INTEGRATION OF CLINICAL DECISION SUPPORT SYSTEMS IN DUTCH RADIOLOGY DEPARTMENTS

Towards the integration of nonknowledge-based clinical decision support systems for treatment evidence analysis into the clinician's workflow and infrastructure of Dutch radiology departments



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"Advances in Artificial Intelligence are running ahead of humanity's ability to absorb and integrate them. Being better at inventing stuff than implementing it, is a lousy strategy for progress."

> Oliver Schabenberger, COO and CTO at SAS, on the implementation of AI

Preface

This is the master thesis of Antonie Berkel for the Business Information Technology master at the University of Twente. This thesis contains a research that has been carried out for SAS Netherlands during a period of five months. The topic of this thesis is the integration of a clinical decision support system (CDSS) into radiology departments. These clinical decision support systems can aid a clinician in his/her decision making and hold the potential to improve practitioner performance and patient care. The CDSS in this research achieves this by using artificial intelligence (AI) to analyze large volumes of unstructured data in the form of imagery to improve the assessment and/or determination of a treatment. Despite the potential, implementation of these CDSS on a large scale is missing. This research set out to solve the integration challenges that arise when implementing a CDSS.

In my five months at SAS and in the world of data analytics in healthcare, it was soon shown that implementation is indeed lacking. During my visits at the Data Driven Healthcare Congress, several knowledge sessions on CDSS implementation and Amsterdam UMC, many organizations, clinicians and data scientists presented their analytics (often AI) and they showed great results. The possibilities were enormous, and they could statistically prove that the system could aid in providing better care. However, when they were asked if the system is actually implemented, the answer is often "no". In one on one conversations with these people, it was clear that they ran into numerous challenges when trying to implement the analytics that they had created. Ranging from ethical barriers to validation barriers to technical barriers to socio-economic barriers. Not a single person had the answer to the question: "how to implement CDSS powered by AI into a clinical environment?" Yet, they were all waiting for it.

SAS ran into the same challenge when they were working on CDSS. SAS firmly believes in the operationalization of analytics and therefore was so keen on finding an answer to that question. This research sets out to solve one of the major challenge topics in the field of implementation: integration. More specifically, integration into the clinician's workflow and infrastructure of the radiology department without causing disruption. In my search for an answer to this question it was clear why this problem is hard to solve. Implementation of CDSS requires vastly different sectors, actors and organizations to combine their knowledge. Data scientists and doctors speak an entirely different language, but their collaboration is vital to the success of integration.

This was also required in this research. Solving the challenges in this research brought the implementation of CDSS into clinical practice one step closer. It has produced two artifacts that contribute to the goal of implementation: 1) a way of classifying CDSS that will improve communication and crystalizes implementation designs for specific types and 2) a concrete design for the integration of nonknowledge-based CDSS for treatment evidence analysis (one of the types) into the clinician's workflow and infrastructure of radiology.

I would like to thank Marten van Sinderen en Fons van Wijnhoven for their support and advice as supervisors in this research. Also, I would like to thank SAS for the opportunity and a special thanks to Alfredo Iglesias Rey and Joost Huiskens for their valuable support while working there. Finally, I would like to thank the Amsterdam UMC for their help in navigating the complex workflows, systems and standards in healthcare.

Antonie Berkel

Executive summary

Healthcare is transitioning towards personalized medicine. A patient-centered model which allows for the tailoring of treatments to the needs of the individual instead of the masses in order to improve patient care. Clinical decision support systems (CDSS) powered by artificial intelligence (AI) can provide the diagnostics that are needed to achieve this individual care by analyzing vast amounts of medical data. SAS, a data analytics company, together with the Amsterdam UMC are developing a CDSS called CAESAR. The goal is to use CT-images to assess and determine treatments for patients with colorectal liver metastases. Despite the potential of these systems, successful implementation is rare. Numerous challenges arise when implementing these systems and thus many of the systems never live up to their potential. This research sets out to solve two of the major challenges that arise when implementing these systems: 1) integration into the clinician's workflow without disruption and 2) integration into the infrastructure of the hospital. It does so, specifically for the type of CDSS that is developed by SAS.

To achieve this goal, the field of CDSS implementation was analyzed. In this analysis, a list of 26 implementation challenges was identified. Challenges regarding the integration of a CDSS into the workflow and infrastructure were the most frequently mentioned. Also, it was found that solving these challenges for the whole spectrum of CDSS was unachievable as the systems are vastly different. However, there was no typology available that could aid in the classification of ideal types of CDSS. Since this research sets out to create a reference solution rather than a point solution, a typology was created. The created typology consists of two dimensions. One dimension allows for the specification of the data input and analysis technique that the CDSS uses, the other allows for the determination of the impact that the CDSS has on the context in which it is integrated. Using the typology, CAESAR was identified as a nonknowledge-based CDSS for treatment evidence analysis in the radiology department.

Based on literature and interviews, an extensive list of system requirements for the integration of the CDSS into the radiology department was created. The solution design that fulfills these requirements depicts that this type of CDSS can best be integrated by allowing it to present its findings in a separate study in the centralized information environment of the clinician. This would allow every clinician to access the outcomes in a form that they recognize (the same images and reports as in radiology) through a centralized access point and ensures that the system can support the clinician without disruption in the workflow or work environment. In the infrastructure, the CDSS can be modelled as a substitution for the system components that are normally responsible for the creation of outcomes in a regular imaging examination: the evidence creator, report creator, post-processing manager and report manager. Challenges that arose during the design of the infrastructure could be solved by using order management and existing transactions. Using this solution design and the radiology standards, process models, a transaction model and a reference architecture for the integration of a nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure of radiology was designed. The artifacts showed that workflow and infrastructure disruption was indeed minimized. These artifacts were validated by expert opinion. Also, to illustrate its use in practice, the artifacts were applied to the real-world case of CAESAR.

The contribution of this research is threefold:

- 1. Scientific The typology can be used to classify types of CDSS in order to focus the implementation effort to specific types of CDSS rather than the entirety of the CDSS field.
- 2. Scientific In the field of health informatics, the reference architecture is a first of its kind reference design for the integration of CDSS into workflow and infrastructure.
- 3. Business It allows SAS to use the artifacts and approach as concrete designs in the communication with partners and the development and integration of their systems.

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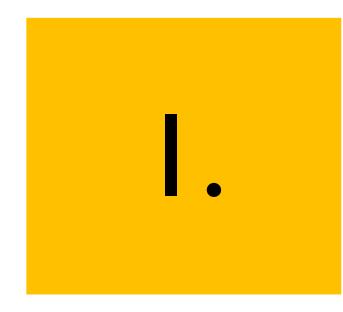
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List of abbreviations

Abbreviation	Meaning
ANN	Artificial Neural Network
ADM	Architecture Development Method
ADT	Admit – Discharge - Transfer
AI	Artificial Intelligence
Amsterdam UMC	Amsterdam Universitair Medische Centra
BPMN	Business Process & Modelling Notation
CAESAR	Cancer center AmstErdam and SAs join forces to improve outcomes
	in patients with coloRectal cancer through advanced analytics
CDSS	Clinical Decision Support System
CNN	Convolutional Neural Network
CPOE	Computerized Physician Order Entry
CRC	Colorectal cancer
CRISP-DM	Cross-Industry Standard Process for Data Mining
CT-scan	Computer-Tomography scan
DICOM	Digital Imaging and Communication in Medicine)
DM	Data Mining
EHR	Electronic Health Record
GP	General Practitioner
HIS	Healthcare Information System
HL7	Health Level 7
IHE	Integrating the Healthcare Enterprise
IT	Information Technology
MDO	Multi-disciplinair overleg
ORM	Order Response Message
ORU	Object Result Unsolicited
PACS	Picture Archiving and Communication System
RIS	Radiology Information System
SAS	Statistical Analysis System
STR	Stakeholder Requirement
SYR	System Requirement
TOGAF	The Open Group Architecture Framework
UID	Unique Identifier
VNA	Vendor Neutral Archive
ZiRA	Ziekenhuis Referentie Architectuur

List of concepts

Concept	Definition
Artificial Intelligence	The creation of machines that perform functions that require
0	intelligence when performed by humans
CAESAR	An endeavor of the Amsterdam UMC and SAS to build a CDSS for
	the improvement of care for patients with colorectal cancer
CDSS	Computer systems designed to impact clinician decision making about
	individual patients at the point in time that these decisions are made
Clinician's workflow	In this research, the series of activities performed by a clinician that
	together enable the ordering, scheduling, creating, storing, processing,
	assessing, presenting and discussing of a medical imaging examination
DICOM	The standard for the communication and management of medical
	imaging information related data
HL7	A set of international standards for transfer of clinical and
	administrative data between software applications used by various
	healthcare providers
HIS	A central information system that manages healthcare data
IHE	An initiative by healthcare professionals and industry to improve the
	way computer systems in healthcare share information and support
	workflows
Knowledge-based systems	Systems that use explicitly specified knowledge to create outcomes.
	Often comprising of a knowledge base, inference or reasoning engine
	and a mechanism to communicate
Modalities	Systems capable of creating medical imaging
Nonknowledge-based	Systems that use a form of AI to create outcomes by learning from past
systems	experiences and recognizing patterns in clinical data.
Nonknowledge-based	Computer systems designed to impact a clinician's treatment decision
CDSS for treatment	of individual patients by analyzing evidence using nonknowledge-based
evidence analysis	mechanisms at the point in time that these decisions are made
PACS	A medical imaging information system which provides storage and
	convenient access to images from multiple modalities
Personalized medicine	The transition from a disease-centered model (where decisions are made
	based on generalized clinical expertise and data from tests instead of
	individual needs) to a patient-centered model. Here, patients receive
	services and treatment focused on individual needs and preferences,
	informed by advice and oversight from their healthcare providers that
RIS	will lead to better, efficient and cost-effective care
K10	A specialized form a HIS, specifically tailored to suit the needs of the
	radiology department



Introduction

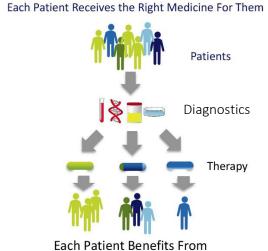
This research sets out to improve the implementation of clinical decision support systems (CDSS) powered by artificial intelligence (AI) by solving two of the major implementation challenges: 1) integration of CDSS into the workflow without disrupting it and 2) integration into the infrastructure. These systems can aid in the clinician's decision-making and improve patient care by analyzing large volumes of (un)structured medical data. The problem with these systems is that although they have potential, the implementation into clinical practice is complex and lacking in the industry. Therefore, this technological advancement is not utilizing its full potential to directly impact daily patient care and improve the life of patients. This research sets out to improve this implementation. This chapter introduces the motivation, problem statement and research questions of the research.

I.I Motivation

I.I.I THE FUTURE OF HEALTHCARE: TOWARDS PERSONALIZED MEDICINE

Healthcare is a field that dates to the earliest civilizations thousands of years ago. From then, we have learned how to cure diseases, prolong life span and in the process, make the quality of life superior to any civilization that came before us. We have found a treatment for almost every disease and have

overcome devastating plagues. And now, healthcare is on the brink of another major transition. Too often, we prescribe treatment on a population level, instead of an individual one. Given a person's uniqueness, this results in situations where one patient responds to a treatment, whereas another with the same diagnosis might experience no effect at all. This disease-centered model (where decisions are made based on generalized clinical expertise and data from tests instead of individual needs) is transitioning to a patient-centered model [1]. Here, patients receive services and treatment focused on individual needs and preferences, informed by advice and oversight from their healthcare providers that will lead to better, efficient and costeffective care [1] (Figure 1). Determining these individual care needs requires diagnostics that allows clinicians to make a better decision regarding the tailored prescribed treatment.



With Personalized Medicine:

Individualized Treatment

1.1.2 THE EMERGENCE OF AI AND CDSS IN HEALTHCARE

Artificial intelligence (AI) can enable these diagnostics. One field of AI focuses on the creation of machines that perform functions that require intelligence when performed by humans [2]. These machines are able to find patterns in and learn from vast amounts of (big) data [3]. Given that big data is on the rise in healthcare [4], there lies a huge potential for this technique to provide new insights that help a clinician's decision making. Scientists and clinicians alike were captivated by the potential that this technology might have on medicine. This led to the research into clinical decision support systems (CDSS). CDSS are "computer systems designed to impact clinician decision making about individual patients at the point in time that these decisions are made" [5]. Given the individual nature and direct impact on care, these systems can contribute to personalized healthcare.

1.1.3 ARTIFICIAL INTELLIGENCE AND CDSS AT SAS

SAS, a company specialized in data analytics (more information in Appendix A), is developing a CDSS for the Amsterdam UMC. This system will be used to aid in the decision making regarding treatments. Its output is valuable for oncology and uses imaging that is created in the radiology department. The system focuses on colorectal liver metastases. These metastases emerge from an earlier or synchronous form of colorectal cancer (CRC). They are manifested in 50% of the colorectal cancer cases and the 5-year overall survival rate of these patients is (only) 20% [6]. The radiology imaging data that is available for these patients holds valuable information that can help clinicians in determining and assessing a treatment. SAS sets out to create and implement a CDSS powered by AI that can analyze these images. It will make care more accurate, efficient and cost-effective (as it will prevent unnecessary surgery and chemo). The name of the project is CAESAR (Cancer center AmstErdam and SAs join forces to improve outcomes in patients with coloRectal cancer through advanced analytics) and its implementation is the main motivation for this research.

Figure 1: Tailored treatment using personalized medicine.

I.2 Problem statement

Despite the potential benefits of CDSS [7] [8] [9] [10] [11], they are not yet common in patient-care settings [12]. Literature (see section 3.3) shows that implementation of a CDSS poses many challenges. Many different aspects have to be accounted for when implementing a system that will support a clinician's decision using artificial intelligence. Being able to build the AI algorithms however does not seem to be the problem given the many analytical models and startups that show great promise in the healthcare sector. Rather, all other aspects surrounding implementation are unaccounted for. Numerous aspects are missing in the current literature and practice to implement CDSS [12] [13] [14]. The, in this case often used, best practices for implementation are absent [14] [15]. Two major implementation challenges are the integration of CDSS into the clinician's workflow without disrupting it [14] [13] [16] [17] [18] [19] and the integration within infrastructure of hospitals [12] [17] [20] [21] [22] [23]. Disruption here means any alteration or addition to the current activities that the clinician performs to achieve a certain goal. Solving these two challenges will contribute to the implementation of CDSS.

Before discussing the problem statement, it is important to note that CDSS is an enormous field with very diverse systems. Ranging from "simple" electronic patient records (EHRs) to full-fledged digital doctors trying to simulate the clinician. Researching a one-size-fits-all solution for the integration of these systems is undesirable since a solution will either be too complex or too vague. A type is therefore specified. With a typology missing in the literature, this research has proposed one itself (Chapter 4). One of these types is a nonknowledge-based CDSS for treatment evidence analysis in the radiology department. The term is further explained in section 4.6, but in short describes a CDSS that analyses evidence to support the treatment decision by using AI-techniques and (un)structured data. For this type, disruption means a change or addition to the workflow and infrastructure that enables the ordering, scheduling, creating, storing, processing, assessing, presenting and discussing a medical image examination. Given that CAESAR is an instance of a system of this type, this is the focus of the research.

All of the statements above mark the problem that this research is trying to solve. The problem statement can be formulated as:

It is unknown how to integrate a nonknowledge-based CDSS for treatment evidence analysis into the current workflow and infrastructure of radiology departments in Dutch hospitals whilst minimizing the disruption in the clinician's workflow and systems

I.3 Research goal

The goal of this research is to solve two of the major implementation challenges that CDSS face: integration into workflow and infrastructure without disruption. To do so, the research first analyses related work regarding CDSS, AI and care processes. Then, a generalizable type for the system is determined. Then, the current situation is analyzed to gain an understanding of what has to be integrated and where. After that, requirements for the integration of such a system are elicited. Then, an artifact is created that can show how this system can be integrated into a clinical context using enterprise architecture. This architecture provides an overview of all components of an organization and allows for the modelling of a current and future vision. On top of that, it allows for modelling of the connection between business processes (workflow), application components and infrastructure nodes and shows how each of them contributes to a service that provides value to the organization [24]. Given the desire to create a generalizable design for integration, a reference architecture will be created. In summary, the goals of the research are:

- 1 To establish the generalizable type of CDSS that CAESAR represents
- 2 To determine the workflows and infrastructure in which the CDSS has to be integrated

- 3 To determine the requirements for integration of the CDSS into the current workflow and infrastructure.
- 4 To design a reference enterprise architecture for nonknowledge-based CDSS for treatment evidence analysis in radiology departments of Dutch hospitals depicting the integration of this system into the workflow and infrastructure.

I.4 Research question

This research is a typical design science research. The challenges stated in section 1.2 poses a design problem since it calls for a change in the world, the solution is a design, there might be many different solutions, this solution is evaluated by (hypothetically) utilizing it and the value of the solution depends on the stakeholder goals [25]. Furthermore, a clear artifact and context can be distinguished: a reference architecture for nonknowledge-based CDSS for treatment evidence analysis and the radiology department in a Dutch hospital respectively. Design science research answers "how?"-questions. With the problem statement and goal defined, the research question will be:

How to integrate a nonknowledge-based CDSS for treatment evidence analysis into the workflow and infrastructure of the radiology department of Dutch hospitals whilst minimizing disruption in the clinician's workflow and systems in order to improve the implementation of these types of systems?

