.

LIST OF ABBREVIATIONS USED

AHA	American Heart Association
ABC	Airway, Breathing and Circulation
ACC	American College of Cardiology
ACEP	American College of Emergency Medicine
ACS	Acute Coronary Syndrome
ANN	Artificial Neural Network
BMP	Basic Metabolic Panel (a collection of blood investigations)
CAEP	Canadian Association of Emergency Physicians
CCB	Calcium Channel Blocker
CDSS	Clinical Decision Support System
CIG	Computer Interpretable Guideline
CK	Creatine Kinase
CP	Clinical Pathway
CPG	Clinical Practice Guideline
DKAP	Domain Knowledge Acquisition Process
DTD	Document Type Definition
EBM	Evidence Based Medicine
ECG	Electrocardiograph
ED	Emergency Department
EMR	Electronic Medical Record
EP	Emergency Physician
ER diagram	Entity Relationship Diagram
FOL	First Order Logic
FST	Fuzzy Set Theory
GEM	Guideline Elements Model
GEOWL	Guideline Elements in OWL

GLIF	Guideline Interchange Format
GP	Glycoprotein
HL7	Health Level Seven International
ICU	Intensive Care Unit
IV	Intravenous
KB-DSS	Knowledge Based Decision Support System
KON	Knowledge on ONcology through Ontology
LFT	Liver Function Test
MACSON	Management of Acute Coronary Syndrome Ontology
MET	Mobile Emergency Triage
MI	Myocardial Infarction
MLMs	Medical Logic Modules
MRP	Most Responsible Physician
NICHE	kNowledge Intensive Computing for Healthcare Enterprises
Non-STEMI	Non ST-segment Elevation Myocardial Infarction
OCL	Constraint Language
OKBC	Open Knowledge-Base Connectivity
OLAP	Online Analytical Processing
OOP	Object Oriented Programming
OR	Operational Research method
OWL	Web Ontology Language
PACS	Picture Archiving and Communication System
PAL	Protégé Axiom Language
PCI	Primary Coronary Intervention
RDF	Resource Description Framework
SAGE	Standards-Based Active Guideline Environment
SIGN	Scottish Intercollegiate Guidelines Network
SNOMED	Systematized Nomenclature of Medicine
STEMI	ST-segment Elevation Myocardial Infarction

SWRL	Semantic Web Rule Language
TIMI score	Thrombolysis in Myocardial Infarction score
TNM	Task Network Model
UA	Unstable Angina
UFH	Unfractionated Heparin
UML	Unified Modeling Language
UMLS	Unified Medical Language System
URI	Uniform Resource Identifier
W3C	World Wide Web Consortium
XML	Extensible Markup Language

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CHAPTER-1 INTRODUCTION

Cardiology is one of the most research-intensive disciplines in medicine, producing a vast range of literature covering clinical studies, best practices, therapeutic options and outcomes, and innovative surgical procedures. Various national level cardiac organizations, such as the American Heart Association (AHA), produce evidence-based Clinical Practice Guidelines (CPG) for health professionals. Despite the availability of CPGs, the challenge always is applying them in clinical care, especially at the point of care that may range from inpatient specialized services to the emergency department (ED).

Practice of emergency medicine is interprofessional in nature and involves collaboration with consultant, such as cardiologists. As a result, the application of CPGs in a multidisciplinary environment is challenging, but at the same time the benefits of following evidence-based guidelines that offer standardized care help to ensure patient safety and quality of care. In recent years, we note that the incorporation of CPGs in emergency medicine has been on the rise, and some of the reasons for their adoption in emergency medicine can be summarized as follows [1]:

1. Emergency physicians (EPs) are confronted with a broad range of acute illnesses. CPGs provide summaries for the acute management of these diseases;
2. CPGs provide common channels of communication between EPs and other consultants; and
3. Adherence to CPGs is used as a benchmark to measure quality of care.

We note that the level of training of practitioners in emergency medicine has an impact on the quality of care[2]. However, it is difficult to staff EDs with fully trained EPs [3], especially in developing countries and in rural areas of developed countries; further to this is the issue of compliance to CPGs in ED. A study conducted to determine the rate of nurses compliance to emergency triage guidelines showed more compliance of nurses trained in emergency departments than non-trained nurses [4]. However, a similar finding

among physicians is not clear in the literature; yet it is observed that physicians who maintain their training level by doing recertification are more likely to follow evidence based practice [5]. Physician resistance to using CPGs is attributed to what is called physician autonomy, which means being independent from any external control. The result is that physicians tend to deviate from CPGs. A study done by Helm *et al.* showed that 41% of physicians tend to justify their deviation from CPGs by using subjective criteria, such as worse patient condition than the guidelines predict [6]. Another factor that increases the subjectivity of decision-making is the cognitive processes through which physicians take the decision. Calder *et al* investigated a cognitive psychological theory in emergency medicine, called the dual process theory. This theory classifies the decision-making into two types, the experiential decision-making that is based on intuition, and the rational decision-making that is based on evidence. They enrolled only expert and trained physicians in this study. Although they found that EPs are using rational decision-making more than the experiential decision-making, they also found that physicians who are trained in family practice and have a shorter duration of emergency medicine training are likely to adopt the experiential decision-making method [7]. For our purposes, we note that most EDs are staffed with physicians having a lower level of ED training compared to the kind of physicians studied by Calder [8]; hence we argue that to effectively disseminate CPGs it is important that EPs are able to access CPG in order to help them in evidence-driven decision-making, because poor adherence to the CPGs in the ED may jeopardize the quality of care and patients' outcomes [9-11].

Hence, despite efforts to develop and publish CPGs, the reality is that they are underutilized [9] particularly in EDs [12]. The utilization of CPGs in EDs faces more challenges than in other settings due to the nature of the working environment and the pace of practice. Physicians depend mainly on what they learned of evidence-based practices during their training, because it is difficult to cover the broad spectrum of newly published CPGs [1], [13]. This highlights the need to develop innovative and alternative approaches to embed CPGs in clinical settings. The computerization of CPGs, and rendering them as Computerized Decision Support Systems (CDSSs) for physicians to seek CPG-mediated, patient-specific recommendations, is a potential solution for the

translation of CPGs into practice [14]. Research in computerizing CPGs to produce Computer Interpretable Guidelines (CIGs) is on the rise and a variety of methods are being proposed to develop CPG-based CDSSs. However, it is worth noting that existing methods for producing CIGs do not take into account three important factors pertinent to the validity and uptake of CPGs; these include: (a) mechanisms to update the CIG in response to new evidence; (b) aligning CIG with hospital resources as it has a bearing on the practical application of the CIG in a real clinical setting; and (c) handling ambiguity inherent in the narration of clinical decisions and recommendations in a CPG [15].

Literature shows that using CIG-based applications increases the adherence to CPGs [16], [17] and improves clinician performance [18]. More recent studies showed some improvement in patients' outcome; however, they lack power because of small sample size [19], [20]. However, CIGs may improve other aspects of health care quality and performance. A recent systematic review done by Sahota *et al.,* involving different types of CDSSs, such as alerts and CPG based CDSSs, concludes that there is no significant impact of CDSSs on patients' outcomes[21]. The authors attributed that to many factors, such as the scope of the studies they involved, which focused mainly on process improvement rather than on patient outcomes[21]. This review did not focus on the quality of the CPGs that were used to designs these systems. Non-valid or non-evidence based CPGs can lead to these results as well. The author found a significant improvement in the care process [21], which, through using CPGs, was found to predict patients' outcomes in Acute Coronary Syndrome (ACS) management, especially the mortality rate [22]. Additionally, care process improvement decreased the time to reperfusion thereby in ACS to meet the standard benchmarks (door-to-needle time less than 30 minutes and door-to-balloon time less than 90 minutes) [23]. Thus, we argue that developing CDSSs can indirectly improve a patient's outcome; however, determining a direct relationship between CDSSs and patients' outcomes warrants more research.

Latoszek-Berendsen and colleagues described the general components of CIG-based applications. These components are:

1. CPG model: It contains the building blocks of the CPGs, such as tasks and rules. Often, the model uses a concept called the task network model (TNM) to represent

the clinical pathway, which is abstracted from the CPG. More details are in Chapters 3 and 4. In our research we focused on the development of a CPG model.

2. Formal language and execution engine: For any CPG to be computer interpretable, it has to be represented in a formal computer language, such as Web Ontology Language (OWL). The final model needs a separate application called the execution engine to execute it [16].

In this thesis, we investigate the development of a modular CPG knowledge model that can be used to instantiate an ACS CPG for ED; i.e. computerize the CPG for ACS (for ED) so that it can serve as a knowledge base for the ACS management CDSS. We propose to address the shortcomings of the evidence update and resource-driven prioritization of clinical tasks at the knowledge modeling level. It is anticipated that the computerized ACS CPG can be executed via a CPG execution engine to serve as a computerized ACS management CDSS.

1.1. Research Motivation & Problem Statement

Adherence to CPGs in clinical practice is not optimal. Cabana *et al.* identified barriers preventing physicians from using CPGs [24]. Related barriers to our research are mentioned here:

1. **Lack of awareness and familiarity**: Physicians who are trained in a certain discipline are unlikely to be interested in other disciplines' CPGs. Some evidence shows that more than 70% of physicians working in EDs are general practitioners [3].
2. **Inertia of previous practice:** Physicians who have no training in emergency medicine, such as general practitioners, or who come from a different background, such as family practice, may have difficulty changing their previous practice to comply with emergency medicine CPGs [8].
3. **Environment-related barriers:** Incorporation of the knowledge of hospital resources is required to apply CPGs.

Therefore, CPG adherence is a complex problem due to multiple factors. In our research

we are proposing a solution to improve adherence to CPGs, whereby the CPG is computerized and presented to physicians as a CDSS, thus allowing physicians to consult the computerized CPG in clinical settings and improve the process care [21], [22]. Designing this CDSS will facilitate the future assessment of the relationship between the CDSSs use and patient outcomes.

The level of accuracy of this model will be estimated using clinical scenarios. Also, the model will be compared to domain experts' management of the same clinical scenarios.

The scope of research is limited to ED management of ACS, which adds another component to the research question; i.e., its capability to accommodate ED settings.

1.2. Research Objectives

Our research objective is to provide decision support to physicians regarding the treatment of ACS in the ED, guided by CPGs prepared by the American College of Cardiology (ACC) and the AHA. In this regard, we promote adherence to the CPG by computerizing it and allowing physicians to seek rapid patient-specific recommendations.

To meet our overall objectives, we pursue a number of goals, as follows:

1. **Development of an ACS Management Knowledge Model:** Our goal is to develop a semantically rich knowledge model that can represent the medical and procedural knowledge, encapsulated in CPGs published by AHA and ACC, pertaining to the management of ACS in ED. The knowledge model is anticipated to serve as the knowledge base for an ACS management CDSS. To deploy the CPG in an ED, we aim to develop a clinical pathway that is based on clinical scenarios for patient management.
2. **Development of mechanisms at the knowledge modeling level to incorporate updates to the CPGs as new evidence becomes available:** The objective is to update the knowledge model without the need for re-developing a knowledge model to capture the CPG updates.
3. **Addressing the issue of variations across multiple hospitals, in terms of policies and resources that influence the deployment of a computerized CPG**

in a specific clinical setting: Our objective is to manifest local operational constraints in the knowledge model and to prioritize clinical tasks based on the prevalence of these tasks in different institutions; the idea is to streamline the CPG recommendations with the clinical practices in an institution to promote the adherence to the CPG.

4. **Prioritizing clinical interventions according to specific criteria, such as the best evidence and most used practice in the hospital**.

1.3. Research Challenges

The proposed research objectives are expected to face challenges at the knowledge modeling and clinical CPG uptake levels:

1.3.1. Modeling Challenges

1. **Knowledge source selection:** There exist many ACS CPGs that are designed with respect to a specific region, a city, or an institution. Then, there are rather generic CPGs that cover typical cardiac care needs; for example, CPGs published by the AHA and the European Society of Cardiology [25], [26]. The challenge is to select the 'right' CPG, which addresses the domain needs and setting-specific constraints.
2. **Knowledge abstraction:** Managing ACS using the CPGs can vary according to the interpretation of the domain experts. Such variations are caused by heterogeneous working environments and are handled as options in the CPG. The challenge is to find a generic model that accommodates all of these options.
3. **Handling complications or unexpected events in the CDSS:** ACS has many complications. Management of these complications requires extra knowledge to be modeled and used by the CDSS. Therefore, the challenge is to connect our knowledge model with related CPGs to handle these complications.
4. **Integration with management workflow:** Many decision steps taken by physicians during ACS management need patient data, such as laboratory values from the laboratory information system, vacancy of the catheterization laboratory from the bed management system, and available medications form the pharmacy

information system. The challenge is to account for all the data elements in the knowledge model and then to connect the knowledge model with the respective data sources.

1.3.2. Clinical Challenges

Improve the efficiency in the ED: In any ED, time is a major factor in treating patients with ACS. Therefore, for a CDSS to be useful it is important that it provides the right recommendations in a short time frame. This time frame should be shorter than the gold standard time mentioned by CPG [27]. We expect to face this challenge at the implementation phase; however, the modeling phase should also consider ease of use issues, while realizing that the ED has a mix of both outpatient and inpatient care features in addition to its unique features; hence the CDSS should accommodate all these features.

1.4. Solution Approach

Our solution approach is in the realm of healthcare knowledge management, focusing particularly on the modeling and computerizing of CPGs. Our solution approach is to (a) model the ACS CPG in a semantically-explicit and executable knowledge model; (b) computerize the ACS CPG using the knowledge model; i.e., instantiate the model with an instance of the ACS CPG; and (c) execute the computerized ACS CPG to offer CPG-mediated recommendations for ACS management; i.e., develop a CPG-driven ACS management CDSS.

For knowledge modeling, we propose to exploit semantic web technologies, in particular using ontologies as a semantic knowledge model. Our approach for knowledge modeling is to build on an existing CPG knowledge model, in this case a CPG ontology developed at the NICHE research group [28], to model the selected ACS CPG by capturing both the domain and procedural aspects of a paper-based CPG. Typically, methodologies for developing ontology based models start from just the knowledge artifact. However, our approach is to exploit the Domain Knowledge Acquisition Process (DKAP) methodology [29], a methodology for building ontology models by using similar domain ontology, to specialize and extend the existing CPG methodology to develop a specialized ACS CPG

model that meets our functional objectives. Our research methodology has the following steps (for more details see Chapter 3):

1. **Determine the domain and scope of the model:** In this step we defined the scope of the solution; i.e., the problem in question.
2. **Determine the most suitable solution:** CDSS has many types, and each type is designed for a specific purpose with certain characteristics. We intend to do an extensive literature review to explore these types and determine the most suitable one.
3. **Knowledge source selection and analysis:** Due to the availability of many CPGs, we should choose one CPG source. Then the chosen knowledge source will be analyzed to abstract the knowledge concepts.
4. **Source ontology selection and analysis:** A similar medical ontology will be used as the foundation for the modeling process. The candidate ontology models will be analyzed to determine their suitability for our domain. Then the most suitable ontology will be analyzed to determine the required modifications to comply with our domain.
5. **Ontology engineering:** Reusing ontologies is a known research field. This field is divided into two main areas; ontology integration and ontology merging. Our research falls under the ontology integration category, where we use an ontology model to create a new model that serves our subject (see Chapters 3-4) [29], [30].
6. **Validate and test the final ontology**: Testing will be done by running clinical scenarios through the model. It also includes technical testing to check the consistency of the model.
7. **Recommendations**: The lessons learned during the modeling phase will be incorporated into the model to be used in the next phase of the CDSS creation.

This research is intended to serve as the first phase of implementing a CDSS for the management of ACS in the ED.

1.5. Research Contribution

This thesis makes the following contributions to the knowledge about ontology-driven CPG computerization:

1. **Specialization of a generic ontology model:** This thesis has extended and specialized an existing CPG ontology in order to accommodate the specific knowledge for ACS management in an ED setting. In this regard, the thesis demonstrates how to specialize a generic CPG ontological model to account for disease-specific knowledge, institution-specific procedural considerations, and evidence driven CPG updates. In addition, we have provided descriptions of decision logic, which can be subsequently, modeled as logic-based rules.
2. **New CPG update mechanism:** This thesis has investigated the provision of updating modeled domain knowledge/clinical procedures in response to CPG models. We have developed mechanisms, embedded within the CPG ontology model, to enable rapid knowledge updates in response to CPG updates. This is achieved by changing evidence values at the knowledge model level, obviating the need to reconstruct the entire CPG model.
3. **Incorporate the hospital resources knowledge:** This thesis extends the CPG model to incorporate information about resources present at an institution, as this information is crucial in determining the actions to be taken. Our CPG model captures information about resource availability and uses it in making clinical decisions.
4. **Computerization of ACS CPG:** This thesis presents a unique ACS management knowledge model that has been instantiated with the AHA CPG, leading to the development of a unique Management of ACS Ontology (MACSON) that incorporates mechanisms to track CPG updates and prioritize clinical actions based on institutional constraints.

1.6. Thesis Organization

The thesis will be organized as follows: Chapter 2 will be a literature review covering all the concepts we are discussing in this research and concludes by choosing our modeling

technique; Chapter 3 will be an overview of the research methodology; Chapter 4 will describe the ontology engineering methodology and the final ontology model; Chapter 5 will be about testing and validating the final model; and Chapter 6 provides the conclusion and includes our future directions

CHAPTER-2 BACKGROUND

In this research, various concepts were explored in order to achieve the goals and objectives mentioned in chapter 1. This chapter will be the foundation of these concepts.

2.1. Acute Coronary Syndrome (ACS)

ACS is a spectrum of heart diseases characterized by ischemic injuries to the heart's muscles (myocardium). Figure-2.1 shows the pathophysiology of this syndrome. The process starts slowly over time, even before the symptoms appear. This early phase can have many abnormalities, such as high blood pressure or high cholesterol. Management of the early phase includes controlling the blood pressure and lipid level and modifying life style. If the pathological process continues, the coronary arteries will suffer from narrowing of their lumen, which limits the amount of blood delivered to the myocardium. This stage can remain without changes for years; however, any further injury to the arteries may lead to sudden excessive narrowing or blocking of the lumens. The sudden cessation of the blood flow to the myocardium varies, and as a result of this variation the ACS presents in many forms. These forms are:

1. **Unstable angina** (UA): not easily defined because its symptoms overlap with myocardial infarction and stable angina symptoms. From the patients' symptom perspective, UA can be one of the following: (a) rest angina, (b) new onset severe angina, or (c) increasing angina. Cardiac markers such as troponin and creatine kinase (CK) are not elevated,
2. **Non-ST Segment Elevation Myocardial Infarction (Non-STEMI)**: a more severe disease that differs from UA in the symptoms and degree of the myocardium's oxygen deprivation. Electrocardiogram (ECG) may show non-specific ischemic changes, except for ST-segment elevation. Unlike UA, patients with Non-STEMI will have elevated cardiac markers,
3. **ST Segment Elevation Myocardial Infarction (STEMI):** the extreme of the ACS spectrum with either severe or complete cessation of blood flow to all or part

of the myocardium. Patients suffering from STEMI will have an elevated ST segment in the ECG and elevated cardiac markers in the blood [27].

After successful treatment of ACS, patients will be managed using a long-term regime that is designed to prevent further damage to the heart and limit the chance of recurrence.

2.1.1. ACS Epidemiology

The American Heart Association (AHA) reported that about 16 million Americans above the age of 20 had coronary heart disease; at least one million of them were presented acutely as ACS, and ≈ 29% of ACS cases were STEMI. The lifetime cost of ACS reached 1.1 million dollar per patient [25].

Similarly, in Canada there are about 70,000 heart attacks annually, 16,000 of which end with death [31]. More than 60,000 patients were admitted to hospitals in 2005/2006 after suffering from heart attacks. Patients suffering from ACS have significant mortality and morbidity, and the cost of care is huge, measured in millions of dollars [32].

2.1.2. Management of ACS

Management of ACS, which includes diagnosing the diseases and treating them, is a very long subject; this section offers a concise overview. For more details see [27], [33-35].

1. Diagnosis of ACS:

The process of diagnosing ACS begins with the usual assessment of the patients such as taking history and doing physical examination, in addition to doing the initial ECG, which can certainly show the diagnosis or increase the ACS index of suspicion.

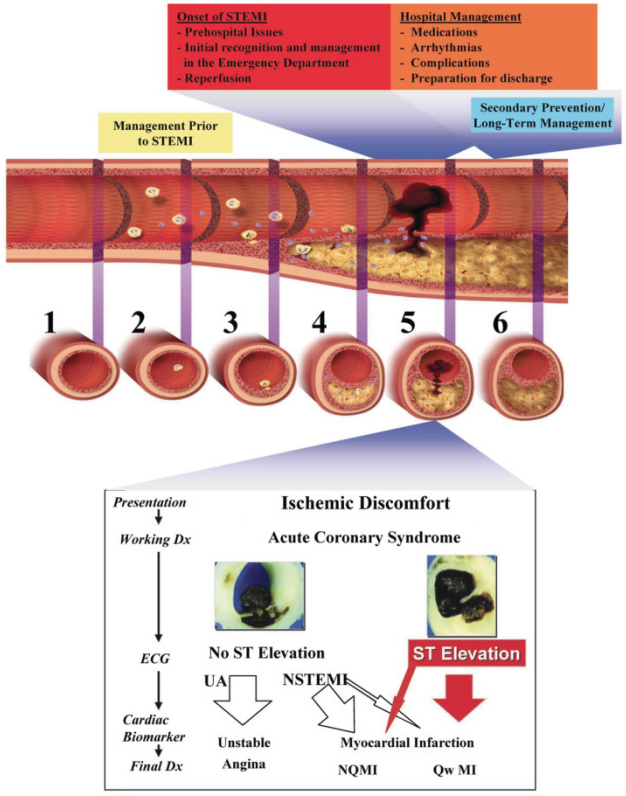

Figure 2.1 Classification and patho-physiology of ACS. Taken with permission from [27].

Patient history is very important to increase the accuracy of the diagnosis. If the diagnosis is still not certain, cardiac enzymes can help in ruling in/out ACS with a high level of accuracy. Dealing with uncertainty of diagnosis is out of scope of this research; however, some terminologies, which will be mentioned frequently during this research, are worth mentioning:

A. **ELECTROCARDIOGRAM (ECG):** The myocardial muscle's electrical signals can be received from the body's surface. These electrical signals are sensitive to any damage that happens to the myocardium. By putting many electrodes over the body, the exact location and extension of the damage can be accurately determined.
B. **CARDIAC ENZYMES:** The damaged myocardium cells release specific biochemical markers, which can be measured by taking a blood sample. Troponin and Creatine Kinase (CK) are examples of these markers.

There are other diagnostic modalities, such as other blood tests that help in the diagnosis; for more details about these modalities consult the ACC/AHA guidelines.

2. Treatment of ACS:

The optimal goal of acute treatment of ACS is to restore the blood flow through the coronary arteries and prevent further damage to the myocardium. There are two main modalities for blood flow restoration:

A. **CARDIAC CATHETERIZATION:** a mechanical type of treatment done by inserting an instrument (catheter) through the body, usually through the femoral artery, to reach the coronary arteries and open the blockage by inflating a balloon. Usually this procedure ends by leaving a stent to help prevent re-blockage, and the whole process is visualized using a special x-ray technique (fluoroscopy). Cardiac catheterization is a type of angiography.
B. **THROMBOLYTIC:** a type of medication that works on the thrombus blocking the arteries in order to dissolve it. There are many drugs classified as thrombolytic; these will be discussed later.

Treating ACS is not confined to these two modalities, as there are other adjunct modalities not mentioned here; for more details consult [27], [33-35].

2.1.3. ACC/AHA Guidelines for ACS Management

The American College of Cardiology (ACC) and the American Heart Association (AHA) have been publishing Clinical Practice Guidelines (CPGs) for ACS since 1990. The guidelines are frequently updated. In 2004 they were completely revised, and then updated in 2007, 2009, and 2011.

We chose to use their CPG in our project for several reasons:

1. **Universality**: this CPG was published to be used by different healthcare institutes. Using it helped in avoiding institute-specific terminologies and knowledge and will also promote our project's usefulness to various healthcare institutes.

2. **Comprehensiveness**: The CPG has a detailed description of ACS and its management. Although it is not a complete description, it has helped in solving a lot of ambiguities,
3. **Continuous updates**: The CPG is supported by two big organizations, ACC and AHA. That will guarantee the continuity of the updates using the same system,
4. **Description of the evidence**: One of the strengths in the CPG is providing the level of evidence for particular interventions, which serves our goals in modeling the evidence's levels and guidelines' updates.

Major challenges we faced in the CPG were in the length of each edition and the fact that the CPG did not differentiate between emergency department treatment and inpatient treatment.

2.2. The Setting (Emergency Department)

Before 1960's, there was no emergency medicine specialty; hospitals were recruiting general practitioners, other specialists, and even nurses to cover emergency departments (ED). The Alexandria plan was the first initiative to provide 24/7 coverage of emergency departments by specialized physicians in the United States. This initiative and others led to establishing the American College of Emergency Physicians (ACEP) in 1968, which became responsible for supervising the training of emergency physicians in USA [36].

In Canada, similar efforts were ended by establishing of the Canadian Association of Emergency Physicians (CAEP) in 1977, and the designation of emergency medicine as an independent specialty in 1980 [37].

2.2.1. Shortage in Emergency Medicine Specialty

Despite three decades of continuous training and graduation of emergency medicine physicians (EP), there is still a huge shortage of them. In 2001, some reports showed that eighty percent of physicians working in Canadian emergency departments were not trained to be EPs [38]. This shortage may affect the quality of practice because of non-adherence to CPGs. It is common to have many non-specialized practitioners working in the EDs, and they often are unaware that CPGs exist. Since knowledge dissemination

can help in mitigating this problem, one of our research goals is to disseminate the knowledge in form of computerized CPGs to the physicians covering EDs.

2.2.2. Decision Support Systems in ED

J. Handler *et al* recommended that all clinical decision support systems (CDSS) used in ED should have certain characteristics such as:

- **Non-fragmented system**: CDSS should be integrated with ED workflow and should be linked to evidence's sources,
- **Online access:** The system should support online access and should not limit the physician's access to web resources [39].

A study was conducted in the University of Alberta Hospital Emergency Department to explore the sensibility of computerized clinical practice guidelines using eCPG©. This study shows that physicians were not using the system frequently, especially the new physicians. The authors related this finding to several reasons, one of which is the fact that physicians will use it when they need it to make decisions regarding rare diseases or conditions [40]. Also, this finding can be related to the fact that eCPG© is a stand-alone system and not integrated to the clinical workflow.

Others found that CDSSs were used successfully in ED. ACAFE is a CDSS used to assess patients with bronchial asthma, which showed improvement in physician documentations and discharge plans [41].

Overall, CDSS in ED has potential benefits when directed to the right users and the right usage.

2.3. Decision Support in Medicine

The healthcare domain is rich in data, information, and knowledge. Practitioners face huge challenges in keeping up with that. The concept of decision support in healthcare is not new; it was started early as the beginning of computing technology. However, the degree of adoption is lagging behind, compared to other domains such as banking [42].

Healthcare is a complex domain, often described as a complex adaptive system, which means being dynamic and exponentially growing [43]. This nature of healthcare goes side by side with its knowledge. The complex nature and inadequate use of technology has contributed to the higher rate of preventable medical errors [44].

The following is a description of the common types of systems used to support clinical decisions:

2.3.1. Data and Information Retrieval

The debate continues about classifying these systems as CDSS. Systems such as laboratory result viewers can help physicians in taking the right decision [45]. However, there are no differences between these systems and a printed result from the laboratory, except the speed. What is clearly missing in these systems is the ability to analyze and reason the data and provide meaningful conclusions.

Some systems, such as online analytical processing (OLAP), can analyze the data retrospectively; however, other systems or users are needed to make the decisions for current tasks. These systems do not support decisions for current tasks or cannot reason the data. Therefore, they should not be classified as decision support systems by themselves [46].

2.3.2. Non-Knowledge Based Decision Support Systems

In the early sixties, CDSSs were developed to mimic human thinking to solve problems. The interaction between these systems and users were either full acceptance when the results are satisfactory or complete rejection when they are unsatisfactory. In healthcare, these systems were directed to find diagnoses for patient conditions by mimicking clinician's thinking.

These types of systems depend on two major components, data and inference. Inference is performed by using tools such as statistical probabilistic tools [47].

Operational Research method (OR) was one of the earliest tools used in the medical domain by Robert Ledley, 1962 [48], [49]. The card sorting system described by Ledley

was one of the systems that are using the probabilistic method to find differential diagnoses for certain symptoms.

The other component is the data, which is collected by users or other part of the system such as databases, then analyzed by the system. Ladley described a learning system which could recalculate the probability during each use of a new data set [48].

An interesting system was developed in 1969 in Beth Israel Hospital, Boston, to diagnose acid base balance disturbance. The diagnostic functionality did not differ much from the previous systems; however, it had a unique functionality at that time. The system recommended the treatments for the diagnosis and linked the user to related literature. It seems that was one of the earliest uses of knowledge base decision systems in medicine. The simplicity of the conditions this system analyzed (acid base disorders) helped in its success [50].

Another tool used in dealing with uncertainty in clinical decision support systems is the ***Bayesian network***, which is a statistical tool founded by Thomas Bayes (1763) [51]. This tool was popular during the 1970's and 1980's, and is still used now. For example, TraumaSCAN was developed in 2000 for predicting the trajectory of penetrating injuries, which uses the principle of the *Bayesian network* [52].

In 1965 Lofti Zadeh introduced Fuzzy Set Theory (FST). FST was the foundation of ***Fuzzy logic*** that is used to deal with uncertainty in artificial intelligence [53]. Computer Assisted Diagnosis (CADIAG-2) was developed to deal with fuzzy descriptions of patients' symptoms and signs [54]. Warren Beliakov and Berend Van Der described the potential use of Fuzzy Logic in dealing with uncertainty in the textual clinical practice guidelines [53].

Part of the continuous effort to mimic human thinking was the contemporary neural networks theory by Alexander Bain and William James. They, independent of each other, theorized that neurons have connections between them, and these connections are strengthened or weakened by the magnitude of their interaction [55]. This theory inspired researchers to develop ***the Artificial Neural Network (ANN)***, which consists of Nodes representing the neurons and weighted connections representing the neurons' connections

or Axons. Yan and his colleagues developed a system used multilayer processing of ANN to diagnose heart diseases [56].

Decision tree is a simple yet powerful tool in making decisions. It was used in CDSS for simple tasks. The tree has nodes and each node has weight. The total weight determines the final probability of a certain condition. This method was used in the medical domain, such as in predicting kidney transplant survival [57] and determining the severity of asthma patients [58]. Decision trees are used also in knowledge based systems (see decision model section below).

Hybrid systems use more than one method to make decisions. AptaCDSS-E is a system designed to predict cardiovascular diseases. It uses Decision Tree, ANN, Support Vector Machine, and Bayesian Network [59].

These systems share a common objective, which is finding the most likely diagnosis or diagnoses. Some of these systems have the advantage of using machine-learning techniques.

Most of above-mentioned systems were designed to operate as stand-alone systems, which limits their uses. Other systems, such as HELP system [47], were integrated with the clinical workflow.

2.3.3. Knowledge Base Decision Support System

Non-knowledge based systems have many disadvantages:

1. They aim to replace the role of users by giving the final diagnosis or decision. Usually, clinicians refuse that because of their autonomy.
2. They lack flexibility; coupling the decision logics with the systems' codes makes updating the system difficult.
3. These systems are often not reusable outside their domain.

Knowledge base decision support systems (KB-DSS) help users to take the decision by recommendation rather than giving the final decision. Usually, users have more acceptances to this type of systems. This acceptance is due to the choice that is given to the users to deviate from the systems' recommendations. Additionally, users can always

refer to the knowledge base, which is created by domain experts. In this type of system, the knowledge base can be separated from the technical coded part. That guarantees the flexibility when knowledge needs to be updated or shared.

KB-DSS has three main components, ***Knowledge Base, Inference engine, and user interface*** [46]

2.3.4. Knowledge Base

Knowledge in healthcare comes in many forms. It can be explicit knowledge, such as a written book or guidelines, implicit form, such as a daily workflow in a clinic, or tacit knowledge, such as the knowledge in the experienced physician's mind [60]. Health Care Knowledge Management is a science that aims to capture these types of knowledge. Going through that is out of our research's scope; however, it is appropriate for our research to go through the clinical practice guidelines.

Nowadays, **Evidence Based Medicine (EBM)** is dominating most of the medical practices. The first real initiative in implementing the evidences in medicine was by Archie Cochrane and his colleagues, which ended by creating Cochrane Reviews in the early nineties [61]. Since that time, research studies were increasing in frequency, making it hard for health professionals to keep up with them.

Clinical Practice Guidelines (CPGs) are defined by the Institute of Medicine as:

> *"Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances"* [62].

CPGs played a role in easing the overwhelming number of clinical research studies by collecting the strongest evidence (or the agreed on evidence) for a particular medical condition, and then summarizing and presenting this evidence to health professionals. However, the benefits of the CPG were built on several assumptions, the first of which is assuming that users will easily access, accept, use, and share these guidelines [62]. These assumptions were proven to be inaccurate when testing the adherence to the CPGs in

clinical practice. The result of that is what we see as a gap between the existing evidence and what really happens in practice. This phenomenon is known as knowledge-gap [63]

To close the knowledge-gap, researchers suggested some strategies to disseminate and encourage using CPGs, which can be passive, such as sending CPGs by mail to practitioners, or active, such as education and sending feedback [64]. A study by Kryworuchko and colleagues showed that the benefits of these strategies are limited [64].

Another stream of research was conducted to computerize CPGs. The goals of these research studies include dissemination of the CPGs, in addition to their standardization, reuse, and sharing.

Successfully computerized CPGs are used as knowledge bases for CDSS [16].

Modeling CPGs aims to produce Computer Interpretable Guidelines (CIGs). There are many formalisms produced in this field. Most of the CIG projects started with conceptualizing the content of the CPGs to produce models capable of accommodating different CPGs, then finding or creating formal languages to represent the model, and finally, creating an execution engine to execute the CIG.

Modeling started by defining the CPGs' scope and the intended use . For example, Arden Syntax was developed for simple guidelines and was used in simple tasks such as laboratory result alerts. This purpose was served perfectly by the simple design of Arden Syntax, which consisted of three components; Medical Logic Modules (MLMs), Maintenance and Library Slots, and Knowledge Slots [65].

On the other hand, Guideline Interchange Format (GLIF), PROforma, Asbru, and EON were developed to handle more complex CPGs, and intended to be integrated with the clinical workflow. Therefore, these formalisms were started initially as flowcharts, then transformed to computer interpretable models using formal languages. They share common concepts, such as actions, and decision with different nomenclature [65]. These concepts are the buiding blocks of the CPGs.

There are many approaches for knowledge representation in the literature. The following section provides overviews of these approaches.

2.4. Knowledge Representations

Knowledge representation is a methodology for transforming the knowledge from one form to another. In the context of our research, it means transforming a medical domain's knowledge (such as a CPG) from textual form to a computerized form (CIG).

There are many knowledge representation methodologies in the literature. The following are overviews of some of them:

2.4.1. Rule-Based Systems

Rule-based systems embed the knowledge in rules to make the decision. They are used in simple guidelines for simple tasks, such as alerts. For example, MLM is one of the modules in Arden Syntax, which is a rule-based knowledge representation.