To support the search for a solution to this question, several knowledge questions will be asked:

- 1. What is CDSS and how can we classify types of CDSS?
- 2. What do the processes and systems on which the CDSS have an impact look like and how can the CDSS support these?
- 3. What are the requirements for the integration of this CDSS into the clinician's workflow and infrastructure?

Then, to validate the designed artifact, the following questions will be asked:

4. Does the designed artifact show the desired effects?

I.5 Reading guide

The thesis is structured as follows. Chapter 2 discusses methods that are used in this research to answer the research question. Chapter 3 discusses related work. In Chapter 4, a typology for CDSS is presented together with specifics on the CAESAR-case. Chapter 5 then presents the reference architecture for the integration of nonknowledge-based CDSS for treatment evidence analysis. Chapter 6 discusses the validation of the solution. The thesis is concluded with a discussion and recommendation in Chapter 7 and a conclusion in Chapter 8. Additional information can be found in Appendices A through H.



2. Methods

Achieving the goal stated in section 1.3 and answering the questions posed in section 1.4 requires a welldefined research design. This chapter discusses the scope, the deliverables, and the approach that is taken to perform the research.

2.1 Scope

In this research, a number of important scoping decisions have been made in order to make the project manageable, valuable and doable in five months' time.

Starting from the desire to implement a CDSS in hospitals (the initial motivation of the research) the first scoping decision was made in terms of the challenges that will be solved in this research. Implementation is a large and complex undertaking. Wanting to address all aspects of the effort is too much for one research. Therefore, the focus is applied to two major challenges: integration of a CDSS into the current clinician's workflow and infrastructure without disrupting these.

The second scoping decision applies to the context of focus. Hospitals (and their departments), naturally, have very diverse infrastructures and processes in place given their different focuses and specializations. Creating a framework that will facilitate all of them will take tremendous effort and resources. A clear subset will thus be more manageable (and valuable). The CDSS created by SAS focuses on utilizing imaging provided by radiology. Given this focus, the reference architecture will be made so that it can be implemented into the radiology department of Dutch hospitals. The focus is put on Dutch hospitals since care is organized very nationally and might differ substantially. The solution might still apply to hospitals in other nations, but the focus lies on Dutch hospitals.

The third scoping decision was made in terms of the artifact of focus. CDSS is a large field that concerns all computer systems designed to impact clinician decision making about individual patients at the point in time that these decisions are made. This results in a vast amount of types of CDSS. The integration effort will focus on nonknowledge-based CDSS for treatment evidence analysis in the radiology department (see section 4.6). This crystalizes the functionalities and requirements that the architecture has to fulfill and is therefore more valuable then higher abstractions where conflicting requirements lead to vagueness.

The fourth scoping decision was made in relation to the workflow in which the CDSS will be integrated. The research assumes a well-functioning workflow where no failures and errors occur. In reality, the integration has to cope with these imperfections. However, these imperfections will differ per implementation effort and are therefore not accounted for in the reference architecture.

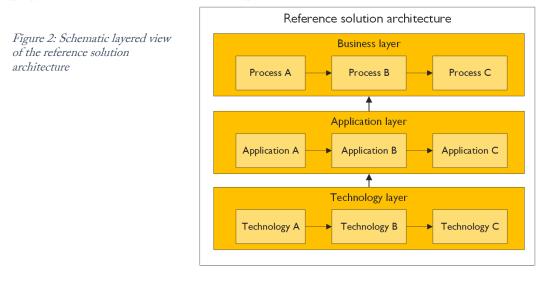
2.2 Deliverable

The deliverable of the research will be a reference enterprise architecture that depicts the integration of the system in the workflow and infrastructure. The choice for this kind of architecture has been made based on three main reasons.

First, a reference enterprise architecture allows for capturing all components and their relationships within an organization. The connections between value delivery, workflows and the underlying IT infrastructure are important aspects for integration and an architecture can provide a holistic overview of this end-to-end integration of value, processes, applications and technology. Enterprise architectures relate requirements (derived from a process) and the external world to a solution structure, including both hardware and software, so that the effectiveness of a system design concept can be communicated [26]. Second, an architecture depicts the current situation as well as a target situation. Third, a reference architecture is desirable in order to create generalizable knowledge instead of a point solution. It has to show a to-be situation where organizations need to migrate to in order to integrate these systems. Reference architectures capture the essence of existing architectures, and the vision of future needs and evolution to provide guidance to assist in developing new system architectures [27].

Independent from the framework or language used to create the architecture, in schematic form, it will show a layered overview of the integration between business/process, software/application and technology [28] (Figure 2).

The reference architecture will be accompanied by process models to show the current and target workflows in more detail, add chronology to the activities in the workflow and assess the validity of the proposed solution by assessing the disruption in the current workflow.



2.3 Research design

In design science, the design cycle proposes an iterative approach composing of several activities that can be carried out one or more times. The design cycle describes the following activities [25]:

- Problem investigation: what phenomena must be improved and why?
- Treatment design: design one or more artifacts that could treat the problem.
- Treatment validation: would these designs treat the problem?
- Treatment implementation: treat the problem with one of the designed artifacts.
- Implementation evaluation: how successful has the treatment been? This then may be the start of a new iteration through the design cycle.

This design cycle is used as the backbone of the research. We run through it twice with some adjustments in some of the steps. The design cycle is complemented with a research design for the development of architectures: The Open Group Architecture Framework (TOGAF) Architecture Development Method (ADM) [29]. The steps taken in this ADM can be mapped onto the design cycle and therefore functions as a valuable deepening of the design cycle. The ADM consists of nine activities who can, again, form an iterative cycle for design (see Apendix C). The method forms a state-of-the-art standard in architecture design and a strongly process-oriented development process as it starts with analyzing the new processes and only then focuses on the supporting infrastructure. This ensures that the value that the system delivers within the process is well-warranted and allows for the monitoring of workflow disruptions. Mapping the steps of the ADM to the design cycle provides a method that will be used in this research (Figure 3). One major change however needs to be made to fit this research. The implementation phase as specified in the design cycle cannot be executed due to limited resources. Implementation requires the actual implementation at the hospital. Since the algorithm has not been certified, no trials have been done yet and the agreement between the hospital and SAS is not fully completed, this is undoable. The research will thus provide a design for integration that is validated by stakeholders and experts in the hospital and by an assessment of workflow disruption. How this will be achieved is discussed next.

In the problem investigation phase of the design cycle, information is gathered about the problem context. This is done using a systematic literature review and interviews with stakeholders. Deliverables in this phase (A) are a problem analysis, a typology of CDSS (to classify the object of interest), current situation (including a process model and architecture of the radiology department of the hospital), stakeholder analysis and requirements.

Then, based on literature and interviews, a solution design is introduced that presents the general solution to the integration challenges. Based on this, a process model and reference architecture are designed that depicts the new workflow and infrastructure when the CDSS is integrated (B, C and D). This method shows one of the major benefits of the ADM in this case. Deliverables in this phase are a target process model and reference architecture.

To validate this reference architecture, its use is illustrated by applying it to the case study of CAESAR. This will show that the reference architecture fits the requirements once it is placed in a context and will depict a target situation for the CAESAR case. Then, experts and stakeholders (sometimes overlapping) provide feedback on the created artifacts. Deliverables in this phase are an illustration of the reference architecture and expert opinions (E).

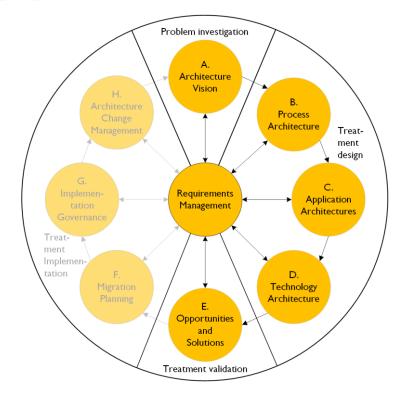


Figure 3: Research design based on the design cycle and ADM



3. Related work

This chapter discusses the state of the art in important concepts used in this research based on a systematic literature review (Appendix C). Discussing this current state of the art establishes a foundation upon which the rest of the research can build. In general, this chapter discusses two perspectives: the perspective of the system that has to be integrated (object of interest) and the perspective of the workflows and infrastructure in radiology (context). For the first perspective, the concepts of CDSS will be examined to establish a common understanding of the object of interest. Then, an analysis of all challenges regarding CDSS implementation is presented. This list will function as input for the list of requirements for integration. Finally, an analysis of artificial intelligence shows how these CDSS can benefit from AI. For the second perspective, the primary care process and therapeutic cycle is discussed to show the general process on which the CDSS can have an impact. The process and underlying mechanisms of medical decision making are examined to understand how a CDSS can support these decisions. Finally, the international standards that are used in the radiology workflow and infrastructure are discussed.

3.1 Clinical decision support systems

3.1.1 OVERVIEW OF CLINICAL DECISION SUPPORT SYSTEMS

Many different innovations are pushed to the sector in order to improve patient care, reduce cost or to make healthcare more efficient. One of these innovations are CDSS. CDSS are "computer systems designed to impact clinician decision making about individual patients at the point in time that these decisions are made" [5]. At first, CDSS was created to simulate the clinician's decision making. However, current CDSS focus on assisting the clinician's decision making. The system is expected to provide information for the user, rather than to come up with a decisive recommendation/answer that cannot be overruled [12].

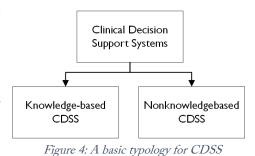
CDSS, in any domain or application, have several shared characteristics [30]:

- 1. The general aim of CDSS can be one or both of the following:
 - a. To make data more readily available for, or easier to asses by a human.
 - b. To create optimal problem-solving, decision-making and action capabilities for a human.
- 2. The decision support is provided to a user who can be any stakeholder in the clinical environment (from clinician to patient).
- 3. A primary task of the system is to select knowledge that is pertinent, or to process data to create pertinent knowledge.
- 4. The selection of knowledge and processing of data requires the carrying out of some inferencing process, algorithm or association method.
- 5. The result of the CDSS is to perform some action, usually to make a recommendation.

Many taxonomies for CDSS have been proposed that scope the CDSS field and classify observable instances of CDSS. Berlin et al. [31] describe CDSS using five dimensions: context of use, knowledge and data sources, nature of decision support offered, information delivery, and workflow impact. The context describes the setting, objectives and other contextual factors of the system. The knowledge and data source dimension look at the sources that are made available for the CDSS. The nature of decision support category looks at the reasoning aspect of the system. Information delivery focuses on the data formats that are used in the delivery of information. The final category workflow relates the systems to the actors that are involved with the system. This taxonomy greatly focuses on functionalities of the CDSS and can provide insight into the design and intent of the CDSS. Osherhoff et al. [32] provide a prescriptive taxonomy that lays out clinical decision support methods: documentation forms/templates, relevant data display, order creation facilitators, time-based checking and protocol/pathway support, reference information and guidance, and reactive alerts and reminders. It is a useful taxonomy to use when determining a method of intervention for a particular problem. It does however not provide guidance for the design and implementation of these systems. Perrealt and Metzger [33] classify CDSS along a number of dimensions. They can differ among themselves in the timing at which they provide support; before, during or after the clinical decision is made (in the latter case, we will not classify it as a CDSS). Also, they differ in support: active (providing alerts autonomously) or passive (reacting to the physician input). They can provide general or specialty-based information and finally, they differ in their ease of use. In general, this is a taxonomy focusing on the functionalities of CDSS. Other taxonomies are created for special types of CDSS like computerized physician order entry (CPOE) systems [34] or rule-based CDSS [35].

Another categorization framework is whether the CDSS is knowledge-based or nonknowledge-based [12] (Figure 4). Knowledge-based decision support systems arose out of earlier expert systems research and exist of three parts: the knowledge base, the inference or reasoning engine and a mechanism to communicate with the user [12]. The knowledge base is made up of vast amounts of information that

are often in the form of if-then rules. The inference or reasoning engine is used to combine the rules or associations with patient data using formulas. Finally, the communication mechanisms present the output of the system in some way to the user. Often, this is computer-based. These systems are often found in electronic health records (EHRs) or computerized physician order entry (CPOE) systems.



Nonknowledge-based systems use a form of AI to learn from

past experiences and recognize patterns in clinical data. Forms of AI include Artificial Neural Networks (ANN) and genetic algorithms. In terms of structure, they show some resemblance to knowledge-based CDSS, but instead of having a knowledge base, a model analyzes patterns in the patient's data to create knowledge. Thus, the knowledge does not have to made explicit to the system. It learns from examples when supplied with known results for a large amount of data. Section 3.2 discusses how this is done. Artificial neural networks can be applied to diagnosis, imaging, analysis of wave forms, outcome prediction, identification of pathological specimens and clinical pharmacology [36].

Apart from the classification between knowledge-based and nonknowledge-based, the taxonomies described in this section do not provide the level of abstraction needed to create a reference architecture for integration of these systems into workflow and infrastructure. Overall, the issue with these taxonomies is that they focus on classifying empirically observable instances of CDSS instead of describing ideal types [37]. Using one of these taxonomies as a way of classifying the CDSS in this research will lead to a point solution instead of generalizable knowledge. Typologies do provide this level of abstraction as its dimensions represent concepts rather than empirical cases. It can then separate a given set of items along these dimensions [37]. Therefore, chapter 4 will propose one.

3.1.2 CDSS IMPLEMENTATION CHALLENGES

The reported effects on practitioner performance due to clinical decision support systems are positive as stated by meta-analysis studies [7] [8] [10] [11]. These studies also state that there is an indication that patient outcome is improved as well, but this needs to be further researched. Despite these positive effects, implementation of these systems is still limited. Many challenges have been identified that contribute to the limited uptake of this technology. Table 1 shows the challenges as they are described in the literature. All of them are related to CDSS in the broad definition of the concept (as introduced in section 3.4.1). These challenges might not all be directly relevant to the type of CDSS in this research, but they are valuable to mention to ensure awareness of these challenges when integrating such a type of CDSS. They can also provide a starting point for the requirements for such a system as some challenges discuss desirable functionalities. Developing a good understanding of all obstacles will help in developing an effective solution [38]. In total, 27 papers that focused primarily on the effects or barriers of CDSS use and implementation were used to identify 26 challenges. In all papers combined, 76 challenges were discussed and there was thus overlap between the papers. The most discussed challenges were mentioned six times. The least discussed challenges were mentioned once. Challenges that are mentioned an equal amount of times are ordered randomly.

#	Challenge	Mentioned
		by
1	Systems causing a disruption in the regular workflow which leads to physicians	[14] [13]
	having to spend more time and be less efficient when working with the system	[16] [17]
		[18] [19]
2	Lack of integration into existing systems and architectures which results in	[12] [17]
	many problems relating to governance, management, availability, data	[20] [21]
	interoperability and efficiency.	[22] [23]