Although, these systems are very efficient for simple tasks, they cannot handle more complex CPGs because of four main reasons:

1. Complex CPGs need a huge set of rules to represent them.
2. Textual CPGs are designed to be executed sequentially in clinical practice. Therefore, rule-based systems need connections between the rules to run them sequentially.
3. Ambiguity is an issue with complex CPGs. Most of the rules have Boolean decision outcomes (true/false). However, most of the decisions in the CPGs are not defined clearly, making them difficult to be represented as Boolean decisions.
4. It is difficult to deal with conflicting rules, especially with complex guidelines [66].

The rule engine is the responsible component in CDSS for firing and terminating the rules using one of two methods, (a) forwarded chaining or (b) backward chaining [66].

Rule-based systems are still used because of the simplicity of their design and coding. They are used in relatively non-complex problems, such as glucose monitoring in the Intensive Care Unit (ICU) and alerting nurses to adjust the insulin infusion [67].

Other systems such as ontology-based systems use the rules as an adjunct representation method of some knowledge parts that are difficult to be modeled using ontology alone. These systems are not called rule-based because the majority of the knowledge is modeled using other formalisms.

2.4.2. Decision Model

In this approach all possible decisions' alternatives for certain conditions are modeled. Then the system navigates through these alternatives according to criteria that determine the most suitable alternative for that condition. Thus, the knowledge is represented as a decision model, such as decision tree. ALCHEMIST is a system that uses the decision models to reconstruct the guidelines [68]. Other commonly used decision models in Decision Support Systems are influence diagrams and state-transition models [68]. This approach shares the same limitations of the rule-based systems in dealing with complex guidelines.

2.4.3. Semantic Modeling

Compared to other methods, this method focuses on modeling the CPGs as a separate object from the CDSS and tries to represent the meaning of the CPGs.

In rule-based and decision model methods, the final model focuses only on decisions. However, CPGs contain more than only the decisions; they include knowledge such as literature review, foundation knowledge about medications, patho-physiology, and evidence levels.

This representation method addresses the need for the sequential execution of the CPGs as clinical workflow. The sequential execution of the CIG (to represent the clinical pathway) facilitates the integration of the CDSS in patient management. Research studies in semantic modeling are active and continuously producing new methods and tools, including languages and specifications.

The following sections will highlight semantic modeling techniques under separate headings.

2.5. Simple Markup Languages

These tools aim to represent the meaning of the CPGs model's elements by marking them. It is also called the Document-Centric approach [57].

2.5.1. XML-Based Formalisms

Guideline Elements Model (GEM) was developed using **Extensible Markup Language (XML)** to compensate for the deficit inherited in GLIF2. It provided the flexibility to include more valuable information in the guidelines compared to GLIF2, which focused more on the recommendations [58]. GEM's authors argued that using XML can help in (a) indexing and searching, (b) being open standard helps in developing applications capable of parsing the guidelines, and (c) being an intrinsic part of the web, which can promote its use [70]. Despite these benefits, GEM has some limitations inherited from the nature of the XML, which is not a knowledge representation language and thus cannot handle the complex content in the guidelines [71].

Markup method can help in developing a simple hierarchical model but cannot handle complex multidimensional models.

2.5.2. RDF-Based Formalisms

Resource Description Framework (RDF) was created by the World Wide Web Consortium (W3C) to represent data and information for semantic web. Element identification is based on the Uniform Resource Identifier (URI).

In the RDF graph, XML syntax is used to markup the RDF's elements. This markup method is known as RDF/XML.

RDF graphs are represented as triples. Each triple has three elements: Subject, Predicate, and Object. The RDF schema was created to define the vocabulary used in the RDF graph [72].

The RDF is better than XML as a representation language; however, it is not enough to do reasoning on the RDF model.

The RDF model is used to fit other ontological modeling specifications, such as FRAME and Web Ontology Language (OWL) [73].

2.6. Ontological Methods

Ontology is defined as "an explicit specification of a conceptualization"[74].

The new trends in CPGs modeling are to develop ontologies, which can accommodate most of the knowledge in the CPGs (depending on the model).

Integration of the CPGs in the clinical workflow requires sequential execution, which can be performed using the task network model (TNM). TNM is the representation of the clinical pathway (CP) or the flowchart. This approach is used in many CDSS, such as Asbru, EON, GUIDE, PROforma, GLIF, and PRODIGY [75]. PROforma used a langauge derived from Red Representaion Language, while Asbru used Document Type Definition (DTD) and XML, and GLIF2 used GLIF syntax at the early stages, then changed to RDF in GLIF3 [76], [77].

Nowadays, ontologies are built using two languages, Frame and Web Ontology Language (OWL).

2.6.1. Frame-Based Representation

Marvin Minsky described Frames theory in 1974, and that was the beginning of a new method of knowledge representation [78].

Open Knowledge-Base Connectivity (OKBC) put a protocol to help in interoperability between the applications that use Frame. Many editing applications, such as Ontolingua, Loom, and Protégé-2000, comply with this protocol. Most of the recently published Frame-Based CDSS used Protégé-2000 Knowledge Modeling Editor.

Often, Protégé-2000 is used to build the model as an RDF graph. The model is composed of the following elements:

1. **Classes:** These represent the concepts in the domain arranged as a hierarchy of classes and subclasses. Multiple inheritance is allowed in this method; i.e., class A can be a subclass of both class B and Class C. Generally, classes are called class frames and instances are called frames.
2. **Slots:** These represent the relationships between the classes or the instances in the classes. There are two types of slots: (a) own slots, which are applied only to the frames (instances), and (b) template slots, which are applied to the classes and inherited by the subclasses.
3. **Facets:** These represent the attributes of the slots, or, in other words, the restrictions [79].

The Frame-based approach was used in many CPGs formalisms, such as GLIF3, EON, and GASTON. Standards-Based Active Guideline Environment (SAGE) was developed using the Frame-based approach and was targeting the following features:

1- Responding to the clinical information system's (CIS) workflow rather than controlling it. SAGE was designed to respond to the decision events when reached by the workflow of the CIS. This feature allowed SAGE to be part of other bigger systems and guaranteed its integration with clinical workflow.

2- Information standards: SAGE supports common standards such as HL7 and SNOMED.

3- Flow-of-Control Standards: SAGE adopted a standard that was created by Workflow Management Coalition [80].

The followings are systems using Frame:

- **Knowledge ON ONcology through Ontology** (**KON^3**) was based on the SAGE model to provide decision support for practitioners working with oncology cases. However, KON^3 uses Semantic Web Rule Language (SWRL) compared to GELLO in SAGE [80-82].

  KON^3 is separate from hospital information systems. Clinicians use KON^3 interface to guide them through the decision steps. Simultaneously an Electronic

Medical Record (EMR) responds by providing and recording the required data to make the decisions [82].

- **Mobile Emergency Triage** (**MET-2**) uses a Frame-based approach to represent the knowledge bases (application model). Three different triaging systems were implemented using MET-2: (1) Triage of pediatric abdominal pain (MET2-AP), (2) triage of pediatric scrotal pain (MET2-SP), and (3) postoperative management of radical prostatectomy (MET2-RP). The system was designed to operate in different platforms. Therefore, ontology technique was used to model the configuration of the system in four other ontologies: configuration, interface, data, and support ontologies [83].
- **SAPHIRE** is an intelligent home exercise monitoring system for patients with cardiovascular disease. It uses GLIF to model a guideline published by the American Heart Association (AHA). This guideline is used to reason the data captured from monitoring devices attached to the patient during home exercise and then to sends these data to the hospital information system [84].

2.6.2. Web Ontology Language (OWL)

OWL was founded by The World Wide Web Consortium (W3C) to build semantic web ontologies. W3C exploited the concepts in the Extensible Markup Language (XML) and the Resource Description Framework (RDF) to build the OWL. Compared to Frame, OWL has an extra layer of semantic richness [85].

OWL comes in three sublanguages:

1. **OW-Lite** has a lower level of complexity than other sublanguages, which makes it suitable for simple taxonomies and thesauruses.
2. **OWL DL** is a more complex sublanguage than OWL-lite, and guarantees full computer interpretability when compared to OWL Full.
3. **OWL Full** gives the user the freedom to articulate the full meaning but does not guarantee full computer interpretability [85]. The major distinction between OWL Full and OWL-DL is the fact that the former supports multiple inheritances, while the later does not.

The following are examples of systems used OWL:

- **Guideline Elements in OWL (GEOWL)** was created in the top of GEM to exploit the functionalities of OWL. The initial work was transforming the elements in XML to classes in the OWL, then translating the properties in XML file (most of them are part-whole) to OWL properties (such as is-a) [71].
- **Preoperative risk assessment CDSS** was designed in Manchester University. Initially it was based on databases; then OWL ontologies were involved in the design to add the following components:
    a. **Decision support ontology**, which models the preoperative tests clinical guidelines that were issued by National Health System in UK.
    b. **Questionnaire ontology,** which models the necessary patient information to be collected by the system. The system exports this information as an OWL file to maintain the semantic interoperability of patient history record.

  The final preoperative assessment is performed by a hybrid process that involves rules calculation and ontology reasoning [86].
- **HEARTFAID** is a project designed to provide decision support for physicians dealing with heart failure cases. It is based on an OWL model of AHA heart failure guidelines. The unique feature of this project is the fact that it is not only modeling the descriptive part of the guideline's knowledge, but also the procedural knowledge. The authors tried to include all the rules in the ontology model and had some success. They identify challenges preventing them from embedding all the rules in the OWL model. These challenges include the following:
    a. OWL does not support certain operators, such as mathematical operators.
    b. OWL does not support control flow, such as loop, branch, and jumping. This challenge was partly overcome by other research [28], [87].
    c. OWL is an open world language, while rules can be open or close world language, giving more freedom for the modeler [88].

Similar research was performed with different modeling techniques for different purposes, such as a decision support system for prostate cancer, which can handle the variation in the guidelines between different institutes [89] and execution of Nursing Care Plans [90].

OWL and Frame are well-developed languages; however, they are not capable of representing all the knowledge in the CPGs. Therefore, Rules are still used with OWL and Frame to fill these gaps. Rules' languages are called expression languages and will be discussed in the following section.

2.7. Expression Languages

Expression languages are utilized to express the rules and conditions that are used in decision steps. These rules and conditions are difficult to model and usually need to be executed as rules.

First Order Logic (FOL) is the precursor of most rule languages, such as Protégé Axiom Language (PAL) [91].

Guidelines expression language (GEL) and GELLO (an object oriented expression language) are used by GLIF, while PROforma used a formal expression language derived from Red Representation Language. EON used three different languages for different purposes: Boolean Criteria for simple Boolean decisions, Protégé Axiom Language (PAL) for more complex decisions, and Asbru temporal expression language to represent temporal driven decisions [65].

W3C created a special expression language for OWL called Semantic Web Rule Language (SWRL) to be used in a semantic web. Although SWRL has some limitations, the research continues to overcome them. For example, XSWRL is an extension of SWRL that adds more expressivity than SWRL when using it with OWL-DL [92], and SWRL-FOL is proposed to enable SWRL to support more of first order logic characteristics, such as the unary and binary functions [93].

2.8. Execution Engines

Some of the aforementioned formalisms have specific execution engines, such as PROforma, Asbru, and EON. The other execution engines are developed by third parties to support many formalisms, such as GESDOR [65].

2.9. User Interfaces

User interfaces (UI) play a significant role in physician satisfaction and acceptance for any hospital information system such as CDSS [94]. Some studies show that systems which allow users to learn how to use the UI gradually during the daily working tasks have a higher acceptance rate than those that require dedicated training sessions [94]. Also, the way a system's interactions (such as alerts) are presented in the UI can influence the physician reaction; i.e., acceptance or rejection [95].

User interfaces and execution engines are important parts of any CDSS. However, our scope does not include these two parts and they will be handled in the future implementation phase.

2.10. Choosing the Solution's Approach

Our literature review on decision support systems and computerizing clinical practice guidelines yielded many options to choose from. The following criteria helped in making our choice:

1. **The knowledge base versus non-knowledge base systems:** The main goal of our research is to produce a model of ACS management based on the ACC/AHA guidelines. Most non-knowledge-based systems are targeting diagnoses or replacing the clinicians' role by providing the decisions (commonly using probabilistic methods). On the other hand, knowledge-based systems provide recommendations, which has the same function as the ACC/AHA guidelines. Probabilistic functions still can be used as part of the CDSS to provide decisions; however, this method will not be the main focus.
2. **Object orientated programming (OOP):** OOP has many powerful characteristics, such as polymorphism, inheritance, reusability, and overloading

[96]. A rule-based CDSS is not object oriented because it distributes all the knowledge about a certain concept over the entire model. Ontological modeling supports OOP and was chosen to be the method of choice for this project.

3. **Monolithic versus non-monolithic methods: A** monolithic (closed) approach uses databases to change or extend the application [97]. The non-monolithic model is extensible and expandable when more knowledge needs to be added through the knowledge model itself [65]. Our domain (management of ACS) knowledge is rapidly expandable and amendable. Thus, the ACS model is expected to change in the future. Therefore, the non-monolithic model is the appropriate method to use. Both Frame and OWL are capable of producing non-monolithic models [65], [98].
4. **Semantic versus non-semantic modeling methods:** Semantic web languages have many advantages on other CPG formalisms. Firstly, using a formal language in modeling the CPG increases the chances of being supported by other researchers in other domains. Secondly, most applications and tools, including reasoning applications and editing tools, are available at no cost, in order to encourage their use. Thirdly, promoting the reuses of OWL ontologies supports knowledge scalability. Currently, there are web repositories for OWL ontologies, which can be explored through search engines such as swoogle.umbc.edu. These ontologies can be reused to accommodate the growing knowledge in any particular domain [86].

   Semantic representation is useful in our domain. For example, Non-ST Segment Elevation Myocardial Infarction (Non-STEMI) is the new name of sub-endothelial myocardial infarction. However, some references still use the old name. Semantic representation will help to match both terms with one meaning.
5. **Frame-Based versus OWL-Based ontology modeling:** Most of the CDSSs were based on a frame-based knowledge modeling approach. In recent years OWL gained popularity as a method of choice in knowledge modeling. The following aspects show the differences between them:

a. **Open world versus close world assumptions: A** Frame model assumes that everything is false unless it is explicitly mentioned in the model (closed world), while the OWL model assumes the opposite (open world) [99], [100]. In medicine nothing is one hundred percent true or false, and there are always possibilities for unknown facts. An example from our domain is Aspirin, which is classified as an anti-platelets drug in the ACS CPG and was not mentioned under the analgesic class. However, not mentioning Aspirin under the analgesic class does not mean it is not an analgesic. The Frame model will not consider Aspirin as analgesic unless the opposite is stated, while the OWL model will consider it analgesic unless it is stated otherwise.

   Usually physicians act on the basis of close world assumptions, but their documentations are based on open world assumptions. For instance, giving Aspirin for the first time to a patient will not be held because of unknown Aspirin allergy. However, physicians will document the allergy history as "unknown allergy". The open world and the close world assumptions are used frequently in the medical domain. Therefore, the best method to represent that is a hybrid method which supports both. We argue that OWL can support both, by being both an open world language and a closed world, by adding closure axioms [99]

b. **Asserted versus inferred model:** Frame has only one model, the asserted model, while OWL has the asserted and inferred models. Inferred models can be any combination of classes that satisfy the necessary and sufficient restrictions and do not violate other restrictions and properties' characteristics [100]. Most workflow models, such as EON and GLIF, describe the flow-control explicitly by using properties (or slots) called next step or next procedure, making workflow model an asserted model. CDSSs that use these models were dependant on the workflow model and did not require the other inferred model; hence Frame was the suitable option here [83].

In conclusion, OWL and Frame Ontology methods are the two most appropriate for our project. However, after comparing them we found OWL is richer in semantic and widely supported by researchers. We chose to use OWL.

2.11. Summary

In this chapter, a foundation for the research domain was established. Also, an extensive literature review of the known medical decision support solutions helped us to identify specific criteria to select our solution approach; i.e., OWL modeling of ACS management guidelines.

CHAPTER-3 METHODOLOGY

This chapter presents our research methodology, which comprises a sequence of systematic steps leading to the eventual computerization of the ACS CPG. The research methodology involves steps for knowledge modeling, ontology engineering, and computerization of ACS CPG and knowledge evaluation framework. In the discussion below, we describe the individual steps, in conjunction with the inspiration and rationale for the methodological steps pursued in this research thesis.

3.1 Reference Ontology Engineering Methodologies

Our CPG ontology engineering methodology is guided by two well-known ontology-engineering methodologies; i.e., DKAP [29] and Pinto *et al* methodology [101]. Our approach is to select the relevant ontology engineering steps from these methodologies and then adapt them according to our domain-specific needs to formulate our CPG ontology engineering methodology. Below, we provide a brief overview of the reference ontology engineering methodologies.

3.1.1. DKAP Methodology:

DKAP methodology was designed to facilitate sharing and reusing ontologies. It was created to serve a teamwork environment, where more than one team works in the same ontology using previous teams' ontologies [29].

Although the domain addressed by DKAP is different from ours, we adapted the methodology to serve for a medical problem. Below we discuss how the DKAP methodology has been applied in our research program:

a. Determine the domain and scope of the ontology;
b. Check the availability of existing ontology;
c. Organize the project: although it is an important step in large projects, it was not followed closely in our research because of the fact that we did not have a big team to manage;

d. Collect and analyze Data: in this step, the domain data are analyzed in order to extract the knowledge. This step is modified in our methodology because of the different knowledge source we used (see below);
e. Develop initial ontology: in this step ontology engineering activities are performed to construct concepts and relationship hierarchies. Authors suggested two approaches to perform that include (1) top-down development, which starts with the most general concepts and ends with the most specialized concept, and (2) bottom-up approach, which involves collecting all concepts and grouping similar ones in more general concepts until reaching the top of the hierarchy;
f. Refine and validate the ontology;
g. Check the consistency and accuracy of the ontology;
h. Collect and analyze additional data; and
i. Incorporate lessons learned and publish the ontology [29].

DKAP methodology targeted sharing and reusing of ontologies at the level of project organization rather than ontology engineering. It provided a generic method of ontology engineering, which can be used in reusing ontology or building it from scratch (see Step-e).

In summary, DKAP helped us in building our methodology in two ways:

1. We built a general framework of our research methodology, which is similar to DKAP but not identical.
2. Part of our knowledge base required new ontology modules to be constructed from scratch. Therefore, we used the DKAP generic engineering method to build these modules.

The next section provides another methodology, which is more specific to ontology engineering.

3.1.2. Ontology Integration Methodology

The authors of this methodology were motivated by the lack of formal methodology for ontology integration. They described a comprehensive set of steps for integration. These

steps can be run sequentially or in parallel depending on the situation. The methodology has ten steps as follows (Figure 3.1):

a) Identify the integration possibility: in this step, the engineer evaluates the overall situation to identify obstacles that could hinder the integration, such as the lack of tools that support the ontologies' integration;
b) Identify modules: the authors described the fact that in any ontology (new or integrated) a set of modules (or sub-ontologies) exist and form the building blocks of the whole ontology. These modules should be identified before starting the integration process;
c) Identify assumptions and ontological commitments: the original ontology building blocks should have documented assumptions and commitments, which should be compatible with each other in order to facilitate the reuse;
d) Identify knowledge to be represented in each module: this step is an attempt to determine the essential concepts in the knowledge base, then to evaluate the ability of the original ontology to accommodate these concepts with some modifications to produce the integrated ontology;
e) Identify candidate ontologies: the authors mentioned two tasks in this step. The first step is finding the ontologies by searching in the ontologies' repositories, and the second is choosing the most suitable candidate ontology. They provided detailed criteria to help make this choice. This step is the initial filtration of the ontologies using general criteria, such as same domain, same or similar formalism, and the availability of the ontologies. More specific filtration criteria are described in Step-h;
f) Get candidate ontologies: the candidate ontologies should be publicly available or provided by their authors with the appropriate permission to reuse them. The availability does not include only the ontology formalism, but also all the documentation related to the ontology, the conceptual design, and the original knowledge source. Authors suggested alternative solutions to reconstruct these materials in case they cannot be found;

g) Study and analyze the candidate ontologies: the domain expert assesses the need to change the candidate ontology to conform to the new domain does the performed tasks in this step. This is also done by the users to assess the need for changes to comply with the intended use (such as a programmer assessing the suitability of using the ontology in CDSS);
h) Choose source ontologies: this is the final filtration step of the candidate ontologies. The authors provided two taxonomies of criteria to be checked in two stages (Figures 3.2 and 3.3);
i) Apply integration operations: in this step, integration operations, such as inclusion, polymorphic refinement, restriction, and mapping, are applied on the source ontologies to produce the new ontology [102], [103];
j) Analyze resulting ontology: in this step, the new ontology is evaluated in respect of its consistency, coherence, and balance level of knowledge detail in all parts [101].

In this methodology, there is an assumption regarding the presence of an overall ontology. The authors assumed that there are many candidate ontologies to choose from, and therefore, this methodology focuses on the selection and filtration of the candidate ontologies. In our work, we did not need to perform a search and selection of ontologies; rather we had to work with a single available CPG ontology [28].

The discussion about the two research methodologies guides the design of our research methodology, as both the source methodologies have a number of overlapping steps and then at some points do not address the specific needs of the medical domain. We present our research methodology as an adaptation of these two methodologies.

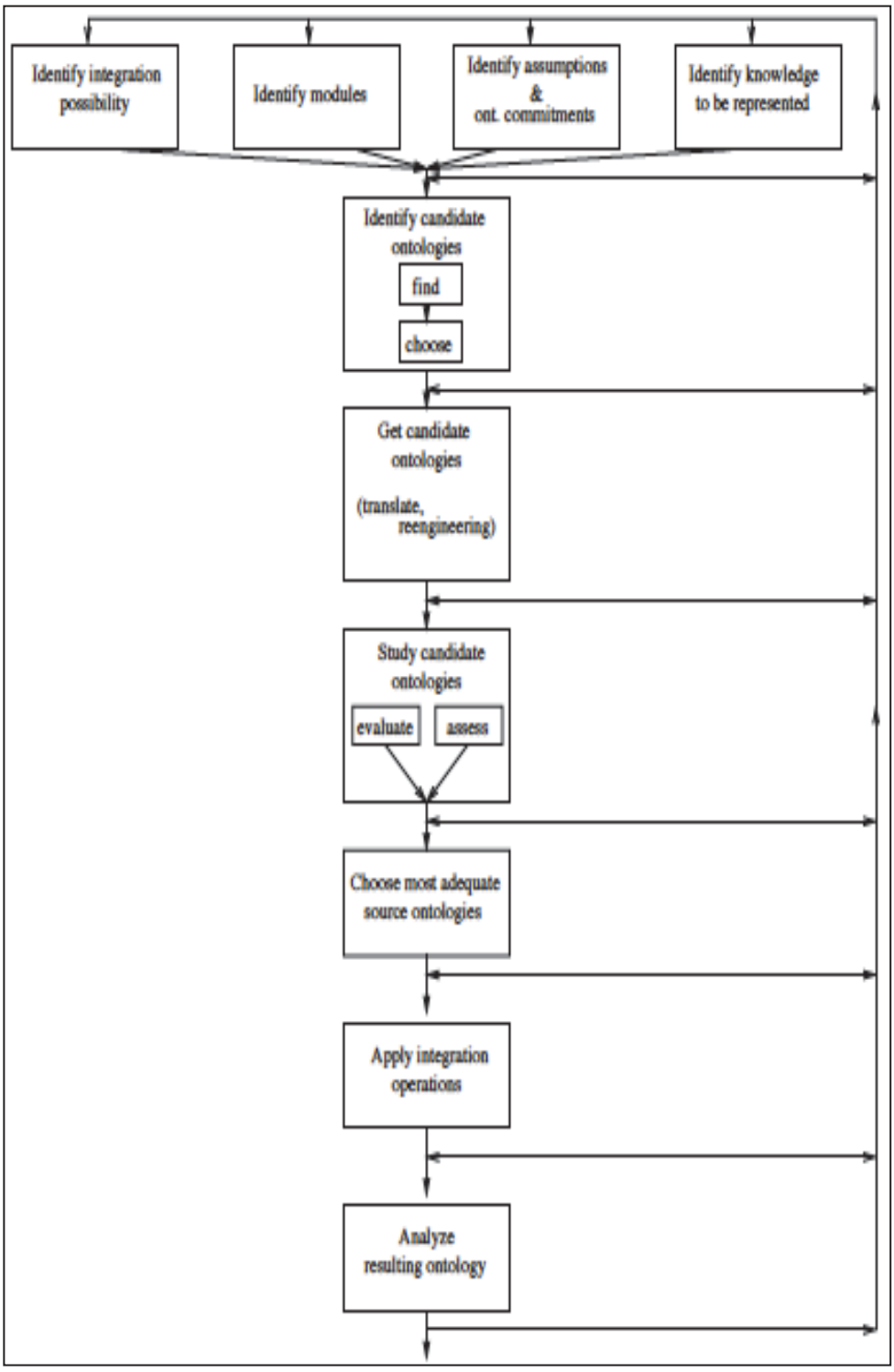

Figure 3. 1 Steps of ontology integration. Taken with permission from [101].

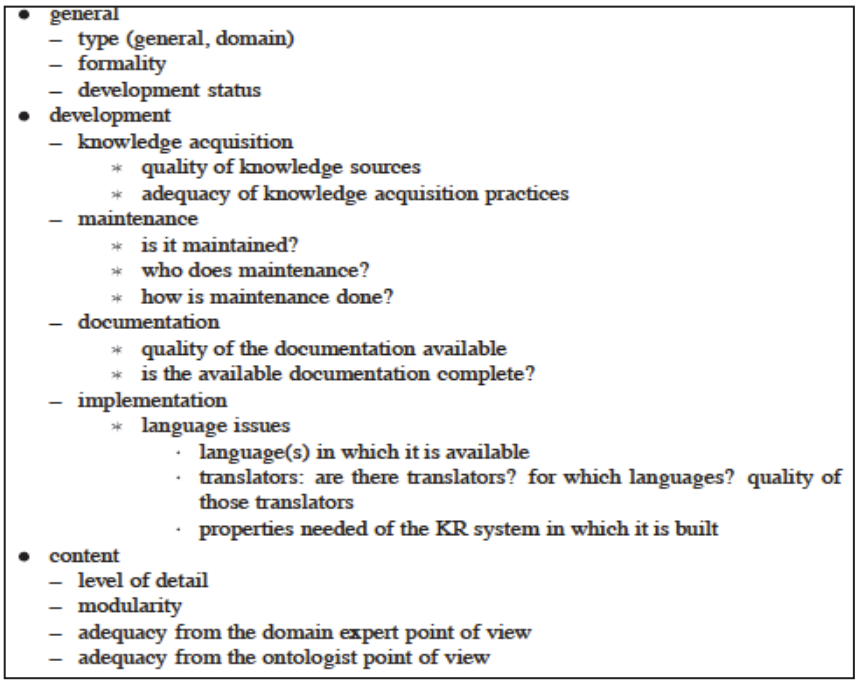

Figure 3.2 Choosing the source ontology, stage-1. Taken with permission from [101].

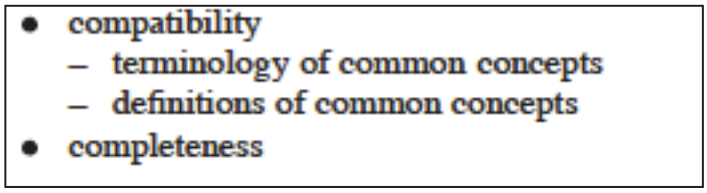

Figure 3.3 Choosing the source ontology, stage-2. Taken with permission from [101].

3.2. Our Research Methodology:

Our research methodology to computerize an ACS CPG for its use in a CDSS for ACS management comprises seven steps, each targeting a specific research task with a defined output, that are described below in detail.

3.2.1. Defining the Research Scope:

The scope of our research can be defined using three boundaries:

a. **Domain scope**: The research is conducted to model acute coronary syndromes (ACS) management in the emergency department. Thus, it does not include inpatient or outpatient management of ACS; however, it

should not be restricted to a specific emergency department. The research can be generalized to different emergency departments with minor modifications.

At this stage, management of ACS does not include finding the diagnosis of ACS or part of it; rather it focuses on recommending the appropriate interventions according to the selected guideline.

b. **Technical scope**: This research is the first part of designing and implementing a CDSS for ACS management, which will be a knowledge based system. This research will end by producing a knowledge model for that CDSS [104].

   Modeling technique will be an ontology modeling technique represented in OWL.

c. **Knowledge base scope**: The knowledge base was restricted to include mainly CPGs, which is satisfactory at this stage. However, to implement a full functional CDSS, other knowledge bases should be incorporated into the CPGs, such as drug formulary and domain experts' tacit knowledge.

3.2.2. Literature Review

In this step we aimed to explore the solutions found by previous researchers and deciding which category our research belongs to. In Chapter Two we conducted a thorough literature review of the various CDSS, especially knowledge based ones, then we narrowed our review to focus on the techniques of knowledge modeling.

3.2.3. Studying the Specialized Clinical Environment

Our experience in emergency medicine came from the practice in different emergency departments in tertiary and secondary hospitals in Saudi Arabia. We used this experience to interpret the AHA/ACC guidelines for management of ACS. This interpretation means filling the knowledge gap in the CPG and solving the ambiguity inherited in most of the CPGs.

3.2.4. Engineering and Instantiating the CPG Ontology

In this step we reused a published CPG ontology (the reference ontology) to model the ACS management. We started by extending the reference CPG ontology to accommodate specific parts of the ACS CPG, such as interventions. Then we added new modules to represent other parts of the CPG that cannot be accommodated by the reference CPG ontology. The final two tasks in this step were removing the redundancies and instantiating the model.

The ontology engineering process will be emphasized more under separate headings below.

3.2.5. Evaluating the Knowledge Model and Computerized CPG

Testing MACSON[1] was performed at three levels:

A. **Testing the consistency:** Ontology consistency testing is technical testing that aims to check the conflict between classes due to their restriction. Running a reasoner such as Pellet reasoner accomplishes that.
B. **Testing the completeness: T**he completeness of any knowledge base is a subjective issue. Even the CPG we used cannot be considered perfectly complete. However, testing the ontology by using clinical cases can help us to find any missing part of ACS management that is not addressed in the ontology.
C. **Testing the validity**: In addition to using the clinical cases to test the completeness, they can also be used to find if the recommendations given by the ontology are right and conform to the knowledge base. This part tests our interpretation of the CPG.

In this step, MACSON[1] was refined using the tests' results to produce MACSON[2].

Figure 3.4 shows the major steps in our ontology engineering method. For more details see Chapter Four.

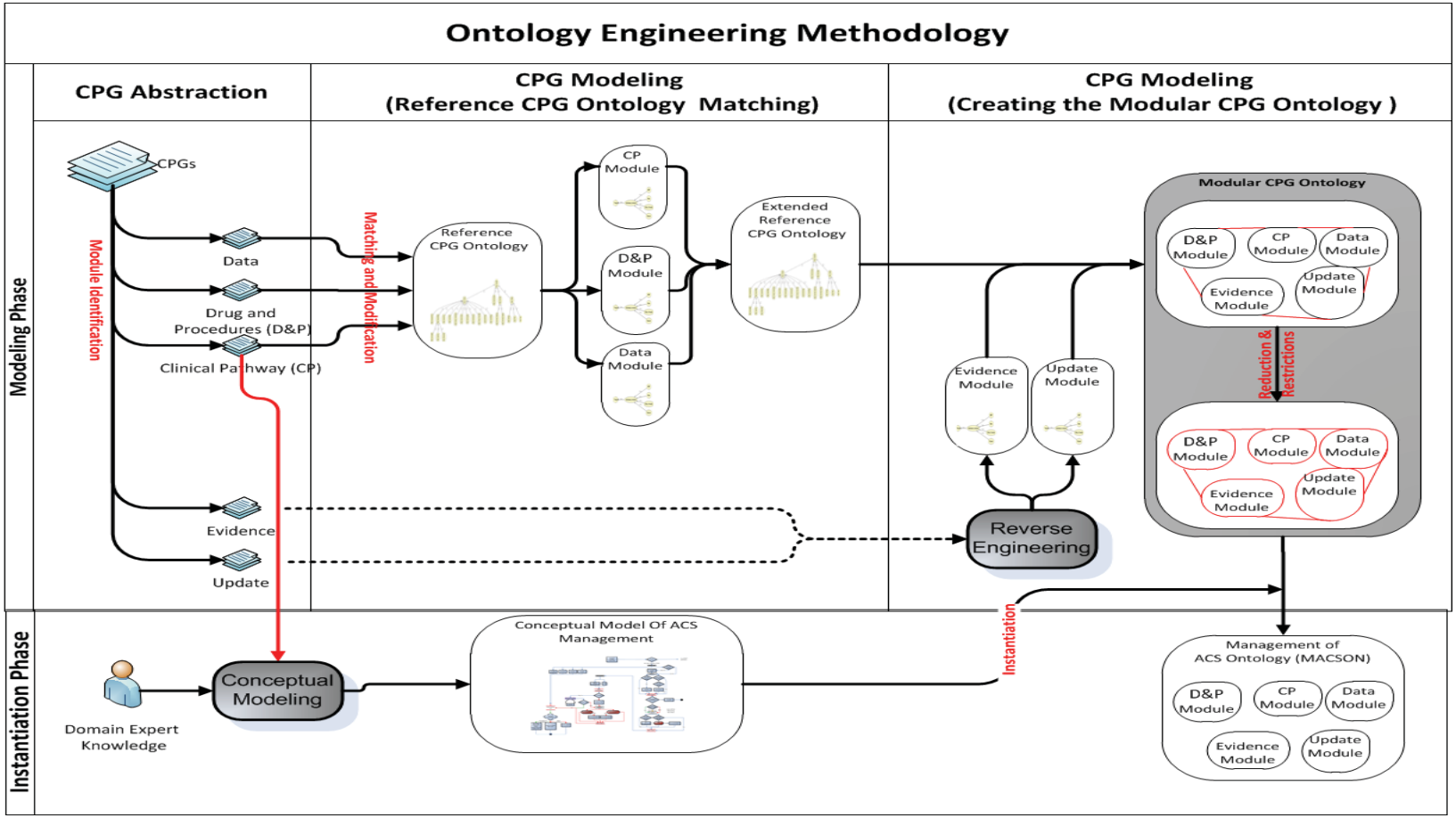

Figure 3. 4 ontology engineering methodology

3.4. The Generic CPG Ontology-Engineering

6.1.1. Knowledge Source Selection and Analysis

A. **Knowledge source selection:** Management of ACS is a huge subject. There are many guidelines published to cover this subject, such as those published by AHA, Scottish Intercollegiate Guidelines Network (SIGN), and the European Society of Cardiology [105], [106]. The choice for this project was the guideline published by AHA and ACC. We chose this CPG for many reasons, such as its universality and being regularly updated (See Chapter Two).

B. **CPG Abstraction:** In our CPG analysis we found five main modules that require modeling in terms of an ontology structure; namely:

    1. Clinical pathway module (or task network (TNM) module), which is required to represent the steps in the clinical pathway;
    2. Drug and procedures module, which represents all the interventions done by health professionals during patient management;
    3. Data elements module that represents all the data needed to make the decisions and the data generated in each step;
    4. Evidence-based medicine module, which represents the evidence classification. Evidence classification is used to annotate the CPG recommendations. This annotation allows the CDSS to prioritize the recommendations according to their evidence level;
    5. CPG update module, which allows adding new updates without changing the basic structure of the model.