Table 1: Challenges related to the implementation of CDSS

3	Physicians having a high regard of their own skill or having experience with	[13] [19]
	faulty/imperfect systems resulting in distrust or disagreement with the	[22] [23]
	recommendations of systems (patients perceive this distrust in the system as well).	[39] [40]
4	Inadequate training of staff leading to misunderstanding or misuse of the	[13] [16]
	system.	[17] [39]
		[41] [42]
5	Lack of deep knowledge of the domain (resulting among other things in the	[14] [17]
	lack of prioritization of important topics and wrong conclusions in data). This	[22] [43]
	produces faulty/imperfect systems	[44]
6	Due to a lack of integration into systems and workflow (specifically to the	[12] [13]
	order entry system), physicians are sometimes required to input data twice.	[22] [23]
	This double data entry is cumbersome and inefficient.	
7	The place, time and content of notifications and recommendations is often not	[12] [14]
	optimal. This gives rise to problems like alert fatigue and information overload	[23] [41]
8	Physicians fear of computer competition and a loss of decision autonomy	[13] [23]
		[40] [42]
9	The lack of availability of adequate computer and peripheral devices and IT	[18] [19]
	skills	[23] [40]
10	Issues regarding liability where it is unclear who is responsible in case of a	[22] [23]
	wrong decision	[45]
11	Many systems score low on user friendliness	[14] [13] [40]
12	The improvement of patient outcome due to CDSS in diagnostics is not	[7] [8] [10]
	convincingly positive and remains understudied	[11]
13	Difficulties in maintaining an algorithm/knowledge base	[23] [43]
14	Lack of robustness and flexibility when facing an altered problem	[13] [44]
15	Ethical issues regarding care standards, appropriate use and users and	[23] [45]
	professional relationships	
16	The fear of automation bias where physicians will blindly trust the outcome of	[46] [47]
	a computerized system instead of their own decision	
17	Lack of best practices in design, development and implementation of CDSS	[14] [15]
18	No standards in vocabulary among physicians and therefore CDSS which leads	[12] [22]
	to wrong use of recommendations	
19	Inability to accurately explain why a system makes a certain recommendation.	[17] [44]
	This black-box contributes to the distrust in the system and makes it hard for a	
	clinician to account for his choices to himself and the patient.	F 7
20	Shifting or eliminating people in a critical process without the proper	[41]
<u> </u>	substitutions in place	F4 (1
21	CDSS cost too much	[16]
22	Lack of existing systems to integrate into (mainly the case in	[16]
~~~	underdevelopment environments)	[40]
23	Concerns about privacy and security of full text notes	[13]
24	No utilizations of freetext in the CDSS	[14]
25	Difficulties in acquiring, organizing and utilizing large clinical datasets	[14]
26	Difficulties in communicating an outcome to the patient	[18]

Successful implementation of a CDSS is thus rare [12] - [14]. Identifying and overcoming the challenges mentioned in Table 1 can lower or remove barriers for implementation. Other research has added to this notion by specifying additional factors for design and implementation that can increase success. Research by Kawamoto et al. [48] that reviewed the success of CDSS in randomized controlled trials

showed a number of features that are deemed critical to the success of a system. These features were (other than solving the challenges of Table 1):

- 1. The provision that prompt the clinician to record a reason when not following the advised course of action.
- 2. The provision of a recommendation instead of just an assessment.

3. The provision of decision support at the time and location of decision making.

Roshanov et al. [49] adds that:

- 4. Providing the advice of a CDSS to both physician and patient can increase success. This is possibly due to the involvement of the patient in their own care.
- 5. The number of alerts presented to a physician should be limited.

Bates et al. [50] adds that:

6. Speed is everything. In their research it showed that users valued this the most.

7. Monitorization of decisions and feedback from users is essential to improve the system.

Khorasani et al. [51] builds on the Bates et al. [50] research and adds that:

- 8. Sources of evidence embedded in CDSS must be diverse
- 9. Evidence must be current and up-to-date

Other research specifies guidelines and best practices for design of CDSS. Wright et al. [52] discusses eight best practices for the implementation of CDSS: deliver CDSS in the most appropriate ways, develop effective governance structures, consider use of incentives, be aware of workflow, keep content current, monitor and evaluate impact, maintain high quality data, and consider sharing content. The most notable guideline is the "CDS Five Rights Framework" [32]. These five rights describe that for a CDSS to become effective, the right information must be presented to the right people, in the right formats, through the right channels at the right points of the workflow.

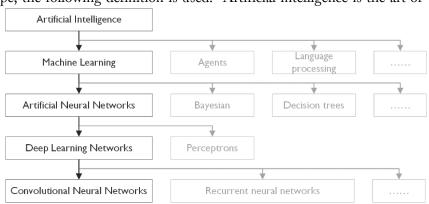
### 3.2 Nonknowledge-based techniques: Artificial intelligence

CAESAR, as introduced in the first chapter, uses artificial intelligence to analyze the radiology images. To assess how this technique works and contributes to decision support it is discussed in this section.

#### 3.2.1 AN OVERVIEW OF ARTIFICIAL INTELLIGENCE

Artificial intelligence (AI) could be considered one of the most promising technologies of the 21st century. While the root of the field lies in the early 40s, it has experienced many breakthroughs recently due to a vast increase in available data and computing power [3] [12]. The field is incredibly large with potential implications in many sector, but this means that a definition is hard to provide. Artificial intelligence research sets out in many different directions ranging from making efforts to creating computers with minds in the full and literal sense [53] to studying computations that make it possible to perceive, reason and act in a rational way [54]. In this research however, we are interested in AI that can perform a task that a human can do; namely, the collection and analysis of evidence needed to make a medical decision. In that scope, the following definition is used: "Artificial intelligence is the art of

creating machines that perform functions that require intelligence when performed by people." [2]. There are numerous ways to create artificial intelligence (Figure 5). One technique that is specialized in recognition is machine learning. Machine learning allows a computer to adapt to new circumstances and to detect and extrapolate





patterns in order to perform functions that require intelligence [3]. Machine learning again is a broader family that consists of multiple methods. One of these methods is artificial neural networks (ANN). A way of programming that is inspired by the biological neural networks in our brain [3]. ANNs again, can be subdivided into multiple categories primarily depending on the number of layers the network contains (more on this in Appendix E). Single-layer neural networks are often referred to as perceptrons and multi-layer networks are often referred to as deep learning networks. Deep learning allows computational models that are composed of multiple processing layers to learn representations of data with multiple levels of abstraction used to recognize and identify objects of interest [55]. Deep learning discovers intricate structure in large data sets by using the backpropagation algorithm to indicate how a system should change its internal parameters. These parameters are used to compute the representation in each layer from the representation in the previous layer. Finally, convolutional neural networks are a type of deep learning network that is often used in image recognition. Deep convolutional networks have brought about breakthroughs in processing images, video, speech and audio, whereas recurrent nets (another type of deep learning network) have shined light on sequential data such as text and speech [55]. Convolutional neural networks are a technique often used in the field of computer vision. A popular science of endowing computers or other machines with vision, or the ability to see [56]. This specific technique is used the most in CAESAR. For more information on the inner workings of ANNs (see Appendix E).

#### 3.2.2 DEVELOPING AI: DATA MINING AND KNOWLEDGE DISCOVERY PROCESS

Artificial intelligence, as shown above, merely describes a technique. The process for creating an artificial intelligence is described in the larger field of data mining and knowledge discovery. Artificial intelligence is a form of data mining as it turns a large collection of data into knowledge [57]. The data mining (DM) and knowledge discovery field has proposed numerous methodologies for the development of these systems/algorithms. CRISP-DM (cross-industry standard process for data mining) is the most well-known standard in this field and provides a sector and technique independent methodology for data mining and knowledge discovery [58]. The model is presented in a hierarchical process model comprising of four levels of abstractions (going from general to specific actions). The phases that are presented in the top level form a generic overview of tasks that have to be carried out in order to do data mining. Lower levels provide sector specific tasks. The following phases are described [58]:

- Business understanding focuses on understanding the project objectives from a business perspective. This is a managerial task.
- Data understanding focuses on activities that are used to get familiar with the data.
- Data preparation described activities that are necessary to obtain and create a final (verified) dataset from the initial raw (ad hoc) data. This task will oftentimes be performed by a human actor in the development and automatically when the system is deployed.
- Modelling focuses on applying various models that will result in the most optimal outcomes.
- In the evaluation phase, the models will be evaluated to prove their value.
- The deployment phase is concerned with activities necessary to deliver the result to the end user.

### 3.3 Using AI in clinical decision support

Baxt et al. [36] described the applications of artificial neural networks in clinical decision support systems. Diagnosis, imaging, analysis of wave forms, outcome prediction, identification of pathological specimens and clinical pharmacology are all possibly valuable fields to implement CDSS powered by ANN. In a more structured way, there are three general categories of application for neural networks in medical decision support [59]:

- Tools for attention focusing
- Patient-specific assessments and advice (the application in this research)
- Interactive tools for critiquing and planning.

To assess why ANN is a good tool to use in CDSS, it is discussed from three different perspectives: solutions to major causes of medical errors, evidence from meta-analysis and common sense.

### SOLUTIONS TO MAJOR CAUSES OF MEDICAL ERRORS

ANNs provide solutions to three major causes of medical error [60]:

- There is a huge amount of available information to use in decision making. In medical image assessment, this is represented not only through what is seen on one image, but on every image of that patient and all other patients that have similar images.
- The human mind has limitations regarding analysis, evaluation and summarizing of a complex problem. In medical image assessment, by for instance recognizing what the different structures are, the classification of their function and threat and the decision on what treatment should be applied.
- The uncertainty surrounding the decision. In this case, uncertainty arises about for instance the effects of treatments.

ANNs are specialized in solving problems that satisfy the above criteria of information, complexity and uncertainty. Following the guidelines for the specification of the appropriate artificial intelligence technique in CDSS specified by Aljaaf et al. [60] again confirms that ANN indeed is the best technique to utilize for this case.

#### **EVIDENCE FROM META-ANALYSIS**

In addition to the meta-analysis of Garg et al. [7], Hunt et al. [8], Jaspers et al. [10] and Johnston et al. [11] who have shown that CDSS as a whole improve practitioner performance, a meta-analysis of Lisboa [9] stated that artificially intelligent CDSS are advised to be used in a clinical supporting role. This is based on evidence that they improve practitioner performance. Unfortunately, not by direct evaluation of changes in patient outcome (more research needs to be done into this). This at least shows that ANN in CDSS proves to be worthwhile for the right applications.

#### COMMON SENSE

Combining what is stated in section 3.1 & 3.2 it makes sense that ANN is used in the case of this research. Clinicians often base their decisions on what is shown to them through medical imaging. ANN has shown that it does a very good job at recognizing and classifying object in images and since the aim of a CDSS is to impact clinical decision making of clinicians, ANN is a useful tool to utilize. Being able to automatically and autonomously recognize and classify anomalies from medical imaging would tremendously help a clinician's decision-making process and would limit the amount of medical errors.

In conclusion, it is clear that ANN and AI in general is a useful technique to use in CDSS. Not only due to the functionalities that ANN provides to CDSS, but also due to the proven positive effects on practitioner performance and indicative improvement in patient care.

### 3.4 The primary care process and medical decisions

With the perspective of the CDSS discussed, the context in which the CDSS must be integrated is analyzed now. To understand which decisions the CDSS will support, the processes that contain these decisions need to be discussed. Therefore, the primary care process and the therapeutic cycle within this process is discussed. This also provides a very general overview of the current workflow in hospitals.

#### 3.4.1 THE PRIMARY CARE PROCESS FOR ONCOLOGY

The title of this section suggests that the process discusses the process for oncology specifically. It does not mean that the process is very different from other primary care processes. It is just the relevant process for this research as CAESAR focuses on patients with colorectal liver metastases. To accurately describe the primary care process, guidelines for oncology are used.

The process can be subdivided into four general phases: referral, diagnostics, treatment and aftercare (according to the guidelines¹).

- Referral. The process starts with a patient visiting a general practitioner (GP) for a regular consult or with some complaints. When the GP thinks that further research is needed to determine what is happening to the patient, he/she refers the patient to a specialist in the hospital.
- Diagnosing. The specialist at the hospital starts the process of diagnosing. The main question is: what complication does this patient have and how does this effect his quality of life? This might require all kinds of examinations. Examples of frequently used examinations are medical imaging, pathological research, historical features of the patient, consultation (speaking to a patient) and physical examination. Based on the evidence that this yield, a specialist can determine a diagnose on the spot (during a consultation) or in a multi-disciplinary meeting (an MDO in Dutch).
- Treatment. Of course, the diagnosis has tremendous impact on the treatment that will be prescribed to the patient and is used as the main input for the decision of prescribed treatment. Guidelines that are created and authorized by the occupational group describe possible treatments that could be effective given a certain diagnosis. Oftentimes, a group of specialists determine the most suitable treatment from those guidelines or from most recent studies (again at an MDO). Prescribed treatment has one of two goals: curative treatment focuses on healing the patient and palliative treatment focuses on the principle "for as long and well as possible". During treatment, these specialists constantly monitor the effect of the treatment. In general, they have three options: continue with the treatment, alter the treatment or stop the treatment. Together with the diagnosis step, this is called the therapeutic cycle: a cycle of constantly determining the as-is situation and deciding on what the treatment decision should be.
- Aftercare. When the treatment is done, the patient will be monitored and examined for a period of time. If a former cancer patient has been free from the cancer that once afflicted him/her for five years, then the patient is cured. The intervals between examinations will slowly increase when the five-year mark draws near.

#### 3.4.2 A PROCESS MODEL FOR THE PRIMARY CARE PROCESS

The primary care process can be translated to a process model for every department in every Dutch hospital. This claim is supported by the ZiRA (Ziekenhuis Referentie Architectuur)²: a collection of models for the design of the organization and information utilities in Dutch hospitals. Their primary care process spans across all departments and thus supports the claim that this process can be modelled universally. From the guidelines for oncology and the ZiRA Figure 6 follows.