3.4.2. Knowledge Representation Formalism Selection and Analysis

As mentioned in Chapter Two, our literature review yielded that using the ontological modeling in the form of OWL is the most suitable method to capture the CPG knowledge for the purposes of executing it within a CDSS.

This step is divided into two main tasks:

A. **Reference CPG ontology selection:** In our research we explored different ontologies for acute coronary syndrome, such as Acute Coronary Syndrome (Common Terminology Criteria for Adverse Events) and Acute Coronary Syndrome (SNOMED Clinical Terms) from the bioPortal ontology repository. Most of these ontologies lack the satisfactory level of granularity required for our research [107].

   The NICHE research group has developed a comprehensive ontology to model the CPGs [28], such that the CPG ontology offers a generic model that can instantiate multiple CPGs from different domains [28]. This CPG ontology (the reference CPG ontology) was our choice.

   Our choice of reference CPG ontology was guided by the following characteristics of that ontology:

   - **Domain similarity:** The domain of the reference CPG ontology is medical guidelines. Our domain is a more specialized domain, which is the ACS guideline in the emergency department. However, both domains are similar;
   - **Granularity**: The reference CPG ontology has a satisfactory level of granularity to describe most of the concepts in our domain;
   - **Access to the required materials**: We had permission to reuse the reference CPG ontology from the authors. All

documentations were available as published articles and dissertation; and

- **Possibility of integration:** The reference CPG ontology was constructed in FRAME and our goal is to use OWL-DL. Protégé, the modeling tool we used, comes in two types, FRAME and OWL. Protégé-FRAME has the ability to export the FRAME ontologies to OWL. However, the exported file will lose some of the FRAME features such as the metaclasses feature. Despite this loss we argue that integration is possible but requires repair of the ontology after the conversion [99].

B. **Analysis of the reference CPG ontology:** During the analysis of the reference CPG ontology, we identified similar modules in reference CPG ontology to what we identified during the CPG analysis (Figure 3.4); namely, pathway module, interventions module, and data module. The latter module was scattered throughout the ontology. The additional modules in the CPG have no similar modules in the reference CPG ontology.

3.4.3. Ontology Integration

In this step we used a concept found in the literature called ontology reuse. In the following section we provide an overview of this concept.

One of the advantages of using OWL ontology is the ability to reuse and expand the knowledge to meet new goals and objectives [108]. However, using previous ontology poses its own set of problems and requires significant ontology engineering efforts. Syntactic and semantic interoperability is one of the major challenges. Syntactic interoperability can be solved by matching terminologies and creating a repository of synonyms for each concept used in the knowledge base [109]. On the other hand, semantic matching is a more difficult task and needs deep understanding of the model. Bontas and colleagues developed a generic method to do such matching [109].

For the purpose of this research, we pursue ontology reuse, whereby we performed a kind of ontology integration to yield a new ontology that is derived by mapping the identified modules in the paper-based CPG to the modules in the source ontology (Figure 3.4). We modified these ontology modules to capture all the concepts in the CPG modules. By the end of this step we created the extended reference CPG ontology. More details about this step can be found in Chapter Four.

3.4.4. Modeling the New CPG Modules

The reference CPG ontology has no match for two of the CPG modules; namely, the evidence and the updates modules. Therefore, these modules were engineered from scratch using the reverse engineering technique (see Chapter Four for more details). By the end of this step we had a CPG ontology with many redundancies.

3.4.5. The CPG Ontology Reduction

The resultant ontology is an inclusive model that had all the concepts from the reference CPG ontology, in addition to the concepts from the paper-based ACS CPG. However, it had a lot of redundancies. Therefore, the reduction process was done to remove the redundancies while maintaining the same level of representation.

The result of the last two steps is the modular CPG ontology (Figure 3.4).

3.4.6. Conceptual Modeling of the ACS Management

By using the result of the clinical environment study and the interpretation and the analysis of the CPG, we were able to produce conceptual models that represent the clinical pathways. Details about these conceptual models can be found in Chapter Four.

3.4.7. Modular CPG Ontology Instantiation

The last step in our engineering method was the instantiation of the modular CPG ontology using the conceptual model. Instances were extracted from the CPG

using domain expert knowledge. The end result of the engineering process was the creation of MACSON[1].

3.5. Summary

Our methodology is a hybrid of the aforementioned two methodologies, with some modification to fit our research situation. During ontology engineering, there were two options to construct the ontology model, manual and automatic methods. Automatic integration using tools such as PROMPT and MoA is an active research field which is out of this research's scope [110], [111]. Therefore, manual integration was chosen.

The next chapter discusses the ontology engineering in more detail.

CHAPTER-4 ONTOLOGY ENGINEERING

4.1. Introduction

In chapter 3, we presented the two major phases of the ontology engineering methodology:

1. Generic CPG ontology engineering, and
2. Management of ACS Ontology (MACSON) creation.

This chapter will provide more details about these Phases.

4.2. Phase-1: Generic CPG Ontology Engineering

The main goal of this phase is to create a generic CPG ontology model that offers a better representation of the management of the ACS CPG than the source CPG ontology.

4.2.1. Analysis of the Subject-Specific Knowledge Base

The American College of Cardiology (ACC) and American Heart Association (AHA) CPGs for management of acute coronary syndrome (ACS) is a set of textual guidelines that have been published since the early nineties. In this research, we chose the following editions of these guidelines, following the reasons mentioned in Chapter Two under the Management of ACS heading:

1. ACC / AHA guidelines for the Management of Patients with ST-Elevation Myocardial Infarction. A Report of the American College of Cardiology / American Heart Association Task Force on, 2004 [27];
2. ACC/AHA guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction, 2007 [112];
3. Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction, 2007 [113];
4. Focused Updates: ACC/AHA Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction (updating the 2004 Guideline and

2007 Focused Update) and ACC/AHA/SCAI Guidelines for Percutaneous Coronary Intervention, 2009 [35]; and

5. ACCF/AHA focused update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 guideline), 2011 [114].

A quick view of these knowledge sources illustrates that a significant amount of knowledge has been compiled in textual form (approximately 500 pages). This lengthy textual format hinders access to the needed knowledge at the point of care. From the above-mentioned knowledge resources, we identified specific modules in the guidelines that were deemed relevant for the purposes of our research. These modules are highlighted in the next section.

4.2.2. Knowledge Base Modularization

Knowledge modularization is the process of dividing a large knowledge repository into smaller parts called modules [115]. Sauro defined a module as "a functional unit that is capable of maintaining its intrinsic properties irrespective of what it is connected to" [116].

The main challenge in modularizing large knowledge is how to define the stable intrinsic properties of each module.

Some authors identified the general requirements of each identified module. These requirements include the ability of the module to be managed separately from the rest of the knowledge base and that it should represent a specific part of the knowledge base [117].

Modularizing the knowledge (including ontologies) has many benefits, such as facilitating the reuse by defining the functionalities of each module. These definitions allow users to reuse the modules separately instead of reusing the whole knowledge base. Another vital benefit related to the ontologies is the fact that ontology size is expected to grow, making it difficult to be handled by applications such as reasoners [115]. The new emerging semantic web research has addressed the benefits of modularization to manage large ontologies [115].

Starting the modularization process at the level of the CPG before creating the ontology will help in creating a modularized ontology.

Modules identification process: Patient management is divided into general components that exist in most medical practices regardless of the specialty. These components include diagnosis, treatment, assessment, and disposition; similar components exist in emergency medicine.

The American College of Emergency Physician (ACEP) created a model for emergency medicine practice [118]. This model has three parts: physician tasks, patient acuity, and conditions [118]. Figure-4.1 shows the components of the physician tasks, which reflects the general patient management components in any specialty, with some modifications.

Physician Tasks	Patient Acuity		
	Critical	Emergent	Lower Acuity
Prehospital care			
Emergency stabilization			
Performance of focused history and physical examination			
Modifying factors			
Professional issues			
Diagnostic studies			
Diagnosis			
Therapeutic interventions			
Pharmacotherapy			
Observation and reassessment			
Consultation and disposition			
Prevention and education			
Documentation			
Multitasking and team management			

Figure 4. 1 Physician tasks and patient acuity in the 2007 model of the clinical practice of emergency medicine. Taken with permission from [118].

We divided these components into two layers, as shown in Figure 4.2. The first layer (Red) contains the main steps that are required to be followed by the physician during the patient management. This layer represents the clinical pathway (CP), which varies from one specialty to another. The CP shown here is

specific for our domain (management of ACS) but can be generalized to other domains with some modification. Most of the CPGs' heterogeneity is due to the variation in this layer.

The second layer (Blue) is the supportive layer, which contains the components required by the first layer. For example, drugs and procedures are a component needed in the treatment and diagnosis components. On the other hand data is needed in most of the components. The data can be fed to the components or generated from them. The maintenance components are used to store the long-term knowledge about the other components. For instance, practitioners need to know when a certain treatment becomes obsolete.

Our method to modularize the management of ACS CPG follows the practice model published by ACEP [118]. Each component in the practice model is represented in one or more modules. This method can be generalized to other CPGs. For this research, we have identified the following modules:

1. **Clinical pathway (CP) module:** The CP is not expressed clearly in the guidelines, and most of its elements are embedded in the text without clear connections between the steps that are required to build the patient management sequence. The conceptual design process (see below) yielded a complete CP for ACS management. This module is the result of applying our experiential knowledge, derived from clinical practice in the emergency department, to interpret the CPG. This module was iteratively refined to produce the Task Network Model (see below).
2. **Drug and Procedure Module:** All of the interventions in the CPGs that are required during the management can be categorized as either treatments-interventions or diagnostic-interventions. The CPG has a list of medications used in the management, which facilitate the module's identification. On the other hand, diagnostic interventions are scattered all over the CPG and require a domain expert to gather them under one module.

3. **Data values module:** During each step of the management, two types of data values are involved: (a) data required by the physician in order to perform the step in question (for example, risk stratification criteria are required to determine the severity of patients' conditions), and (b) data generated during step execution, such as the value of risk stratification generated by using the criteria in the decision step (i.e., high, moderate, or low risk). The data can be numerical, such as the values of cardiac enzymes result; Boolean, such as the answer of "Is Aspirin contraindicated"; date and time, such as time of giving thrombolytics therapy; or strings, such as documenting why the physician chose to deviate from the system's recommendations.
4. **Evidence levels module:** One of the major advantages of the chosen CPG is the presence of evidence levels for most interventions used during the management. ACC and AHA use a specific classification scheme for the evidence (Figure 4.3). Each classification consists of two parts:
    A. **Treatment effect:** This part shows how the intervention is effective on ACS management, starting from level I, which is the most effective level, to level III, which denotes harmful interventions.
    B. **Evidence strength:** This part shows how strong is the evidence that supports certain interventions, starting from A, which is the strongest evidence level, to C, the weakest one [27].

    This module is used mainly with the therapeutic interventions (see unique feature section below).
5. **Guidelines updates module:** ACC and AHA guidelines are updated frequently. The newly updated editions may or may not involve the previous unchanged interventions. Usually, the updates focus on the interventions that are required to be changed, so instead of rewriting the whole guideline when the update is due, they publish only the new changes.

There are other elements that also exist in the CPGs but are not modularized (such as literature review and disease pathophysiology), but this did not affect the overall CPG computerization exercise, as these elements are not involved directly in the decision-making.

Previously (in Figure 3.4 in Chapter 3) we mentioned that the conceptual model came in after creating the modular CPG ontology as part of creating MACSON[1]; however, we are mentioning it here to give an overview of the generic CPG ontology components, which are similar to the conceptual model components.

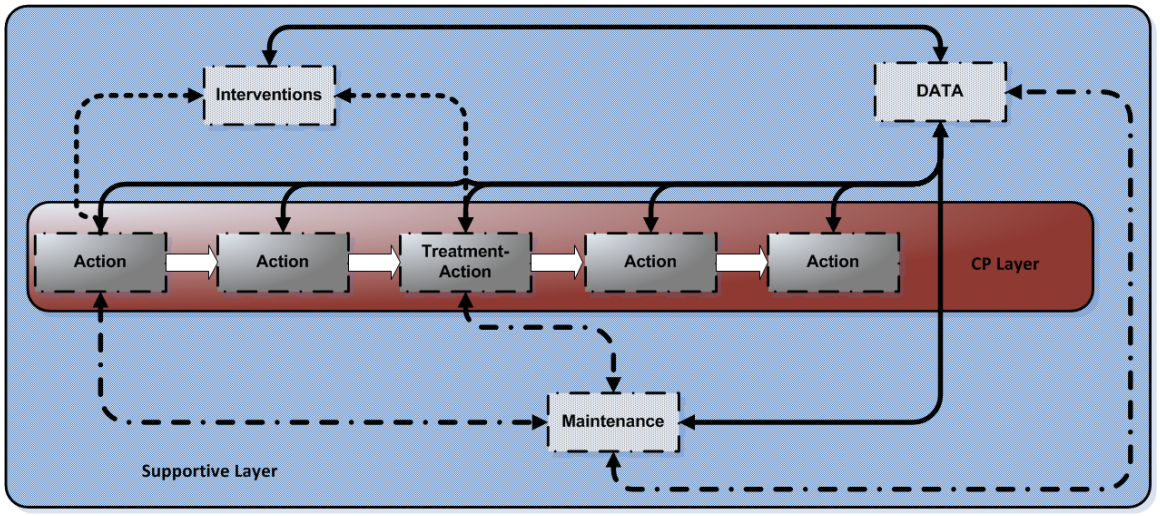

Figure 4. 2 CPG module layers

4.2.3. Conceptual Modeling

A conceptual model is used to represent the domain's concepts. This representation may involve the concepts' attributes, the concepts' relationships, and the domain restrictions [119], [120].

Often the conceptual model is represented as a graphic diagram [119]; however, other representations can also be used. One of the unique characteristics of the conceptual model is its independence from the applications [119]. For example, our conceptual design should not be specific to any CDSS design.

There are many languages and schemas, such as UML, ER diagram, and object constraint language (OCL), used in the conceptual model [119]. We used specific symbols in our model, as defined in Table 4.1.

All the previous modules needed to be modeled conceptually before they are represented in OWL; however, only the CP module will be mentioned in this section, whereas the other modules will be discussed below.

The way CPGs are constructed does not demonstrate a good representation of the clinical workflow. The hierarchy of the CPGs mainly follows the interventions' classifications, such as anti-ischemic treatments, reperfusion techniques, and adjunct treatments. Some of the editions show workflows of the management or pathways (Figure 4.4). However, these pathways lack the granularity needed to design the CDSS. The domain expert can easily interpret them because he/she can solve the ambiguity in the CP from her previous clinical experience. Thus, we require a more expressive conceptual model in order to develop a domain-specific ontology.

Most of the previous research in CPG computerization, such as GLIF and PROforma, was built on conceptual models that represented the textual guidelines [121]. These conceptual models are also called the task network models [121]. Each model is composed of the building blocks representing the individual tasks in the CPGs. Examples of these building blocks are action, diagnosis, branching, and plan. These tasks are reused by many other projects [121].

In our research we used many of the tasks mentioned in the literature. Additionally we identified new tasks such as prioritization steps, which are sub-tasks of action.

Figure 4. 3 Evidence classifications. Taken with permission from [27].

Symbol	Description
	Action step
	Decision step
	Prioritization Step
	Loop Step
	Branching or Synchronization step
	Disposition step
	Consultation step

Table 4. 1 Symbols used in the conceptual model

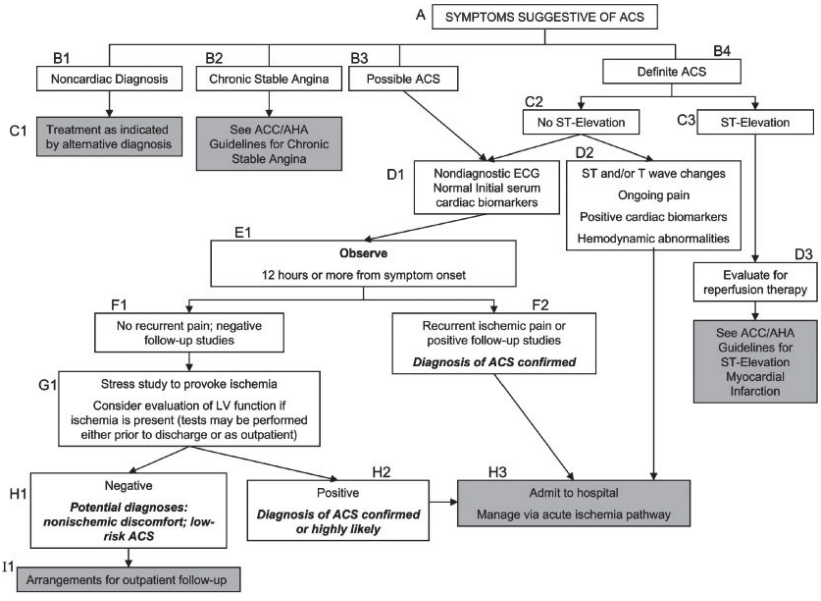

Figure 4. 4 Pathway for management of ACS. Taken with permission from [112].

Constructing the model requires domain expert to connect all the identified tasks correctly. In our approach we used the following steps:

1. **Formalizing the assumptions:** In the first instance, we are setting the operational criterion that will guide pathway formulation**.** Priori rules and assumptions were formalized before the modeling process started. The rationale behind that is to comply with the research's scope and to produce a generic model, which can be used in different situations. In addition to the diagnosis assumption (we assumed that the initial diagnosis of ACS will be done by the physician; the model does not handle the provisional diagnosis), the following were added:
    A. **Assumptions to define the role's responsibilities:** As mentioned before, the guidelines did not assign the interventions to specialties. Some interventions are easily assigned to certain roles, such as cardiac catheterization is done by the cardiologist, and the initial ECG assessment is done by the ED physician. On the other hand, other interventions' assignments, such as thrombolytics and giving Glycoprotein IIb/IIIa inhibitors, are not clear in the CPGs. Thus, interventions mentioned in the model are assumed to be the responsibility of either ED physician or ED nurse, while those not mentioned are assumed to be the responsibility of other roles, including the cardiologist.
    B. **Assumptions regarding clinical pathway sequence:** Some interventions have no preferred order in the CPGs. This is because of the fact that they have no order preference in the real clinical workflow. So, the sequence we put in the model is based on our best clinical knowledge. Manipulating the task network model in the CPG ontology can easily change these sequences.
2. **Simulating all the possible ACS patient presentations**: A patient with ACS can have many different presentations, such as unstable angina, STEMI, non-STEMI, and cardiogenic shock. The tasks and task flow were

constructed by consulting the CPGs to answer common questions, such as what to do if the patient has a certain presentation such as hypotension. And what is the next step after that?

3. **Simulating all different situations in the emergency departments**: The resources in emergency departments influence ACS management. Therefore, all the simulation cases in the previous step were repeated in different situations in the emergency department. For instance, ST-segment myocardial infarction has different managements depending on the availability of cardiac catheterization in the hospital.
4. **Refining the model using feedback from the domain experts:** Other domain experts who worked in the emergency departments in Saudi Arabia reviewed the tentative model. Then their comments were used to refine the model. The final model is more reflective of the work environment in Saudi Arabia.

Figures 4.5 and 4.6 show the final conceptual design of the management of ACS.

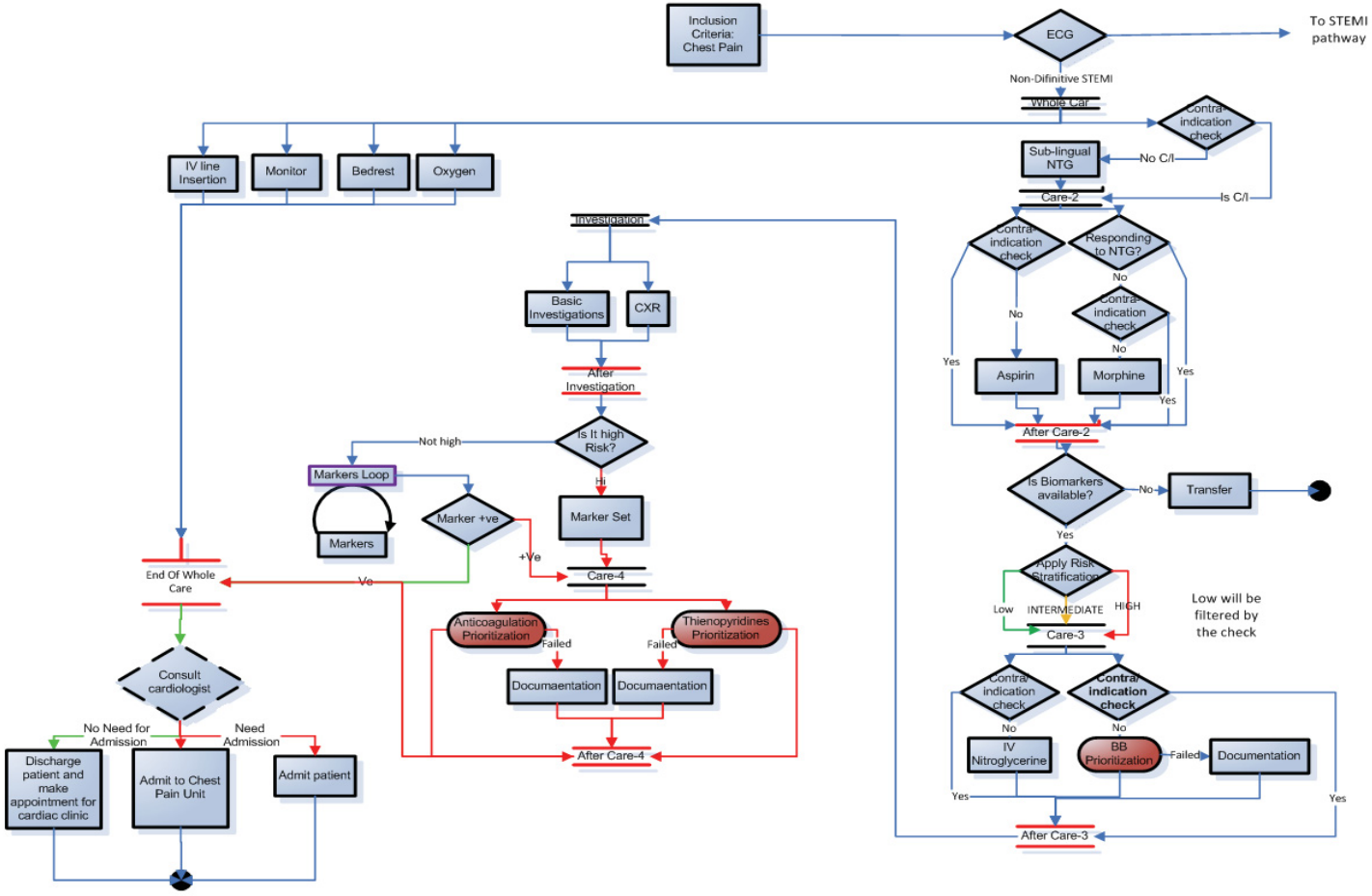

Figure 4. 5 Conceptual model of non-definitive STEMI management

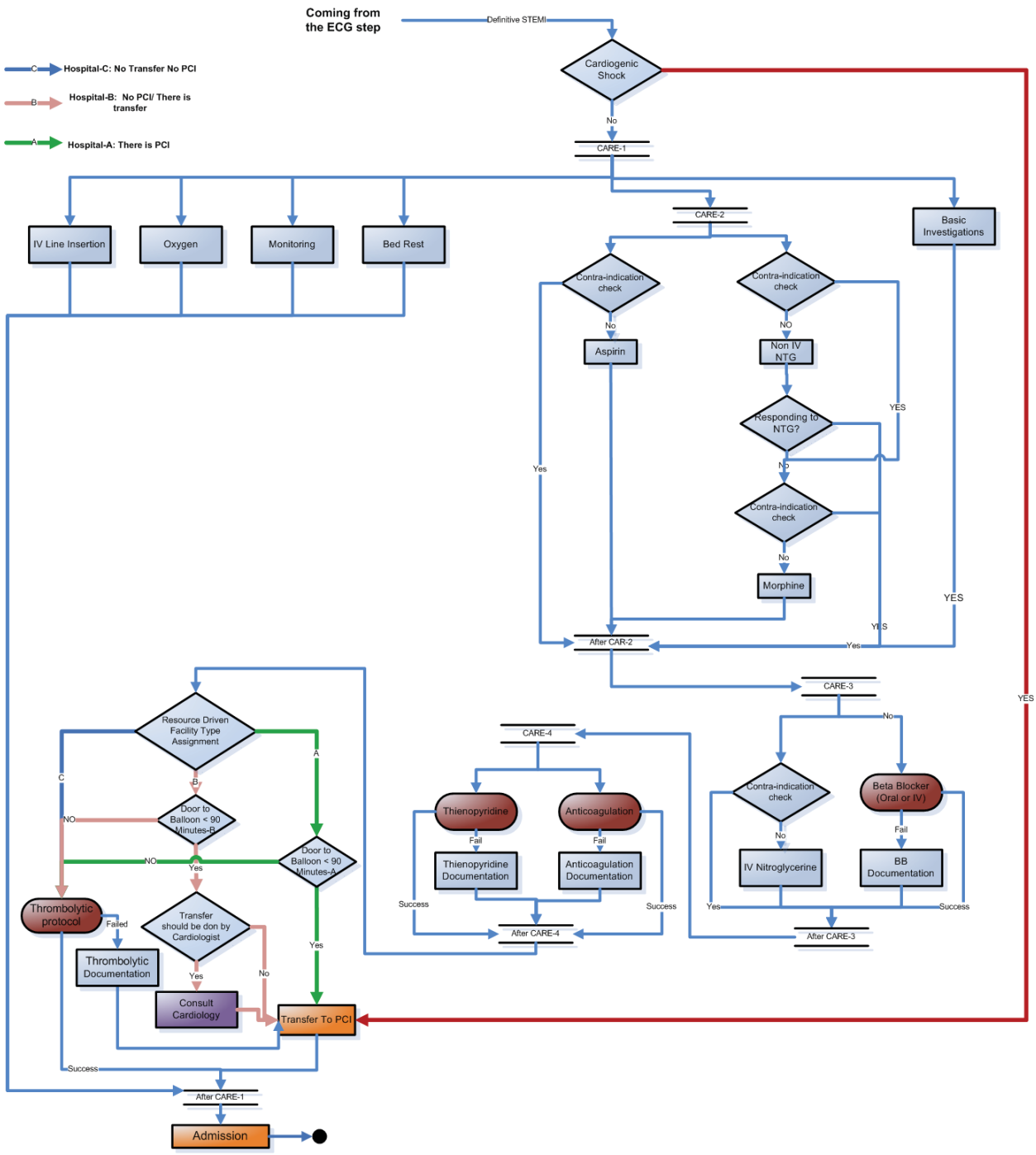

Figure 4. 6 Conceptual model of STEMI management

The starting point of the model is the ECG step, which is a decision step. The result of the ECG step divides the model into two separate pathways; namely, the definitive ST segment elevation myocardial infarction (STEMI) pathway, and the non-definitive STEMI pathway. The model has the following elements:

- **Intervention steps:** In the intervention step there is an intervention done as part of the management. The intervention can be treatment, diagnosis, disposition, or documentation.
- **Decision steps:** These steps are often used to check the indication and contraindication of the intervention before it is executed. For example, the intervention step to give Aspirin is preceded by a decision step to check the indications and contraindications of Aspirin. Some decision steps, such as the risk stratification decision step, are not related to the intervention steps.
- **Prioritization step:** Compared to the intervention step, which has only one intervention to be executed, the prioritization step has at least two interventions to choose from. The physician runs some logics to decide which choice to go with. For example, Beta-Blockers (BB) prioritization step includes approximately thirteen drugs classified as BB, and the physician decides to choose one according to many factors, such as the availability and the strengths of evidence behind the treatment.
- **Branching step:** This is used when physicians need to perform two steps as parallel steps. In our model we used the method mentioned by Abidi and Shayegani in [28], where a designated step called the branching step leads to at least two steps. For example, Care-2 leads to two decision steps to be run as parallel. It is worth mentioning that being parallel does not mean they have to be run at the same time; rather, there is no order preference in running these steps.
- **Synchronizing step:** After the parallel steps finish, the pathway should synchronize to make one flow again. Generally, each branching step has to be followed somewhere in the pathway by a synchronization step.

- **Loop step:** Some interventions needed to be run more than once in a certain sequence. In our model, a loop step is used to repeat cardiac enzymes to diagnose Non-STEMI. Repeating a single intervention is very easy; we need only to specify the number of iteration. On the other hand, multiple intervention steps that should be repeated in a certain sequence is more difficult to be modeled. More detail about modeling multiple steps as a loop can be found below. Synchronization and loop steps-concepts were adopted from the Abidi's and Shayegani's model [28].

4.2.4. Knowledge Representation Formalism Analysis

Selecting the formalism was discussed in Chapter 3. We selected a published CPG ontology done by Abidi and Shayegani [28]. This ontology was built using Protégé-Frames to accommodate different CPGs from different domains. The authors inspired some concepts from previous projects, such as SAGE and GLIF. The ontology model has a satisfactory level of granularity with 50 classes and 161 attributes. Figure 4.7 shows the hierarchy of the ontology.

In this section we attempt to identify potential modules in the source ontology. We looked for modules that are similar to the identified modules in the CPG. As a result, the identification process is based on:

(a) Functional similarity (i.e. doing the same function), and/or
(b) Structural suitability to our purpose.

In functional similarity we were looking for a coherent part of the reference CPG ontology that serves a function in the CPG. For example, The Task network module that is started from the guidelines steps class works as the clinical pathway layer in Figure 4.2.

Structural similarity means a similar hierarchical structure. For example, the intervention modules are used because its classification is serving our purpose to avoid the classification done in the CPGs. The intervention module in the reference CPG ontology is classifying the interventions according to the type (diagnostic and therapeutic). The interventions module can have the same function

with different structure, such as classifying the interventions according to the time of occurrence during patient management (i.e. initial management and advanced management.). The CPGs' intervention is classified according to the time of occurrence. However, we preferred to use the reference CPG ontology intervention module method because it avoids the duplication in the interventions at different stages of the management and it makes the module more generic.

The other factor that governs the identification process is "Minimization of the semantic distance between sibling concepts" criteria, mentioned by Gómez-Pérez and colleagues [122]. These criteria mean that all similar concepts should be grouped under a super-concept [122]. There are many concepts in the reference CPG ontology that are needed to be grouped together and cannot be considered modules (see below).

The following are the identified modules in the reference CPG ontology (Figure 4.7):

A. **Task Network Module:** In Figure 4.7 this module is shaded. It has three main steps: action step, decision step, and route step. Each main step concept is divided further to more sub-concepts. More details about the use of these concepts can be found in [14] and [28]. This module has the potential to model the clinical pathway (CP) module that was identified in the CPGs analysis.
B. **Interventions module:** This module models all the interventions required during management (Figure 4.6). It is divided into two main concepts, intervention for diagnosis and intervention for treatment, which are further divided to more sub concepts. The interventions module can be used to model the drugs and procedures module that was identified in the knowledge source analysis [28],[14].
C. **Other part of the reference CPG ontology:** The ontology has many other classes, which are not part of the previous two modules. These classes are descended directly from the root class (thing). Although it is difficult to collect them under fewer super-classes, they can be

remolded to form well-structured modules, such as data module (see below).

The reference CPG ontology has two potential modules, which can be used to model the knowledge source (A and B). Another impeded module is the data module, which is scattered all over the ontology. Data properties were extracted to form another module (see below). There are more modules in the knowledge source without match and need to be modeled from scratch.

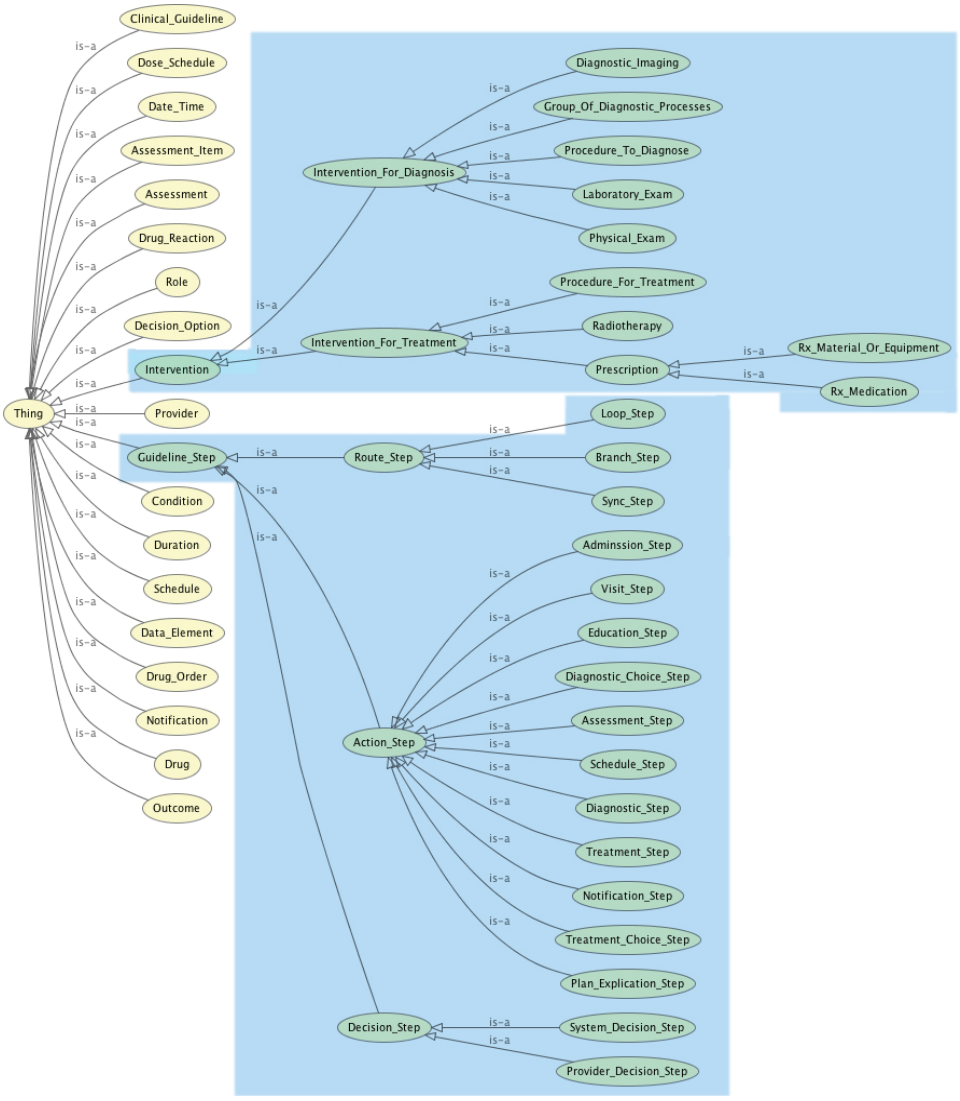

Figure 4. 7 Modules identification

4.2.5. Module Mapping And Creating The New Modules

Although this step was mentioned as two separate steps in Chapter 4, we combined them here because they overlap.

The most used tool during the modeling was *Protégé*-OWL *3.4.5;* another version of *Protégé, version 4.1,* was also used because it supports reasoners such as HermiT beside Pellet reasoner, and has a better view of classes' and properties' usage, which helped in tracking reasoning errors.

Ontology visualization tools are helpful in understanding the ontology structure. We used OWLViz and *Jambalaya Protégé plug*-in to visualize the ontology.

Our ontology engineering method complies with the general principles of the ontology building that are mentioned by Bodenreider and colleagues [123]:

- **Principles of classification:**
  - Presence of single root for the hierarchy.
  - All classes, except the root, must have at least one parent.
  - Non-leaf class must have at least two children.
- **Principles of subsumption**
  - The children should inherit all parents' properties.
  - No cycles are allowed in an *IS A* hierarchy.
  - All roles of a parent class must either be inherited by each child or refined in the child.

Also, the model complies with the fact that OWL should be used and understood by human and machine. Therefore, explicit classes' namespaces were used to make the classes clear to the user. As a result, some classes and properties have long namespaces.

In order to be systematic in our process we followed an iterative algorithmic method to achieve the ontology integration and creation of the new modules. This algorithm is depicted in Figure 4.8.

We started by finding a concept from the CPGs, which were all kept in a registry, and then checking whether the concept was found before (i.e., already exists in the

registry). After that, we checked the reference CPG ontology for a similar concept; if an exact match is found, then the matched class in the reference CPG ontology will be used. For example, the drug class was used “as is” from the reference CPG ontology.

If there is no exact match found, the similarity check is done at two levels: first, looking for syntactic similarity where one concept is named in different ways, such as “Lab” and “Laboratory”, and second, which is done at the semantic level by analyzing the meaning and the usage of the concept. For example, the condition concept in the reference CPG ontology means the logical elements that are required to execute a decision, while in the CPG it means the patient state. The previous example yielded that the two condition concepts are different. In a case where the similarity check yielded nothing, the concept is considered new and added to the new CPG ontology. The algorithm is terminated when there is no new concept found (i.e. all the concepts are in the registry).

During this step we created two versions of the generic CPG ontology (Figure 3.4 in Chapter 3). The first contains the original reference CPG ontology modules after modification and expansion (called the extended reference CPG ontology), and the second has the new modules identified in the CPG analysis (the evidence and the update modules) in addition to the reference CPG ontology (called the modular CPG ontology). Other modules are also created and included in the second version. These modules will be highlighted below.

The resulted ontology is larger than the reference CPG ontology and accommodating the original domain (medical CPGs) along with the new domain (management of ACS) and contains a lot of redundancy. Therefore, the next step is dealing with the redundancies by reducing the ontology.

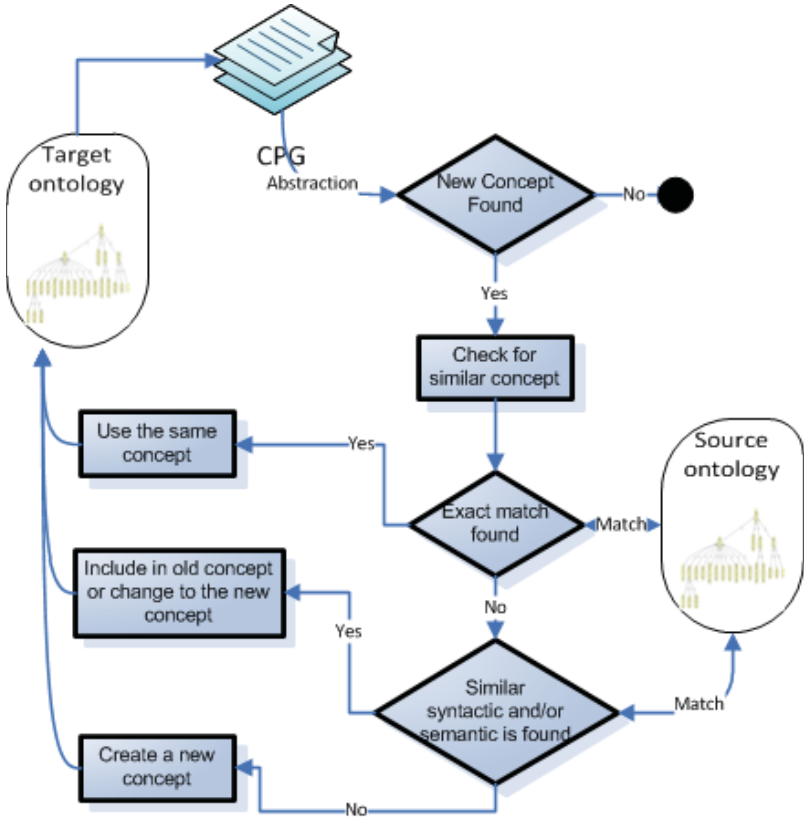

Figure 4. 8 Building the tentative ontology

4.2.6. CPG Ontology Reduction

The aim here is to remove all the redundancies and duplicated classes and properties. It has three phases:

A. **Classes Reduction:** Figure 4.9 shows the algorithm for class reduction. Any class is tested for the presence of usage; i.e., potential instances. For example, with the prescription class, which is part of the reference CPG ontology; there is no instance that can be included in this class, simply because the CPG did not clearly mention giving prescriptions for patients in the emergency department. However, this class was reserved because it has potential use in the future during the implementation. In case the class has no potential usage, it will be deleted (without jeopardizing the ontology consistency); otherwise, it will be checked for possible similarity with other classes. If no similarity is found it would be kept as a unique class. If a similarity is found, it will be

checked for syntactic and semantic similarities in a process identical to the previous stage, with one exception, that there is no reference CPG ontology matching here; the matching is done inside the Modular CPG Ontology. All the similarity checks will end by either merging the classes or sub-setting the classes as sub-classes.

It worth mentioning that we were running a consistency check using Pellet reasoner when we changed or deleted any class, in order to keep a consistent model.

B. **Properties reduction:** Similar to classes reduction, properties redundancy and duplications needed to be removed. The algorithm for properties reduction is depicted in Figure 4.10 and follows the same concept of classes' reduction, except that merging can be done also, using restrictions. For example, taking two properties, "next step" and "branch to", where "next step" is used to navigate to the subsequent step in the task network model while "branch to" is used to navigate to parallel steps, using cardinality restriction (≥ 2) allowed using "next step" properties instead of the "branch to" properties. All the preserved properties are ended by adding other required restrictions if needed.

C. **CPG Ontology final modularization:** After the final reduced CPG ontology version is produced, similar concepts are collected under fewer numbers of classes. For example, the new ontology has the same way of representing the data type properties, which were attached to the other classes, such as treatment intervention, and the way drugs are administered, such as the dose and route. Hence, most of the datatype properties are collected under data elements class, which allow same data type to be reused by other classes.

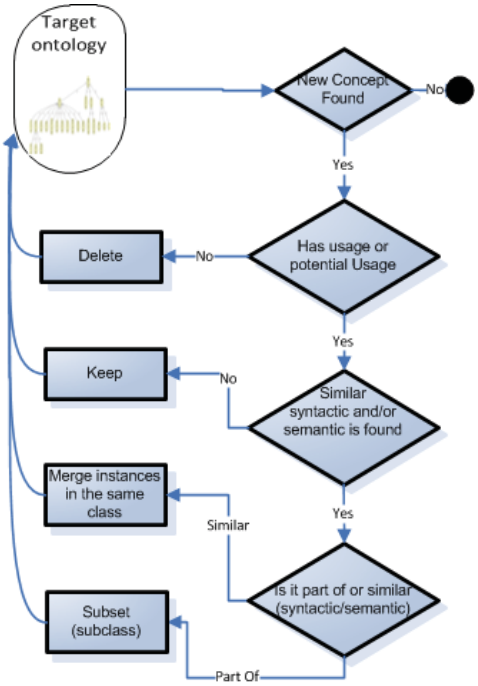

Figure 4. 9 Classes reduction

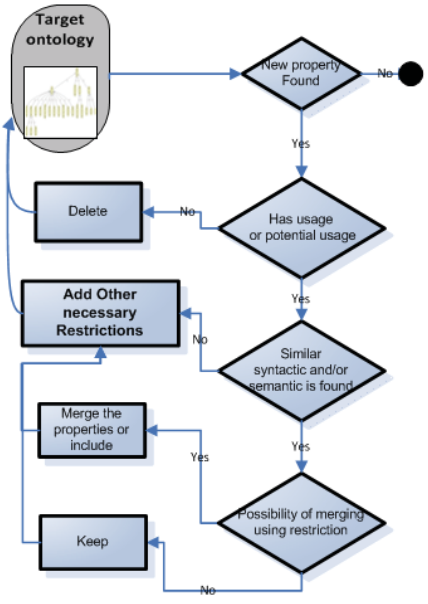

Figure 4. 10 Properties reduction

4.2.7. The Modular CPG Ontology

During the modeling process we took into consideration the concept of modularization. Thus, the CPG ontology model has many modules, which are listed as follows:

1. Task network Model (TNM) module:

In general, most of the components in this module are the same as described in [28] with some modifications. The main knowledge captured in this module is the classification of guideline actions/tasks/steps, represented by the class ***GUIDELINE_STEP***, where the transition from one step to another is achieved by the property ***Next_Step*** that indicates the subsequent step. The property ***responsible*** indicates who should perform the step. Also, we exploited an existed property, the ***Has_Data_Element,*** to connect these steps with the related DataTypes properties in the Data Module—it may be noted that this property was not used in the ***GUIDELINE_STEP*** in the reference ontology. New classes were introduced or merged to represent the CPGs. These classes are listed as the following (Figure 4.11):

1) ***ACTION_STEP****:* This class is preserved as is; however its subclasses are changed:

   a) ***DISPOSITION_STEP*** is a new class that represents the patient movement from the emergency department. It has three subclasses; ***ADMISSION_STEP***, which is adopted from the source model and subsumed under the ***DISPOSITION_STEP***; ***TRANSFER_STEP***, which is used when the patient is transferred to another facility; and ***DISCHARGE_STEP*** when discharging patient home. The setting in the emergency department requires these extra concepts because it is between outpatient and inpatient settings.

   b) ***DIAGNOSTIC_STEP*** is used “as is”, with the same ***DIAGNOSTIC_INTERVENTION*** property that indicates which intervention needed to be performed in this step from the

INTERVENTION_FOR_DIAGNOSIS class in the intervention module (Figure 4.12).

c) ***CONSULTATION_STEP*** is a new class to represent the task done by the emergency physician in order to get the opinion of other specialists such as cardiologist. It has two new properties, ***Has_Action_Steps_As_Consultation_Outcome*** to indicate the step required to be done as a result of the consultation, and ***Has_Consulted_Role*** to indicate the specialist required to be consulted.

d) ***TREATMENT_STEP*** is similar to the ***DIAGNOSTIC_STEP*** and was used "as is".

e) ***DOCUMENTATION*** class is used with another class called ***PRIORITIZATION_STEP*** and will be discussed below.

f) ***TERMINATION_STEP*** is used to stop the flow control.

g) **Preserved classes*:*** Some classes were not used in our model; however, they are preserved because of the potential use in the future. These classes are ***NOTIFICATION_STEP,*** and ***EDUCATION_STEP.***

h) **Removed classes***:* Without a clear definition of the classes, reasoner cannot infer instances correctly. Instances can be forced to belong to the wrong classes. In order to avoid that, some classes were removed from the hierarchy at this stage, such as ***ASSESSMENT_STEP, PLAN_EXPLICATION_STEP, SCHEDULE_STEP,*** and ***VISIT_STEP.*** New classes in our model replaced some classes in the reference CPG ontology, for example, replacing ***DIAGNOSTIC_CHOICE_STEP*** and ***TREATMENT_CHOICE_STEP*** by ***PRIORITIZATION_STEP.***

2) ***DECISION_STEP:*** This class is reused from the reference CPG ontology. It has two subclasses: ***PROVIDER_DECISION_STEP*** represents the decisions taken by the user, and ***SYSTEM_DECISION_STEP*** indicates the decisions taken by the system when all the required elements to run the decision logic can be provided automatically. Instances of these classes have decision options from the ***DECISION_OPTION*** class and connected using ***Decision_Options*** property.

3) ***DECISION_OPTION:*** This class was a separate class in the reference CPG ontology and descended from the root class directly. It represents the options of the decision steps. In another word, it represents the line coming from the decision steps in the pathway (figures-4.5 and 4.6). We moved this class to be part of the TNM module under the ***GUIDELINE_STEP*** class.
4) ***PRIORITIZATION_STEP:*** This is a new class replacing other subclasses in the ***ACTION*** class. When an action step has more than one intervention option for the user to choose from, ***PRIORITIZATION_STEP*** is used to recommend the most suitable option/options to choose from. For example, choosing between Beta-Blocker drugs (there are approximately 13 drugs classified as Beta-Blockers in the CPG) can be left totally to the user, who may or may not be certain which drug to choose, or it can be run through logical processes to filter these drugs and limit the choices. More about these logics can be found in the unique features section below. In case the step failed to recommend the right intervention, and the user has to choose a different intervention, the flow control will be directed to the ***DOCUMENTATION*** step to record the reason behind that; otherwise, it will proceed to the next step using ***Next_Step*** property. At this stage the prioritization step has three levels of protocols, which are part of ***PRIORITIZATION_PROTOCOLS_CDSS*** class in the data module and connected here using ***Has_Data_Element***.
5) ***ROUTE_STEP*** is reused from the reference CPG ontology, with some modifications. It has three subclasses:
    a) ***BRANCH_STEP*** is used for parallel steps. In the reference CPG ontology, ***BRANCH_STEP*** was participating in the ***branching_steps*** property to proceed to the parallel steps. In our ontology we argue that ***branching_steps*** is a sub-property of ***Next_Step*** property with special characteristic. Therefore we used ***Next_Step*** instead of ***branching_steps*** and added cardinality restriction (≥ 2) to limit the participation.
    b) ***SYNC_STEP*** is adopted from the reference CPG ontology to synchronize the preceding branching steps. ***Preceded_Steps_To_Be_Completed***

property is reused from the reference CPG ontology to indicate which steps need to be completed before advancing forward.

c) ***LOOP_STEP*** is a **class** that was changed completely from the reference CPG ontology. In the reference CPG ontology, ***LOOP_STEP*** can handle a single step, which is repeated easily using ***iterations*** datatype to determine the number of repetitions. In case there is more than one step needed to be repeated in a certain sequence, the steps have to be modeled as a separate guideline and the ***LOOP_STEP*** will be just a referral class to this guideline. This method lacks the flexibility and not accurate because this sequence is not a separate guideline. Therefore, the new ***LOOP_STEP*** class (Figure 4.11) has a new property called ***Has_Loop_Sequence*** to indicate the loop sequence required by the loop step. This sequence is taken from a new class called ***LOOP_SEQUENCE.***

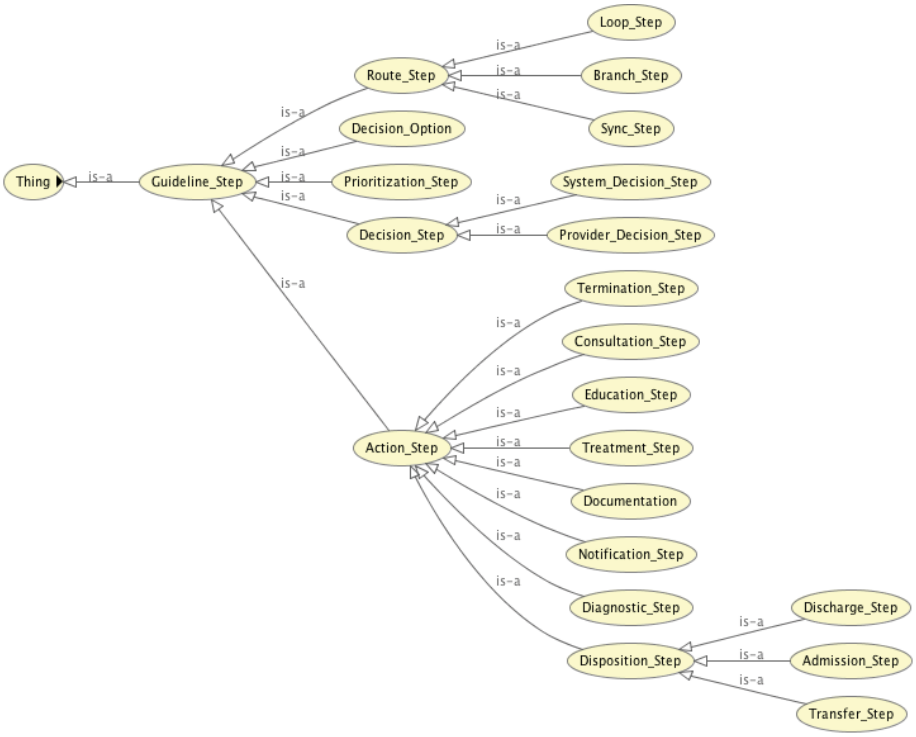

Figure 4.11 The task network module

2. Interventions module:

INTERVENTION class represents all the interventions done in the guideline steps. As in the TNM module, all the datatype properties were separated from this class and put in the data module. ***Allowed_Roles_To_Request*** property was preserved to indicate who could do a specific intervention. ***Has_Evidence_Update*** property is a new property used to show the level of the interventions' evidence that the recommendation was built on (Figure 4.3).
Has_Other_Intervention_Or_Guideline property is new and used if a certain intervention requires other interventions or other guidelines. For example, intravenous nitroglycerine requires vital signs monitoring.

INTERVENTION class has two main sub-classes,
INTERVENTION_FOR_DIAGNOSIS and
INTERVENTION_FOR_TREATMENT (Figure 4.12)**.**

1. ***INTERVENTION_FOR_DIAGNOSIS*** has the following sub-classes:
    a. ***DIAGNOSTIC_IMAGING,*** which is adopted from the reference CPG ontology.
    b. ***GROUP_OF_DIAGNOSTIC_PROCESSES***, which is adopted from the reference CPG ontology and has the diagnostic interventions that are grouped as one, such as Complete Blood Count (CBC) and Renal Profile.
    c. ***LABORATORY_EXAM*** indicates the laboratory investigations that have a single value, such as cardiac troponin and creatine kinas (CK).
    d. ***PATIENT_MONITORING*** is a new class that indicates the procedure done during patients' monitoring, such as cardiac monitor.
    e. ***PROCEDURE_TO_DIAGNOSE*** is the same class in the reference CPG ontology used for procedures that help in the diagnosis, such as the stress test.

f. **Preserved classes:** ***PHYSICAL_EXAM*** has no use at this stage; however, it was preserved because of the potential benefit.

2. ***INTERVENTION_FOR_TREATMENT***: Instances of this class are participating in ***Has_Expected_adverse_Effect*** property, which indicates the adverse effect of the treatments. The adverse effects are instances of the ***MORBIDITY_CONDITION*** class. For example, Aspirin has allergy as an expected adverse effect (from the ***MORBIDITY_CONDITION***). ***Required_Monitoring*** property connects the treatment with its required monitoring from the ***PATIENT_MONITORING*** class. This class has the following subclasses:

    a. ***INTERVENTION_DRUG_ADMINISTRATION*** which is a new class required by the emergency department setting to represent how the treatment is given to the patient during her stay. The name of the drug is coming from the ***DRUGS*** class using ***Drug_Name*** property. The methods of drug administration such as oral or intravenous are in the data module and connected here using ***Has_Drug_Administration_Method.***

    b. **Preserved classes*:*** ***PROCEDURE_FOR_TREATMENT*** and ***PRESCRIPTION*** classes are preserved because of the potential use in future.

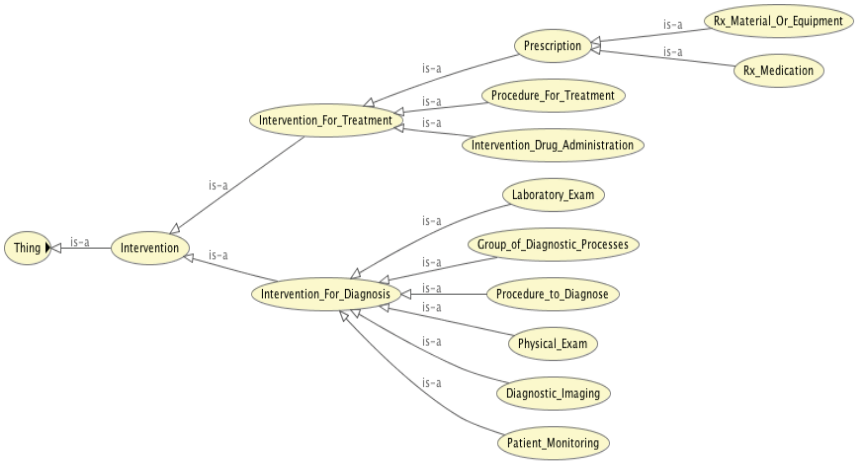

Figure 4. 12 The interventions module

3. EVIDENCE MODULE:

This module contains all the knowledge related to the evidence based medicine classification (EBM) involved in the CPG. Its hierarchy is started from the ***EBM*** class (Figure 4.13).

Figure 4.3 shows the classification of the evidence. This classification is represented in the ***CLASSIFICATION_OF_EVIDENCE*** class, which has the following sub-classes:

1. ***SIZE_OF_TREATMENT***: This class represents the four levels of treatment size depicted in Figure 4.3.
2. ***STRENGTH_OF_EVIDENCE***: This class represents the three levels of evidence strength depicted in Figure 4.3.
3. ***INTERSECTION***: This class represents the intersections between the previous two classes and has 12 instances; namely, ***IA, IB, IC, IIaA, IIaB, IIaC, IIbA, IIbB, IIbC, IIIA, IIIB,*** and ***IIIC.***
4. ***EVIDENCE_SCENARIO***: This class represents the updates' scenarios. In the CPGs, the updates come as scenarios. A careful analysis of these scenarios resulted in identifying two components in each one, the Declarative Knowledge component, and the Procedural Knowledge component, which

can be represented as rules. More detail about these components is in the data module and the unique features section. ***EVIDENCE_SCENARIO*** is participating in the ***Has_Scenario_Data*** property, which connects it to the ***SCENARIO_DATA***, a sub-class in the data module.

Has_Evidence_Intersection indicates the evidence intersection of each scenario. In case the scenario is updating or overriding a previous scenario, ***Updating_Scenario*** property will indicate the old overridden scenario.

Another class in this module is the ***INTERVENTION_EVIDENCE_UPDATE,*** which represents the updates published for a certain intervention. For example, Beta-Blockers have three updates, one in 2004, and two in 2007.

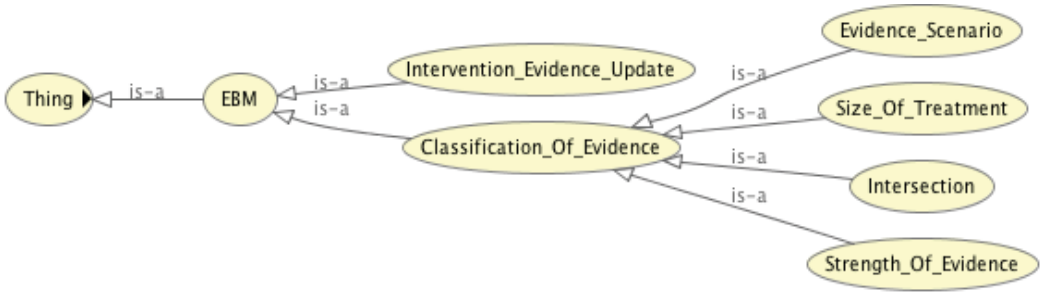

Figure 4. 13 The evidence module

4. DRUGS MODULE:

DRUG class is present in the reference CPG ontology; however. The new CPG ontology adds more granularity to this class by adding six sub-classes representing the common types of drugs used in the CPG (Figure 4.14). These sub-classes are:

1. ***ANTICOAGULATION_CLASSIFICATION***
2. ***BB_CLASSIFICATION***
3. ***THROMBOLYTIC_CLASSIFICATION***
4. ***ANTIPLATELET_CLASSIFICATION***
5. ***ANALGESIC***
6. ***OTHER_DRUG_CLASSIFICATION***

Has_Other_Classification property is used to indicate other classifications of certain drugs. For example, Aspirin is classified as analgesic and antiplatelet. ***Has_Interaction_With*** property is used to indicate other drugs that may interact with certain drugs, such as Aspirin and Ibuprofen. Drug indications and contraindications are presented in the data module and connected here using ***Has_Data_Element*** property.

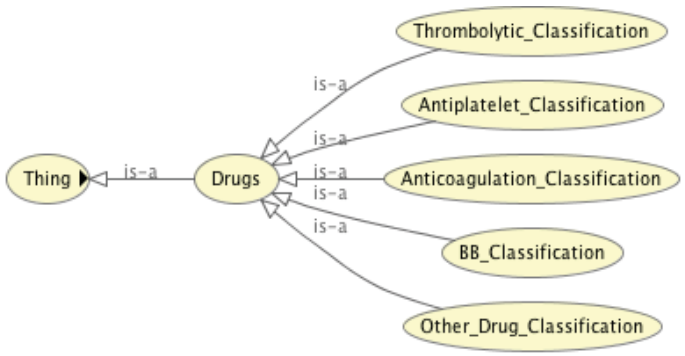

Figure 4. 14 The drugs module

5. DATA MODULE

In the reference CPG ontology, datatype properties are distributed all over the classes. Some datatype properties can be reusable. However, coupling these datatype properties with other classes hinders their reuse. Therefore, most of the datatype properties are collected in one module called the data module.

DATA_ELEMENT class is adopted from the reference CPG ontology and extended to involve all the datatype properties.

CONDITION class was used in the reference CPG ontology to represent the logics required in the decision steps; we subsumed this class under the ***DATA_ELEMENT*** class.

We identified two types of data as the following:

1. **CDSS Data**: This type of data is required by the CDSS to execute the decision logics; for example, criteria for risk stratification and drug contraindications. The source of this data, which has a low turnover rate, is mainly the CPGs.
2. **EMR Data**: This type of data is more specific to the patient. The main source of the data is the ontology execution; i.e., when patient management is guided by the CDSS, data are generated and should be recorded in the EMR. For example, giving certain drugs recommended by the CDSS may lead to some reactions. These reactions are specific to the patient and should be recorded in the EMR. Other sources of this type of data are hospital information systems, such as the laboratory information system and the Picture archiving and communication system (PACS).

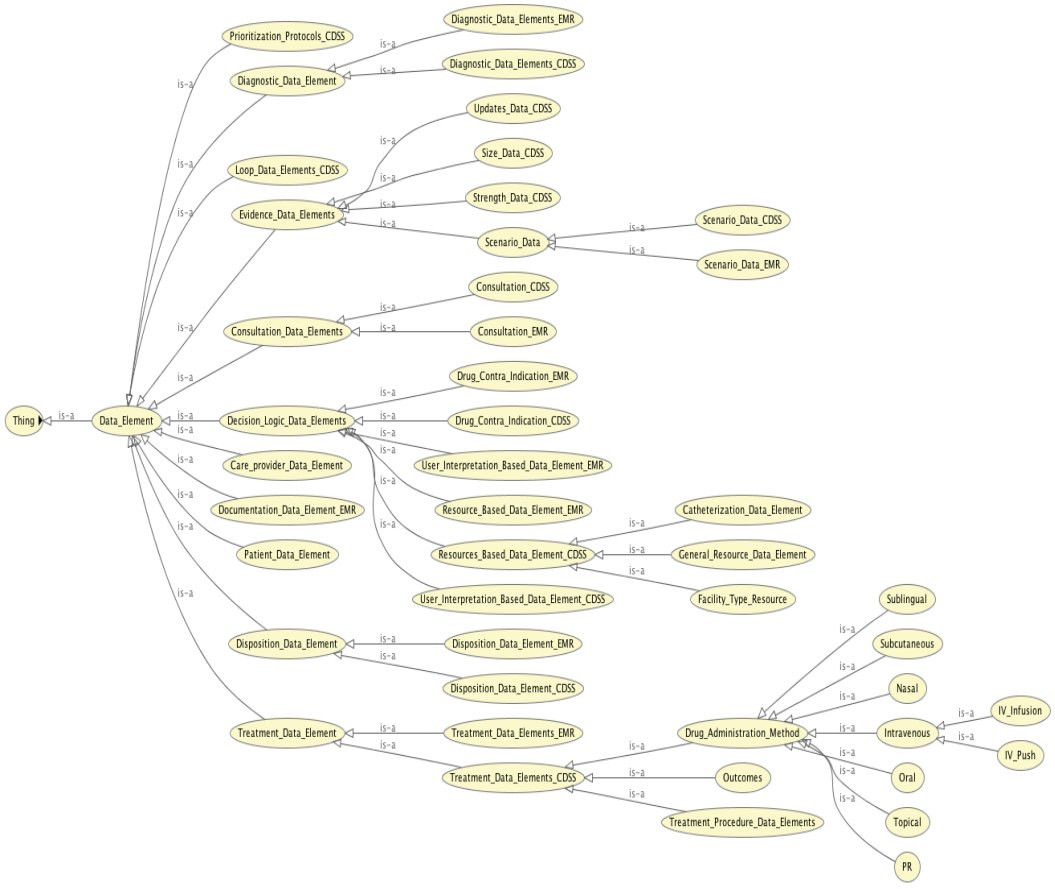

Figure 4. 15 The data module

DATA_ELEMENT class has the following sub-classes (Figure 4.15):

1. ***CARE_PROVIDER_DATA_ELEMENT:*** this class has all the data related to the care providers who are involved in patient management. ***Is_MRP*** is a Boolean datatype property indicating whether or not the provider is the most responsible physician (MRP) for patient management. MRP is usually the emergency physician. However, in some institutes the cardiologist is the MRP. Other self-explanatory datatype properties are ***provider_email, provider_name,*** and ***provider_phone.***
2. ***CONSULTATION_DATA_ELEMENTS*** class represents the data involved in the consultation step. It has two sub-classes:
    a. ***CONSULTATION_CDSS*** is the domain of **Consultation_*Duration_Standard*** datatype property, which means the maximum duration for the consultation to finish, according to the hospital policy. This datatype helps in auditing the efficiency in the emergency department.
    b. ***CONSULTATION_EMR*** represents the data captured in the consultation step. It has five datatype properties: ***Consultation_Issue*** indicates the reason behind the consultation, ***Consultation_Response_Time*** indicates when the cardiologist answered the call for the consultation, ***Consultation_Starting_Time*** indicates the time when the cardiologist is physically present at the point of care, ***Consultation_End_Time*** indicates the time when the consultation's issue is resolved, and ***Further_Instructions*** is used when the consultation step results in agreement between the cardiologist and the emergency physician on a plan other than what is indicated in ***Has Action Steps As Consultation Outcome*** property in the TNM module.

3. ***DECISION_LOGIC_DATA_ELEMENTS***: To some extent, this class is replacing the ***CONDITION*** class in the reference CPG ontology. However, it represents more than the conditions. From the class name, it is clear that the data in this class are used in or generated from the decision logics in either the decision steps or the prioritization steps. It has seven sub-classes:
    a. ***DRUG_CONTRA_INDICATION_CDSS*** represents the indications and contraindication for interventions. It has four main datatype properties, ***Absolute Contraindications, Relative Contraindications, Indications***, and ***Decision Question.*** The last datatype property is used to save the question needed to be answered by the user or possibly by the system. For example, in Aspirin contraindication decision step (Figures 4.5 and 4.6), the users should answer the following question: "Is Aspirin indicated and has no contraindication?" The user will draw her conclusion from interviewing the patient and applying the data represented in the ***Absolute_Contrainddications, Realtive_Contraindications,*** and ***Indications*** datatype properties.
    b. ***DRUG_CONTRA_INDICATION_EMR*** class represents the data captured during the decision logics execution. It has two main datatype properties, ***Question_Answer***, which is a Boolean datatype property to answer the question in the previous class, and ***Answer_Comment***, which is used if the user added any comment to her answer. ***Question_Answer*** and ***Answer_Comment*** are used frequently in the sibling sub-classes.
    c. ***RESOURCES_BASED_DATA_ELEMENT_CDSS*** represents the data related to the resources required in the management of ACS. Resource could be drugs, facility required for treatments' procedure, such as catheterization laboratory, or the availability of transfer from one hospital to another. The ***Description*** datatype property provides descriptions of the resources. This class has three sub-classes:

I. ***GENERAL_RESOURCE_DATA_ELEMENT*** is a generic class that can be applied to any resource. It has five datatype properties, ***Availability, Cost, Decision_Question,*** and ***Intervention_Duration_Standard***, which is the standard maximum duration of the resource usage to finish. For example, chest X-ray has a standard duration to be performed in. This duration depends on the hospital's policy. The last class is ***Rate_Of_Usage***, which is used when there are multiple options of the same resource available to compare and decide on the preferable one. For instance, in using metoprolol and propranolol, both are beta-blockers; however, one of them might be preferable over the other.

II. ***CATHETERIZATION_DATA_ELEMENT*** is a class specific to the catheterization procedure. Figure 4.6 shows that there are two decision-steps required to calculate the time to finish the cardiac catheterization. All the variables required for this calculation are collected in this class.

III. ***FACILITY_TYPE_RESOURCE*** is specific for the facility to determine which type it is. The type depends on the availability of catheterization laboratory, transfer capability, and thrombolytics. The last two classes are not generic. We added them to represent our CPG.

d. ***RESOURCE_BASED_DATA_ELEMENT_EMR*** class is similar to ***DRUG_CONTRA_INDICATION_EMR*** class.

e. ***USER_INTERPRETATION_BASED_DATA_ELEMENT_CD-SS*** is used when the decision logic requires the user's participation. Usually, the user needs materials, such as criteria,

to help in taking the decision. These materials are saved in this class under the ***Provided_Material*** datatype property.

   f. ***USER_INTERPRETATION_BASED_DATA_ELEMENT_E-MR*** class captures the user's response during decision-making.

4. ***DIAGNOSTIC_DATA_ELEMENT*** class captures the data in diagnostic steps. It has two subclasses
   a. ***DIAGNOSTIC_DATA_ELEMENTS_CDSS*** class provides materials to the user when she/he performs any diagnostics procedure. These materials are included in ***Provided_Material*** datatype property.
   b. ***DIAGNOSTIC_DATA_ELEMENTS_EMR*** class captures all the data generated by performing diagnostic procedures. It has four datatype properties: ***Diagnostic_End_Time, Diagnostic_Start_Time, Diagnostic_Name,*** and ***Diagnostic_Result.***
5. ***DISPOSITION_DATA_ELEMENT*** class captures the data related to the disposition step. It has two subclasses:
   a. ***DISPOSITION_DATA_ELEMENT_CDSS*** mainly captures the standard maximum duration for the disposition to finish. That is indicated by ***Disposition_Duration_Standard*** datatype property.
   b. ***DISPOSITION_DATA_ELEMENT_EMR*** class has three datatype properties: ***where*** datatype property, which indicates the place that the patient is moved to, such as discharge home or admitted to the hospital, ***Disposition_End_Time***, and ***Disposition_Start_Time.***
6. ***DOCUMENTATION_DATA_ELEMENT_EMR*** is a class for the data recorded in the documentation steps. It has three datatype properties: ***Prioritization_Name*** is the name of the failed prioritization step, ***What*** is the subject title of a documentation, and ***Why*** is the failure reason.
7. ***EVIDENCE_DATA_ELEMENTS*** is the class where all the related evidences are recorded. It has four sub-classes:

a. ***SIZE_DATA_CDSS*** and ***STRENGTH_DATA_CDSS*** provide the meaning of the evidence's levels in the ***Description*** datatype properties (Figure 4.3).

b. ***UPDATES_DATA_CDSS*** captures data of each intervention's update. It has four datatype properties: ***Date*** records the release date, ***Justification*** records the reason behind the update, ***Source*** records the citation of the updates, and ***Keywords*** helps in finding similar knowledge in the literature.

c. ***SCENARIO_DATA*** includes each update, which is represented as scenarios, and each scenario has two parts: ***Declarative_Knowledge*** which is the condition that should present in order for the scenario to be true, and ***Procedural_Knowledge*** which indicates the applied knowledge in case the declarative knowledge is present. These parts are under the ***SCENARIO_DATA_CDSS*** class. To have a better understanding of the scenario data, the following excerpt of the CPG is analyzed [113]:

> *"It is reasonable to perform rescue PCI for patients with 1 or more of the following:*
> *a. Hemodynamic or electrical instability.* ***(Level of Evidence: C)***
> *b. Persistent ischemic symptoms.* ***(Level of Evidence: C)****"*

It is clear that Hemodynamic or electrical instability and Persistent ischemic symptoms are the declarative knowledge, while performing the rescue PCI is the procedural knowledge.

d. ***SCENARIO_DATA_EMR*** has two datatype properties: ***Chosen_Scenario*** that records the most applicable scenario for the patient, and ***Captured_Evidence_Level*** that records the evidence level of the chosen scenario.