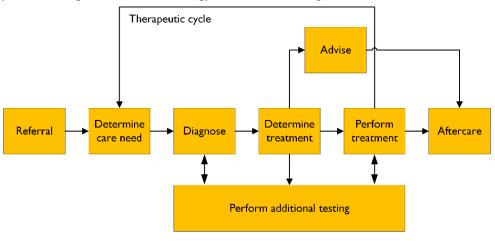


Figure 6: The primary care process in Dutch hospitals

¹ https://www.oncoline.nl/colorectaalcarcinoom

² https://www.nictiz.nl/standaardisatie/referentiedomeinenmodellen/zira/

#### 3.4.3 TYPES OF MECIAL DECISIONS

Disregarding all decisions that are not of a clinical nature (like logistics, planning or finance), the following four types of clinical decisions follow from the discussion in this section:

- Referral. Where the main question is: do I need to refer this patient to a specialist?
- Determining care need. Where the main question is: what does the patient need?
- Diagnose. Where the main question is: what is the diagnosis (or current situation in later cycles)? In the first cycle, this leads to a medical diagnosis of the illness.
- Treatment. Where the main question is: what is the best treatment to apply? In the first cycle, this leads to the creation of a whole treatment plan. In later cycles, it boils down to one of three decisions: continue the treatment, adjust the treatment or stop the treatment.

## 3.5 Medical decision making

Zooming in on each of these medical decisions, it is possible to dissect the process of decision-making itself. Clinicians are trained to make these difficult medical decisions based on the data that is presented to them. To understand the way in which CDSS will have an impact on medical decision making, the process and reasoning behind decision making itself needs to be fully understood. This understanding will help in determining what steps in the medical reasoning process will be supported, automated or optimized by a CDSS.

When asking a clinician: "How do you make a medical diagnosis?", he will often speak of the following aspects. "First, I obtain the case facts from the patient's history, physical examination, and laboratory tests. Second, I evaluate the relative importance of the different signs and symptoms. Third, to make a differential diagnosis I list all the diseases which the specific case can reasonably resemble. Then I exclude one disease after another from the list until it becomes apparent that the case can be fitted into a definite disease category, or that it may be one of several possible diseases, or else that its exact nature cannot be determined." [61]. This process is extensively researched in the field of psychology where it is part of the larger field of decision-making. Many models have been considered to capture the essence and steps that constitutes decision-making. Models presented by Janis and Mann [62] and Guo [63] show such models (the latter specifically for healthcare managers). Although there are some differences in choice of words and number of steps, they all boil down to the same application of logic (Figure 7):

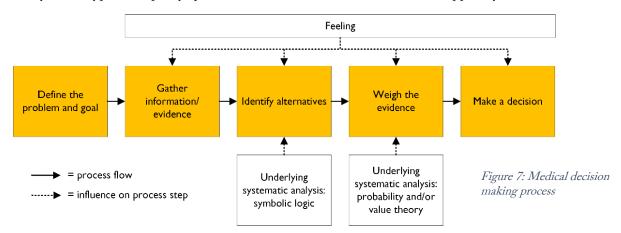
- 1. Define the problem and the goal for the decision. E.g. a patient is ill and must be diagnosed.
- 2. Gather information/evidence. Collect symptoms of the patient.
- 3. Identify alternatives. Determine the possible diseases that might be linked to the symptoms.
- 4. Weigh the evidence. Link the diseases to the symptoms and determine the likelihood of each disease or disease group being prevalent in the patient.
- 5. Make a decision. Identify the most likely disease among all alternatives and either diagnose the patient or go back to step 2.

To further rationalize this decision-making process, one needs to realize that the statements made earlier are still a simplified version of reality. One thing that is missing from this explanation is the "feeling" of the clinician. An intangible aspect consisting of relations between data, facial expressions, own thoughts and experiences, reliability of the patient and so forth. Medical decision making thus involves processes that can be systematically analyzed, as well as those characterized as "intangible" [61]. The hypothesis stating that parts of decision making can be systematically analyzed is vital for the earliest assumptions that computers can aid in this process (Ledley and Lusted already hypothesized this in 1959). Computers (especially in the 40's and 50's) work very systematically and could therefore only aid in the process if some of the steps in decision making thus provides an insight into what computer systems should do to aid in decision making. There are three well-known mathematical disciplines that can be used best to describe the reasoning foundations in medical decision-making that can be systematically analyzed: symbolic logic, probability and value theory [61]. Symbolic logic shows the importance of considering combinations of symptoms or symptoms complexes in conjunction with combinations of diseases or disease complexes. These symptoms and diseases are rarely treated on its own. Probabilistic concepts are necessary to express the uncertainty that is involved with every medical decision. Value theory depicts the decision that a clinician has to make regarding a choice of treatment so that it maximizes the chance of curing the patient given the ethical, social, economic, and moral constraints of the environment.

Logical concepts are mostly used in step 3 of the decision-making process in diagnosis, since it identifies the possible linkage between the symptoms (evidence) and the disease complexes (alternatives). In treatment choice it depicts the linkage between diagnosis (evidence) and the treatment options (alternatives). Logical statements provide conclusive statements such as "If a patient has symptom x, then he must have disease y." Unfortunately, in medical decision making, this conclusiveness is often not present. Probability or chance is a tremendously important concept in medicine as in many cases the previous statement would say: "If a patient has symptom x, there is a probability p that the patient has disease y." Since this is so often the case in medicine, probability concepts are essential. These concepts can be used to weigh evidence in step 4 of the decision-making process.

After a diagnosis has been established, the clinician must further decide upon the treatment. There are one of two options here: the choice of treatment is crystal-clear due to the straightforward application of the currently accepted options or the choice of treatment involves an assessment of a complicated set of variables (not only including the diagnosed disease). To approach the latter type of problems, value theory can be used. This concept allows outcomes of problems to be maximized towards a certain measure (e.d. chance of curing or quality of life). Of the many forms of value theory, game theory is most used and well-known [64]. Again, these concepts are used in step 4 of the decision-making process.

From this analysis, it is clear that decision-making is an activity that can, in part, be systematically analyzed. Since it can be systematically analyzed, computers can, in theory, provide support for this activity. This hypothesis partly sparked the innovation of clinical decision support systems.



## 3.6 Standards in radiology: HL7, DICOM AND IHE

The general workflow of the primary care process describes the decisions that a clinician has to make. It however cannot provide the level of detail needed to model every activity that is necessary to design the integration of a CDSS. Numerous international standards exist who do provide this detail. It can be used to model a generalizable workflow for any radiology department who complies to these standards.

Three relevant standards for radiology are:

- DICOM (Digital Imaging and Communication in Medicine) is the standard for the communication and management of medical imaging information related data [65].
- HL7 (Health Level 7) messaging provides a set of international standards for transfer of clinical and administrative data between software applications used by various healthcare providers [66].
- IHE (Integrating the Healthcare Enterprise). An initiative by healthcare professionals and industry to improve the way computer systems in healthcare share information and support workflows [67]. IHE promotes the coordinated use of established standards such as DICOM and HL7 to address specific clinical needs in support of optimal patient care. It provides a way of organizing HL7 and DICOM into department specific integration profiles. These profiles present detailed workflows for common use cases.

Many hospitals (including the Amsterdam UMC) use HL7 along with DICOM [68] according to the IHE profiles and this compliance proves to be critical to the success of CDSS development [20].

#### 3.6.1 HL7

In the HL7 standard, there are three most important messages relevant to the research [66]:

- Admit, Discharge, Transfer (ADT) carry patient demographic information for HL7 communications but also provide important information about trigger events (such as patient admit, discharge, transfer, registration etc.).
- Order messages (ORM) functions as a general order message that is used to transmit information about an order.
- Observation Result Unsolicited (ORU) messages transmit observations and results from producing systems to the ordering system or a medical record archive. It is used to communicate text, numbers and codes (no images) and can store many types of results.

#### 3.6.2 DICOM

The DICOM standard provides a data format for imaging, operations for data management and an information model for data storage [65]. There are two operation types that are relevant for this research:

- Composite operations (abbreviated by C-...) are independent operations that can exist without reference to other operations. Composite operations like C-STORE allow a client to push data to a server, where C-FIND for instance is a query service.
- Normalized operations (abbreviated by N-...) are simple database operations. For instance, N-CREATE creates a dataset within the server and N-SET updates a single dataset.

DICOM specifies an information model that structures the way in which imaging and accompanying data structures (like reports and evidence) are stored into studies. These structures allow for the standardized storage and usage of imaging studies. The structure within this information model is the following (Figure 8). The top layer is the patient. This patient has one or more studies it that hold relevant insights. Numerous attached to verified departments/entities within the hospital can add studies to a patient that contain information about interventions and examinations that the patient has undergone. These studies are ordered by clinicians and have a worldwide unique Study Instance UID. In radiology, these studies contain one or more series (with a Series Instance UID). These series in turn, act as a container that aggregates zero or more objects (regarded as evidence) with an SOP Instance UID. These objects can be images, raw data, presentation states, structured report (SR) documents etc. This information structure is often used in the Healthcare Information Systems (HIS). The IHE profiles describe this in detail.

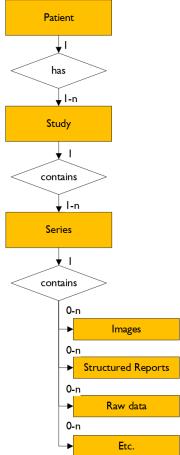


Figure 8: Snippet of the real-world information model of the DICOM standard

#### 3.6.3 IHE

Lastly, the IHE integration profiles provides workflows, generalizable systems and transactions between systems in the radiology department. The following systems can be identified (Figure 9). Healthcare Information Systems (HIS) is a computer system that can manage all the information to allow health care providers to do their jobs effectively. It focuses mainly on centralizing all administrational needs for a hospital and provides a central access points for clinicians to access patient health information and history at the place and time that it is needed. It is here that the radiology department can add details on an examination to a patient in the form of a study (following the DICOM information model). Therefore, it is a vital backbone for the hospital. Oftentimes these systems are called electronic health records (EHRs). The system consists of three important actors that provide a specific function for the radiology department. First, the admit-discharge-transfer actor provides the ability to create a new patient when one presents itself or to update patient demographics information. Second, the order placer allows clinicians to generate and distribute orders. Third, the enterprise report repository stores structured reports so that they can be used by clinicians during decision making.

Then, Radiology Information Systems (RIS) are a specialized form of HIS and they provide specialized administrational functionalities for the radiology department. In this RIS, an order filler manages the orders performed by the radiology department. Also, a reporting manager asserts control over the process of creating reports for examinations.

A Picture Archiving and Communications System (PACS) is a specialized HIS as well and, as the name suggests, allows for the radiology department to long-term store imaging-related data in an image archive. The image manager in this system asserts control over the storing and distribution of these images. The post-processing manager in turn asserts control over the process of post-processing and evidence creation for these images.

A modality is any machine that is capable of creating imagery.

Finally, the radiology workstations are specialized work environments for radiologists and are tailored to the specific needs of an individual radiologist. The image display retrieves and displays images on this workstation whilst the evidence creator can create additional evidence objects by post-processing raw imaging data.

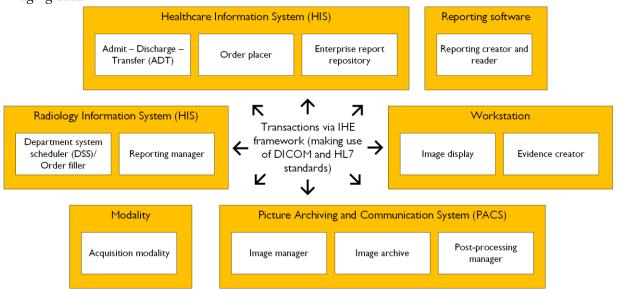


Figure 9: All systems and components in the radiology profile of the IHE

The IHE integration profiles [67] show how these systems interact and integrate with each other by specifying the workflow and transactions in which they participate. Three workflows are relevant to this research as they depict the entire perfect workflow from ordering an examination to delivering insights based on this examination:

- The scheduled workflow establishes the continuity and integrity of basic departmental imaging data acquired in an environment where examinations are generally being ordered. It specifies a number of transactions that maintain the consistency of patient and ordering information as well as defining the scheduling and imaging acquisition procedure steps.
- The post-processing workflow addresses the need to schedule, distribute and track the status of typical post-processing workflow steps, such as image processing. It also ensures the delivery and storage of evidence (new images based on raw imagery) that is created in this workflow.
- The reporting workflow addresses the need to schedule, distribute and track the status of the reporting workflow tasks such as interpretation, transcription and verification. It also ensures allows for the delivery and storage of reports (insights) that are created in this workflow.

In these workflows, the interaction is specified by transactions that make use of HL7 and DICOM semantics. The overview of Figure 10 shows all transactions relevant to the radiology department. This overview provides a combination of all transactions in the three workflows and provides a valuable helicopter view that can later be used to model the integration between the CDSS and this environment. At this moment, not every transaction is discussed in detail as this will be done in the modelling of the current situation in section 5.1.

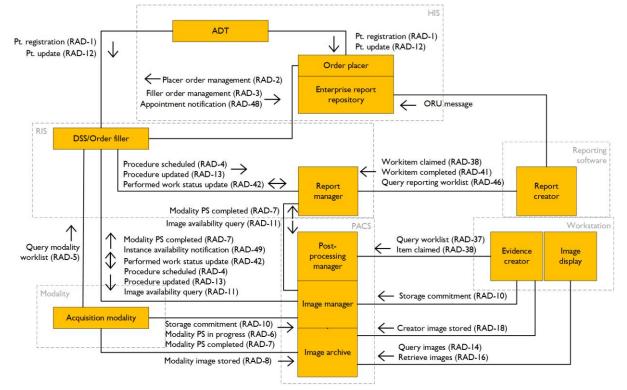


Figure 10: Overview of transactions between system components in radiology according to the IHE

The combination of systems, organized in workflow profiles, using transactions and information models based on DICOM and HL7 allow a radiology department to order, schedule, protocolize, execute, post-process, assess, store and present a medical image examination.



# 4 A typology for CDSS

With the related work on medical decision making, clinical decision support systems and artificial intelligence discussed, attention is shifted towards the artifact for which the reference architecture will be created. Given the vagueness and lack of typologies, CDSS implementation is still a very broad term and related work has shown that there are many places (in a process) where a CDSS can have impact. To apply focus to this implementation effort, specify the artifact in this research and broaden the range of cases for which the architecture can be used, a typology is created. This typology is built upon two dimensions: the impact on the medical decision-making process and the type of data input and underlying technology. The former dimension is a combination of the decision-making process and therapeutic cycle in the primary care process. The latter is an existing dimension drawn from the typology by Berner[12]. The term nonknowledge-based CDSS for treatment evidence analysis is coined to describe the object of study in this research. This chapter presents the typology and underpins the term and introduces a concrete example in the form of CAESAR.