8. ***LOOP_DATA_ELEMENTS_CDSS*** is the class that contains all data to execute the loop step correctly. Loop step needs the number of times it is

needed to be run, which is captured by ***Iterations*** datatype property, the duration between each run, which is captured by ***Interval_Between_Runs***, the logic needed to stop the loop, which is captured in ***Loop_Termination_Logic***, and the indication to run the loop at least once represented in the ***Run_At_Least_Once*** datatype property.

9. ***PATIENT_DATA_ELEMENT*** is the class used for the patient's data such as age, sex, past medical history, allergy, etc…
10. ***PRIORITIZATION_PROTOCOLS_CDSS*** is the class for prioritization steps, which have protocols, as mentioned in the TNM module. The description of these protocols is represented by ***Description_Of_The_Protocol*** property in this class. Each protocol is connected to the ***Decision_Logic_Data_Elements*** by ***Has_Data_Element*** object property to provide the required data to run the protocol. For example, one of the protocols to prioritize Beta-Blockers is ***Prioritization_Protocols_By_Inventory***, which requires data, such as the availability and costs, from ***GENERAL_RESOURCE_DATA_ELEMENT*** class.
11. ***NOTIFICATION_DATA_ELEMENT_CDSS*** is a class that represents notifications required during the management. This class has a datatype property called ***Notification_Trigger***, which is used to represent the triggering factor.
12. ***TREATMENT_DATA_ELEMENT*** illustrates one of the major differences between our ontology's domain (management of ACS) and the reference CPG ontology' domain (medical CPGs), which is the way drugs are given; i.e., the method of administration. Therefore, this class was created to represent the whole data regarding the treatments' interventions. This class has two subclasses: the first is ***TREATMENT_DATA_ELEMENTS_EMR***, which has two datatype properties, ***Description*** to describe the treatment given and ***Reported_Reaction*** if there is any reaction that happened due to the treatment. The second subclass is the

TREATMENT_DATA_ELEMENTS_CDSS, which has three subclasses: the ***OUTCOMES*** indicates the description of the outcomes needed to be achieved by the given treatment;

TREATMENT_PROCEDURE_DATA_ELEMENTS is a class to provide the description data for the treatment procedures; and the ***DRUG_ADMINISTRATION_METHOD*** represents the method of giving the treatment in the emergency department. There are seven methods modeled as subclasses listed as follows:

a. ***INTRAVENOUS (IV)*:** through the veins and divided into two types:
    i. ***IV PUSH***: the whole dose is given in one push
    ii. ***IV INFUSION***: an infusion of the whole dose in certain rate,
b. ***NASAL:*** through the nose,
c. ***ORAL:*** through the mouth,
d. ***PR:*** through the rectum (stands for per rectal),
e. ***SUBCUTANEOUS*:** under the skin,
f. ***SUBLINGUAL:*** under the tongue, and
g. ***TOPICAL:*** through the skin.

Table-4.2 shows the datatype properties representing the administration methods.

Datatype property	IV	IVP	NA	OR	PR	SC	SL	TP	Description
Dose_Unit	√	√	√	√	√	√	√	√	Such as, milligram, milliliter, drops, etc.
Loading_Dose	√	√	√	√	√	√	√	√	Some drugs such as heparin needs initial loading dose before the maintenance dose.
Maintenance_ Dose		√	√	√	√	√	√	√	The continuous dose after the loading dose. This property is not used in the IV infusion; rate of infusion is used instead.

Datatype property	IV	IVP	NA	OR	PR	SC	SL	TP	Description
Maximum_ Maintenance_ Dose	√	√	√	√	√	√	√	√	Self-explanatory.
Maximum_ Total_Dose	√	√	√	√	√	√	√	√	Is the maximum dose of the drug, including the maintenance plus the loading. In case of IV infusion, it includes the total rate of infusion over period of time plus the loading dose.
Minimum_ Maintenance_ Dose	√	√	√	√	√	√	√	√	Self-explanatory.
Recommended_ Dose	√	√	√	√	√	√	√	√	Sometimes, the CPG put a recommended dose between the maximum and the minimum doses.
Special_ Instructions	√	√	√	√	√	√	√	√	In case the drug needs special handling during the administration. For example, Adenosine needs arm elevation immediately after administration.
Max_ frequency		√	√	√	√	√	√	√	What is the maximum number of times the drug should be given?
Min_ Frequency		√	√	√	√	√	√	√	What is the minimum number of times the drug should be given?
Interval_ of_Increment_ Decrement	√								The time between each adjustment of the infusion. For example, IV nitroglycerin is usually adjusted every 5 minutes until target reached.
Rate_Of_ Increment_ Decrement	√								How much, in terms of dose units, should infusion rate increased or decreased with each adjustment?
Rate_Of_Infusion	√								The maintenance initial infusion rate.

Datatype property	IV	IVP	NA	OR	PR	SC	SL	TP	Description
Total_Duration	√								How long the infusion should continue.
Treatment_ Target	√								What is the target of the treatment? For example, lowering the blood pressure.

Table 4. 2 Data elements of drug administration methods (IV: infusion, IVP: IV Push, NA: Nasal, PR: Rectal, SC: Subcutaneous, SL: Sublingual, and TP: Topical)

6. **EXTERNAL RESOURCE MODULE:**

Each class of the data module is saved in or retrieved from other sources. For the purpose of our research, we designed a tentative database to be connected to the Modular CPG ontology. Data module classes are connected to the ***EXTERNAL_RESOURCES*** class through ***Has_DB_Table*** object property to indicate which table in the database has the data of that class. The ***EXTERNAL_RESOURCES*** class has two subclasses: ***DATABASE*** subclass contains the general information of the database, and ***DB_TABLE***, which is divided into two further subclasses, ***CDSS_TABLE*** and ***EMR_TABLE*** (Figure 4.16).

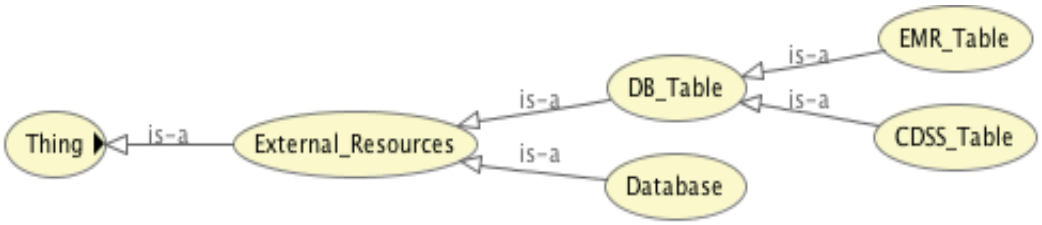

Figure 4. 16 The external resource module

7. **ACTORS MODULE:**

This module represents all the actors during the patient's management (Figure 4.17). These actors can be ***PATIENT***, the most responsible physician (***MRP***), the physician who is primarily treating of the patient, or other providers such as nurses and cardiologists. ***ROLE*** class indicates the role of the actors who

are involved in a certain intervention. For example, let's assume that we have three providers under the ***OTHER_PROVIDER*** class; namely, Alice, Bob, and Oscar. Alice and Bob have the assigned role "cardiologist, and ER-physician", while Oscar has "nurse". Intervention such as ordering thrombolytics will be permitted to Alice and Bob, but not to Oscar.

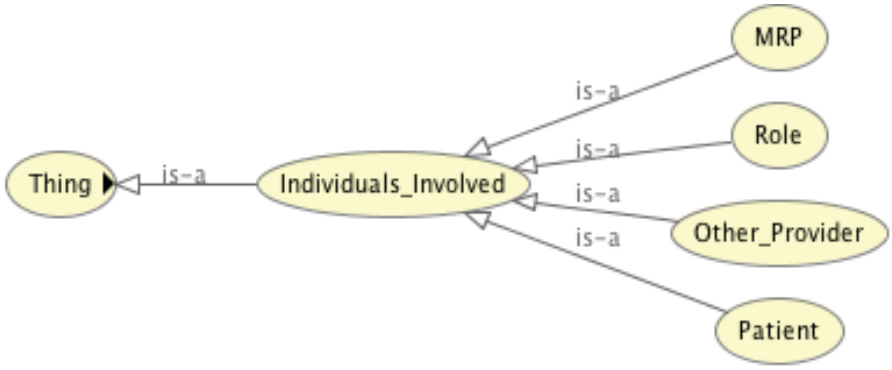

Figure 4. 17 The actors module

8. OTHER CLASSES

Some other classes are difficult to modularize; thus they are kept as subclasses of the root class. The following is a list of these classes:

- ***a. LOOP_SEQUENCE*** class contains the sequences of the loop steps.
- ***b. MORBIDITY_CONDITION*** represents the patient's pathological state. These states can be presentation diseases or adverse effects from the interventions. For instance, bleeding is expected to happen if Heparin is given. Each morbidity condition has its own treatment or guideline to manage.
- **c.** ***NOTIFICATION*** class is adopted for the reference CPG ontology to provide alerts and notifications. This class is connected to the notification step in the TNM.

DURATION class was removed because we found it difficult to model all the varieties of duration as instances. Instead duration was modeled as datatype properties under each class.

4.2.8. OWL Restrictions in the Modular CPG Ontology

Adding restrictions to the ontology helps in reasoning and checking the consistency of the model. This section provides only some examples of the restrictions we used; for more details see the ontology model (the OWL file).

1. PRIMITIVE AND DEFINED CLASSES

The reference CPG ontology and our ontology were designed in a way that all concepts' classifications are asserted, making the automatic classification by the reasoner unnecessary. Therefore, at this stage we used mainly primitive classes. Defined classes are used in the drugs' module, where some drugs have more than one classification. For example, Aspirin is analgesic and antiplatelet in the same time; it was inserted under the ***ANALGESIC*** class, so a necessary and sufficient restriction was applied to the ***ANTIPLATELET*** class to force Aspirin under it (Figures 4.18).

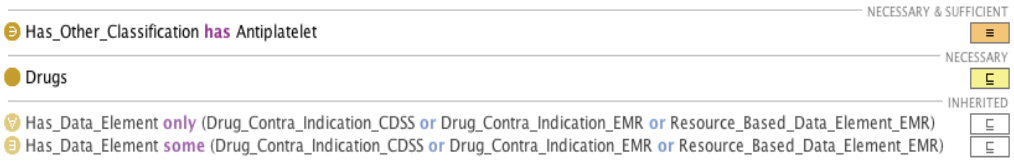

Figure 4. 18 Adding necessary and sufficient restrictions to antiplatelet class

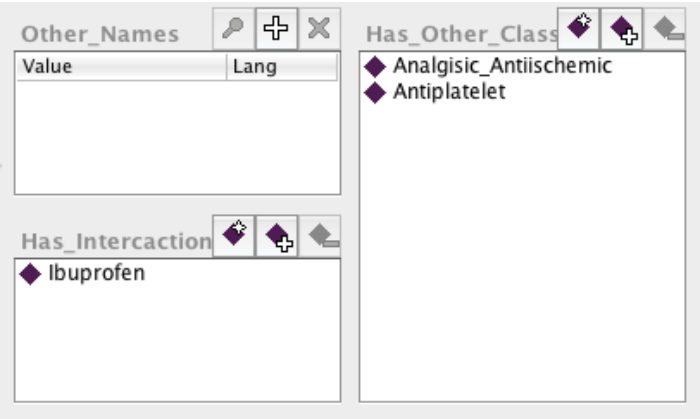

Figure 4. 19 Aspirin has two instances of the classification

It is worth mentioning that, although Aspirin is inferred as Analgesic and Antiplatelet, it was used as Antiplatelet in the context of the CPG.

2. EXISTENTIAL RESTRICTIONS, UNIVERSAL RESTRICTIONS, AND CLOSURE AXIOM

Existential restrictions are used in most of the classes to add more layers of semantic on the classes. Simultaneously universal restrictions and existential restrictions are added to form closure axioms. For instance, ***DOCUMENTATION*** step, like many other classes, is participating in ***Has_Data_Element*** object property; however, this participation is restricted using closure axiom (Figure 4.18). Using such restrictions prevents the reasoner from making wrong classifications and allowed us to reuse many object properties with many classes.

3. CARDINALITY RESTRICTIONS

Minimum, maximum, and exact cardinalities are used extensively in the model. For example, to replace ***Branch_to*** property by ***Next_Step*** property we added minimum cardinality of 2 to the ***Next_Step*** Property. Maximum cardinality was used in situations when we would like to reuse an object property in two axioms, the first axiom needing functional property, while the other needs multiple participations; instead of making the property functional, we added maximum cardinality of 1 to the first axiom and no restriction in the second. For example,

Treatment_Step has only one intervention, so we restricted ***Has_Treatment*** property, which is not functional, with a maximum cardinality of 1.

4. PROPERTY CHARACTERISTICS

Most of the properties we used are non-functional, because of the flexibility provided by adding cardinality restrictions. However, some properties are used as functional, such as ***Has_Drug_Administration_Method.*** Also, symmetric properties are used in drug interactions; for example, Aspirin ***Has_Intercaction_With*** Ibuprofen, which means Ibuprofen ***Has_Intercaction_With*** Aspirin. Other characteristics were not identified in the ontology.

The complete hierarchy of the Modular CPG ontology is shown in Figure 4.20.

4.3. Phase-2: Modular CPG Ontology Instantiation (Creating MACSON[1])

After creating the Modular CPG ontology, we instantiated it to create MACSON. MACSON has 909 instances under 113 classes. Also, it has 161 properties, 52 of which are object properties and 109 are datatype properties.

The following diagrams show snapshots of the instances, object properties, and datatype properties.

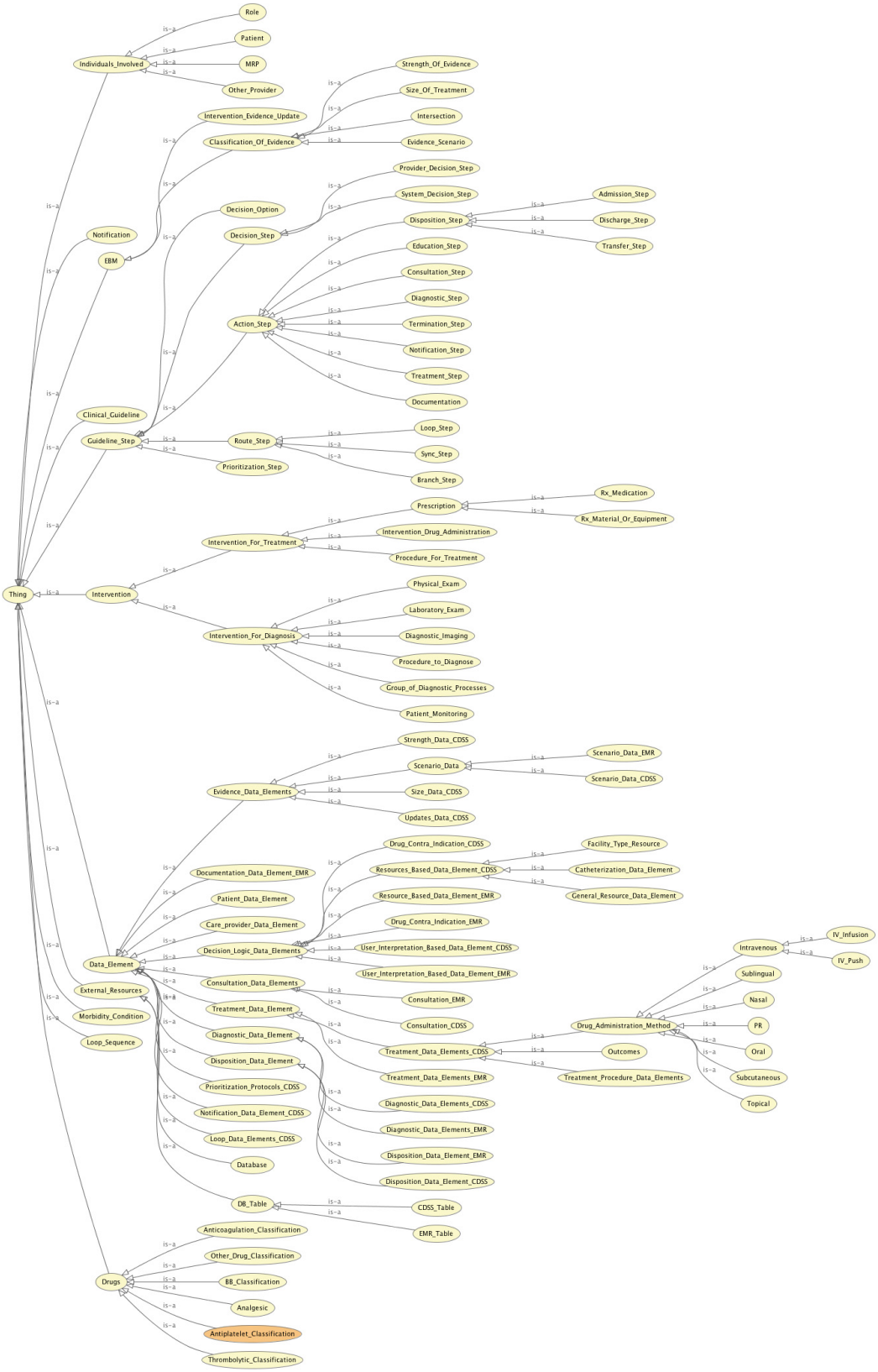

Figure 4. 20 The modular CPG ontology

Figure 4. 21 A snapshot of the TNM module's instances

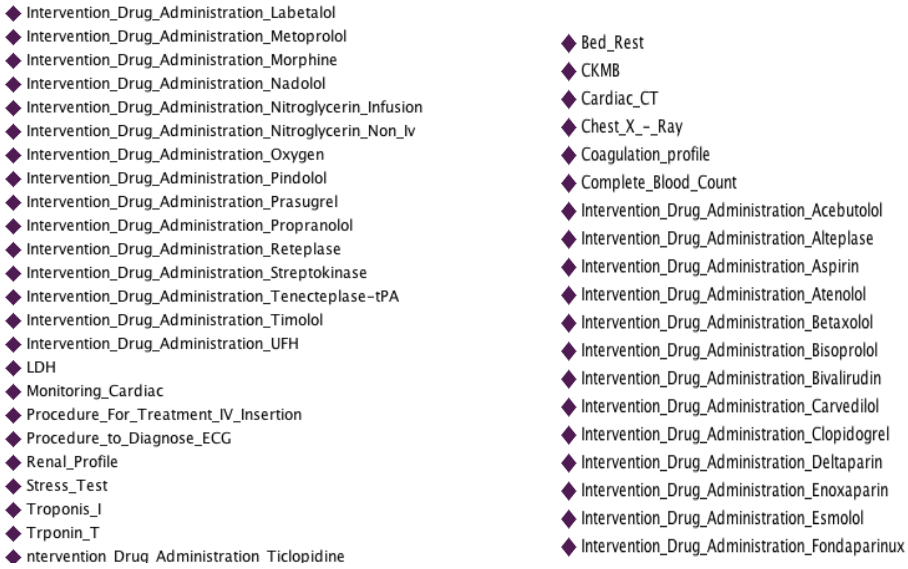

Figure 4. 22 A snapshot of the interventions module's instances

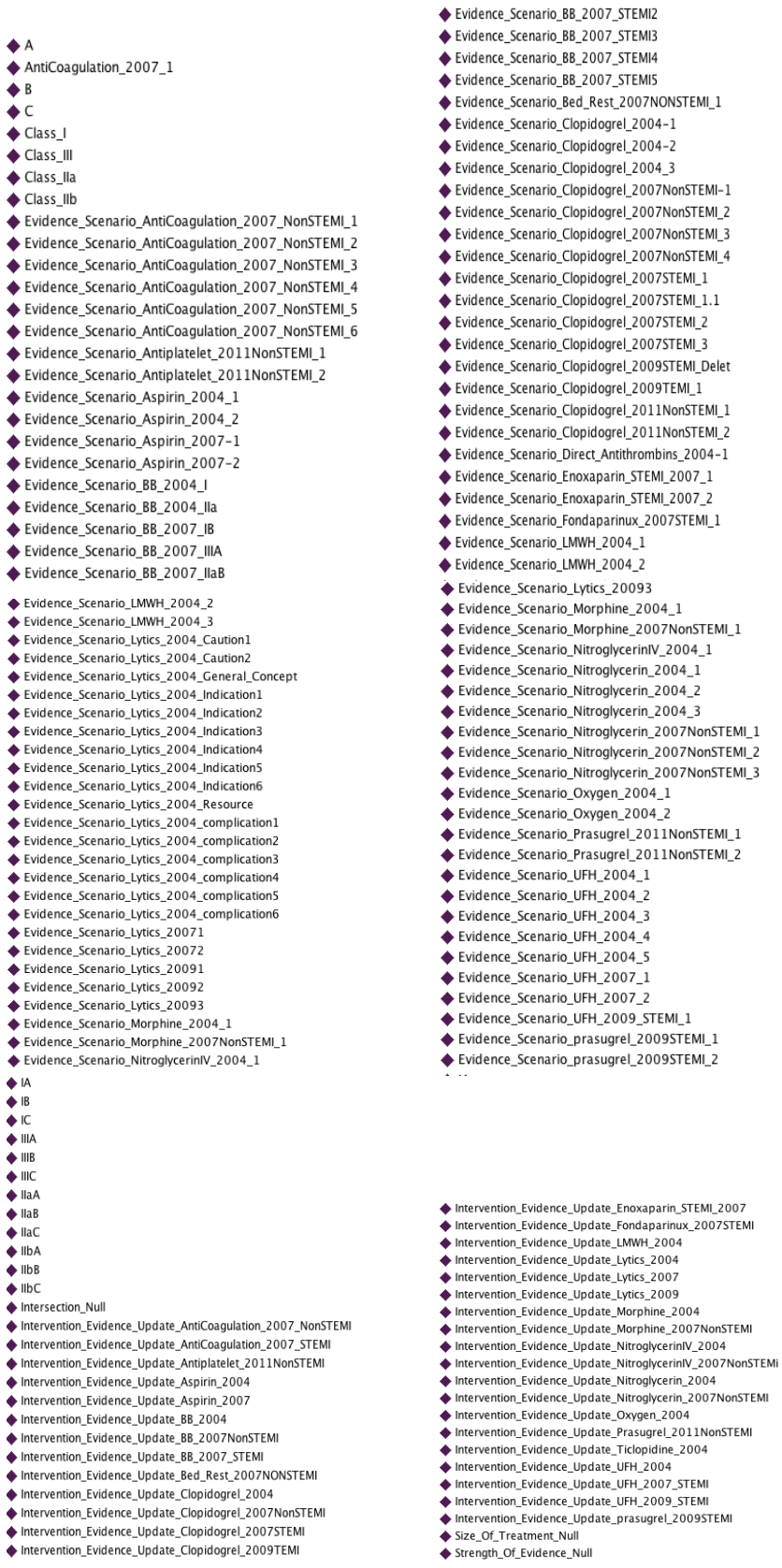

Figure 4. 23 A snapshot of the evidence based medicine module's instances

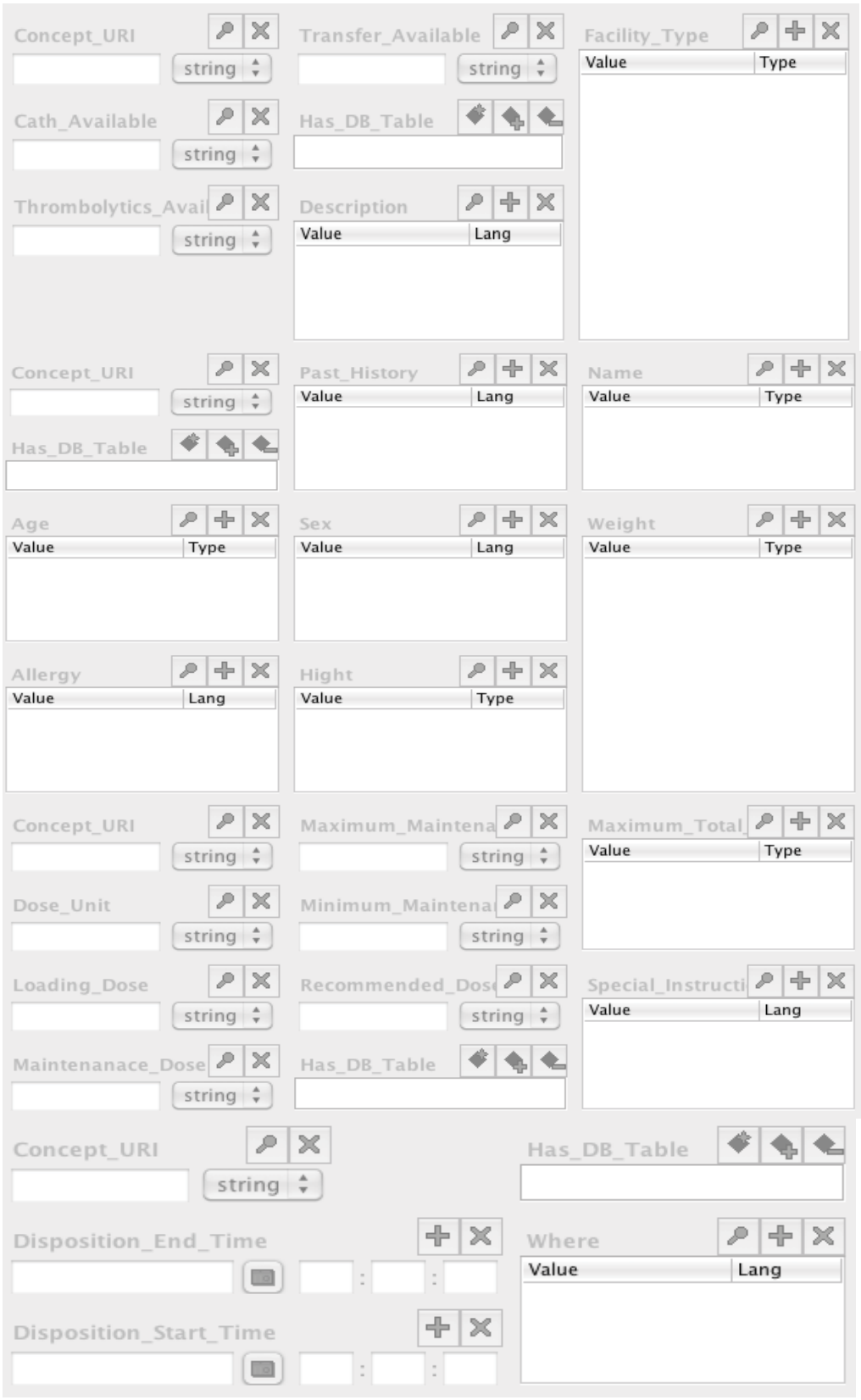

Figure 4. 24 A snapshot of some of the datatype properties in the data

4.4. Unique Features in the Modular CPG Ontology

4.4.1. Modeling the CPG Updates

Usage of the evidence module is depicted in Figure 4.25. Some of the interventions have multiple updates, and each update has many scenarios. The system will show a questionnaire that is built using the declarative knowledge of the scenarios to determine the most suitable scenario that applies to the patient. Then the evidence level of the chosen scenario will be captured from the level intersection class then recorded in the EMR type of Data as mentioned above. This captured evidence will have two main uses:

1. **To prioritize the treatment options in the prioritization step (see below).**
2. **To modify the task network model:** Some of the updates address situations where some steps in the clinical pathway become obsolete, overriding previous recommendations. Capturing these situations through the scenarios can help to avoid giving some interventions by omitting or jumping some of these steps using rules.

   For example, Beta-Blockers, especially the intravenous form, were used generously in treating patients with ACS. The new updates added more restrictions on this type of medication, such as not giving it with the early signs of heart failure. By using scenario to detect the early heart failure signs we can assign level III size of treatment to Beta-Blockers in treating certain patients. Then rules will be fired to skip the Beta-Blockers step in the clinical pathway.

Previous research studies discussed the issue of updates to guidelines. However, this research focused on adding new treatment instances rather than changing the pathway structure. The researchers assumed that the clinical pathway does not change frequently [124]. This assumption is partially true; however, when pathway changes happen they are expensive, in terms of restructuring the model. Using this module helps in saving the monolithicity of the model, as only minimal restructuring is needed when the new updates are published.

M. Peleg and R. Kantor used a versioning annotation method to add annotation to the tasks in the CPG model. These annotations indicate the version of the updated tasks. The

author extended GLIF3 to be able to model this versioning technique [125]. Our modeling technique uses the evidence level to version the tasks.

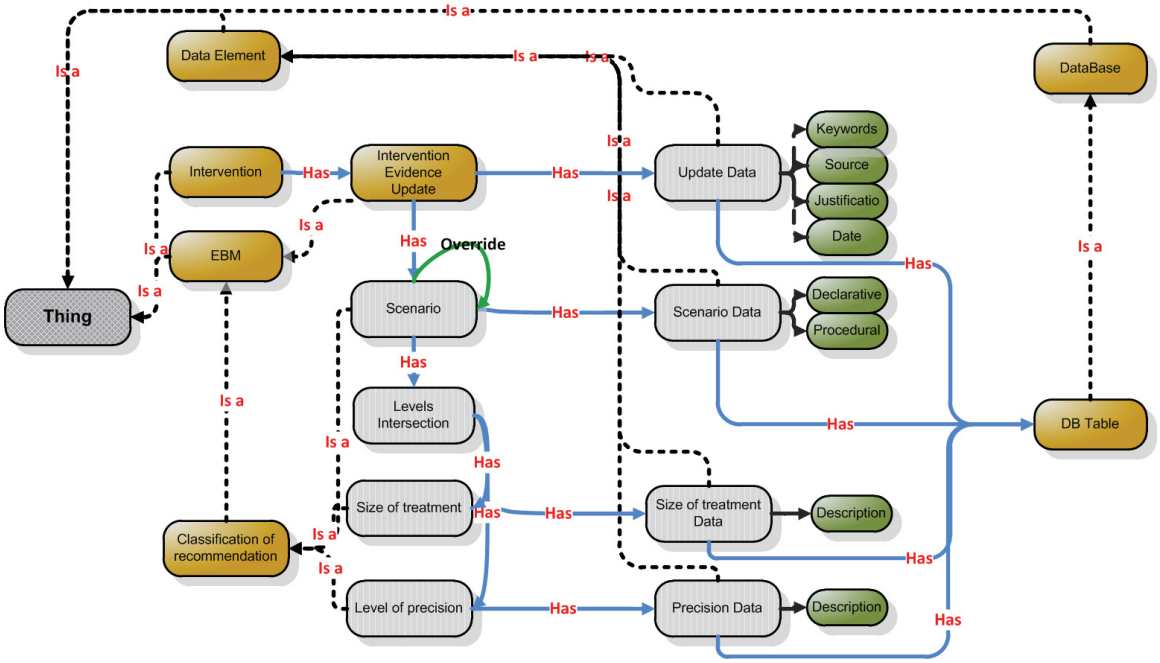

Figure 4. 25 Modeling the CPG update

4.4.2. Shifting to Other Guidelines

The issue of comorbidities was addressed in previous research [126]. The handling of comorbidities in the ontologies needed merging of the guidelines at different levels, such as modeling level and executions level [126]. Handling this issue is out of our research scope; however, the model has the ability to shift from one guideline to another using three ways:

1. At the beginning of ACS management, each patient will have ***MORBIDITY_CONDITIONS***, one of which is ACS, and each condition will have its own Guideline.

2. At the task network model, ***Next_Step*** object property has the ***CLINICAL_GUIDELINE*** as a range allowing the control flow to move to another guideline. This feature is adopted from the reference CPG ontology.
3. At the interventions' level: some interventions can lead to another morbidity, such as bleeding caused by heparin. Any intervention related morbidity (which has its own guideline) is connected through the ***Has_Guideline*** object property. For instance, thrombolytics can lead to intracranial bleeding, which is listed under the ***MORBIDITY_CONDITION*** class. The control flow can shift to the intracranial bleeding guideline. ***TERMINATION*** step indicates when to go back to the original guideline.

This feature has some limitations, such as duplication of common steps and omitting the parallel steps of two different guidelines. The work done in [126] can help in improving this functionality in the future.

4.4.3. Prioritization Protocols

Instead of leaving the physician to choose between many options for a single step, such as giving Beta-Blockers, the system can filter non-suitable options using three-prioritization protocols (Figure 4.26). The first protocol starts by questioning the physician about treatment contraindications. The contraindicated treatments are excluded, and the non-contraindicated treatments enter the second level, which has two filters. The first one is used to filter out-of-stock options, while the second one orders the choices according to the local rate of use. The last level of prioritization happens by ordering the options according to the level of evidence. The final choices will appear with two orders: (1) by the rate of use, and (2) by the evidence level, leaving the last decision to the physician, which guarantees some level of professional autonomy.

Beside the main function of the prioritization step (the suggestion of the most suitable options), it can be used to report the discrepancy between the rate of use and the evidence-based practice.

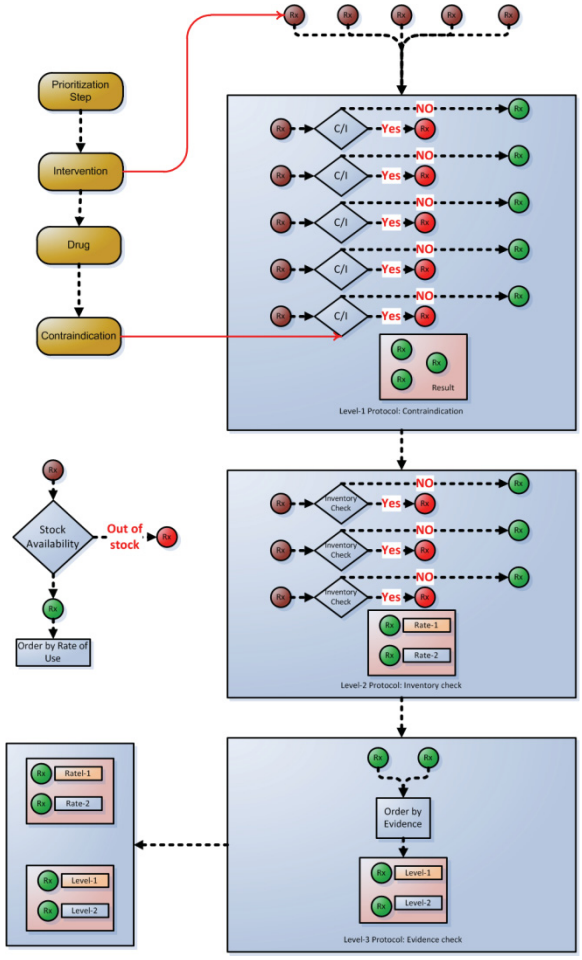

Figure 4.26 Prioritization protocols

4.5. Summary

In our ontology engineering process, we matched the abstracted knowledge from the CPG to the knowledge in the reference CPG ontology, and then we added the missing modules to create the extended reference CPG ontology and the modular CPG ontology. Following that we reduced and normalized the ontology to produce the final modular CPG ontology. The modular CPG ontology is considered a generic model, and it was instantiated to produce MACSON. We followed systematic algorithms to ensure the completeness of the engineering process. Also, we exploited many OWL features in our design, such as reusing properties by adding restrictions. Finally, unique ontology model features were identified and designed, which provided a better representation of the CPG.

CHAPTER-5 ONTOLOGY EVALUATION

5.1. Introduction

Ontology evaluation is needed for many situations, such as: (a) ontologies are intended to be used with certain applications should be evaluated to check how it fits with these applications; and (b) establishing a ranking of ontologies after the evaluation can guide the user to select the best ontology that fits her/his use [127].

Our ontology evaluation will cover the following:

1. **Phase-1: Testing the level of domain representation**
   In this phase we intend to qualitatively evaluate the CPG ontology based representation of the research domain (management of ACS). We have two options to perform an evaluation of the domain representation: (i) consult domain experts to run real clinical cases through the ontology and provide their feedback, and (ii) use published clinical cases to test the ontology.
   The main obstacle in the first option is the fact that domain experts will not be keen to use the ontology in its current format (OWL) because it is not a user-friendly format; therefore, we adopted the second option.
2. **Phase-2: Testing the evidence and update module**
   In this phase we are going to use a clinical case that requires treatment modalities mentioned in the CPG. We will then show how MACSON was able to model the recommendations' update and the evidence behind them that are published in the CPG updated editions.
3. **Phase-3: Testing the prioritization functionality**
   In this phase we will use the above-mentioned case to show how MACSON will help in choosing the best drugs for treating patients and compare it to the expert physician's choices.
4. **Phase-4: Technical evaluation**
   In this phase we intend to test the quality of MACSON. Although there is no widely accepted stranded for this type of evaluation, there is published research

suggesting frameworks to evaluate ontologies [128-130]. This part will be highlighted in phase-4.

5.2. Phase 1: Testing Domain Representation

In this phase, it is important to note that we aim to test the CPG representation rather than the emergency setting representation. The emergency setting has many concepts that are not mentioned in the CPG. For example, usually emergency physicians start the patient's evaluation by assessing three main aspects of the clinical presentation, the airway, breathing, and circulation (ABC). As the ABC was not the main focus of the CPG, the CPG ontology did not mention it. However, any concept mentioned in the ontology is part of the emergency clinical practice.

The aim of this test is to determine if MACSON is satisfactorily representing the CPG based ACS management in the emergency department.

To evaluate MACSON we have selected a mix of clinical cases for management of ACS in the emergency department. To provide a good mix of cases, we have used different sources to capture the diversity of practice. The selection criteria for these cases are mentioned below.

The cases are mainly published for educational purposes. They are directed to different levels, ranging from medical students to attending physicians.

This test is not free of limitations. The main limitation is inherited from the nature of the published cases. These cases are written for specific purposes, such as oral exam, which make them very concise and do not involve all the concepts in ACS management. The other limitation is the fact that these cases do not report what happened during the patient's management; rather they focus on what should be done. Hence, some intervention steps are mentioned without chronological order. These limitations will require testing MACSON in real clinical workflow in the future.

Each case was used to perform the following two tests:

A. **Concept accommodation:** In this test we listed all the concepts captured in the case and tried to find corresponding concepts in the ontology. Missing concepts are reported as gaps in the ontology if there is no justification for their absence. Quantitative measurements are avoided because of the conciseness of the cases. Consequently, we expect to have a limited number of retrieved concepts. Therefore, our sample size will be small to show significant results.
B. **Testing the task network model (TNM):** We tried to construct TNMs from the cases and compare it to the CPG ontology's TNM.

CASES' SELECTION CRITERIA

We selected our cases from literature according to the following criteria (Table 5.1):

A. **Clinical pathways**: Our conceptual model has two separate pathways (Figures 4.5 and 4.6). Each case can be used to test one of these pathways. In our tests we used at least two cases to test each pathway.
B. **Shifting guidelines**: This criterion is present in some of the cases. It means shifting the management of the case as ACS to another condition such as cardiogenic shock. These criteria will test the ability of our model to shift to another guideline.
C. **Resource availability**: Some cases address the importance of resource availability in decision-making during the management. Resource availability is one of the issues that are handled by MACSON.
D. **Time sensitive actions**: Case 2 focused on how to choose between the perfusion strategies according to the duration of the symptoms. Case 5 highlighted the timing to activate and transfer the patient to the catheterization laboratory. Because ACS management is time sensitive, MACSON should effectively handle this issue.
E. **Other criteria:** Case 3 has an explicit clinical pathway reflecting the author's approach in managing NSTEMI/UA. On the other hand, Case 4 was published in the Emergency Medicine Practice journal, which specializes in emergency evidence-based practice. Hence, we chose Case 5 because of the objectivity in

the management approach compared to others that might be more subjective in their approaches.

Case	Pathway-1	Pathway-2	Shifting guidelines	Resource availability	Time sensitive actions	Other
Case 1	✗	✓	✓	✗	✗	
Case 2	✗	✓	✗	✓	✓	
Case 3	✓	✗	✗	✗	✗	Presence of clinical pathway
Case 4	✓	✗	✗	✗	✗	Evidence Based Approach
Case 5	✗	✓	✗	✗	✓	

Table 5. 1 Test cases selection criteria

The cases are listed as follows:

Case 1:

Source: EMERGENCY MEDICINE ORAL BOARD REVIEW ILLUSTRATED**,** 2009 [131].

Author: Nick Genes, MD, and PhD.

Objective: preparation for oral emergency board examination.

Summary: 61-year-old male with epigastric pain, which turned out to be inferior myocardial infarction with right ventricular involvement and possibility of shock.

Final diagnosis: Inferior MI with right ventricular involvement.

Test 1:

Listing and comparing the concepts in Case 1 resulted in identifying some missing concepts:

- Specific types of myocardial infarction were not addressed in the CPG ontology because of its scope, which does not involve the initial diagnosis. Identifying the infarction's site such as inferior, lateral, anterior, or right ventricular is left to the physician, as stated in the research scope. However, documenting the location and the final diagnosis is worth addressing in the ontology. Therefore, a new datatype property in the ***DISPOSITION_DATA_ELEMENT_EMR*** class called ***Final_Diagnosis*** was created to document the diagnosis before moving the patient out of the emergency department.
- Some of the investigations and treatments, such as BMP, LFT, type and cross matching, and IV fluid, were mentioned in this case. However, the CPG did not focus on them because they are not routine tasks in managing ACS. These steps might be important in the implementation phase. MACSON can be connected to other ontologies that classify other routine investigations in the emergency department.
- ECG was named differently in this case (EKG). This name can be captured as a synonym by the ***Other_Names*** datatype property, which has two domains, ***DRUGS*** and ***DIAGNOSTIC_DATA_ELEMENTS_CDSS.***
- The repeated ECG can change the whole TNM because of the unexpected result of the ECG. Therefore, this concept was left for the coding phase when rules can solve this problem.
- Other symptoms of ACS, such as vomiting, require specific treatment. These symptoms are not part of the scope (it was not mentioned in the CPG as part of routine management of ACS). However, MACSON has the ability to model this type of contingencies by classifying vomiting as a ***MORBIDITY_CONDITION***. ***MORBIDITY_CONDITION*** is the domain of ***Has_Guideline*** object property. So vomiting will be a morbidity condition with its own guideline (if it has one).
- Calcium-channel blockers (CCBs) are mentioned in the case as a drug to avoid, so it is not part of the management. CCBs' evidence levels are ranging from IIa to III in the CPG, making them unpopular drugs to use in the emergency setting. In some situations, they are used as alternatives to beta-blockers. We included them as instances in the drug class; however, we did not include them in the TNM.

Adding them to the TNM can be done in the future as a customization if the users request it.

- Activating cardiac catheterization was a physician's task in the case. Depending on the hospital policy, nurses, physicians, or other staff can do cardiac catheterization activation. Assignment of this step is not mentioned clearly in the CPG. Therefore, including it in the ontology will violate our goal to have a generic model. However, this step can be added as a local customization of the system at the implementation phase.
- The physical examination is mentioned in both the case and the CPG. However, physical examination findings rarely affect the management workflow other than shifting to treat other comorbidities. Therefore, we did not create a separate class for physical examination in MACSON. Additionally, the findings in the physical examination and clinical history are indirectly implemented in different steps, such as the beta-blockers contraindication decision step, which requires information captured from the physical examination, such as pulmonary edema, and from history taking, such as history of bronchial asthma.

Table 5.2 summarizes the findings of Test 1

CASE 1			
CASE CONCEPT	**CORRESPONDING ONTOLOGY CONCEPT**	**ALTERNATIVE ONTOLOGY CONCEPT**	**COMMENTS**
Right Ventricular MI		Myocardial Infarction	Specific location of the infarction needed to be addressed
Inferior MI		Myocardial Infarction	Specific location of the infarction needed to be addressed
Age	Patient age		
Oxygen	Treatment step oxygen		
IV-line	Treatment step IV line		

CASE CONCEPT	CORRESPONDING ONTOLOGY CONCEPT	ALTERNATIVE ONTOLOGY CONCEPT	COMMENTS
CBC	CBC		
BMP (basic metabolic panel)			Not mentioned in the CPG as a routine investigation, however, this test is done routinely in EDs
LFT			Not mentioned in the CPG as a routine investigation
Cardiac Enzyme	Cardiac Enzymes		
PT/PTT	PT/PTT		
Type and cross			Not mentioned in the CPG as a routine investigation
500cc NS bolus			Not mentioned in the CPG as a routine treatment
Cardiac monitor	Cardiac monitor		
EKG	ECG		***Other_Names*** datatype property can accommodate the synonyms
Nitroglycerine	Nitroglycerine		
Nitroglycerine Contraindication	Nitroglycerine Contraindication		
Nurse Role	Nurse Role		
CXR	CXR		
Aspirin	Aspirin		
Consult cardiology	Consult cardiology		
Repeat EKG			Omitted in the ontology, to be included in the rules
Right-sided EKG	Right-sided ECG		
Activating cardiac catheterization		Transfer to cardiac catheterization laboratory	Can be added in the implementation phase as local customization

CASE CONCEPT	CORRESPONDING ONTOLOGY CONCEPT	ALTERNATIVE ONTOLOGY CONCEPT	COMMENTS
Vomiting			Omitted as an ACS presenting symptoms; however, it is included as drug adverse effect in the ***MORBIDITY_CONDITION*** class
B-blockers	BBs		***Other_Names*** datatype property can accommodate the synonyms
Calcium-channel			Mentioned in the case as one of the drugs to avoid, but not one of the drug to give routinely.
Physical exam			Helpful in detecting other morbidity conditions. Comorbidity modeling is out of scope.

Table 5. 2 Test 1 results summary of case 1

Test 2:

The constructed pathway from the case is missing a lot of links, because most of the actions are listed without clear chronological orders (Figure 5.1).

We compared this workflow with our pathway (Figure 4.6) and found the following:

- Most of the primary actions are done initially in our pathway, which is consistent with this case. The exceptions to that are the CXR and the investigations. For the investigations it is common for the emergency physician to draw the blood samples and order the investigation as soon as the intravenous (IV) line is inserted. Drawing blood samples does not mean sending them to the laboratory. The final decision of which investigation to order is made when the patient's situation becomes clear. In our pathway and MACSON, ordering the investigations is delayed to give better evaluation for the patient; however, drawing the blood samples is done early during the IV line insertion. The same applied to the CXR.
- Some steps are not shown here because they were contraindicated. For instance, nitroglycerine was contraindicated because of the right ventricular infarction. In

our pathway nitroglycerine contraindication is captured initially using the contradictions decision step.

- The rationale behind omitting the physical examination, some investigations, such as LFT, and some treatments, such as IV fluids, in our pathway are mentioned earlier.
- The case workflow deviated to the management of shock, which is addressed in MACSON as managing other morbidity condition.

Thus, this test shows that MACSON has similar TNM to the case TNM. The variation in the tasks' timing can be handled easily in MACSON if requested by the user.

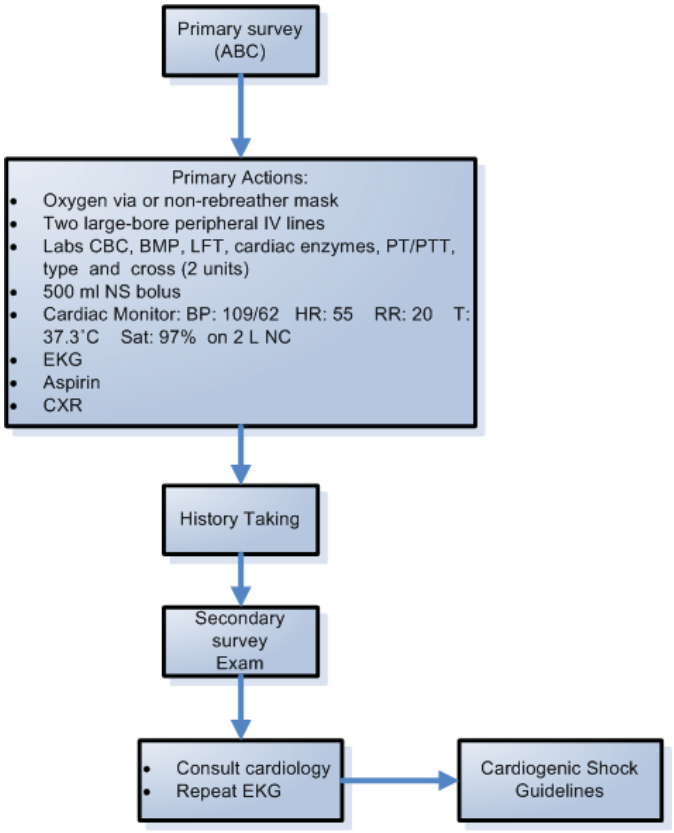

Figure 5. 1 Case 1 management workflow

Case 2:

Source: Case 40-2010: A 68-Year-Old Woman with Chest Pain during an Airplane Flight, The New England Journal of Medicine, 2010 [132].

Author: Dr. Shveta Raju

Summary: A 68-year-old female with a history of intermittent episodes of chest pain over 24 hours was seen in a hospital for another attack of chest pain, then transferred to another hospital for cardiac catheterization within 3 hours of the last chest pain episode.

Final diagnosis: Anteriolateral MI complicated with an acute rupture of the left ventricular free wall.

Test 1

In this test we found the following:

- Glycoprotein IIB/IIIA inhibitors, a drug class used in treatment of ACS, are mentioned in the case as a modality of treatment. . We assumed in the beginning of our research that this class is out of scope because of the fact that it is given by the cardiologist when the patient care is transferred to inpatient care. We acknowledge that some hospitals' policies give the authority to the emergency department physician to give this type of drug; however, it is not the common practice. This drug class can be easily added to the CPG ontology if the user requests it.
- Similar to Case 1 the synonyms and abbreviations can be captured using ***Other_Names*** datatype property.

Summary of Test 1 is shown in Table 5.3.

Case 2			
CASE CONCEPT	**CORRESPONDING ONTOLOGY CONCEPT**	**ALTERNATIVE ONTOLOGY CONCEPT**	**COMMENTS**
Symptoms duration	Symptoms duration		
Blood Pressure	Blood Pressure		
Oxygen saturation 98%		Cardiac monitoring	Oxygen saturation monitoring is usually done with cardiac monitoring
Complete blood count	CBC		Abbreviation

CASE CONCEPT	CORRESPONDING ONTOLOGY CONCEPT	ALTERNATIVE ONTOLOGY CONCEPT	COMMENTS
Electrocardiogram	ECG		Abbreviation
Metoprolol	Metoprolol		
Morphine sulfate	Morphine		Synonym
Heparin	Heparin		
Acetylsalicylic acid	Aspirin		Synonym
Patient Transfer	Transfer step		
Cardiac computed tomography (CT)	Cardiac CT		Although it is not part of routine emergency management at this time, it might be in the future
Pulmonary edema		Morbidity condition	Modeled as an instance of the ***MORBIDITY_CONDITION*** class
Cardiac catheterization	Cardiac catheterization		
Decision logic to give thrombolytics	Decision logic to give thrombolytics		
Decision logic to do cardiac catheterization	Decision logic to do cardiac catheterization		
Glycoprotein Inhibitor/ Eptifibatide			According to our assumptions, this class of drugs is given by the cardiologist

Table 5. 3 Test 1 results summary of case 2

Test 2

This case was reported by a tertiary hospital to discuss mainly the finding in the cardiac catheterization and the inpatient management. The authors stressed the fact that patient management was not optimal in the airplane, confirming the need for decision support for non-trained health professionals in such settings (Figure 5.2). The test result is summarized as follows:

- This case mentioned airplane setting, which is out of our scope.
- The ECG step was similar to our ECG decision step, and the result was the diagnosis of Myocardial Infarction (MI).

- Timing and resource availability were important factors in making treatment decisions in this case. The transfer to a cardiac catheterization laboratory was chosen based on two factors: the first is the duration between the time of the symptoms and the expected time to perform the catheterization, and second is the resource availability; i.e., the availability of catheterization laboratory in the hospital.

  In MACSON (Figure 4.6) the hospitals are categorized into three types according the availability of the catheterization lab. All the other needed variables to calculate the expected time to reach the catheterization laboratory are modeled as datatype properties in ***CATHETERIZATION_DATA_ELEMENT*** class. Patient was received by the first hospital after another pain episode, and that hospital has no catheterization lab but was able to transfer the patient to another facility, making it a type-B hospital according to Figure 4.6. Therefore, the patient was eligible for transfer to the second hospital, which was ready to do the catheterization within 3 hours from the last pain episode.
- All the issues of missing interventions chronological order were also noticed here.

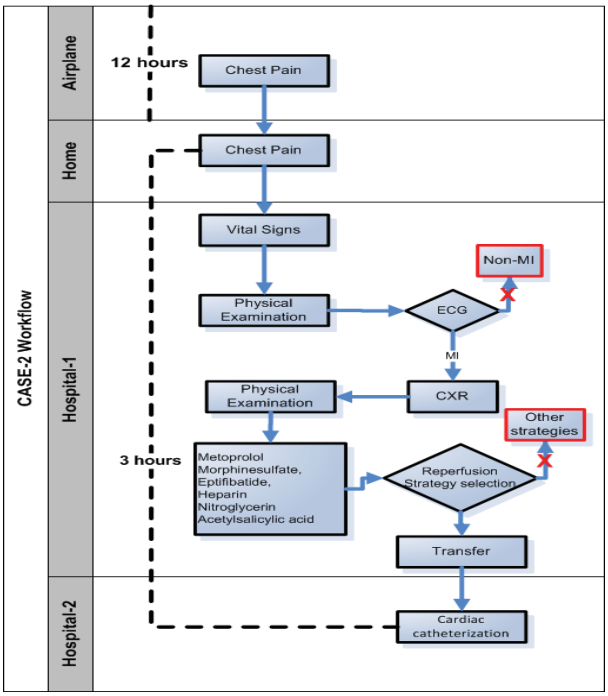

Figure 5. 2 Case 2 management workflow

Case 3:

Source: A 43-Year-Old Man With Angina, Elevated Troponin, and Lateral ST Depression, Management of Acute Coronary Syndromes, JAMA, January 6, 2010 [133].

Author: Amy N. Ship

Summary: A 43-year-old man had a history of chest pain on exertion. Had ST-segment depression in the ECG and positive troponin. Was admitted for diagnostic angiography.

Final diagnosis: NON-ST-Segment elevation MI (Non-STEMI)

Test 1

The following is a summary of the findings in this test:

- The author mentioned specific diagnostic findings in the ECG, such as ST-segment depressions and T-wave inversions. These findings are included in the Non-definitive MI decision option of the first step in MACSON.
- Atorvastatin is a drug used to lower the lipids in the blood. Although it was given to the patient in the emergency department, it is not part of the emergency treatment of ACS according to the CPG.
- Angiography is used sometimes to indicate cardiac catheterization. In this case angiography is used as non-emergent diagnostic intervention for the patient, while our scope includes this intervention as an emergency reperfusion procedure.
- Prasugrel and Ticagrelor are new antiplatelet drugs and will be added as instances in the CPG ontology.
- The author discussed the issue of the new updates and studies that might change the practice in managing ACS such as B-Blockers updates. These issues are covered in the ontology under the updates-module and will be tested later in this chapter.

Table 5.4 shows the summary of Test 1.

Case 3			
CASE CONCEPT	**CORRESPONDING ONTOLOGY CONCEPT**	**ALTERNATIVE ONTOLOGY CONCEPT**	**COMMENTS**
ST-segment depressions		Included in non-definitive MI diagnosis	
T-wave inversions		Included in non-definitive MI diagnosis	
Weight	Weight		
Height	Height		
Atorvastatin			Not mentioned in the CPG as part of Emergency Management of ACS
Angiography			Angiography is similar to cardiac catheterization; here it was done as non-emergent intervention
Risk stratification	Risk stratification		
Prasugrel			New drug added in the 2011 update
Ticagrelor			New drug added in the 2011 update
Low-molecular-weight heparins	Low-molecular-weight heparins		
Bivalirudin	Bivalirudin		
Fondaparinux	Fondaparinux		

Table 5. 4 Test 1 results summary of case 3

Test 2

In this case most of the results are similar to the previous cases except the following:

- There was one discrepancy between the MACSON's TNM and the patient risk stratification in the case (Figure 5.3). The author mentioned that the intermediate risk patient would need an aggressive anticoagulation, while in MACSON anticoagulation is given only to the high-risk patients or patient with positive markers from the other risk groups. Although it seems that the author's suggestion is safer, we argued that our TNM has a safety step before discharging patients with negative markers; i.e., the consultation step (Figure 4.5). The last consultation step was put in to reevaluate patient's risk and discuss it with the

cardiologist, who might suggest starting anticoagulation and admitting the patient even with a low score in the risk stratification.

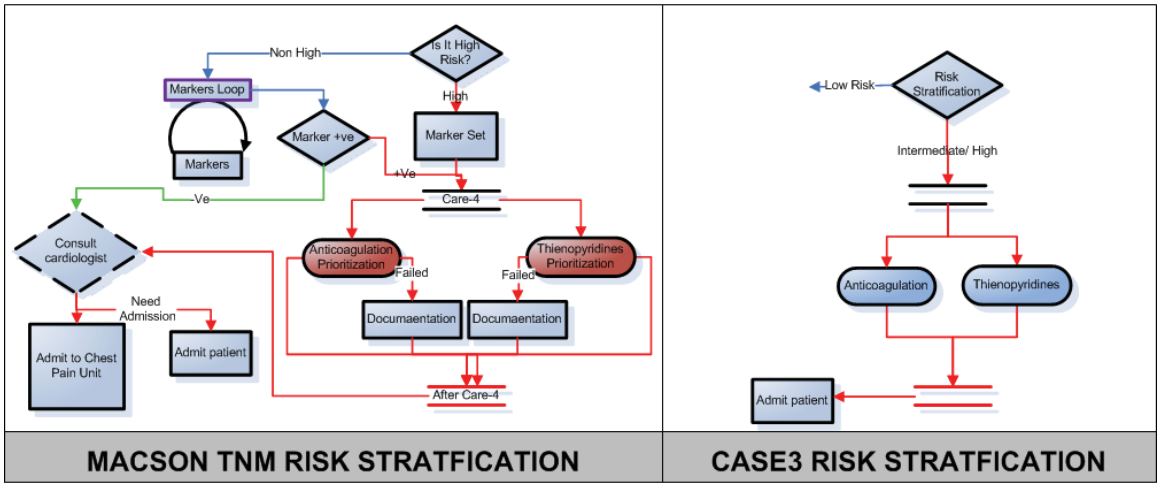

Figure 5. 3 Comparing risk stratification in MACSON and case 3

In MACSON we used TIMI risk stratification as our scoring method. However, we acknowledge that there are many other methods, and MACSON can handle different methods by manipulating the TNM.

Case 4:

Source: Evaluation And Management Of Non–ST–Segment Elevation Acute Coronary Syndromes In The Emergency Department, Emergency Medicine Practice, 2010 [134].

Authors: Ankur A. Doshi, Kara Iskyan, John M. O'Neill, and Kelly N. Sawyer.

Summary: 69-year-old female with a history of chest pain, with no ST-Segment elevation in the ECG and positive cardiac enzymes. Patient was admitted for cardiac Catheterization.

Final diagnosis: NON-ST-Segment elevation MI (Non-STEMI)

Test 1

The author used the clinical case as an introduction for managing Non-STEMI. We chose this article because it is more relevant to practice in emergency medicine.

Most of the concepts found in the article come from the theoretical management of the disease rather than the reported case (Table 5.5). The results are:

- NSTE-ACS is used in the article to stand for Non-STEMI and unstable angina at the initial patient presentation; i.e., before the definitive diagnosis. We used non-definitive MI in MACSON.
- The left bundle branch block is a finding in the ECG, going with the definitive MI diagnosis in certain situations. In MACSON this finding is part the criteria used by the physician in the first ECG decision step.
- Although Myoglobin is one of the cardiac markers, it is not popular because of low specificity. It is included in MACSON as an option.
- Phosphodiesterase inhibitors ***DRUG*** class is mentioned in the article as an interaction with Nitroglycerin because of possible hypotension. In MACSON we mentioned the individual drugs, such as sildenafil, rather than the class.
- Angiotensin-converting enzyme inhibitors are not part of MACSON because of the scope limitation. Usually it is given after the patient is admitted.

Case 4			
CASE CONCEPT	**CORRESPONDING ONTOLOGY CONCEPT**	**ALTERNATIVE ONTOLOGY CONCEPT**	**COMMENTS**
NSTE- ACS		Non definitive MI	Include both non-ST segment elevation MI and Unstable angina
Left bundle branch block	Left bundle branch block		This is not a class; it is part of decision criteria in the first ECG step
Serial ECGs		Repeated ECG	As discussed in Case 1
Myoglobin	Myoglobin		One cardiac markers; troponin is superior to it
Phosphodiesterase inhibitors		Sildenafil	Mentioned in the drug interactions
Angiotensin-converting enzyme inhibitors			Not routinely given in ED for ACS
Calcium channel blockers			As mentioned in Case 1

Table 5. 5 Test 1 results summary of case 4

Test 2

- The management was arranged under four categories:
    - **Anti-ischemic therapy**
    - **Reperfusion therapy**
    - **Antiplatelet therapy**
    - **Antithrombin therapy**
- Unfortunately, there was no clear connection between the management steps. However, the authors provided a pathway in the article, which concentrates more on the risk stratification. This pathway confirms our finding in Test 2 of the third case. This article's pathway agrees to some extent with our pathway by limiting the aggressive treatment to only high-risk patients and discussing other patients with the cardiologist.
- The article mentioned that most of the initial treatments and investigations are performed in parallel. We agreed on this statement with some exceptions, such as morphine and nitroglycerine (non-IV). Although no specific order is suggested by the CPG, it is logical to give morphine only after trying the nitroglycerine.

Case 5:

Source: EMERGENCY MEDICINE ORAL BOARD REVIEW ILLUSTRATED**,** 2009 [131].

Authors: Lisa Jacobson

Summary: 59-year-old male with history of chest pain. His ECG shows ST-Segment Elevation in the anterior and lateral leads.

Final diagnosis: Anteriolateral STEMI.

Test 1

The concepts in this case are identical to those in Case 1, except the Urine analysis, which was ordered for the patient. Urine analysis is not part of MACSON or the CPG because it is not part of routine management of ACS.

Test 2

The findings her were similar to Case 1.

5.3 Summary Of Phase 1

Most of the missing concepts have alternative concepts in the CPG ontology or can be easily added upon request. By the end of Test 1, using all cases we realized that MACSON evaluation and improvement is a continuous process, which is fostered by the flexibility of the model.

At this phase we improved the model by adding all new concepts that were worth modeling.

In Test 2, the main discrepancies were due to the variation of chronological order of steps during the initial management. Due to the time sensitivity of the disease some steps cannot wait until previous steps are done, and some steps are done in parallel to save time. This fact resulted in variable orders of these steps. Our ontology will be used in a CDSS, which will ensure these steps are done safely ordered according to the CPG.

Moreover, MACSON is flexible, allowing changing the order of steps without deletion of the axioms. This characteristic is known as non-monolithicity, which is a benchmark for testing the quality of the ontologies [135].

In conclusion, MACSON showed a satisfactory level of completeness in regard to domain representation and the flexibility to modify the TNM according to users' needs.

5.4 Phase 2: Testing The Evidence And Update Modules

Testing the evidence and update modules was done during the instantiation. At the instantiation phase we modeled the 2004 edition of the CPG; then we incrementally added the updates until the 2011 edition.

These two modules are related. Therefore, we will use treatment modalities that are mentioned in the CPG and updated in different editions to illustrate the testing process. To illustrate this test we will use the following mock case:

> "A 45 year-old male presented to the emergency department with a history of chest pain and vomiting for one hour. His ECG showed an anterior STEMI."

According to the clinical pathway in Chapter 4, this patient will need Thienopyridine as antiplatelet treatment modality and heparin as anticoagulation treatment modality.

We will start by using the unfractionated heparin (UFH) as a simple test for the evidence and update modules. UFH recommendations are updated in the different CPG editions. Table 5.6 shows some of these updates.

These recommendations were successfully modeled in MACSON using the update, evidence, and data modules. Figure 5.4 shows that the UFH update versions (ordered by date) are modeled as instances under the ***INTERVENTION_EVIDENCE_UPDATE*** class. Each version has many scenarios under the ***EVIDENCE_SCENARIO*** class. The evidence of each scenario is captured from the evidence ***INTERSECTION*** class using *Has_Evidence_Intersection* object property. The last part is connecting the scenarios with the Data Module using *Has_Data_Element* Object property. Each scenario has a data element instance that contains the *declarative* and the *procedural* knowledge of the scenario.

Update	Sc#	Scenario description	Eve.
2004	04-1	Patients undergoing percutaneous or surgical revascularization should receive UFH	IC
	04-2	Unfractionated heparin should be given intravenously to patients undergoing reperfusion therapy with alteplase, reteplase, or tenecteplase with dosing as follows: Bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/hr (maximum 1000 U) initially adjusted to maintain activated partial thromboplastin time (aPTT) at 1.5 to 2.0 times control (approximately 50 to 70 seconds)	IC
	04-3	Unfractionated heparin should be given intravenously to patients treated with nonselective fibrinolytic agents (streptokinase, anistreplase, urokinase) who are at high risk for systemic emboli (large or anterior MI, atrial fibrillation (AF), previous embolus, or known LV thrombus).	IB

Update	Sc#	Scenario description	Eve.
2004	04-4	Platelet counts should be monitored daily in patients taking UFH.	IC
	04-5	It may be reasonable to administer UFH intravenously to patients undergoing reperfusion therapy with streptokinase.	IIbB
2007	07-1	For patients undergoing PCI after having received an anticoagulant regimen, the following dosing recommendations should be followed: For prior treatment with UFH, administer additional boluses of UFH as needed to support the procedure, taking into account whether GP IIb/IIIa receptor antagonists have been administered	IC
	07-2	For patients undergoing PCI after having received an anticoagulant regime: Bivalirudin may also be used in patients treated previously with UFH	IC

Table 5. 6 Recommendation scenarios of the unfractionated heparin [17][25][103]. (sc# =scenario number, eve. = evidence level, ovsc = the overriding scenario)

For the sake of simplicity we named the instances here by years followed by the serial number of the scenario. However, in MACSON we used more unique explicit names.

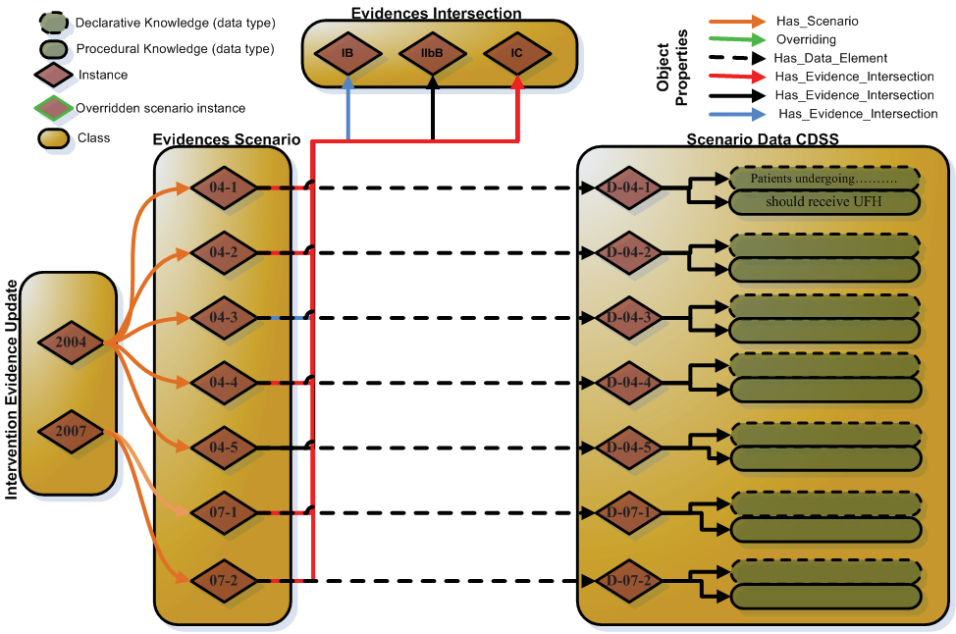

Figure 5. 4 Modeling the recommendations of UFH in MACSON

Moreover, these modules can model more complex recommendations, such as thienopyridines recommendations. Recommendations of the thienopyridines are frequently updated. Table 5.7 shows some of these updates published in different editions of the CPG. Some recommendations became obsolete (red font) because they were overridden by newer recommendations.