# 4.1 Applying focus to the field of implementation

CDSS come in many different shapes and forms. Given the vast differences in their technology, functionality and impact on healthcare, this research does not believe that people and organizations can speak of "the implementation of CDSS" as a whole. An analysis of the primary care process and medical decision making have shown that there are many places where a CDSS can have impact. Attempting to create a reference architecture supporting all types of CDSS would either result in a vague architecture or a complex and messy architecture containing many if's and but's to account for all different configurations of CDSS. Clinical decision support, as demonstrated by the literature, feels like an umbrella term that collects every system that shows the characteristics provided by Greenes [30]. To be clear, this works perfectly well when clinicians and other stakeholders discuss systems that help them in their decision making. It is however too vague and insufficient when one discusses the implementation of these systems. Therefore, an effort is made to define a typology that allows for the classification of CAESAR. This enables the creation of a reference architecture and generalizable knowledge for a type of CDSS. The typology consists of two dimensions. One drawn from the framework of Berner [12] showing the nature of the data and analysis in the system (the input). The other dimension drawn from a combination of numerous fields showing the impact on the process and context (the output). To determine the latter dimension for the typology of CDSS, two candidate dimensions are assessed: the impact in the medical decision-making process and the impact in the therapeutic cycle of the primary care process. It is claimed that these two can be combined to create the second dimension. With these two dimensions, it is claimed that every CDSS in the therapeutic cycle can be accurately classified.

#### 4.1.1 METHOD FOR DEVELOPING A TYPOLOGY

This research creates a typology for CDSS in the therapeutic cycle (thus excluding some of the other decisions in the primary care process) for the sake of precision and clarity. Drawing inspiration from the architectural layers in an enterprise architecture [28], it is claimed that the typology should be able to provide an answer to four questions (one for each layer). The questions are (together with architectural link):

- 1. What is the goal of the system? (Links to motivation)
- 2. What is the impact on the process? (Links to process)
- 3. What are the techniques that will be used? (Links to application)
- 4. What data input does it require? (Links to technology)

The proposed typology uses two dimensions to provide an answer to these questions.

# 4.2 Dimension I: knowledge-based vs. nonknowledge-based

Berner [12] proposes a simple typology for clinical decision support systems. A CDSS is knowledgebased or nonknowledge-based. Despite the simplicity, it does tell a lot about the system. It shows the fundamental differences in techniques that the system uses. A knowledge-based CDSS uses techniques based on a rule-based or inference engine and is therefore used for structured data. A nonknowledgebased CDSS uses techniques based on artificial intelligence (mainly artificial neural networks) and can therefore also use unstructured data. This fundamental difference impacts the integration of systems since it specifies the required input of the CDSS. These distinctions are necessary in the application and technology layer of the architecture (question 3 and 4).

## 4.3 Dimension II: impact on the process

The goal and impact on the process is fundamental for the integration of these systems. Two aspects are considered candidate dimensions:

- The decision-making process. This dimension is considered since it greatly shows which part of the decision-making process is optimized, replaced or supported by a CDSS. The step(s) that it impacts has major impact on the way the system has to be integrated since each step requires different technologies (a different type of analysis is needed for different steps [61]) and a different desired place for presentation of outcomes. For instance, the more a system is involved with later steps in the process (and thus more involved with the actual decision) the later it can be presented in the workflow. Values for this dimension are:
  - Define the problem and the goal for the decision.
  - Gather information/evidence.
  - Identify alternatives.
  - Weigh the evidence.
  - Make a decision.
- The primary care process. This dimension is considered since it shows what the impact of the CDSS will be on the workflow. It indicates which actors will work with the system and what type of medical decisions it supports. This dimension focuses on the process aspects that are impacted by the CDSS. Values for this dimension are:
  - o Referral
  - o Diagnosis
  - Treatment

One could argue that these two dimensions should be assessed separately. However, the dimensions overlap and one dimension can be treated as a zoomed in version of the other. Therefore, it is suggested to combine the dimensions into one dimension.

To do this, we start with the therapeutic cycle as it is described in the primary care process. This therapeutic cycle describes the cyclical process of determining the as-is situation and determining what the best course of action is to get to a to-be situation. This therapeutic cycle and the decision that are made here can be linked with the decision-making process in our brain. To determine the as-is situation, we first need to specify a goal (what is the current situation?), collect information (imaging, patient data etc.), determine the alternatives (what could be happening?), weigh the evidence and then make a decision on what is happening. We then use this current situation to determine what should be done (the problem here is: what is the best course of action?). We do this by collecting information (as-is situation, history etc.), determining alternatives (what can we do?), weighing the evidence (what do we expect will happen?) and then make a decision. In every cycle, this thought process is repeated. This connection shows that the dimensions influence each other and can be summarized into one dimension (Figure 11). This dimension indicates exactly what the impact and goal of the system is and thus allows us to answer question 1 and 2.

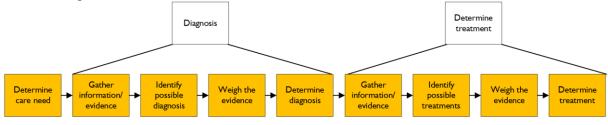
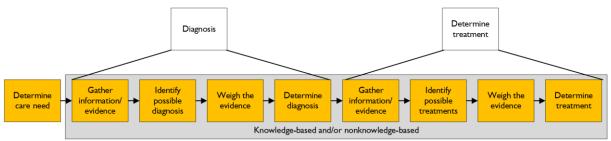


Figure 11: Linking the therapeutic cycle with the medical decision-making process

# 4.4 A typology for CDSS in the therapeutic cycle

Combining the two dimensions provides a typology for CDSS in the therapeutic cycle that indicates the input for the system, underlying technologies, impact on the process and overall goal (Figure 12). With this typology, communication about these systems is clear and by determining a specific type within this technology, a reference architecture can be created.





Some important remarks. The typology specifies that a CDSS in the therapeutic cycle can be used and placed in one of the nine process steps (depicted in orange). CDSS in total can span and support multiple steps, but the different functionalities can always be attributed to a specific process step. Also, this typology clearly shows that CDSS in general do not make the decision. Rather they provide an analysis that a clinician can use so that they can make the decision. The "support" in clinical decision support systems thus cannot be stressed enough as this is vital in ethical discussions regarding machine involvement in clinical decisions. CDSS should support clinicians, not replace them.

In terms of name giving for the types of CDSS, it is proposed to use the scheme as proposed in Figure 13. Here, the prefix in front of CDSS is the data input and analysis techniques dimension, the suffix after the CDSS shows the decision and the most advanced process step within this decision it supports (although it might also impact earlier steps) alongside the department from which it creates, gathers and analyses evidence. This naming scheme is presented to provide guidance in how one could speak about a certain type of CDSS in the therapeutic cycle.

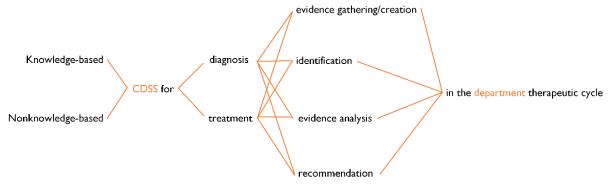


Figure 13: Guidelines for name giving of CDSS in the typology

# 4.5 An example of a CDSS in the therapeutic cycle: CAESAR

To determine the type of CDSS that is the focus of this research, the CAESAR project is explained in detail. This section builds on the general information about care processes that was provided in section 3.1.

#### 4.5.1 THE GOAL

At this point, the goal of CAESAR is to:

- Aid in selecting and assessing the best way of treatment for an individual patient (personalized medicine) and improve patient care. This is done through generating as much valuable and high-quality data and data analysis as possible from medical imaging that can be used by a clinician to decide upon. Outputs can come in the form of images or text.
- Reduce unnecessary treatment (either by minimizing the treatment or not performing it at all) in order to improve efficiency and cost reductions in healthcare.

#### 4.5.2 THE PROBLEM

CAESAR focuses solely on patient with liver metastases (an extensive analysis on this disease can be found in Appendix B). Metastases in general are an indication that a curative treatment is impossible. There is however hope for these specific patients. If the patient only has metastases in the liver (and not in any other organs), then there is a chance to cure these patients. Research has shown that if these metastases can be fully removed from the liver, the patient can be cured [69]. This can be done in two ways: local treatment (like resection) or systemic therapy followed by resection.

There are two main problems here:

- 1. Evaluating the response of a patient to systemic therapy. As will be seen later this section, the criteria for measuring this response are very basic and do not provide a fully accurate picture of current situation and the response to the chemo.
- 2. Determining whether a local treatment strategy for a metastasis is possible or not. This is tricky due to the anatomy of the liver. The liver contains 9 segments. To keep a fully functioning liver, only 2 of these segments need to be present. This is of course remarkable, but it is important to remember that these 2 segments cannot be chosen arbitrarily. The two constraints are that there must be a functioning in- and outflow of blood and that there must be a functioning bile duct. Determining whether a local treatment strategy is possible is not only subject to anatomical constraints, but also to constraints represented by the confidence of the surgeon in his/her own skills.

#### 4.5.3 THE SOLUTION

To address the two problems, SAS wants to create a system that can perform several actions. Development is divided into three phases: generate as much valuable information as possible from CT-scans, auto segment CT-scans, determine resectability using a model of the liver and advise on systemic therapy.

Phase 1. The development starts with the generation of as much valuable metastasis information as possible from CT-scans. To illustrate why this is extremely valuable, Figure 14 shows a CT-scan of a patient with liver metastases. The left image shows a situation before systemic therapy, the right one after systemic therapy. Now, clinicians assess these images according to the guidelines on roughly two criteria: are the metastases smaller and are there less metastases? For this example, it is clear: there are less metastases and they are smaller as well. The treatment works and should continue.

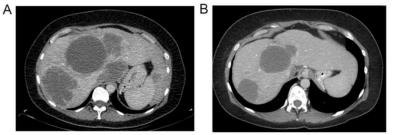


Figure 14: CT-scan treatment effect assessment of liver metastases A

In other images, this assessment is harder to perform. Figure 15 shows that the metastases are smaller but there are more metastases. However, with a bit of logic, we can see that the extra metastasis is actually a former large metastasis split in two due its shrinkage.

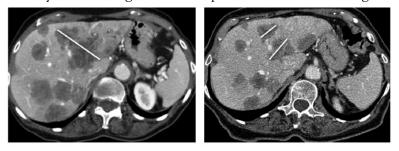


Figure 15: CT-scan treatment effect assessment of liver metastases B

Figure 16 shows that the metastases are not smaller and there are not less of them, so one might say that the treatment stabilizes the disease. However, what we do see is that the edges of the metastases are far clearer and that the greyscale within the metastases is spread evenly and this does represent some sort of progress (whether this is positive is up to the clinician). However, current guidelines do not account for these features.

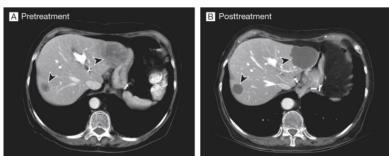


Figure 16: CT-scan treatment effect assessment of liver metastases C

These images illustrate that there are a lot of unused characteristics that cannot be used at this moment. ANN allows us to see and measure the characteristics. Adding the greyscale, volume, density, maximum diameter etc. to the list of available data can lead to a better analysis of the response to systemic therapy.

Phase 2. Once this is done, an effort is made to auto-segment the metastases, organs and other tissues from a CT-scan. The purpose for this is three-fold: 1) it removes the inter-observer variability between radiologists, 2) it gives better insight into the structure of an individual's organs and metastases and 3) it makes the process more efficient and less time-consuming. Early efforts have provided an indication of what this might look like. In Figure 17, the liver (in green) and metastases (in red) can be visualized in the x,y,z-plane and this allows for an easier assessment of 3D-characteristics.

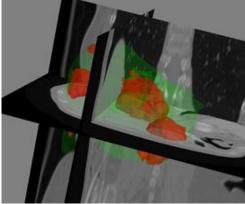


Figure 17: 3D model of a liver and metastases

Phase 3. When the system is able to provide all relevant characteristics of the liver and metastases and can model this in a 3D environment on a patient level (given the differences in anatomy), the next step will be to create a model that can determine the technical feasibility of local treatment strategies of the metastases in the liver. An AI could provide insights into this feasibility if it is presented with enough relevant data. Moreover, the AI would be better at providing an analysis of the needs and possibilities of the individual patient rather than a population of patients (like surgeons often do). This is due to the individual unique data that the AI can analyze.

# 4.6 The typology applied to CAESAR

#### 4.6.1 DIMENSION I: NONKNOWLEDGE-BASED

From the description of the project it is clear that the system will primarily use unstructured data in the form of imagery. In turn, a primary technique used for the analysis is convolutional neural networks. This technique is complemented with other AI techniques in later phases. The system is thus nonknowledge-based.

#### 4.6.2 DIMENSION II: GOAL AND IMPACT ON THE PROCESS

The overall goal of the system remains the same throughout the phases: the system aids and impacts a clinician's treatment decision. The diagnosis decision remains untouched. The impact on the decision-making process however changes throughout the phases. Starting in phase 1, the system gathers and generates evidence that can be used in decision-making. The impact is on evidence gathering. In the

second phase, the system adds to this evidence by auto-segmenting the CT-scans. This ensures a better quality of evidence (no inter-observer variability) and the ability to assess imagery in 3D. The impact doesn't change as it is still concerned with evidence gathering, it is just expanded with another functionality. The third phase introduces impact on a different step in the process. Using all the evidence that it has generated and collected, the system now starts analyzing this information to provide an analysis on local treatment strategy feasibility. The impact shifts towards "Weigh the evidence" step (although it also still impacts the "Gather evidence"-step). Note that it does not actively specify or looks for alternatives. The boundaries of alternatives are still presented by a human actor (to resect or not for instance). Figure 18 shows the places of the different phases of CAESAR in the typology.

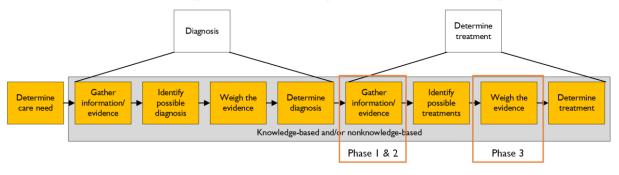


Figure 18: The typology applied to the phases of CAESAR

#### 4.6.3 CAESAR: A NONKNOWLEDGE-BASED CDSS FOR TREATMENT EVIDENCE ANALYSIS IN THE RADIOLOGY DEPARTMENT

CAESAR thus supports the gathering, creation and analysis of evidence in order to provide insights into the effect of treatment and feasibility of future treatments. It is important to remark that CAESAR does not include the actual recommendation of a treatment. It does not tell a clinician what a should do and it will definitely not make a decision autonomously. There is still a lot of debate on whether or not we can let machines decide on the way we should be treated. Whether one agrees or disagrees with this statement, it requires more of a mindset shift then a technological shift. In the current scope, evidence analysis is the most advanced step that the system will impact. Using the naming scheme and the typology we can now accurately describe the system for which the reference architecture is developed. CAESAR can be classified as a nonknowledge-based CDSS for treatment evidence analysis in the radiology department. One could argue that it should specify that the insights are used in oncology as it would have an impact on the place in which the data is used. An understandable consideration. However, it is argued that since the name already specifies that treatment decisions are supported, mentioning of the department in which these treatment decisions are made is redundant as the primary care process and location of these decisions are the same in each department (at an MDO, hospital floor and clinician office). Besides, it could be that future insights are not valuable for oncology, but for the pathology department. It is however very important to remark that the data that is being used originates from the department of radiology as each department does have a different infrastructure when it comes to data management. Building upon the definition by Weaver et al. [5], this type of CDSS is defined as:

"Nonknowledge-based CDSS for treatment evidence analysis are computer systems designed to impact a clinician's treatment decision of individual patients by analyzing evidence using nonknowledge-based mechanisms at the point in time that these decisions are made"



# 5 A reference architecture for nonknowledge-based CDSS for

# treatment evidence analysis

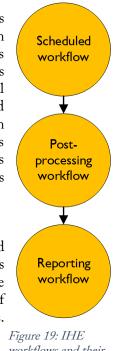
A description of the CDSS that will be integrated in the Amsterdam UMC is given in the previous section. Now, it is time to develop a reference architecture to support this integration goal. Following the TOGAF ADM, the chapter starts with defining a current situation by developing process models and an as-is architecture. Then, an analysis of the stakeholders and requirements for integration is presented. These requirements are elicited from interviews with experts as well as literature. The depiction of the current situation, stakeholders and requirements are part of the architecture vision phase (A) of the TOGAF ADM. Then, a solution is introduced that specifies a novel way of integrating the CDSS without workflow and system disruption. Using the requirements, business understanding and solution design the process models, transaction models and architecture are designed to envision a target situation. This resembles the phase B, C and D of the ADM. Finally, the total reference architecture for the integration of nonknowledge-based CDSS for treatment evidence analysis in the radiology department is presented.

#### 5.1 Current situation: the clinician's workflow and supporting infrastructure

Using the standards that were discussed in section 3.6, the current clinician's workflow and supporting infrastructure can be designed. The IHE integration profiles (Figure 19), in combination with interviews with clinicians and experts allow for the design of a detailed workflow and infrastructure. The goal of this workflow is to order, schedule, create, process, assess, store and present a medical imaging examination in order to obtain insights (in the form of evidence and reports) in a person's health status. Every single (human and machine) activity in this workflow can be modelled. By modelling every activity, every change to this workflow and infrastructure will become visible when integrating the CDSS. This section describes these workflows and supporting infrastructure in text, in process models and then in an as-is architecture.

#### 5.1.1 THE SCHEDULED WORKFLOW

The process starts when a patient presents itself at the hospital (Figure 23). Based on whether or not this patient is already known at the hospital, a patient file is created (RAD-1) or updated (RAD-12). With the updated information, the patient is referred to a clinician. This clinician will assess the patient and if necessary, order a medical imaging examination from a list of predefined protocols. The clinician uses an order placer in the HIS to do this. The HIS creates a study (according to the information model of DICOM) which triggers a process that generates ORM (order) messages towards an Order Filler (often part of a



workflows and their main activities

RIS/PACS) (RAD-2). This order filler presents the order in a worklist. A planner (human or machine) can schedule the order after a radiologist has protocolized the order (determining what procedures have to be executed). After every change, the study is updated in the image manager and the HIS via transactions (RAD-3). When the order is protocolized and scheduled, an appointment is set that is being returned to the clinician via the order placer (RAD-48). He can then notify the patient about this appointment. At the same time, the report manager and image manager are informed about the scheduled procedure so that they are aware and can prepare if necessary (RAD-4). If the procedure changes before it takes place, the order filler updates them (RAD-13). In this manner, the HIS, RIS, modality, PACS (image manager) and reporting manager are constantly aware of the latest relevant changes to the order.

The acquisition modality constantly queries the order filler so that it is aware of the procedures it must execute (RAD-5). When the patient arrives via schedule, the technologists checks whether the information provided by the patient checks out with the order and then sets up the modality according to the ordered protocol. The modality starts working on the order and creates images whilst continuously updating its status towards the order filler and the image manager and archive (RAD-6). Once it is done, the modality stores the images in the study of the image archive (RAD-8) and requests a confirmation of this storage action (RAD-10). Finally, when the status is changed to completed (RAD-7), the study is presented in the post-processing worklist where it awaits processing. The destination of these store, commit and status completed messages can be altered. After receiving the same "complete"-message, the order filler and report manager actively query the image manager to confirm and locate the presence of images for a study (RAD-11). An affirmation of this enquiry leads to the study being added to the reporting worklist in the RIS.

#### 5.1.2 THE POST-PROCESSING WORKFLOW

To start post-processing the images, the workstations can enquire about new work items it has to perform at the post-processing manager (RAD-37). If the workstation (and thus the radiologist) starts working on a work item, it is first claimed (RAD-38) and the images are retrieved from the archive using two transactions (RAD-14, RAD-16) When the images are retrieved from the archive, the radiologist can start post-processing. If the radiologist is satisfied, the new images are stored (RAD-18) in the image archive according to the DICOM standard and form an output of the examination. The workstation asks for a confirmation of the storage of these images (RAD-10).

#### 5.1.3 THE REPORTING WORKFLOW

The third step in the process is the reporting workflow. It starts when the status of the study is updated to completed by the modality as it is then presented to the reporting manager in a reporting worklist (as mentioned earlier) (RAD-7). Again, a report creator can enquire the order filler in order to retrieve work items (RAD-46). After claiming one (RAD-38), a report is created and once it is done, it is finalized in the report manager (RAD-41). To create this report, a radiologist simultaneously opens the images from the image archive so that it can use these in the assessment as well as the report creator software. When the report is finished the radiologist has to sign for the report and an ORU message is sent to a repository on the HIS in order to notify this system about the availability of a report (ORU). This is an output of the examination as well.

#### 5.1.4 ASSESSING AND DISCUSSING INSIGHTS ON A PATIENT AT AN MDO

These three workflows allow to deliver insights into the medical situation of a patient. The outcomes of such an examination are oftentimes not specifically relevant to the radiologist, but to any other clinician who has ordered the examination. Therefore, it is necessary to describe how this clinician absorbs the created insights. Since the CDSS will also develop insights for many different clinicians, it is important to be aware of this process.

Insights are absorbed and used in a clinician's office, the patient's bed or at an MDO. In the first two cases, the clinician simply assesses the outcomes of the examination in the patient file in the HIS. In case of an MDO, a more elaborate explanation is needed. When a clinician deems that it is appropriate to discuss a patient with colleagues, he/she does this at an MDO. This MDO allows for a discussion with professionals of different specializations in order to determine a next step. To achieve this goal, the clinician requests for the patient to be discussed at the MDO using an order that is created in the HIS. HIS processes this order and adds the patient to the next MDO meeting (oftentimes once a week). Other clinicians can then see that the patient will be discussed at the next MDO by looking at the overview that the HIS creates. Simultaneously, the radiologist checks this overview and determines whether every patient that will be discussed has been analyzed and thus has a report. If this is not the case, then the radiologist knows that this has to be done before the MDO. When the MDO starts, clinicians come together and discuss the patient by looking at the patient's information and imagery on two screens. One for lab results, reports, previous MDO's etc. in the HIS. One screen to assess the imagery in PACS. Both screens are opened and operated separately (see Figure 21).

#### 5.1.5 BPMN PROCESS MODELS

Using BPMN (business process model & notation) [70], the workflows are transformed into models that show chronology in all transactions and activities. This overview does not exist in the current IHE framework but is vital when determining the new workflow that is created when the CDSS is implemented. By splitting the workflows into multiple smaller segments, the following processes in radiology were designed using BPMN (Figure 20): ordering and scheduling, acquisition, post-processing, reporting and presentation, assessment and discussion of a patient at an MDO (or consultation or patient's bed).



Figure 20: Segments of the clinician's workflow (each separately modelled in a BPMN diagram)

The process models are designed from two standpoints. One standpoint provides a high-level overview of the total medical imaging examination workflow from a clinician's perspective (Figure 22). In this perspective, only the activities performed by human actors are shown. This allows for the specification of the current workflow from the clinician's perspective and this can later be used to determine the level of disruption in this process. The other perspective shows the system perspective and can be treated as a more detailed version of the first perspective (Figure 21 and 23-26). This is because this perspective, next to the human activities, also shows all system interactions (that are automated in the eyes of a clinician). In the modelling school of BPMN, the pools are often used to model a department or organization. However, this research is not interested in the departments of an organization, but rather in the system's transactions and integrations. These messages can only exist between pool in the syntax of BPMN [70]. Therefore, the pools in these models depict systems.

With this in mind the BPMN diagrams are developed. Using the validation capabilities of Microsoft Visio, the diagrams are validated against the BPMN syntax. To validate the content of the models, two clinicians (one at the Amsterdam UMC, one clinician working for SAS) and the IT coordinator for radiology (at the Amsterdam UMC) have iteratively assessed the models. The final version as presented in this thesis has been approved by them. The processes modelled in Figure 21 through 26 show how medical image examinations are ordered, scheduled, performed, stored, processed, assessed and presented and how the results are absorbed in an MDO or patient consultation (only the MDO is modelled since the patient consultation is a trivial process).

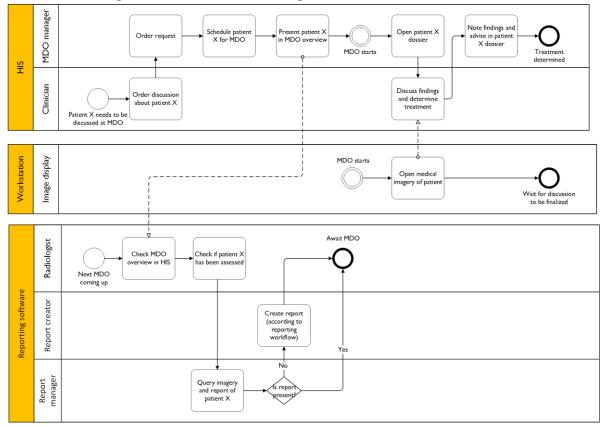


Figure 21: Process of discussing and assessing a patient at an MDO

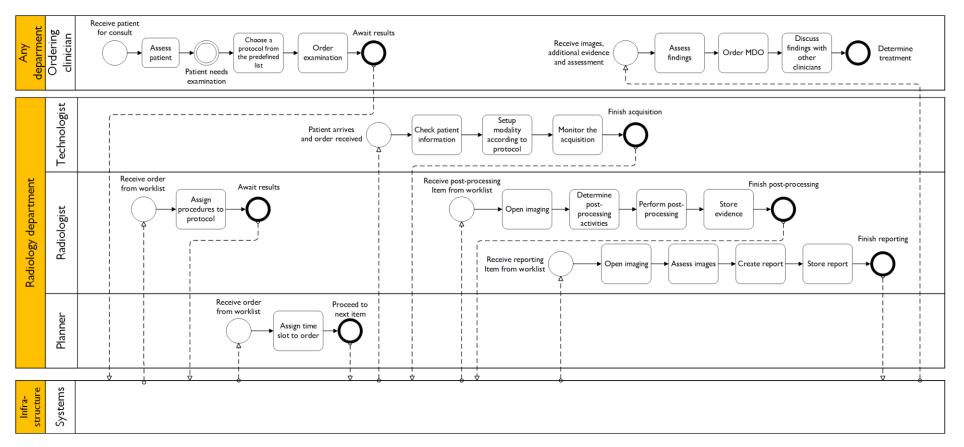
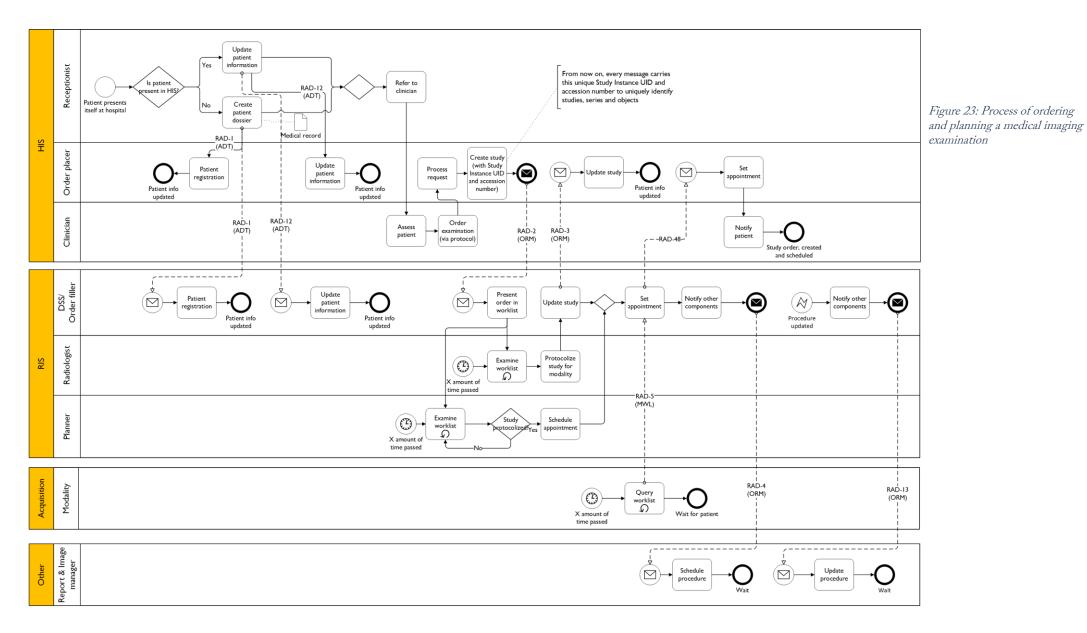


Figure 22: The clinician's workflow



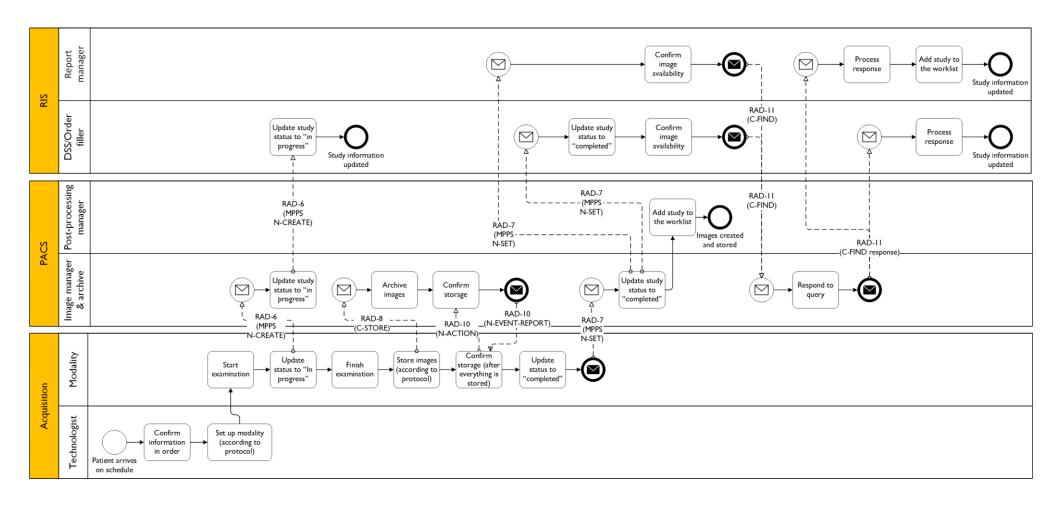


Figure 24: Process of creating medical imaging

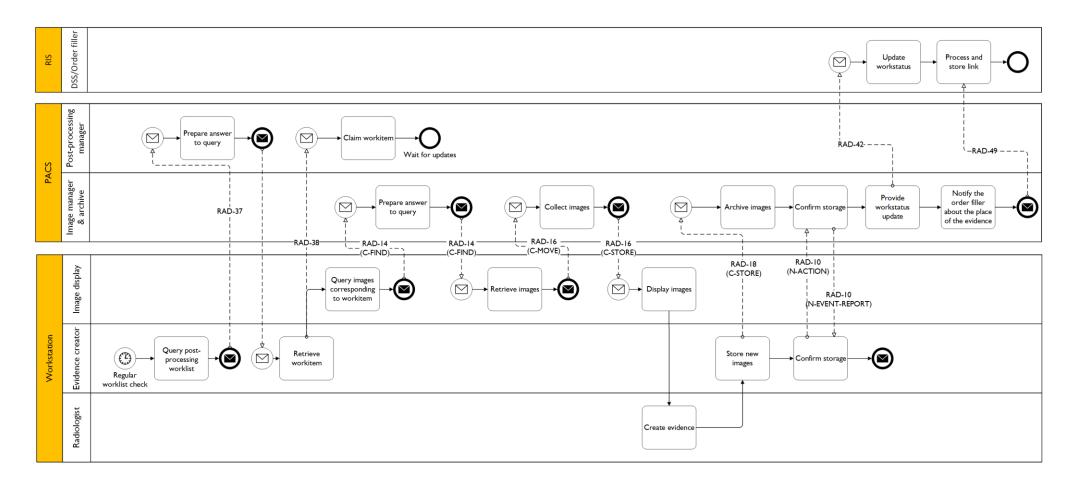


Figure 25: Process of post-processing medical imagery

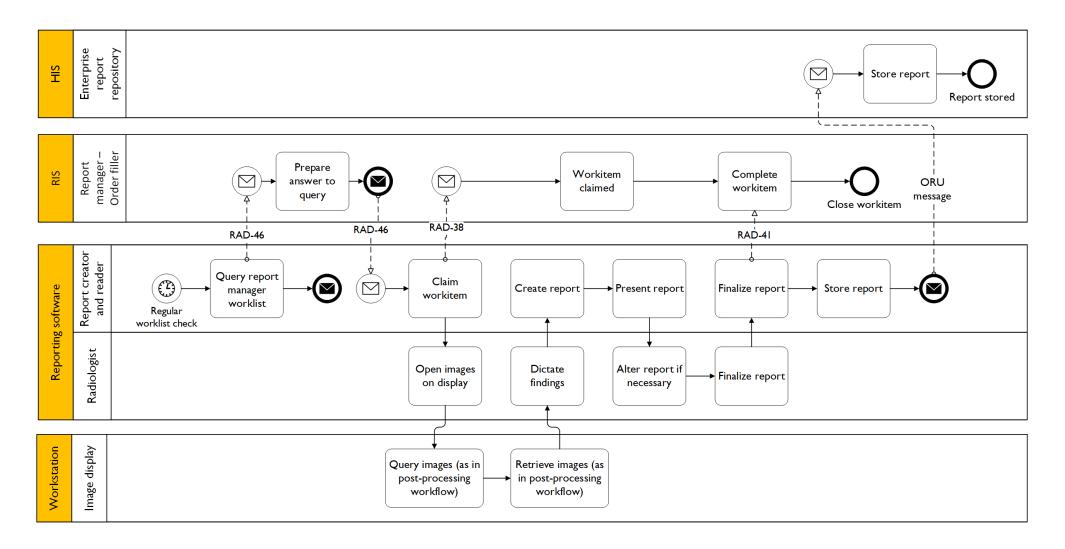
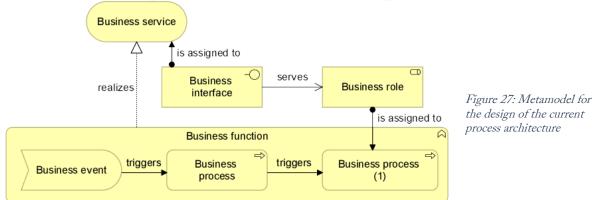


Figure 26: Process of reporting on a medical imaging examination

#### 5.1.6 THE CURRENT PROCESS LAYER

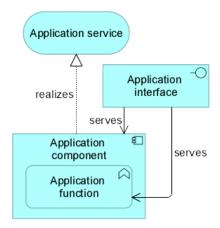
ArchiMate is used as the language for the architectures in this research. It is an industry standard and the native language that is supported by TOGAF [71] (see Appendix H). Although transforming the BPMN process models into an architecture results in the loss of chronology of activities, it does enable the connection of the process to application components and in turn infrastructure nodes. Given the tremendous detail that the BPMN process models provide about each activity in this process, in the process layer the number of steps in each process are reduced in favor of readability. Each process now provides a well-organized summary of activities that together form a business function, with business interfaces, actors and most importantly, services that are realized by the process. The process architecture uses standard modelling patterns as described in the ArchiMate specification [71] (Figure 27).



Using this design pattern, the process layer depicts the same processes as described in the BPMN process models. This thus results in five business functions: ordering and scheduling a medical image examination, performing a medical image examination, post-processing images, assessing medical imagery and determining treatment (at an MDO, consult or patient's bed).

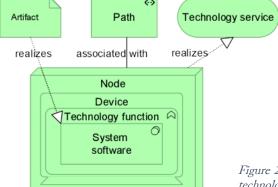
#### 5.1.7 THE CURRENT APPLICATION LAYER

The processes modelled in the previous layer are supported by services presented by an application layer. These services in turn are realized by application components. All of them have been discussed during the presentation of the BPMN models. What is however important to note (something that is not clearly visible in the BPMN models) is that the PACS software does not have an interface that directly allows for image viewing. This interface is provided by the workstations. Furthermore, the application layer explicitly shows the application functions that are provided by the components. The design pattern used to model the application layer again follows the ArchiMate specification [71] (Figure 28).



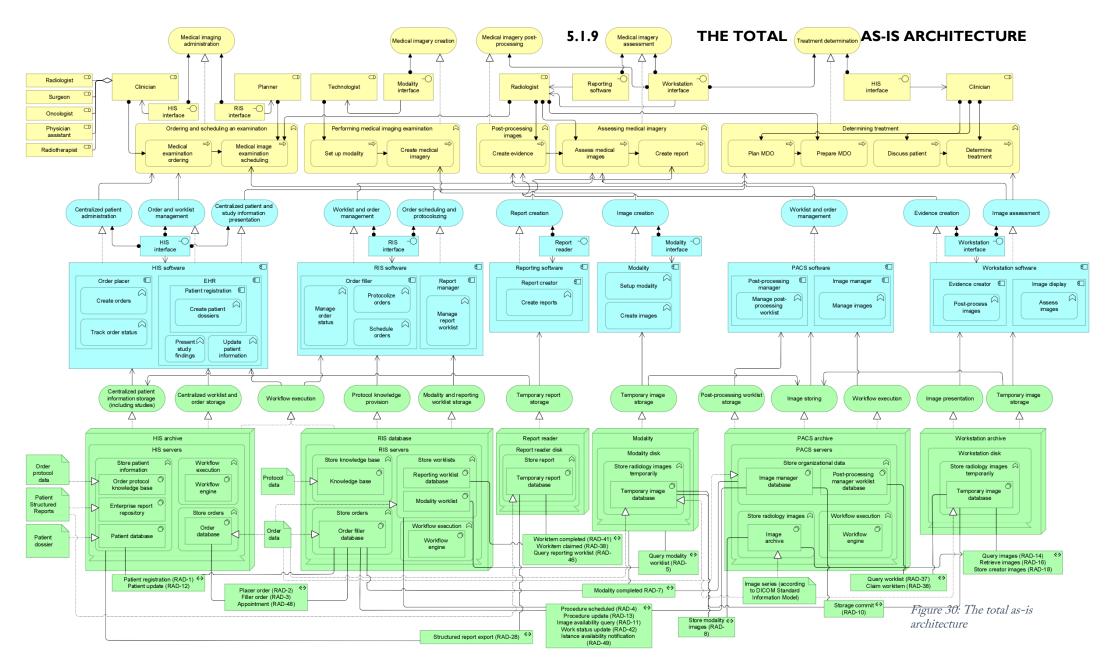
*Figure 28: Metamodel for the design ot the current application architecture* 

#### 5.1.8 THE CURRENT TECHNOLOGY LAYER



As the BPMN models show, there are a lot of transactions necessary to create an integrated healthcare enterprise. This is no surprise given the complex and many systems implemented at the hospital. The technology layer is able to summarize which systems communicate with each other and which transactions they use to communicate and achieve data synchronicity, interoperability or data access. The metamodel is shown in Figure 29 [71].

Figure 29: Metamodel for the design of the current technology architecture



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By connecting the three layers, an as-is architecture can be depicted that shows the current workflow and infrastructure of a hospital who complies to the IHE, DICOM and HL7 standards (Figure 30). A

service realization viewpoint of this architecture is shown in Figure 32 (to increase readability) [71].

### 5.2 Integration requirements

This section presents the requirements for the integration of a CDSS into clinical radiology practice. Getting to these requirements is done in a number of steps: 1) stakeholders identification, 2) stakeholder requirements elicitation based on interviews and literature and 3) integration requirements elicitation based on the stakeholder requirements.

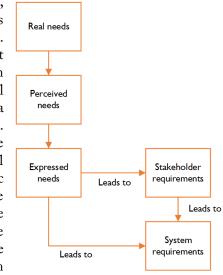
#### 5.2.1 STAKEHOLDERS

Four main groups of stakeholders can be distinguished to determine the whole environment of stakeholders in which the CDSS is placed (according to the Alexander taxonomy [72]): stakeholders interacting with the artifact, stakeholders in the immediate environment, stakeholders in the wider environment and stakeholders involved with the development. The first group is closest and most involved with the system, the last group is the least involved. These four categories can be split up into multiple stakeholder types. Each type of stakeholder is then represented by an actual person, group of persons or institution and each of these persons have their own goals (Table 2).

#### 5.2.2 REQUIREMENTS FOR THE SYSTEM

The requirements posed by the stakeholders are the most vital input for the architecture of the system that is designed. These requirements are derived from stakeholder needs and lead to system

requirements. Numerous forms of needs can be identified [73], and this can help in determining the underlying, sometimes hidden or subconscious, motivation for the new system. Oftentimes, stakeholders start with perceived needs; needs that express an awareness that something is wrong, and an opportunity is presented. These perceived needs emerge from real needs. Needs that show a generic urge to achieve something in a certain context. Perceived needs in turn lead to expressed needs. The purpose of this type is to accurately specify, from all the needs of the stakeholder, which needs will be satisfied in the final product. Expressed needs transform perceived needs into generic actions and prioritize them. They can be used to generate stakeholder requirements. Finally, system requirements are the translation of the stakeholder needs to represent the views of the supplier, keeping in mind the potential, preferred, and feasible solutions. These needs can be translated into system requirements (Figure 31).



*Figure 31: Adaptation of the cycle of needs* [73]

Since the clinicians (all normal operators) are the main stakeholder in this case, their needs are expressed in this section. They form the main input for the system requirements. Their perceived needs are expressed in section 4.5 and can be stated as:

- P1. The need for extra and improved explainable, valuable and accurate assessment of response to chemotherapy in patients with colorectal liver metastases.
- P2. The need for an explainable, valuable and accurate analysis of local treatment strategies of liver resectability metastases.

All of these needs ensure that the decisions that the clinicians make are improved.

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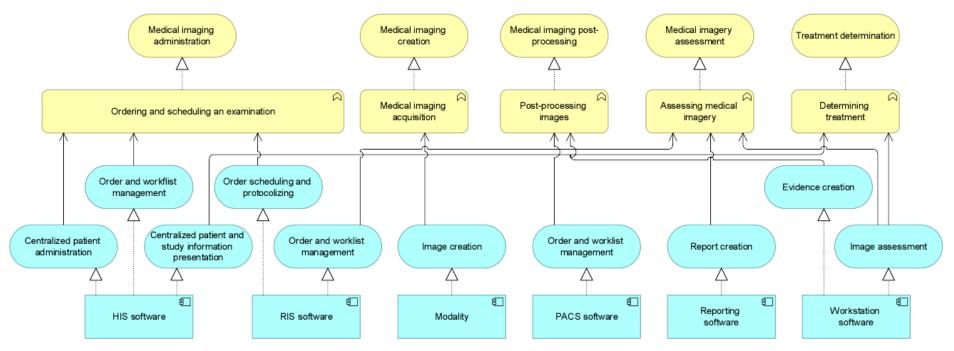


Figure 32: Service realization viewpoint of the as-is architecture

#### Table 2: Stakeholders for nonknowledge-based CDSS for treatment evidence analysis

Category	Туре	Definition	Stakeholder	Motivation
Interacting	Normal	Give routine commands to	Radiologists,	These clinicians will all be using the system in everyday life.
with the	operators	the artifact (end users)	Radiotherapists,	
artifact	_		Oncologists, Surgeons	
	Maintenance	Interact with the system to	IT support staff	Joint effort of maintaining the system
	operators	keep it running		
	Operational	Supports normal operators in	IT support staff	Joint effort of keeping the system operational as well as performing
	support	their use of the system and		updates
		keep the system operational		

Immediate	Functional	Benefit from the output	Patients	Better care and efficiency   Provide better care, work more efficient and make better decisions				
environment	beneficiaries	produced by the system	Radiologists, Radiotherapists, Oncologists, Surgeon					
	Interfacing systems	Have an interest in the requirement and scope	Researchers Hospital board Dutch hospitals	Successful implementation might lead to other implementation efforts				
Wider environment	Financial beneficiaries	Benefit from the system financially	Hospital board Dutch government Insurance companies	Provide more efficient and cheaper care				
	Political	Benefit from the system in	Amsterdam UMC and	Increase presence and knowledge in the medical sector				
	beneficiary	terms of status, power, influence etc.	Dutch government	Increase image of providing state-of-the-art care				
	Negative stakeholder	Are worse off when the artifact is introduced	Lab assistants	Might have less work due to automation of processes				
	Threat agent	Wants to hurt the system by compromising its integrity	Conservative/stubborn clinicians	Might be reluctant to use the new technology and might influence others in the process				
Involved in development	Sponsor	Initiates and provides a budget for development	Hospital board/ research group	Has to give a "go" for the development of the system				
	Purchaser	Responsible for terminating development successfully.	Hospital board (AUMC)	Will terminate development when successful				
	Developers	Build the system	IT developers	Will develop the system				
	Consultants	Support development of the artifact	IT developers	Will aid the hospital and development team				
	Suppliers	Deliver components of the	IT developers	Delivers the full system				
		artifact	IT support at AUMC	Delivers knowledge on IT infrastructure				
			Clinicians	Deliver business understanding				
			Third party data providers	Provides data and knowledge for the system to utilize				
			Clinical departments in the hospital					

These perceived needs emerge from the real need (R1) that clinicians want to be able to tailor medicine to each individual patient in the form of personalized medicine and improve their decision making in order to achieve this.

These two types of needs form the basis for the expressed needs of the clinicians. The following expressed needs can be derived:

- E1. To use advanced analytics for treatment assessments using medical imaging
- E2. These assessments should be performed immediately after a new relevant medical image is acquired as well as for historical medical images
- E3. To always be able to access any analytics outcome in combination with the relevant input data from the interfaces and formats that I am used to (the HIS) during an MDO, consultation or patient's bed.
- E4. To get an understanding of the analytical process and outcome in order to explain it to patients (at the ward and during consults), my colleagues (at an MDO) and to myself (in my office)
  - a. To achieve this, I want to receive clear and helpful explanations when using and applying for advanced analytics.
  - b. Also, I want to be able to trace and govern the creation of the analytics.

Stakeholder requirements can now be expressed. This is done using user stories whom add value and context to the requirement as they mention the stakeholder for which the requirement has value. To do this, we first need to specify a number of business roles. The patient (functional beneficiary) and IT support staff (maintenance operator and operational support) are added to the already existing stakeholders (normal operators) as we are slowly moving towards requirements for the system and their requirements have to be stated and monitored as well. The following roles can thus be identified:

- Surgeons
- Radiotherapists
- Radiologists
- Oncologists
- Physician assistant
- IT Support staff
- Patient

The surgeon, radiotherapist, radiologist, physician assistant and oncologist business roles are combined into the business role of clinician for simplicity.

Semi-structured interviews (with three clinicians and an IT coordinator), literature and earlier work of SAS were used as input in this effort. The business roles are represented in the following requirements:

- STR1. As a patient, I would like to receive the best possible treatment so that I can be cured, or I can for as well and long as possible.
- STR2. As a patient, I would like to receive adequate information on how a clinician has come to the decision to prescribe a certain treatment or on what the progress is of the treatment that I am currently receiving.
- STR3. As a patient, I want the hospital to handle my data appropriately and ensure that it is safe and secure.
- STR4. As a clinician, I would like to receive more characteristics of liver metastases that I can use to get a clearer picture of the current situation.
- STR5. As a surgeon, oncologist and radiotherapist, I would like to see an analysis of the response to chemotherapy in patients with liver metastases to see how well/bad they are doing.
- STR6. As a surgeon and oncologist, I would like to receive an analysis on the feasibility of local treatment strategies of liver metastases to help in determining the best course of action.
- STR7. As a clinician, I would like these analyses to be made when a new examination is requested so that I can immediately use the information in my decision making.

- STR8. As a clinician, I would like these analyses to be made on demand for any previous examination so that I can adjust my decision making or use a newer and better form of information source for existing patients.
- STR9. As a clinician, I would like to receive clear explanations about the models and outcomes at the time of requesting the examination and at the time of receiving the outcomes.
- STR10. As a clinician, I would like to easily communicate the results with my colleagues at an MDO and with my patients during a consult.
- STR11. As a clinician and IT support staff, I would like to examine KPIs regarding the performance of the model. I want to see what the accuracy of the model is in order to keep trusting the system.
- STR12. As an IT support staff, stability and availability KPIs should also be monitored so that I can monitor whether the system is operating as it should be.
- STR13. As a clinician, I want to see the metadata regarding the outcomes of the AI so that I can explain myself regarding the choices I have made at any point in time. I want these kinds of metadata for the aspects of the model itself (like outcome) as well as for the traceability of the entire process.
- STR14. As a clinician, IT support staff and patient, I have to be sure that the systems that are used are validated and approved by the department and that they comply to Dutch and European law and data standards. This approval and compliance must be present.
- STR15. As an IT support staff, I want an easily maintainable and operational system so that I do not have to spend an excessive amount of time on maintaining the system and keeping it operational.
- STR16. As an IT support staff, I want mechanisms in place that will ensure that facilitate access management functionalities so that people with the wrong authorization cannot perform not allowed actions. One (or some) of us should be able to handle authorization.
- To these stakeholder requirements, a number of constraints are added (together with their source):
  - C1. As a clinician, I want to be interrupted in my current workflow as little as possible as otherwise I will not use the system. I have to work efficiently and effectively and I do not want to perform or be disturbed by extra tasks and information (challenge 1 [16] [17] [18] [14] [19] [13]).
    - a. This also means that as a clinician, I do not want to use a new system interface to receive the results of the system. At this moment, I have enough systems that I have to use, and I do not want another one [IT coordinator and clinicians].
    - b. Furthermore, as a clinician, I do not want to wait for the outcomes of the system. I have to work efficient and effective and I cannot afford to wait for results [IT coordinator and clinicians].
    - c. As a clinician, I do not want to be bothered by information that is not meant for me as I will eventually ignore (alert fatigue) it or cannot use it (challenge 7 [41] [12] [14] [23]).
  - C2. From an IT support staff standpoint, many of the software systems cannot be changed and are dependent on their supplier. To speed up integrations and make the new system scalable, this dependency should be kept in mind and disruption in this infrastructure should be limited (challenge 2 [20] [12] [21] [17] [22] [23]).
  - C3. The system cannot under any circumstances overwrite or alter any data in the rest of the environment. This is because the original files should always be kept original [IT coordinator].

With the stakeholder requirements, expressed needs, constraints and challenges and success factors in literature identified, the system requirements can be stated. Note that the system in this case is the integrated current infrastructure with the addition of the CDSS. The mentioned references for each requirement refer to the source that discusses the challenges from which the requirements have emerged. Requirements were validated by the same clinicians and IT coordinator. This system should fulfill the following requirements:

- SYR1. The system should provide advanced and relevant treatment analysis for surgeons, radiologists, radiotherapists, physician assistants and oncologists using medical imaging (challenge 1 & 5 [39] [40] [13] [19] [23] [43] [22] [17] [44] [14]). In CAESAR, it does so by:
  - a. Analyzing CT-scan images of liver metastases in order to create valuable new insights
    - i. The user should be able to request this function simultaneous to a medical imaging examination.
    - ii. The user should be able to request this function for an already performed medical imaging research.
  - b. Preferably, the system should be built in such a way that it can also easily use data from other departments in the future (scalability).
- SYR2. The system should change/interrupt the current workflow as little as possible. Meaning that the clinician and any actor in the process will not have to wait or perform excessive actions to receive advanced analytics. Change of the workflow should solely make the workflow more efficient in terms of the number of actions required or substitute an action for an equally labor-intensive one (challenge 2 [16] [17] [18] [14] [13] [19]).
  - a. Data presentation. This means that the outcome of the analytics should be available and presented using the right interface, at the right time, in the right format, to the right actor and at the right step in the process [32] (C1b, C1c, challenge 7 [41] [12] [14] [23]).
  - b. System activation. This in turn means that the system should be called (or activated) at the right time, by the right system in the process so that it has enough time to achieve system requirement 1a [32].
  - c. System requests. This in turn means that requests for the analytics (at the start of the workflow) should happen at the right time, by the right actor (the one who values the information), at the right step in the process and using the right interface [32]. This will allow requirement 1a and b to be satisfied.
- SYR3. The system should provide the clinician and the patient with information on how a certain decision/analysis was made. This is to allow a clinician to understand why a certain decision was made and this will help him in making a conscious decision (challenge 19 & 26 [17] [44] [18]).
  - a. The information should be easily findable from the actual outcome of the analytics (originating from low user friendliness (challenge 11 [40] [14] [13])).
  - b. Also, the system should prevent automation bias as much as possible. When information is presented in the system, this threat should be taken into consideration (challenge 16 [46] [47]).
- SYR4. The system should be fully integrated so that the CDSS can use useful functionalities of other parts of the infrastructure and deliver an integrated experience for a user (challenge 2 and 6 [20] [12] [21] [17] [44] [14] [19]. For this requirement, a number of constraints are vital [IT coordinator]:
  - a. The HIS, the electronic health record, is leading. The rest of the applications should follow. This means that the HIS has the gold record in the department.
  - b. It is not possible to create a new interface for the clinicians as this is a constraint (C1a).
  - c. The rest of the systems interacting with the new CDSS are very limited in their flexibility and the hospital's power to change them is thus limited as well. Major changes are not possible and can only be achieved due to a collaboration between the supplier and SAS (C2).
- SYR5. The system should comply to the data standards and handling in terms of internal standards (C3) international standards like HL7. This also means that it complies to the standards in terms of altering data (challenge 5 [12] [22]).
- SYR6. The models run in the CDSS should be validated and thoroughly examined before deployed. The system should therefore have mechanisms implemented that allows the model to acquire these characteristics (challenge 3 and 5 [39] [40] [13] [19] [23] [43] [22] [17] [44] [14]).

- SYR7. The CDSS' outputs and metadata should be traceable at any point in time (challenge 2 [20] [12] [21] [17] [44] [14] [19].
  - a. Governance practices should allow for storing of the metadata for each analysis that it has ever performed. What version of the system is/was running at the time of the analysis, who asked for it, what data was used, which results were shown and how this has changed since are examples of important metadata.
  - b. Support staff and users should be able to access this metadata in an easy manner.
- SYR8. The system should provide an analysis that give insights into the performance and impact of the CDSS in terms of validity, availability and stability of outcome and the process. Users, support staff and board should be able to see and reflect on these numbers. This results in the clinicians trusting the outcomes of the system (challenge 3, 12, 19 and 26 [8] [7] [10] [11] [17] [44] [18] [39] [40] [22] [19] [13] [23].
- SYR9. The model and the system surrounding the model should be compliant to the European law and Dutch guidelines so that hospital departments can and will adopt the system [IT coordinator and clinicians].
- SYR10. The system should be very easy to use so that even someone with little computer skills can use it (challenge 4 and 9 [41] [16] [17] [39] [42] [13]).
- SYR11. The system should provide the ability for easy and continuous maintenance actions on the algorithm by the support staff and SAS (challenge 13 [43] [23]).
- SYR12. The system should use a vocabulary that is agreed upon by clinicians in the environment in which it is placed (challenge 18 and 26 [12] [22] [18])
- SYR13. The system should support the clinician in communicating the outcome to the patient (challenge 26 [18]).