Update	Sc#	Scenario description	Eve.	OvSc
2004	04-1	In patients taking clopidogrel in whom CABG is planned, the drug should be withheld for at least 5 days, and preferably for 7 days, unless the urgency for revascularization outweighs the risks of excess bleeding.	IB	
	04-2	If true aspirin allergy is present, preferably clopidogrel (75 mg orally per day) or, alternatively, ticlopidine (250 mg orally twice daily) should be substituted.	IC	07-2
	04-3	Clopidogrel is probably indicated in patients receiving fibrinolytic therapy who are unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance.	IIaC	
2007	07-1	In patients less than 75 years of age who receive fibrinolytic therapy or who do not receive reperfusion therapy, it is reasonable to administer an oral loading dose of clopidogrel 300 mg	IIaC	09-4
	07-2	For patients with an absolute contraindication to aspirin, it is reasonable to give a 300-mg to 600-mg loading dose of clopidogrel, administered at least 6 hours before PCI, and/or GP IIb/IIIa antagonists, administered at the time of PCI.	IIaC	
	07-3	A loading dose of clopidogrel, generally 600 mg, should be administered before or when PCI is performed.	IC	09-1
	07-4	In patients undergoing PCI within 12 to 24 hours of receiving fibrinolytic therapy, a clopidogrel oral loading dose of 300 mg may be considered.	IC	
2009	09-1	Loading dose of Thienopyridine is recommended for STEMI patients for whom PCI is planned. At least 300 to 600 mg of clopidogrel should be given as early as possible before or at the time of primary or non-primary PCI.	IC	

Update	Sc#	Scenario description	Eve.	Upt
2009	09-2	Loading dose of Thienopyridines is recommended for STEMI patients for whom PCI is planned: Prasugrel 60 mg should be given as soon as possible for primary PCI.	IB	
	09-3	For STEMI patients undergoing non-primary PCI: If the patient has received fibrinolytic therapy and has been given clopidogrel, clopidogrel should be continued as the Thienopyridine of choice	IC	
	09-4	For STEMI patients undergoing non-primary PCI: If the patient has received fibrinolytic therapy without a Thienopyridine, a loading dose of 300 to 600 mg of clopidogrel should be given as the Thienopyridine of choice	IC	
	09-5	For STEMI patients undergoing non-primary PCI, and the patient did not receive fibrinolytic therapy, either a loading dose of 300 to 600 mg of clopidogrel should be given or, once the coronary anatomy is known and PCI is planned, a loading dose of 60 mg of Prasugrel should be given promptly and no later than 1 hour after the PCI.	IB	

Table 5. 7 Recommendation scenarios of the thienopyridines taken from [17][25][103]. (sc# =scenario number, eve. = evidence level, ovsc = the overriding scenario, upt=update)

These recommendations were successfully modeled in MACSON using update, evidence, and data modules. As in Figure 5.4, Figure 5.5 shows the modeled instances of Thienopyridines recommendations. Some of the new Thienopyridines recommendations scenarios override other older scenario instances. The overridden scenarios are shown in Figure 5.5 as instances with green borders. Connecting the overridden instance with the overriding instance is done by the *Override* object property (green arrow). As in the UFH example, each recommendation is divided into declarative and procedural parts, and these parts are represented in the data module.

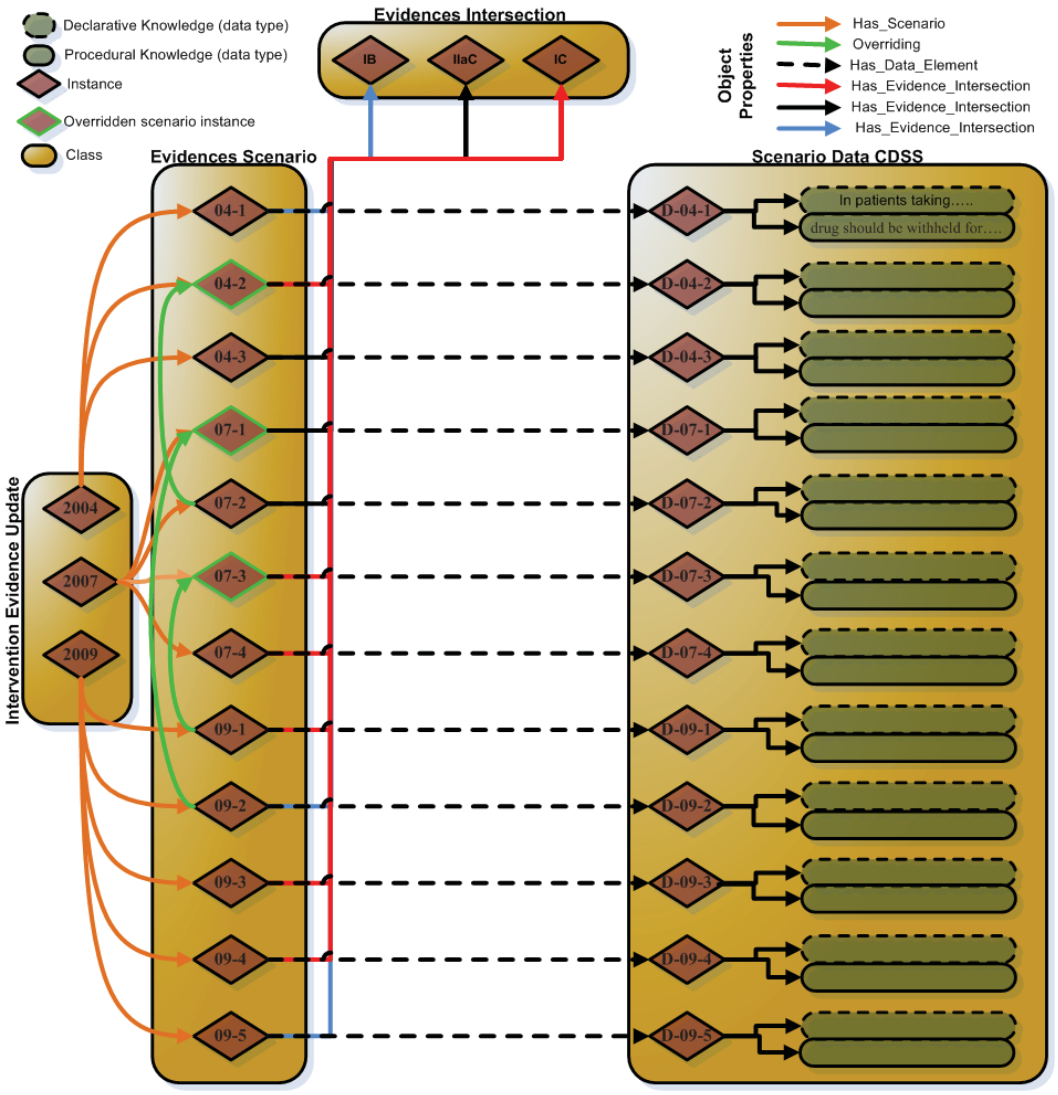

Figure 5. 5 Modeling the recommendations of thienopyridines in MACSON

In this phase we showed how MACSON is capable of modeling any new update of the guidelines as long as the update format stays the same.

5.5 Phase 3: Testing the Prioritization Functionality

In the above-mentioned mock case, the patient will require a Thienopyridine drug. In the clinical pathway in Chapter 4, we classified the Thienopyridine step as a prioritization step because it has more than one option.

Physicians usually choose one the following drugs:

- Ticlopidine
- Clopidogrel
- Prasugrel

An expert physician will choose Clopidogrel for certain reasons, such as the supported evidence behind it or because it is commonly used. Ticlopidine has many adverse effects, and Clopidogrel came as an alternative to this drug. On the other hand, Prasugrel is a new drug and most of the physicians will not know about unless they read the new update of the CPG.

So, the prioritization step is used to recommend the best option of these drugs. The recommended choice should be consistent with (or better than) the expert physician's choice.

To test this functionality we will add the following to the mock case:

> **Medical History:** No bleeding or bleeding disorders, no neutropenia, and no thrombocytopenia. Patient had a history of Ticlopidine sensitivity but no history of other allergies.
>
> Cardiac Catheterization (PCI) is available and the patient is eligible for it.
>
> We also added the following table to show the pharmacy inventory of these drugs.

Drug	Stock (mg)	Rate of Usage Dose/Month	Expiry Date
Ticlopidine	2500	300	29/10/2014
Clopidogrel	2000	800	03/12/2015
Prasugrel	400	20	07/12/2014

Table 5. 8 Pharmacy inventory of the thienopyridines

The prioritization process starts when the control flow reaches the Thienopyridine prioritization step (Figure 4.7). Then the intervention choices needed in this step are represented as instances under the ***INTERVENTION*** class and connected here using *Has_Items_To_Prioritize* object property. Each intervention is connected to the ***Drug*** class using the *Drug_Name* object property. Ticlopidine Clopidogrel, Prasugrel are instances of the ***DRUG*** class. Each drug instance is connected to the ***DRUG_CONTRA_INDICATION_CDSS*** class, which is part of the data module, using the *Has_Data_Element* object property. This class contains the indications and contraindications of the drugs as datatype properties.

The prioritization process has many levels. Each prioritization step instance has protocol instances. For the system to know which protocol to start first, we ordered the protocols by numbers. For example, Protocol 1 will be started first. The protocols are instances of the **PRIORITIZATION_PROTOCOLS_CDSS** class. This class is also part of the data module.

Each protocol has descriptions of the rules. The rule engine will fire these rules in order to execute the prioritization level. The following are the protocols used in this test:

1. **Protocol 1:** compares patient's history with the drugs contraindications datatype properties; if equal then it excludes that drug.
2. **Protocol-2**: has two functions:
    a. If the drug stock is less than stock-threshold then exclude the drug, and
    b. Order drugs by the rate of use in the hospital.
3. **Protocol-3:** has three functions:
    a. Determine the most suitable evidence level of the drug,
    b. Exclude the drugs that have level III evidence level, and
    c. Order drugs by the evidence level.

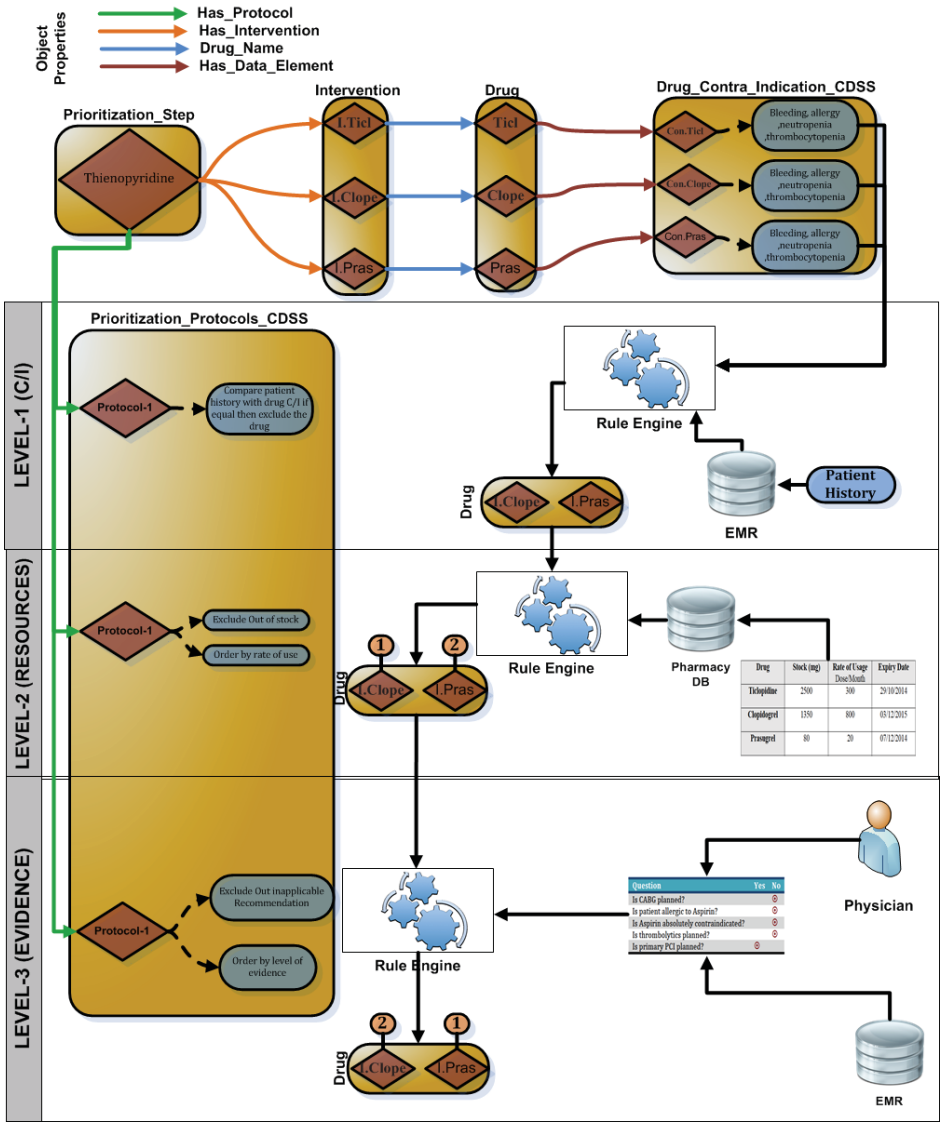

Figure 5. 6 Thienopyridines prioritization process

Thus, in the first protocol we need the patient history, which is saved in the EMR, and the contraindications of the drugs, which are captured by the *contraindications* datatype property in the data module. Then, the rule engine will fire the rules that are associated with Protocol 1 to compare the values in the *contraindications* datatype properties with the patient history values in the EMR.

As expected Ticlopidine will be excluded because of the match between the patient history "Ticlopidine sensitivity" and the *contraindications* value "allergy".

Clopidogrel and Prasugrel will enter the second prioritization level. In this level, the rules require hospital resources data taken from the pharmacy database. These data are shown in Table 5.8. The first rule is fired to exclude out of stock drugs. In our case, both Clopidogrel and Prasugrel are in stock. Then, the rule will calculate the minimum required dose (stock-threshold) and compare it to the available stock. Stock threshold is the total dose that is required to be given over a specific number of days. In our case we need to start one of the drugs and guarantee that we have enough doses to be given for at least five days. Stock threshold is calculated as the following:

$$Stock\text{-}Threshold=(Nd)(Ld+(Rd\ (Fr)))^{*}$$

Nd = Number of the days

Ld = Loading dose

Rd = Recommended dose

Fr = Maximum Frequency per day

All of the variables in this formula are captured by MACSON. Figure 5.7 shows the datatype properties of Clopidogrel administration method under **DRUG_ADMINISTRATION_METHOD** class, which is part of the data module.

So, the Stock-Threshold for clopidogrel is:

$$5(300+75 \text{ X } 1)=1500 \text{ mg}$$

And the calculated Stock-Threshold of Prasugrel is 350 mg.

Then the rule will compare the Stock-Threshold with the stock amount in table-5.8. Both drugs have more stock amount than their Stock-Thresholds. So, the rule will not exclude them.

* This formula is used for demonstration only. Other validated formulas should be used in implementation phase.

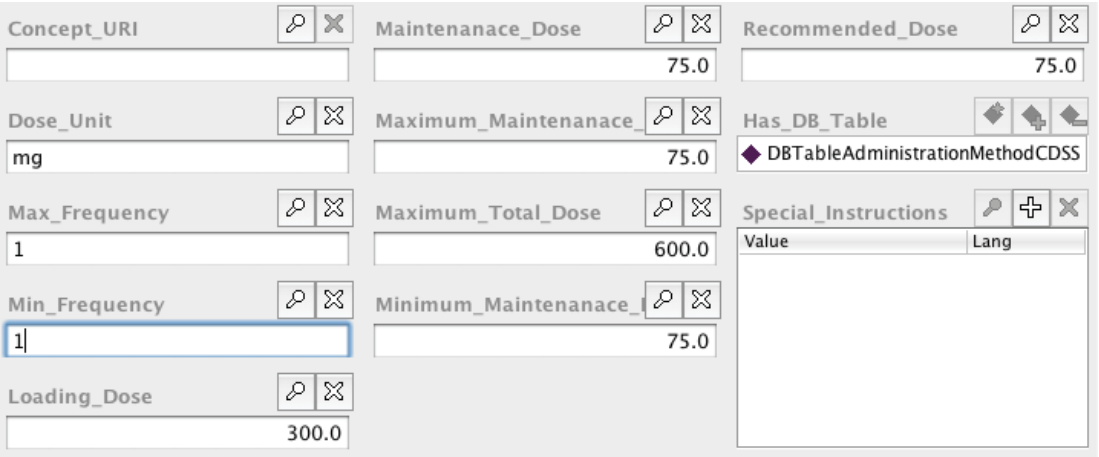

Figure 5. 7 Datatype properties of the oral drug administration in MACSON

The last task in Level 2 is to order the two drugs by their rate of use. Clopidogrel will be the first, followed by Prasugrel, according to the values in Table 5.8.

The prioritization step will end by executing Protocol 3 in the third level. In this level, there are three functions: the first function is to assign the most appropriate evidence level to the drugs. Analyzing the evidence scenarios in Table 5.7 showed that each scenario has declarative and procedural parts. These two parts are modeled under the *declarative* and *procedural* datatype properties (Figure 5.5).

All the declarative parts can be transformed to Boolean questions (Figure 5.8). These questions can be answered by the user or by the system if the answer exists in the EMR database. Figure 5.8 shows the answers of the declarative parts of the Clopidogrel and Prasugrel scenarios.

The rule engine will use the answer values of these questions to exclude all non-applicable scenarios. Question 1 will exclude scenario 04-1 in Table 5.7, question 2 will exclude scenario 07-2, question 3 will exclude scenario 04-3, question 4 will exclude scenario 07-4, and question 5 will exclude scenarios 09-3 to 09-5. So, this rule will conclude by assigning IC Evidence level to Clopidogrel (scenario 09-1) and IB to Prasugrel (scenario 09-2).

In case there are many suitable evidence levels for the same drug, the higher level will be assigned to that drug, except if one of the levels is III, which is the harmful scenario. If

one drug has two applicable scenarios and one of them has evidence level III, this level will be assigned to that drug.

#	Question	Yes	No
1	Is CABG planned?		¤
2	Is patient allergic to Aspirin?		¤
3	Is Aspirin absolutely contraindicated?		¤
4	Is thrombolytic therapy planned?		¤
5	Is primary PCI planned?	¤	

Figure 5. 8 Scenarios' declarative knowledge questionnaire

The second function in this level is excluding all the drugs that carry evidence level III. In our case both Clopidogrel and Prasugrel do not have this level.

The last function in this level is responsible for ordering the drugs by the evidence level. Therefore, Prasugrel is the first (IB) and Clopidogrel is the second (IC).

In conclusion, the prioritization step was able to choose the best two drugs to be given to the patient ordered by two methods. The first method is by the rate of use in the hospital, which is the same choice of the expert physician mentioned earlier. The second method is ordering the drugs by the evidence level. The last method is more valuable to the quality of practice, because it recommended the best evidence-based drug and drew the physician's attention to a new drug, the Prasugrel. Ideally both methods should have the same order.

5.6 Phase 4: Technical Evaluation

In this section we focus on evaluating the CPG ontology model from the engineering quality point of view. Ontology quality can be evaluated at two levels. Level one is used for evaluating the CPG ontology model using general ontology quality criteria. Examples of this level are the criteria mentioned by Gomez-Perez and Gruber [136], [137], and

Bodenreider [123]. On the contrary, Level two uses more domain-specific criteria, such as the criteria mentioned by Peleg to test common computerized CPG formalisms [130].

As we are more interested in medical domain specific criteria, Level two is going to be explored first.

5.6.1. Comparison Dimensions of Ontologies by Peleg *et al*:

This framework has eight dimensions. Our model is tested against these dimensions as follows:

1. **Organization of guideline plan components:**
    a. **Plans and plan components:**

    Our model uses most of the plan components used in the reference CPG ontology, which is designed by Abidi and Shayegani [28]. These components are mentioned under the TNM module in Chapter 4. Also, we introduced new components, such as documentation, consultation, and prioritization steps, to accommodate our domain (management of ACS).

    b. **Aspects of plan organization:**
        i. **Computational Models of Plan Networks:** Our model is designed to be executed sequentially as a flowchart; similar to EON and GLIF [130].
        ii. **Nesting:** The model supports nesting in two ways: firstly, by shifting to a new guideline when a morbidity condition happens, such as shifting to intracranial hemorrhage management guidelines if it happened due to thrombolytic treatment; and secondly, by using loop-step, which can accommodate any sequence of interventions asserted according to the users' need; this sequence can be run once or repeated several times.
        iii. **Sequential execution:** This is similar to the reference CPG ontology**;** MACSON uses Next_Step property to indicate the next step in the sequence.

iv. **Parallel execution:** This is achieved by using branching and synchronization steps.

v. **Cyclical and iterative plans:** This is achieved by using loop-step. More details about this step are mentioned in Chapter 4

vi. **Entry points into guideline plans:** Entry to the guidelines is indicated by the morbidity condition. When a patient comes to the emergency department, the physician will determine the most likely diagnosis, which is a morbidity condition. This condition (ACS in this context) has a guideline, and each guideline has a first step that initiates the guideline execution. In MACSON the first step is the ECG decision step.

2. **Specification of goals/intentions:**

   Most of the goals and intentions are formally expressed in the model. The **OUTCOME** class in the data module models the desired interventions' outcomes. *Decision_Question* datatype property indicates the intention behind the decision steps by providing the question needed to be answered during the execution of these steps. Also, termination steps and termination logic are used to define the completion goal of certain sequences of steps.

3. **Model of guideline actions:**

   a. **Structured medical actions:** all medical tasks are categorized in a hierarchy according to their types. The relation used for this classification is "is-a" object property. For instance, ***Treatment_Step_Clopidogrel*** is classified under **TREATMENT_STEP** class, which is an **Action_Step:**

Treatment_Step_Clopidogrel -------is_a---->**Treatment_Step** -------is_a----> **Action_Step**

   b. **Action refinement: T**he model provides refinement for the treatment steps by specifying which drug should be given. This drug is classified under the drug modules according to its pharmacological characteristics. Further refinement is done by connecting this drug to the data module,

which provides the indications, the contraindications, other names, the method of administration, etc…

c. **Temporal constraints:** Our scope is limited by the CPG. Many temporal concepts for the action steps were not addressed by the CPG. However, addressing this concept is important for the future implementation in the emergency department. Therefore, the model addressed only the relevant temporal concepts at this stage by using datatype properties in the data modules, such as ***Diagnostic_Start_Time*** and ***Diagnostic_End_Time***. These properties have OWL temporal ranges, such as time and date.

d. **System actions:** System is an instance of role-class in the model. This means that system can be assigned as an actor in some steps when all the needed parameters are available automatically. For example, the STEMI_Contraindication_to_IVNTG decision step can be executed by the system because the answer of the contraindication is captured during a previous step executed by the user (Figure 4.6).

e. **Representing and reasoning with effects of actions:** This criterion tests common CPG formalisms for their ability to change the plans according to the results of previous plans, or at least mentions the effect of plans [130]. PROforma and Asbru have these characteristics [130].
Our ontology addresses some of these effects under the ***Has_Expected_Adverse_Effect*** object property of the interventions, which are instances of the ***MORBIDITY_CONDITION*** class. Further actions for these effects are modeled by using the ***Has_Guideline*** object property of the ***MORBIDITY_CONDITION*** class instances. The model does not handle the issue of changing its TNM in response to the actions' effects because it was not mentioned clearly in the CPG. The CPG handles these situations as sub-guidelines. The other option is to use the rules to change the TNM according to the plans' outcomes.

4. **Decision Model**

Peleg *et al* mentioned many types of decision models when they compared the CPG formalisms. In our model we used two types; the first is "switch constructs",

which is used in deterministic decisions, such as contraindication checks prior to the drug's administration. The flow control is forced to choose only one option and leave the other options. For example, a contraindication check for Aspirin yields either it is contraindicated or not.

The other type of decision models is "Argumentation rules for/against choice alternatives", which, according to Peleg et al, is used for increasing the preference of one decision choice over another and used in non-deterministic decisions. Prioritization steps use this type of decisions model. Peleg et al mentioned four types of rules used in the Argumentation rules for/against choice alternatives decision models; namely, (1) "Rules that strictly exclude the alternative", (2) "Rules that argue against the alternative", (3) "Rules that argue for the alternative", and (4) "Rules that confirm or expresses strong preference the alternative". The first type of these rules is used in the Prioritization step to exclude contraindicated drug choices and out of stock drugs. The last type of these rules is used in ordering the drug choices according to their level of evidence strength and other resource criteria, such as cost and rate of use. For more details see Chapter 4.

In addition, Peleg et al mentioned other criteria in their comparison. These criteria are listed as the following:

a. **Extensibility of the decision model**: In our model we used OWL-DL language which can handle other types of decisions models, such as decision trees [138].
b. **Expressing preferences for alternatives to a choice**: Intervention choices are modeled in MACSON using the **PRIORITIZATION_STEP** class**.** Figure 5.5 shows how the prioritization protocols are used to express the best choice and the alternative choices ordered, according to the hospital resources and the evidence levels.
c. **The relationship between decision-making and commitment to a decision alternative:** Like most of the formalisms in the Peleg et al

article, our model explicitly connects the decision steps to the next step, using the ***Next_Step*** object property.

d. **Authorizing decisions**: Each decision step has to be authorized by a role. This authorization is modeled by the ***Responsible*** object property of the ***DECISION_STEP*** class.

5. **Expression/criterion language:**
   At this stage we did not choose or design the decision expression language. However, using OWL will promote SWRL as the candidate expression language for future development.
6. **Interpretation of data:**
   Because we are using ontology, the abstractions of the concepts are derived from the hierarchy. For example, heparin is an instance of anticoagulation, which is a subclass of the ***DRUG*** class. This means that heparin is an anticoagulation drug.
7. **Medical concept model:**
   Similar to the reference CPG ontology, we used a datatype property to link the concepts to the standard medical concept repository. This datatype property is called *Concept_URI*. At this stage, the source of standard concepts is not yet defined; because it depends on where do we intend to use this ontology. The standard medical concept repository can be SNOMED or UMLS.
8. **Patient information model:**
   Patient information is modeled in the data modules as part of the EMR data type (Chapter 4). This information is not complete because we modeled only the relevant information mentioned in the CPG. However, the model should include more of the patients' information for future implementations.

In conclusion, our model addressed all the dimensions mentioned by Peleg et al. The model is comparable to other formalisms used in their study and exceeds these formalisms in some aspects, such as nesting, and cyclical and iterative plans.

5.6.2. General Standards in Ontology Engineering

Gómez-Pérez and colleagues mentioned several criteria for standard ontology engineering [122]. Our ontology is tested against these Criteria as follows:

1. **Clarity and Objectivity**: The ontological concept should be written clearly in natural language and not biased by the implementation field, such as computer science [136]. In our ontology we used simple and clear names of the concepts. We strived to make the names very expressive, allowing the user to know the meaning of the concepts from the names only. As a result, some concepts' names are very long.
2. **Completeness:** Gruber explained the completeness at the level of the axioms, not at the overall ontology. He preferred the axioms to be defined completely by necessary and sufficient restrictions [136]. In our ontology we used mainly the necessary restriction. Sufficient restriction was not needed for our scope.
3. **Coherence:** Coherent ontology allows the inference of knowledge without conflicting with other facts defined previously [136]. We used reasoners to check the consistency of the CPG ontology, which is an indicator of coherence. For example, we used Pellet reasoner in Protégé 3.4.5 and HermiT in Protégé 4.1. All the consistency checks resulted in a consistent and satisfied ontology.
4. **Maximum monotonic extendibility:** A good ontology should accommodate new concepts without changing the old definitions [136]. Testing these criteria will require introducing new updates into the model. Update module is mentioned in Chapter 4 and aims to maintain the model monotonicity.
5. **Minimal ontological commitments:** The ontology model should not strictly define the domain to allow other users to modify this definition[128]. In the beginning of this chapter we found that it is difficult to define the right sequence of the initial ACS management steps because it is different from one place to another. So, changing these sequences is very easy because the model has all the terminology and concepts required for that.
6. **Ontological Distinction Principle**: Disjointness adds more semantic richness to the ontology. However, it is not easy to be added in the ontology and maintain the consistency [122], [136], [139], [140]. Therefore, a trade-off between disjointness and consistency helps to design consistent ontology with a

satisfactory semantic level. In our ontology most of the classes are disjoint, except those that are overlapping.

7. **Diversification of hierarchies:** Using different criteria in different classifications in the ontology allows it to accommodate different concepts easily [136], [141]. In our model we used a different type of classification criteria, such as drug classification according to the pharmacological characteristics and evidence-based updates classification.
8. **Modularity:** Our ontology engineering method is based on identifying and designing separate modules of the ontology to promote ontology reuse.
9. **Minimization of the semantic distance between sibling concepts:** In compliance with these criteria, all similar concepts in the CPG ontology are grouped under one super-class [122], [141].
10. **Standardization of names whenever is possible:** Vega et al mentioned that relationship names should reflect the subjects and objects [122], [141]. This criterion was not followed in our ontology because different subjects and objects reuse most of the relationships.

In conclusion, our ontology model complies with all of the previous criteria.

5.7 Summary

In this chapter, we evaluated our CPG ontology at 4 levels; level one showed that the ontology is effectively representing the research domain with minor exceptions. These exceptions are easily mitigated by the flexibility provided by the model.

The second and third levels showed that our evidence module, update module, and the prioritization functionality are working effectively and accurately.

The fourth level showed that the ontology complies with quality standards and that it is comparable to other popular CPG formalisms, such PROforma, GLIF, EON, and Asbru.

CHAPTER 6 DISCUSSION

In Chapter 1 we stated our goals as the following:

1. Development of an ACS Management Knowledge Model.
2. Development of mechanisms at the knowledge modeling level to incorporate updates to the CPGs as new evidence becomes available.
3. Addressing the issue of variations across multiple hospitals, in terms of policies and resources that influence the deployment of a computerized CPG in a specific clinical setting.
4. Prioritizing clinical interventions according to specific criteria, such as the best evidence and most used practice in the hospital.

This chapter discusses achieved goals and research contributions.

6.1. Achievements

Research achievements are listed as the following:

6.1.1. Management of ACS Ontology (MACSON^2)

During our modeling process, we built sophisticated clinical pathways that represent the management of ACS in the ED based on a CPG. The pathways were successfully computerized and modeled in MACSON^1.

At the end of the ontology evaluation we concluded that MACSON^2 is satisfactory as a model to represent the CPG. However, it needs further evaluation at the clinical setting during the CDSS implementation phase.

6.1.2. Better Non-Deterministic Decision Model

Compared to the reference CPG ontology, MACSON^2 added more expressivity to the no-deterministic decision steps. These steps are modeled as prioritization steps. In these prioritization steps we introduced three levels of logical processes to recommend the best

choices for certain situations. The reference ontology did not include these decisions, leaving them for the implementation phase to be modeled as rules.

6.1.3. Improving the Model Non-Monolithicity

CDSS obsolescence is a major factor affecting the rate of adoption and success of these systems, because of rapidly evolving evidence [132]. In MACSON^2 we provided a solution to improve the flexibility to update the model with minimal change of its structure. More details will follow in the next section.

6.1.4. Handling the CPG Updates

CDSS obsolescence is frequently discussed in literature. This problem can be handled at the maintenance level to maintain the system update; however, maintaining systems is costly, especially with non-flexible systems.

Some other approaches have attempted to tackle this problem at the design level by developing more flexible systems. For instance, non-knowledge based approaches, such as ANN, were used to maintain the currency of the CDSS algorithms [142]. Our approach is to solve this problem at the design level by creating a flexible knowledge base, since MACSON^2 has the flexibility to handle the CPG updates. Additionally, MACSON^2 will ensure that all the CPG updates are evidence based, because it depends on the evidence levels to add these updates.

Moreover, the CPG that we used is highly complex in terms of detailed recommendations and lengthy text, and the updated recommendations are often overwhelming in number and difficult to follow. MACSON^2 provided a practical method to computerize these recommendations. Hence, they can be summarized and simplified to run the decision logics that are required in the decision steps (Table 5.6 and Figure 5.6).

6.1.5. Handling the Effect of Resource Availability on CPG Recommendations

Availability of resources is a major barrier in adopting the CPGs [8], [24]. Often, CPGs are designed to be used in different institutions. Therefore, they don't handle local issues, such as the availability of resources. On the other hand, many CPGs cover all the possibilities of the resources' availability. In either case, the adoption rate of the CPGs

will be low compared to the adoption rate of the local customized CPGs that handle the issues of local resources [8].

MACSON^2 handles this issue in two ways:

1. The design of the TNM took into consideration the effect of catheterization laboratory availability and the ability to transfer the patient within the time limit on the management workflow (Figure 4.6). The hospital types are assigned according to these resources. Users do not need to choose which option is more suitable because the system will assign the hospital types automatically.
2. Level-2 prioritization protocol (Figure 5.6) incorporates the resource data into the decision logics. Hence, all the prioritization steps execution will be based on availability of hospital resources.

6.2. Limitations

The limitations are classified according to the research components as follows:

6.2.1. Scope Limitation

Our scope is to model the guidelines for management of ACS. However, emergency management of ACS involves many other concepts than what are addressed by guidelines. For example, the universal approach for managing any patient in the ED follows three common steps; namely, Airway, Breathing, and Circulation. These steps are known as the (ABCs). The ABCs were not mentioned in the CPG. However, to implement a CDSS based on MACSON^2 we should add these concepts to the model.

6.2.2. Limitations Inherited from the Knowledge Base:

The modeled CPG is a generic one. It avoided addressing areas where there are disagreements between practitioners to perform certain management steps. For instance, there was no clear chronological order for the initial management steps because it varies from one location to another. During our modeling we had to make assumptions about these steps. However, these assumptions might not be applicable to different locations.

So, the model should be fine tuned or customized to fit the location for which it is intended.

6.2.3. Limitations Inherited from the Representation Language

MACSON^2 was created using OWL-DL, which is part of the semantic web technology. Some parts of the CPG were difficult to model in OWL-DL. For example, modeling the repeated ECG step is omitted, because it is difficult to put in the TNM. Therefore, the model does not include this step and will be added as rules in the implementation phase.

6.2.4. Limitation in the Evaluation Tests

Ideally, MACSON^1 should be tested in real clinical practice. However, its current format, OWL-DL, is not user friendly to be tested by physicians. Hence, we used clinical cases to test MACSON^1. Unfortunately, these cases were not published to report what happened during patient management; instead, they were published to discuss certain aspects of patient management or to test practitioners. As a result, the cases are concise and missing many management concepts. This means that MACSON^2 evaluation will need to be repeated after the CDSS is created and used in real clinical practice.

6.3. Future Directions

6.3.1. Customizing MACSON^2

After creating the model, we intend to study several emergency departments to capture the variation in ACS management. The goal of this study is to generate more than one version of MACSON^2. These versions will allow hospitals or even clinicians to choose which model to use. Hopefully, this will eliminate the practice variation issues.

Customization of the model will involve adding more concepts to reflect the general management in the emergency setting, not only those mentioned in the CPG.

Also, we will code the rules used in the decision steps and the prioritization steps using an expression language such as SWRL.

6.3.2. Developing the CDSS

Creating the whole CDSS will be the next project. The CDSS should address one of the challenges mentioned in Chapter 1, which is related to the pace of emergency practice. Since emergency practice is time sensitive, using the CDSS should be efficient and effective, quickly providing the best recommendations based on evidence. So, the future CDSS should comply with this rule.

6.3.3. Reevaluation

After creating the CDSS it should be reevaluated. The revaluation results will be used to refine the MACSON^2.

6.4. Conclusion

The modular CPG ontology and its instantiation (MACSON^2) will be the knowledge base for ACS management CDSS. The primary users for this system will be novice physicians who work in EDs, especially in rural areas. The system will help in disseminating CPGs and translating them into practice; hence, we anticipate that this system will help in improving quality of care in these areas. Expert physicians will also benefit from the system because it will provide an easy method for organizing and presenting CPG updates. Thus, the system will facilitate the adoption and implementation of current and updated knowledge in patient care. Additionally, expert and novice physicians will be able to know the real time availability of their hospitals' resources, and the system will build decisions based on these resources. Expeditious, resource driven decision-making will shorten the time to definitive management, a crucial factor in patient outcomes.

Our model is based on patient management workflow. Hence, the model can be used as a knowledge base for teaching tools which interactively simulate patient conditions as scenarios and present them to medical students and junior physicians [143]. The model is rich enough to present different levels of scenarios, in terms of difficulty, according to the trainee level (such as medical student or junior resident). Thus, due to the nature of emergency practice, which is fast-paced, risky and limits the extent of hands-on training, these simulation tools can become an alternative solution for training in emergency medicine.

As mentioned earlier, management of ACS is time sensitive. These time frames are used as benchmarks to measure the compliance with CPGs. The most commonly used benchmarks in ACS management are door-to-needle time (less than 30 minutes) and door-to-balloon time (less than 90 minutes). These benchmarks are barely met in EDs [144]. Our model provides a mechanism to estimate the expected door-to-needle time and door-to-balloon time and choose the procedure that is more likely to be completed within the time frame. All the values that are needed to calculate the expected time frames are modeled in the modular CPG ontology. Examples for these values are the average time needed to transfer the patient to the catheterization laboratory and the average time needed to dispense the thrombolytic therapy. These time values differ from one hospital to another, and MACSON^2 needs to be customized according to these values.

At the level of quality management, the system can serve as a tool to measure the compliance with CPGs. The prioritization function can measure the ratio of practice that is based on the local hospital usual practice to the practice that is based on evidence. Moreover, the system will provide a method to measure one of the most important benchmarks in treating ACS, the timing.

The decision to implement any new tool in patient care should depend on its effect on patient outcomes. Research about the relationship between CDSSs and patient outcomes is limited and did not show any significant improvement over the standard care, which can be partly attributed to the quality of the CPGs that are used to design these systems. In our research we targeted a high quality CPG that is based on valid evidence that shows improvement in patient outcomes. Furthermore, literature shows that CDSSs improved the care process. Improving the process of care is found to have a significant positive impact on outcomes of certain diseases such as ACS. Direct impact of our model on patient outcomes will need investigation after developing the ACS CDSS.

Our model is built using a semantic modeling technique and supports health care standards such as HL7 and SNOMED. Therefore, the CDSS that is going to be built on this model will be interoperable with any hospital information system. Integrating the CDSS with the hospital information system will help to avoid the disadvantages of standalone CDSSs, such as being non-proactive systems, where the user should initiate

the process of decision support, and time consuming in terms of data entry, where the system needs the data to be entered manually by the user, compared to the integrated CDSSs which can retrieve the data from the hospital information system [47]. Moreover, the interoperability of our model enhances knowledge sharing [145]; our model can be reused by other researchers and developers due to the high level of expressivity inherited from the semantic modeling technique, and the fact that each element of the model has enough properties to describe it clearly, thus eliminating any ambiguity. The reuse can be partial because of the fact that our model is a modular one; i.e., each module can be reused separately from the whole model.

During the modeling process we experienced challenges in interpreting the knowledge of the AHA and ACC CPG and representing it as an OWL model because of its complexity. We believe that the modular CPG ontology can be a guideline to restructure the AHA and ACC CPG to be less complex without affecting the content.

We believe that a MACSON^2-based CDSS will have an impact on the care process of managing ACS in EDs. The workflow in EDs is complex and multidimensional because of the fact that multiple patients are managed in the same time. Therefore, the CDSS should not control the workflow in EDs; rather it should respond to it.

Because of the shortage of trained EPs in Saudi Arabia and lack of systems that measure the compliance with ACS management benchmarks, our proposed solution is expected to have a positive impact on the quality of care.

REFERENCES

[1] P. V. Scribano, T. Lerer, D. Kennedy, and M. M. Cloutier, "Provider adherence to a clinical practice guideline for acute asthma in a pediatric emergency department.," *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, vol. 8, no. 12, pp. 1147-52, Dec. 2001.

[2] R. M. McNamara and J. J. Kelly, "Impact of an emergency medicine residency program on the quality of care in an urban community hospital emergency department," *Annals of Emergency Medicine,*, vol. 21, no. 5, pp. 528-533, 1992.

[3] Y. P. C.D. Miller and J. W. H. B.L. Lytle, A.Y. Chen, W.B. Gibler, E.M. Ohman, C.V. Peterson Jr., M.T. Roe, E.D. Peterson, "Emergency Department Factors That Predict Adherence to American College of Cardiology/American Heart Association Guidelines for Treatment of Patients With Non–ST-Segment Elevation Acute Coronary Syndromes: Results From the CRUSADE Initiativ," *Annals of Emergency Medicine*, vol. 44, no. 4, p. S46-S46, Oct. 2004.

[4] M. Bhimani, G. Dickie, S. McLeod, and D. Kim, "Emergency medicine training demographics of physicians working in rural and regional southwestern Ontario emergency departments.," *CJEM : Canadian journal of emergency medical care = JCMU : journal canadien de soins médicaux d'urgence*, vol. 9, no. 6, pp. 449-52, Nov. 2007.

[5] A. Turchin, M. Shubina, A. H. Chodos, J. S. Einbinder, and M. L. Pendergrass, "Effect of board certification on antihypertensive treatment intensification in patients with diabetes mellitus.," *Circulation*, vol. 117, no. 5, pp. 623-8, Feb. 2008.

[6] E. A. Halm et al., "Understanding physician adherence with a pneumonia practice guideline: effects of patient, system, and physician factors.," *Archives of internal medicine*, vol. 160, no. 1, pp. 98-104, Jan. 2000.

[7] L. A. Calder et al., "Experiential and rational decision making: a survey to determine how emergency physicians make clinical decisions.," *Emergency medicine journal : EMJ*, pp. 1-7, Nov. 2011.

[8] M. B. Harrison, F. Légaré, I. D. Graham, and B. Fervers, "Adapting clinical practice guidelines to local context and assessing barriers to their use.," *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, vol. 182, no. 2, pp. E78-84, Feb. 2010.

[9] S. Vikman et al., "Improved adherence to practice guidelines yields better outcome in high-risk patients with acute coronary syndrome without ST elevation: findings from nationwide FINACS studies.," *Journal of internal medicine*, vol. 256, no. 4, pp. 316-23, Oct. 2004.

[10] T. Jernberg, P. Johanson, C. Held, B. Svennblad, J. Lindbäck, and L. Wallentin, "Association between adoption of evidence-based treatment and survival for patients with ST-elevation myocardial infarction.," *JAMA : the journal of the American Medical Association*, vol. 305, no. 16, pp. 1677-84, Apr. 2011.

[11] M. Komajda et al., "Adherence to guidelines is a predictor of outcome in chronic heart failure: the MAHLER survey.," *European heart journal*, vol. 26, no. 16, pp. 1653-9, Aug. 2005.

[12] B. Tremey et al., "Teaching improves adherence to clinical guidelines in the treatment of oral anticoagulation-related severe bleeding in the emergency department.," *Intensive care medicine*, vol. 35, no. 8, pp. 1444-8, Aug. 2009.

[13] G. P. Purcell, "What makes a good clinical decision support system.," *BMJ (Clinical research ed.)*, vol. 330, no. 7494, pp. 740-1, Apr. 2005.

[14] S. Shayegani, "Knowledge Modeling to Develop a Clinical Practice Guideline Ontology: Towards Computerization and Merging of Clinical Practice Guidelines," *Master's thesis, Dalhousie University*, 2007.

[15] M. Kastner, E. Estey, and O. Bhattacharyya, "Better guidelines for better care: enhancing the implementability of clinical practice guidelines.," *Expert review of pharmacoeconomics & outcomes research*, vol. 11, no. 3, pp. 315-24, Jun. 2011.

[16] A. Latoszek-Berendsen, H. Tange, H. J. van den Herik, and A. Hasman, "From clinical practice guidelines to computer-interpretable guidelines. A literature overview.," *Methods of information in medicine*, vol. 49, no. 6, pp. 550-70, Dec. 2010.

[17] R. Goud et al., "The effect of computerized decision support on barriers to guideline implementation: a qualitative study in outpatient cardiac rehabilitation.," *International journal of medical informatics*, vol. 79, no. 6, pp. 430-7, Jun. 2010.

[18] A. X. Garg et al., "Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review.," *JAMA : the journal of the American Medical Association*, vol. 293, no. 10, pp. 1223-38, Mar. 2005.

[19] M. W. M. Jaspers, M. Smeulers, H. Vermeulen, and L. W. Peute, "Effects of clinical decision-support systems on practitioner performance and patient outcomes: a synthesis of high-quality systematic review findings.," *Journal of the American Medical Informatics Association : JAMIA*, vol. 18, no. 3, pp. 327-34, May 2011.

[20] J. Roukema, E. W. Steyerberg, J. Van Der Lei, and H. A. Moll, "Randomized trial of a clinical decision support system: impact on the management of children with fever without apparent source," *Journal of the American Medical Informatics Association*, vol. 15, no. 1, pp. 107–113, 2008.

[21] N. Sahota et al., “Computerized clinical decision support systems for acute care management: A decision-maker-researcher partnership systematic review of effects on process of care and patient outcomes.,” *Implementation science : IS*, vol. 6, no. 1, p. 91, Aug. 2011.

[22] E. Peterson, M. Roe, and J. Mulgund, “Association Between Hospital Process Performance and Outcomes Among Patients With Acute Coronary Syndromes,” *Medical Association*, vol. 295, no. 16, pp. 1912-1920, 2006.

[23] S. W. Glickman et al., “Care Processes Associated With Quicker Door-In-Door-Out Times for Patients With ST-Elevation-Myocardial Infarction Requiring Transfer: Results From a Statewide Regionalization Program.,” *Circulation. Cardiovascular quality and outcomes*, vol. 4, no. 4, pp. 382-8, Jul. 2011.

[24] M. Cabana, C. Rand, and N. Powe, “Why Don’t Physicians Follow Clinical Practice Guidelines,” *JAMA: the journal of*, vol. 718, 1999.

[25] V. L. Roger et al., “Heart disease and stroke statistics--2011 update: a report from the American Heart Association.,” *Circulation*, vol. 123, no. 4, p. e18-e209, Feb. 2011.

[26] E. Braunwald, “ACC/AHA Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction--2002: Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidel,” *Circulation*, vol. 106, no. 14, pp. 1893-1900, Oct. 2002.

[27] E. M. Antman et al., “ACC / AHA PRACTICE GUIDELINES — FULL TEXT ACC / AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction,” *Circulation*, vol. 6083, 2004.

[28] S. Shayegani and S. S. R. Abidi, “Modeling the Form and Function of Clinical Practice Guidelines : An Ontological Model to Computerize Clinical Practice Guidelines,” *Knowledge Management for Health Care Procedures*, pp. 81-91, 2009.

[29] M. B. Sarder, S. Ferreira, J. Rogers, and D. H. Liles, “A Methodology for Design Ontology Modeling,” *PICMET ’07 - 2007 Portland International Conference on Management of Engineering & Technology*, pp. 1011-1018, Aug. 2007.

[30] H. S. Pinto, A. Gómez-Pérez, and J. P. Martins, “Some issues on ontology integration,” in *IJCAI-99 workshop on ontologies and problem-solving methods (KRR5)*, 1999, no. 1997, pp. 1-12.

[31] P. H. A. Canada, “Tarcking Heart Disease and Stroke in Canada,” 2009.

[32] J. Johnson, “Management of non-ST segment elevation acute coronary syndrome: the managed care perspective,” *Journal of Managed Care Medicine Vol*, vol. 9, no. 2, p. 23.

[33] R. Desk, L. Williams, and K. Health, "ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Com," *Circulation*, vol. 116, no. 7, pp. 803-877, Aug. 2007.

[34] E. M. Antman et al., "2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaborat," *Circulation*, vol. 117, no. 2, pp. 296-329, Jan. 2008.

[35] F. G. Kushner et al., "2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guid," *Circulation*, vol. 120, no. 22, pp. 2271-306, Dec. 2009.

[36] R. Krome, "Twenty-five Years of Evolution and Revolution : How the Specialty Has Changed Twenty-five Years of Evolution and Revolution : How the Specialty Has Changed," *Annals of Emergency Medicine*, no. November, 1997.

[37] R. Elyas, "THE BIRTH OF A NEW SPECIALTY: THE HISTORY OF EMERGENCY MEDICINE IN CANADA," in *Proceedings of the 16h Annual History of Medicine Days Melanie Stapleton- March 2007*, 2007, no. 2007, pp. 277-286.

[38] I. P. Steiner, P. W. Yoon, and B. R. Holroyd, "C OMMENTARY • C OMMENTAIRE Manpower crisis in emergency medicine : Can residency programs make an impact ? A Northern Alberta perspective," *Annals of Emergency Medicine*, vol. 2, no. 2, pp. 1999-2001, 2001.

[39] J. A. Handler et al., "Computerized physician order entry and online decision support.," *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, vol. 11, no. 11, pp. 1135-41, Nov. 2004.

[40] T. A. D. Graham, M. J. Bullard, A. W. Kushniruk, B. R. Holroyd, and B. H. Rowe, "Assessing the Sensibility of Two Clinical Decision Support Systems," *Journal of Medical Systems*, vol. 32, no. 5, pp. 361-368, Mar. 2008.

[41] R. Kwok, M. Dinh, D. Dinh, and M. Chu, "Improving adherence to asthma clinical guidelines and discharge documentation from emergency departments: implementation of a dynamic and integrated electronic decision support system.," *Emergency medicine Australasia : EMA*, vol. 21, no. 1, pp. 31-7, Feb. 2009.

[42] L. Schoff, "Comparing the Challenges of Implementing Decision Support Systems in the Healthcare and Financial Industries," *Health Care and Informatics Review Online*, vol. 13, no. 3, pp. 3-10, 2009.

[43] W. B. Rouse, "Health Care as a Complex Adaptive System : Implications for Design and Management," *Organization Science*, 2007.

[44] (US) C. on Q. of H. C. in America, “CROSSING THE QUALITY CHASM: A NEW HEALTH SYSTEM FOR THE 21ST CENTURY,” *Health (San Francisco)*, no. March, 2001.

[45] E. H. Shortliffe and J. J. Cimino, *Biomedical Informatics: Computer Applications in Health Care and Biomedicine*. Springer Verlag, 2006, pp. 600-639.

[46] E. S. Berner, *Clinical decision support systems: theory and practice*, vol. 6. Springer Verlag, 2007, pp. 3-12.

[47] A. Wright and D. F. Sittig, “A four-phase model of the evolution of clinical decision support architectures.,” *International journal of medical informatics*, vol. 77, no. 10, pp. 641-9, Oct. 2008.

[48] R. Ledley, “Reasoning foundations of medical diagnosis,” *Science*, 1959.

[49] J. November, “Early Biomedical Computing and the Roots of Evidence-Based Medicine,” *Annals of the History of Computing, IEEE*, pp. 9-23, 2011.

[50] H. L. Bleich, “Computer evaluation of acid-base disorders.,” *The Journal of clinical investigation*, vol. 48, no. 9, pp. 1689-96, Sep. 1969.

[51] H. Markowitz, “God, ants and Thomas Bayes.,” *THE AMERICAN ECONOMIST*, vol. 55, no. 2, p. 5, 2010.

[52] O. Ogunyemi, J. R. Clarke, and B. Webber, “Using Bayesian networks for diagnostic reasoning in penetrating injury assessment,” in *Computer-Based Medical Systems, 2000. CBMS 2000. Proceedings. 13th IEEE Symposium on*, 2000, pp. 115–120.

[53] J. Warren, G. Beliakov, and B. V. D. Zwaag, “Fuzzy logic in clinical practice decision support systems School of Computing and Mathematics , Deakin University,” *Computing*, vol. 0, no. c, pp. 1-10, 2000.

[54] K. P. Adlassnig, “Fuzzy Set Theory in Medical Diagnosis,” *IEEE Transactions on Systems, Man, and Cybernetics*, vol. 16, no. 2, pp. 260-265, 1986.

[55] Y. Huang, L. J. Kangas, and B. a Rasco, “Applications of artificial neural networks (ANNs) in food science.,” *Critical reviews in food science and nutrition*, vol. 47, no. 2, pp. 113-26, Jan. 2007.

[56] H. Yan, Y. Jiang, J. Zheng, C. Peng, and Q. Li, “A multilayer perceptron-based medical decision support system for heart disease diagnosis,” *Expert Systems with Applications*, vol. 30, no. 2, pp. 272-281, Feb. 2006.

[57] S. Krikov et al., “Predicting kidney transplant survival using tree-based modeling.,” *ASAIO journal (American Society for Artificial Internal Organs : 1992)*, vol. 53, no. 5, pp. 592-600, 2007.

[58] K. Farion, W. Michalowski, S. Wilk, D. O’Sullivan, and S. Matwin, “A tree-based decision model to support prediction of the severity of asthma exacerbations in children.,” *Journal of medical systems*, vol. 34, no. 4, pp. 551-62, Aug. 2010.

[59] J. Eom, S. Kim, and B. Zhang, "AptaCDSS-E: A classifier ensemble-based clinical decision support system for cardiovascular disease level prediction," *Expert Systems with Applications*, vol. 34, no. 4, pp. 2465-2479, May 2008.

[60] N. Wickramasinghe and J. Gupta, "Creating knowledge-based healthcare organizations," 2005.

[61] H. M. Shah and K. C. Chung, "Archie Cochrane and his vision for evidence-based medicine.," *Plastic and reconstructive surgery*, vol. 124, no. 3, pp. 982-8, Sep. 2009.

[62] I. of Medicine, *Guidelines for Clinical Practice: From Development to Use*. Washington, D.C: National Academy Press, 1992, p. 27.

[63] J. R. Geddes and P. J. Harrison, "Closing the gap between research and practice," *The British Journal of Psychiatry*, vol. 171, no. 3, pp. 220-225, Sep. 1997.

[64] J. Kryworuchko, D. Stacey, N. Bai, and I. D. Graham, "Twelve years of clinical practice guideline development, dissemination and evaluation in Canada (1994 to 2005).," *Implementation science : IS*, vol. 4, p. 49, Jan. 2009.

[65] P. A. D. Clercq, J. A. Blom, H. H. Korsten, and A. Hasman, "Approaches for creating computer-interpretable guidelines that facilitate decision support, Artif," *Intell. Med.*, vol. 31, no. 1, pp. 1-27, 2004.

[66] P. M. Nadkarni, "Metadata-driven Software Systems in Biomedicine," *Health (San Francisco)*, pp. 143-155, 2011.

[67] R. Barendse, J. Lipton, M. V. Ettinger, and S. Nelwan, "Implementing a Clinical Decision Support System for Glucose Control for the Intensive Cardiac Care," *Screen*, pp. 161-165, 2009.

[68] G. D. Sanders, R. F. Nease, and D. K. Owens, "Design and Pilot Evaluation of a System to Develop Computer-based Site-specific Practice Guidelines from Decision Models," *Medical Decision Making*, vol. 20, no. 2, pp. 145-159, Apr. 2000.

[69] S. Hussain and S. Abidi, "An Ontology-based Framework for Authoring and Executing Clinical Practice Guidelines for Clinical Decision Support Systems," *Journal On Information Technology In Healthcare*, vol. 6, no. 1, pp. 1-15, 2008.

[70] R. N. Shiffman, B. T. Karras, A. Agrawal, R. Chen, L. Marenco, and S. Nath, "GEM: a proposal for a more comprehensive guideline document model using XML.," *Journal of the American Medical Informatics Association : JAMIA*, vol. 7, no. 5, pp. 488-98, 2000.

[71] N. Tran, G. Michel, M. Krauthammer, and R. N. Shiffman, "Embedding the guideline elements model in web ontology language.," *AMIA ... Annual Symposium proceedings / AMIA Symposium. AMIA Symposium*, vol. 2009, pp. 645-9, Jan. 2009.

[72] W3C.org, “RDF Primer,” 2004. [Online]. Available: http://www.w3.org/TR/2004/REC-rdf-primer-20040210/. [Accessed: 09-Jun-2011].

[73] N. Prapakorn, “A Frame-based Resource Description Framework Expert System,” *WSEAS International Conference.*, pp. 499-503, 2009.

[74] T. R. Gruber, “A translation approach to portable ontology specifications,” *Knowledge acquisition*, vol. 5, no. 2, pp. 199–220, 1993.

[75] Y. Ye, Z. Jiang, X. Diao, D. Yang, and G. Du, “An ontology-based hierarchical semantic modeling approach to clinical pathway workflows.,” *Computers in biology and medicine*, vol. 39, no. 8, pp. 722-32, Aug. 2009.

[76] L. Ohno-Machado et al., “The guideline interchange format: a model for representing guidelines.,” *Journal of the American Medical Informatics Association : JAMIA*, vol. 5, no. 4, pp. 357-72, 1998.

[77] M. Peleg et al., “GLIF3 : The Evolution of a Guideline Representation,” in *Proceedings of the AMIA Symposium*, 2000, p. 645.

[78] M. Minsky, “Minsky’s frame system theory,” in *Proceedings of the 1975 workshop on Theoretical issues in natural language processing*, 1975, pp. 104–116.

[79] N. Noy, R. Fergerson, and M. Musen, “The knowledge model of Protege-2000: Combining interoperability and flexibility,” *Knowledge Engineering and Knowledge Management Methods, Models, and Tools*, no. 1, pp. 69–82, 2000.

[80] S. W. TU et al., “The SAGE Guideline Model: achievements and overview,” *Journal of the American Medical Informatics Association*, vol. 14, no. 5, pp. 589–598, 2007.

[81] M. Ceccarelli, A. Donatiello, and D. Vitale, “KON^3: A Clinical Decision Support System, in Oncology Environment, Based on Knowledge Management,” *2008 20th IEEE International Conference on Tools with Artificial Intelligence*, pp. 206-210, Nov. 2008.

[82] M. Ceccarelli, A. D. Stasio, A. Donatiello, and D. Vitale, “A Guideline Engine For Knowledge Management in Clinical Decision Support Systems (CDSSs),” *Proceedings of the 21st International Conference on Software Engineering & Knowledge Engineering (SEKE 2009), Boston, Massachusetts, USA, July 1-3, 2009*, pp. 252-257, 2009.

[83] K. Farion, W. Michalowski, S. Wilk, D. O’Sullivan, S. Rubin, and D. Weiss, “Clinical decision support system for point of care use--ontology-driven design and software implementation.,” *Methods of information in medicine*, vol. 48, no. 4, pp. 381-90, Jan. 2009.

[84] A. Hein, O. Nee, D. Willemsen, T. Scheffold, and A. Dogac, “SAPHIRE - Intelligent Healthcare Monitoring based on Semantic Interoperability Platform - The Homecare Scenario -,” *Middle East*, pp. 1-11, 2006.

[85] W3C.org, “OWL Web Ontology Language Overview,” 2004. [Online]. Available: http://www.w3.org/TR/owl-features/. [Accessed: 03-Jun-2011].

[86] M.-M. Bouamrane, A. Rector, and M. Hurrell, “Development of an ontology for a preoperative risk assessment clinical decision support system,” *2009 22nd IEEE International Symposium on Computer-Based Medical Systems*, pp. 1-6, Aug. 2009.

[87] F. Baader, M. Knechtel, and R. Peñaloza, “A Generic Approach for Large-Scale Ontological Reasoning in the Presence of Access Restrictions to the Ontology ’ s Axioms,” pp. 49-64, 2009.

[88] M. Prcela, D. Gamberger, and A. Jovic, “Semantic web ontology utilization for heart failure expert system design,” *Studies in health technology and informatics*, vol. 136, no. October, p. 851, 2008.

[89] A. Daniyal, S. R. Abidi, and S. S. R. Abidi, “Computerizing clinical pathways: ontology-based modeling and execution.,” *Studies in health technology and informatics*, vol. 150, no. iii, pp. 643-7, Jan. 2009.

[90] D. MA, S. S. R. Abidi, and B. Jafarpour, “Ontology based modeling and execution of Nursing Care Plans and Practice Guidelines.,” *Stud Health Technol Inform*, no. 160, pp. 1104-1108, 2010.

[91] N. Chungoora, O. Canciglieri, and R. I. M. Young, “Towards expressive ontology-based approaches to manufacturing knowledge representation and sharing,” *International Journal of Computer Integrated Manufacturing*, vol. 23, no. 12, pp. 1059-1070, Dec. 2010.

[92] W. Li and S. Tian, “XSWRL, an Extended Semantic Web Rule Language and prototype implementation,” *Expert Systems with Applications*, vol. 38, no. 3, pp. 2040-2045, Mar. 2011.

[93] H. H. Wang, J. S. Dong, J. Sun, and J. Sun, “Reasoning support for Semantic Web ontology family languages using Alloy,” *International Journal*, vol. 2, pp. 455-471, 2006.

[94] H. J. MURFF and J. KANNRY, “Physician Satisfaction with Two Order Entry Systems,” *Journal of the American Medical Informatics Association*, vol. 8, no. 5, pp. 499-510, 2001.

[95] H. M. Seidling et al., “Factors influencing alert acceptance: a novel approach for predicting the success of clinical decision support.,” *Journal of the American Medical Informatics Association : JAMIA*, vol. 18, no. 4, pp. 479-84, Jul. 2011.

[96] O. Nierstrasz, “A survey of object-oriented concepts,” *Object-Oriented Concepts, Databases and Applications*, 1989.

[97] P. Terenziani, E. German, and Y. Shahar, “The temporal aspects of clinical guidelines.,” *Studies in health technology and informatics*, vol. 139, p. 81, 2008.

[98] P. A. de Clercq, A. Hasman, J. A. Blom, and H. H. M. Korsten, “Design and implementation of a framework to support the development of clinical guidelines.,” *International journal of medical informatics*, vol. 64, no. 2-3, pp. 285-318, Dec. 2001.

[99] O. Dameron, D. L. Rubin, and M. A. Musen, “Challenges in Converting Frame-Based Ontology into OWL : the Foundational Model of Anatomy Case-Study Converting the FMA into OWL-DL,” *Symposium A Quarterly Journal In Modern Foreign Literatures*, vol. 1, pp. 181-185, 2005.

[100] H. H. Wang et al., “Frames and OWL side by side,” in *9th International Protégé Conference, Stanford, California, USA*, 2006, p. 54.

[101] H. S. Pinto and J. P. Martins, “A methodology for ontology integration,” *Proceedings of the international conference on Knowledge capture - K-CAP 2001*, p. 131, 2001.

[102] E. Jim, B. C. Grau, I. Horrocks, and R. Berlanga, “Ontology Integration Using Mappings : Towards Getting the Right Logical Consequences,” pp. 173-187, 2009.

[103] R. Fikes and A. Farquhar, “Tools for assembling modular ontologies in Ontolingua,” *Proceedings of the Fourteenth National Conference on Artificial Intelligence*, 1997.

[104] E. R. Melnick, N. G. Genes, N. K. Chawla, M. Akerman, K. M. Baumlin, and A. Jagoda, “Knowledge translation of the American College of Emergency Physicians’ clinical policy on syncope using computerized clinical decision support.,” *International journal of emergency medicine*, vol. 3, no. 2, pp. 97-104, Jan. 2010.

[105] J.-P. Bassand et al., “Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes.,” *European heart journal*, vol. 28, no. 13, pp. 1598-660, Jul. 2007.

[106] S. I. G. Network, *Acute coronary syndromes A national clinical guideline*, vol. 2007, no. June. Edinburgh : SIGN, 2007.

[107] “NCBO BioPortal.” [Online]. Available: http://bioportal.bioontology.org/.

[108] M. Uschold, M. Healy, K. Williamson, P. Clark, and S. Woods, “Ontology Reuse and Application,” *Information Systems*, vol. 98, pp. 1-15, 1998.

[109] E. P. Bontas, “Towards affreuse-oriented methodology for ontology engineering,” *on Terminology and Knowledge Engineering (*, pp. 1-12, 2005.

[110] N. Fridman Noy and M. A. Musen, “PROMPT: algorithm and tool for automated ontology merging and alignment,” *AAAI/IAAI*, vol. 2000, pp. 450–455, 2000.

[111] J. Kim, M. Jang, Y.-guk Ha, J.-chan Sohn, and S. J. Lee, “MoA : OWL Ontology Merging and Alignment Tool for the Semantic Web,” pp. 722 - 731.

[112] J. L. Anderson et al., "ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise th," *Circulation*, vol. 116, no. 7, pp. e148-304, Aug. 2007.

[113] E. M. Antman et al., "2007 Focused Update of the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: developed in collaborat," *Circulation*, vol. 117, no. 2, pp. 296-329, 2008.

[114] R. S. Wright et al., "2011 ACCF/AHA focused update of the Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction (updating the 2007 guideline): a report of the American College of Cardiology Foundation/American Heart Association T," *Journal of the American College of Cardiology*, vol. 57, no. 19, pp. 1920-59, May 2011.

[115] C. Parent and S. Spaccapietra, "An overview of modularity," in *Modular Ontologies*, S. Stuckenschmidt, Heiner and Parent, Christine and Spaccapietra, Ed. Berlin, Heidelberg: Springer-Verlag, 2009, pp. 5–23.

[116] H. M. Sauro, "Modularity defined.," *Molecular systems biology*, vol. 4, no. 166, p. 166, Jan. 2008.

[117] J. Meyer-Fujara, B. Heller, and S. Schlegelmilch, "Knowledge-level modularization of a complex knowledge base," in *KI-94: Advances in Artificial Intelligence*, Berlin ; New York: :Springer-Verlag, 1994, p. 214.

[118] D. G. Perina et al., "The 2007 Model of the Clinical Practice of Emergency Medicine: the 2009 update.," *Academic emergency medicine : official journal of the Society for Academic Emergency Medicine*, vol. 18, no. 3, p. e8-e26, Mar. 2011.

[119] M. R. Kogalovsky and L. a Kalinichenko, "Conceptual and ontological modeling in information systems," *Programming and Computer Software*, vol. 35, no. 5, pp. 241-256, Sep. 2009.

[120] G. Simons, "Conceptual modeling versus visual modeling: A technological key to building consensus," *Computers and the Humanities*, no. 3, pp. 303-319, 1996.

[121] P. de Clercq, K. Kaiser, and A. Hasman, "Computer-interpretable Guideline Formalisms," *Studies in health technology and informatics*, vol. 139, p. 22, 2008.

[122] A. G. Pérez and V. R. Benjamins, "Overview of knowledge sharing and reuse components: Ontologies and problem-solving methods," in *IJCAI-99 workshop on Ontologies and Problem-Solving Methods (KRR5), Stockholm, Sweden*, 1999, pp. 1-15.

[123] O. Bodenreider, B. Smith, A. Kumar, and A. Burgun, "Investigating subsumption in SNOMED CT: An exploration into large description logic-based biomedical terminologies," *Artificial Intelligence in Medicine*, vol. 39, no. 3, pp. 183-195, Jul. 2007.

[124] M. Peleg et al., "Reasoning with Effects of Clinical Guideline Actions using OWL: AL amyloidosis as a Case Study," in *Artificial Intelligence in Medicine*, 2011, pp. 95-108.

[125] M. Peleg and R. Kantor, "Approaches for guideline versioning using GLIF.," in *AMIA ... Annual Symposium proceedings / AMIA Symposium. AMIA Symposium*, 2003, pp. 509-13.

[126] S. Abidi, "Towards the Merging of Multiple Clinical Protocols and Guidelines via Ontology-Driven Modeling," *Artificial Intelligence in Medicine*, pp. 81–85, 2009.

[127] S. Tartir, I. B. Arpinar, and A. P. Sheth, "Theory and Applications of Ontology: Computer Applications," R. Poli, M. Healy, and A. Kameas, Eds. Dordrecht: Springer Netherlands, 2010, pp. 115-130.

[128] A. Gangemi, C. Catenacci, M. Ciaramita, and J. Lehmann, "Modelling ontology evaluation and validation," *The Semantic Web: Research and Applications*, pp. 140–154, 2006.

[129] J. Baumeister and D. Seipel, "Smelly Owls–Design Anomalies in Ontologies," in *Proc. FLAIRS*, 2005, pp. 215–220.

[130] M. Peleg et al., "Comparing Computer-interpretable Guideline Models: A Case-study Approach," *Journal of the American Medical Informatics Association*, vol. 10, no. 1, p. 52, 2003.

[131] Y. Okuda and B. P. Nelson, *Emergency medicine oral board review illustrated*. Cambridge University Press, 2009.

[132] M. H. Picard, K. Rosenfield, S. Digumarthy, and R. N. Smith, "Case 40-2010 : A 68-Year-Old Woman with Chest Pain during an Airplane Flight," *The New England Journal of Medicine*, vol. 363, pp. 2652-61, 2010.

[133] D. S. Pinto, "A 43-year-old man with angina, elevated troponin, and lateral ST depression: management of acute coronary syndromes.," *JAMA : the journal of the American Medical Association*, vol. 303, no. 1, pp. 54-63, Jan. 2010.

[134] A. A. Doshi, K. Iskyan, J. M. O'Neill, and K. N. Sawyer, "Evaluation And Management Of Non–ST Segment Elevation Acute Coronary Syndromes In The Emergency Department," *Emergency Medicine Practice*, vol. 12, p. 2, 2010.

[135] D. Vrandecic, "Ontology Evaluation," in *Handbook on Ontologies*, S. Staab and R. Studer, Eds. Berlin, Heidelberg: Springer Berlin Heidelberg, 2009, pp. 293-313.

[136] T. Gruber, "Toward principles for the design of ontologies used for knowledge sharing?," *International Journal of Human-Computer Studies*, vol. 43, no. 5-6, pp. 907-928, Nov. 1995.

[137] A. Gómez-Pérez and M. Rojas-Amaya, “Ontological reengineering for reuse,” *Knowledge Acquisition, Modeling and Management*, pp. 139–156, 1999.

[138] A. Mechouche, N. Abadie, and S. Mustière, “Alignment-Based Measure of the Distance between Potentially Common Parts of Lightweight Ontologies,” *Ontology Matching*, p. 49, 2010.

[139] S. Borgo, N. Guarino, and C. Masolo, “Stratified ontologies: the case of physical objects,” in *Proceedings of ECAI-96 Workshop on Ontological Engineering*, 1996.

[140] J. Völker, D. Vrandečić, Y. Sure, and A. Hotho, “Learning disjointness,” *The Semantic Web: Research and Applications*, pp. 175–189, 2007.

[141] J. C. A. Vega, A. Gómez-Pérez, A. L. Tello, and H. S. A. N. P. Pinto, “(ONTO) 2 Agent: an Ontology-based WWW broker to select ontologies,” in *Applications of Ontologies and Problems Solving Methods 13th European Conference on Artificial Intelligence ECAI’98*, 1998.

[142] M. Frize, E. Bariciak, and S. Weyand, “Suggested criteria for successful deployment of a Clinical Decision Support System (CDSS),” *2010 IEEE International Workshop on Medical Measurements and Applications*, no. i, pp. 69-72, Apr. 2010.

[143] V. López, E. M. Eisman, and J. L. Castro, “A Tool for Training Primary Health Care Medical Students: The Virtual Simulated Patient,” in *2008 20th IEEE International Conference on Tools with Artificial Intelligence*, 2008, vol. 2, pp. 194-201.

[144] D. Vlahaki, M. Fiaani, and W. K. Milne, “A door-to-needle time of 30 minutes or less for myocardial infarction thrombolysis is possible in rural emergency departments.,” *Cjem*, vol. 10, no. 5, pp. 429-33, Sep. 2008.

[145] E. Sanchez et al., “An Architecture for the Semantic Enhancement of Clinical Decision Support Systems,” *Knowlege-Based and Intelligent Information and Engineering Systems*, pp. 611–620, 2011.

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