Table 3 shows a summarizing overview of the connection between all requirements and their source.							
Table 3: Overview of all requirements and their originating source							

	R1	R2	R3	R4	R5	R6	R7	R8	R9	R10	R11	R12	R13
CH1	Х												
CH2		Х		Х			Х						
CH3						Х		Х					
CH4										Х			
CH5	Х				Х	Х							
CH6				Х									
CH7		Х											
CH9										Х			
CH11			Х										
CH12								Х					
CH13											Х		
CH16			Х										
CH18												Х	
CH19			Х					Х					
CH26			Х					Х				Х	Х
C1		Х		Х									
C2				Х									
C3					Х								
CLI	Х	Х	Х			Х	Х	Х	Х	Х		Х	Х
IT	X	Х	<u> </u>	Х	Х	Х	X	X	Х	X	Х	11 X	0.10

Some of the challenges of section 3.1 have not been used as a basis for requirements. Challenges 8, 10, 14, 15, 17, 20, 21, 22, 23, 24 and 25 were not mentioned in the requirements. This is because these challenges are out of scope as they either describe aspects that cannot be solved by integration (for instance, challenge 15: ethical issues) or describe quality measures of the algorithm within the CDSS (for instance, challenge 14: flexibility when facing an altered problem).

# 5.3 Solution design

This solution design presents the high-level design choice that has been made regarding the integration of the CDSS into the clinician's workflow and infrastructure. It was found that there are numerous possibilities to do this and this section explains these options and the choice for a final solution design. With this solution design, the new integrated workflow and infrastructure can be designed.

Osheroff et al. [32] describes in the CDS Five Rights Framework that for a CDSS to become effective, the right information must be presented to the right people, in the right formats, through the right channels, at the right point in workflow. These factors can be used to present an ideal solution design which can be used to assess the quality of the proposed solution designs:

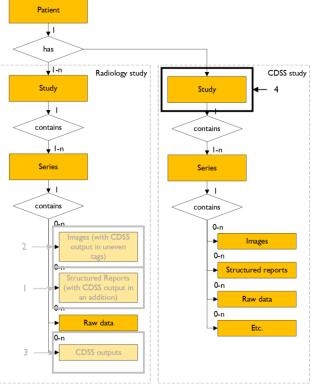
- The right information: out of scope as this concerns the quality and clinical relevance of the outcome of the CDSS.
- The right people: the outcomes can be relevant for many clinicians (surgeons, oncologists, etc.). All of these people must have access to this data.
- The right formats: the CDSS produces output in the form of images and/or text. The clinician is used to these formats.
- The right channels: the HIS. This is the central access point for clinicians and given the applicability of the analysis in multiple departments, the outcomes should be presented here.
- The right point in workflow: as fast as possible after the imaging has been acquired. Since the outcomes are used in evidence analysis (an advanced step in the decision-making process) there is some room for delay here (consults and MDOs are rarely scheduled right after an examination). However, as constraint 2 mentions, clinicians do not want to wait for outcomes and speed is therefore important.

For the considered solution designs, the information and point in workflow are the same. They do however differ on the other points: the formats, people and channel. In terms of channel, this mostly concerns the presentation of outcomes in a certain place according to the information model that is depicted in Figure 33. The following options were considered:

- 1. Present the outcomes in an addition of the report of a radiologist and present this data before the radiologist starts dictating its own findings. Outcomes are presented to radiologists, in a text format, through the radiology reports in the HIS. Besides the misalignment with the ideal type, clinicians have to (morally and explicitly) sign for their findings in the reports and this results in the fact that clinicians do not like to sign for things that they have not created or do not concern their expertise.
- 2. Present the data in the uneven tags of images using the DICOM standard. Uneven tags in the DICOM standard are empty and can be used according to the preferences of the hospital. In theory, they can thus be used for data from a CDSS. Outcomes are presented to radiologist, in a text format, through the tags of images in the PACS. Besides the misalignment with the ideal type, this data would not be easily visible to every stakeholder (especially the ones who are not in the radiology department) and this will leave no room for explanations or images.
- 3. Present the data in a dedicated area of an HIS. Adding data to this part of the system would require a collaboration with the HIS provider since these fields do not exist yet. Outcomes are presented to all clinicians, in a text and/or imaging format and through a dedicated field in the HIS. Although this aligns with the ideal type, this would come with extra challenges regarding the organization of such a collaboration. Also, implementation of the CDSS would then be specific to one HIS provider and if the CDSS were to operate in a different HIS environment, that would mean that the whole collaboration must be setup again.
- 4. Present the data in an entirely new study that is presented next to the original radiology study. This extra study can then hold all evidence that the CDSS creates. This option presents outcomes to all clinicians, in a text and/or imaging format, and through a dedicated study in the HIS.

Option 4 represents the ideal type of CDSS integration. To further assess the benefits of this option, the "five rights" are discussed in more detail. In the explanations, the requirements that this option satisfies will be shown as well.

- The right information: out of scope.
- The right people: the new study would provide centralized access to CDSS outcomes for every clinician without any disruption in their own work environments (SYR2). People are not disturbed by information that is not for them (C1c).
- The right formats. Given the similarities in outputs that the CDSS will provide when compared to a "regular" study performed by radiology, it is logical to make use of the environment that the HIS provider has created for these studies. Reports, images and other evidence can be stored in the same manner and thus the whole system is not bothered by the lack of flexibility in many of the systems



*Figure 33: Options for the presentation of CDSS outcomes in the DICOM information model* 

(SYR1, SYR4, SYR12, C2). Also, it allows the CDSS to utilize this new space to enhance the data presentation in reports as these reports could also link to visual, more appealing forms of presentation including accurate explanations (SYR3, SYR13). Finally, in the future, when new datasets from other departments are necessary for new advanced analytics, integration with these other departments and application of value in other departments is way easier when the CDSS can create its own study (SYR1b). This is because the CDSS can present the data in a separate view from anyone's work environment/flow and request the data on its own without having to comply to the goals of that department. If this were not the case, each department will have to create their own CDSS implementation as clinicians do not want insights that do not belong to their expertise in their work environment/workflow (C1c). On the other hand, the departments already can and will exchange data with each other freely.

- The right channel. Besides the fact that clinicians are not disrupted in their own work environment, the new environment and information model is one that they are used to. The CDSS study can adopt the same look and feel of a regular radiology study, which makes the outcomes easily findable and usable (SYR10).
- The right point in the workflow. Further discussed in section 5.4. It is however clear that clinicians are not bothered by the CDSS outcomes in their workflow (C1, SYR2) and there is no need for a new interface (C1a).

Allowing the CDSS to create a dedicated study resembles the current hospital as well. Each department can add their own studies within a patient file. Each department delivers evidence and insights that together can be used to make a decision regarding the treatment of a patient. This solution design would introduce a new entity that is capable of providing its own evidence: the CDSS. This claim is supported by the typology that was created. Here it was clear that the CDSS should not replace the clinician, but function as an extra way of receiving evidence that can help in his/her decision making. It is therefore logical to not present and deliver the outcomes of the CDSS in a study where the clinician creates his/her own evidence, but in a separate supporting study.

One could however argue that the output of the CDSS is also relevant within the radiology study of a radiologist as this might improve the insights when the evidence is assessed. This is however where the distinction in the typology between CDSS for treatment evidence gathering/creation and evidence analysis becomes apparent. The former type solely generates evidence. A CDSS of this type cannot create insights and thus it still needs to be included in the human analysis of the clinician before it can become insightful. Since studies mostly consist of evidence together with insights based on this evidence, CDSS of this type should be included inside the study of the clinician. The latter type however, relies to large extent on the insights that emerge from the analysis that the system itself performs on the evidence it has gathered/acquired/created. By itself, this thus resembles the characteristics of a study (evidence plus insights) and can thus be presented in a separate supporting one. Also, it allows for the logical separation of machine and human made assessments. Together with the regular study, clinicians can absorb the insights and evidence from both and use this towards a decision at an MDO, a patient's bed or the office.

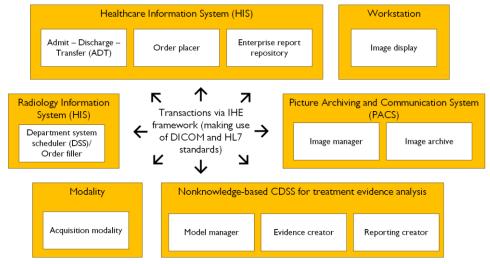
In order to implement this solution design, the three layers in the architecture are each tailored to the new situation. This is done by first determining what will change in the current situation and how the CDSS will interact with the rest of the layer. Then, the details of the concepts of the CDSS itself in that layer will be designed. This latter activity depicts a product architecture of the CDSS. Together with its connection to the context of the as-is situation in radiology departments, a reference architecture for nonknowledge-based CDSS for treatment evidence analysis in radiology can be presented.

# 5.4 Designing the process architecture

When the current business landscape was described in section 5.1, the systems involved with radiology and their transactions according to the IHE framework were described first. This is done here as well, but with the transaction model now presented in the technology layer (section 5.6). The overviews of Figure 9 and Figure 10 show these actors and transactions and they can now be changed to resemble the target situation. In terms of systems involved, two functions can be completed removed as they are substituted by the CDSS: the reporting and the evidence creation. The evidence and insights that these components normally generate are now substituted by the CDSS. (Remember, these components are not completely removed from the hospital, they are just not present in the workflow (and study) of the CDSS.) The post-processing manager, evidence creator, report manager and report creator can be removed and replaced by the CDSS in form of an evidence creator, reporting creator and a model manager (Figure 34). The workstation now solely provides capabilities to view evidence created by the CDSS. This prevents data contamination between human- and machine-made evidence.

To create full integration with the system, the current infrastructure should communicate with the CDSS in order to provide information on orders and images. The following changes should be made for each of the as-is process models.

Figure 34: Overview of all system components in the target situation



Ordering and scheduling an examination. The biggest challenge here is to initiate the workflow and create the two separate studies in the HIS without disrupting the normal workflow. The as-is workflow shows that an ordering clinician can order an examination according to a protocol which translates to a single ORM message that initiates the workflow. Luckily, orders can be divided into multiple ORM messages that each hold a unique Study Instance UID. This already occurs, for instance, when a biopsy is combined with a medical imaging examination, only one order is placed, but with some intelligence of the order filler and placer of the HIS/RIS, two studies are created (one for imaging, one for lab examinations). The HIS automatically provides a separate space for every unique study. Protocols can specify the way in which these orders are treated and thus, the hospital should add new protocols to the list that can initiate this workflow. In the eyes of the ordering clinician nothing changes as he only orders the examinations that he wants performed. Then, in the last phase of this subprocess, where all systems are notified about the order, the CDSS receives both the regular order as well as the CDSS order as this will solve a challenge in the next subprocess. Also, the CDSS will receive information about the creation and updates of patients so that it can store and maintain the created outcomes for that patient (necessary for historical analysis of all imaging of a patient).

Medical imaging acquisition. The creation of two separate studies and workflows creates another challenge. Both studies need the imaging that is acquired by the modality. However, this modality should only execute one order as otherwise the same procedure would run twice. To limit disruption, the regular order should contain the acquisition of the images. To ensure that the CDSS is aware of the acquisition of these images, the modality is set up (again using that same protocol) to send "modality completed" messages to the CDSS. Given that the CDSS is aware of the regular order and CDSS order, it can link this incoming message (carrying the regular order information) and link it to its own order. From then on, it can query the archive for the images of the regular order and use it for post-processing and reporting. Also, before the images are acquired, the CDSS is capable of prefetching historical data of the patient to perform a historical analysis (as no new images are needed).

Post-processing and reporting. These two subprocesses can be merged together as both of the activities are carried out within the CDSS. Since the internal creation of this evidence and reports is outside of the scope, it is treated as a black box. The workflow in general (worklist querying, item claiming, image querying, image storage, creation, item completion) will be the same as the current situation as this resembles the current practice in the hospital. The CDSS can then store and present the outcomes depending on their form in the enterprise report repository (automatically signed reports) or image archive (images) using the details of the study. This will normally be done in the CDSS study but can even occur for the radiologist's study (if the outcomes were only useful in the workflow of the radiologist). In the sub-process of the presentation, assessment and discussion of a patient at an MDO, the only change is that the clinicians can now assess an additional study that is created by the CDSS.

The general workflow of Figure 20 is now updated to resemble this new workflow Figure 35. The target BPMN models are shown in Figure 36-39 (the MDO is not shown since there are no relevant changes). These models were validated by a clinician, an IT coordinator and an independent integration specialist.

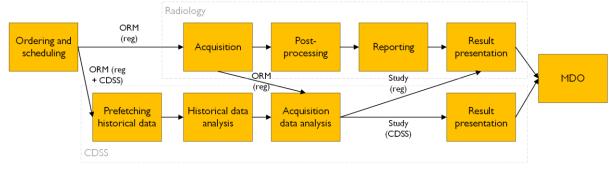
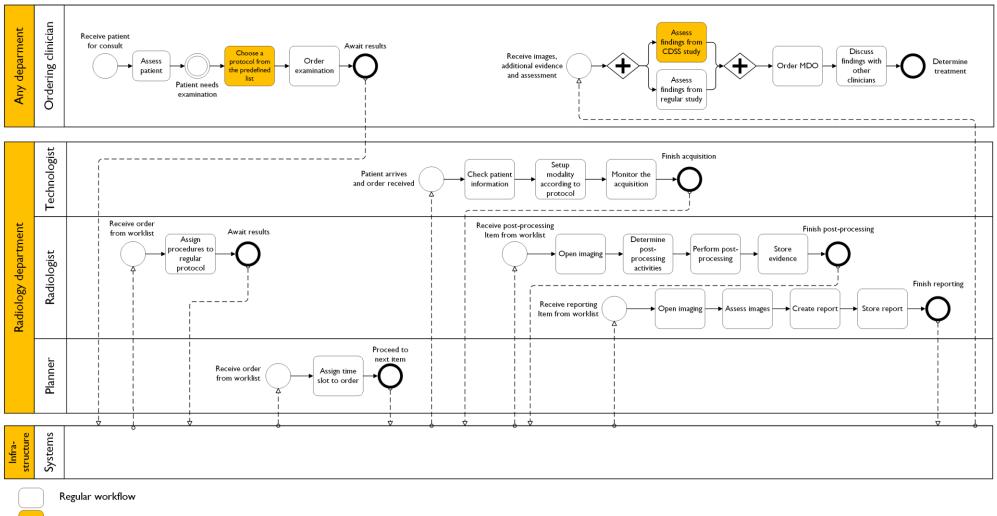


Figure 35: The CDSS workflow in combination with the regular radiology workflow



CDSS workflow

Figure 36: The clinician's target workflow

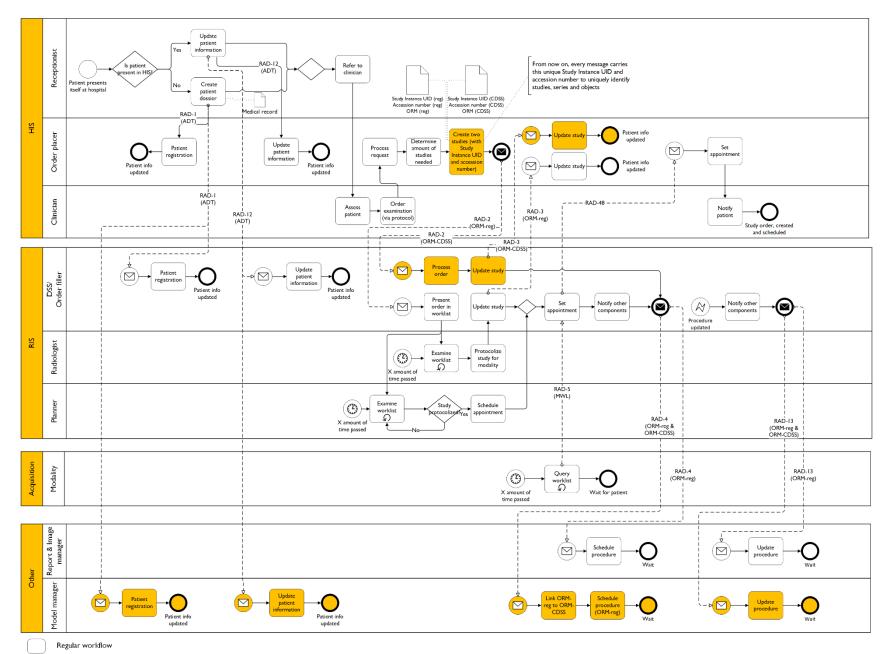
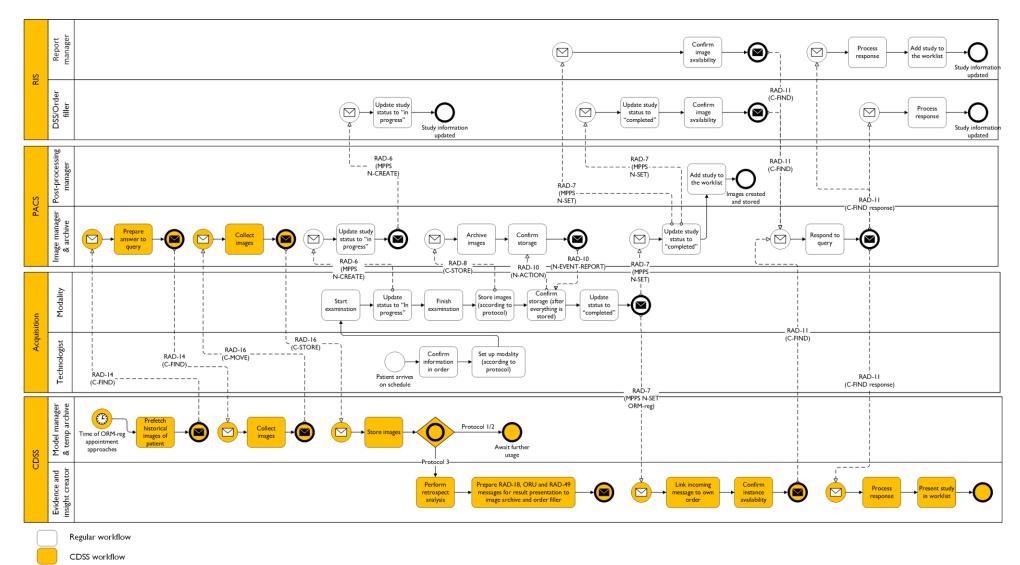
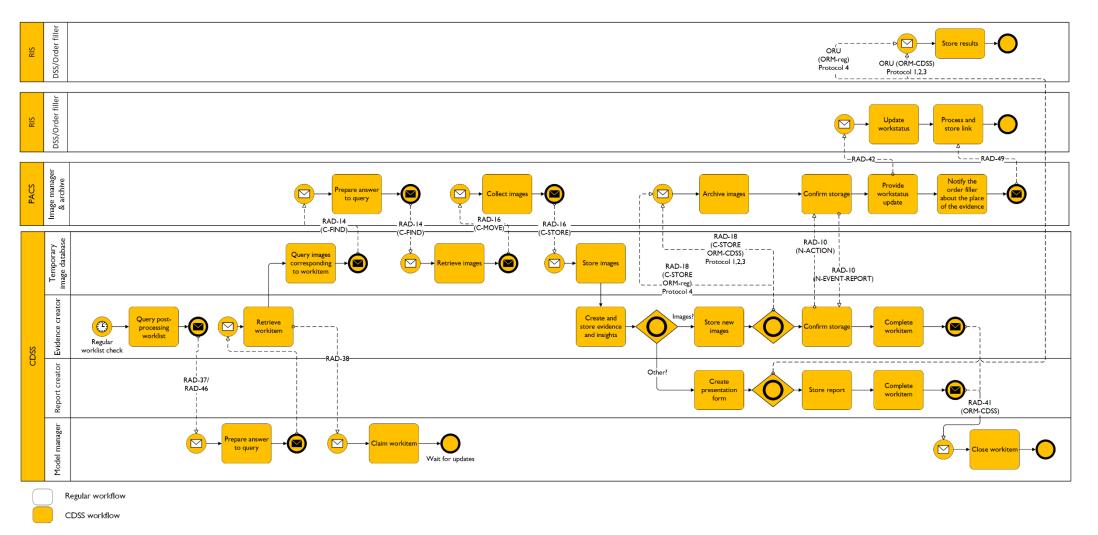


Figure 37: The process of regular and CDSS examination ordering and scheduling (target)











With this workflow, four protocols providing different functionalities can be implemented:

- 1. CT + CDSS: produce a regular CT-examination and in parallel, perform analysis on the acquired raw images by the CDSS and present these in a study.
- 2. CT CDSS: produce a CT-scan and only use the acquired images for the CDSS.
- 3. CDSS historic: produce an analysis on all historic data of a patient (could be part of a CT + CDSS or CT CDSS protocol).
- 4. CT + CDSS Radiology: produce an analysis on acquired images but present the results in the radiology study (only applies when the outcomes are only relevant and useful for the radiologist)

In addition to the changes in the current processes, three new process should be added. Requirements state performance, impact that and metadata tracking should be possible (SYR7 and SYR8). This is done to trace the validity and impact of the CDSS outcome as well as create a traceable path for each analysis that the CDSS has made. Two new processes should be added to the layer that allow stakeholders to do this: outcome performance tracking and process performance tracking

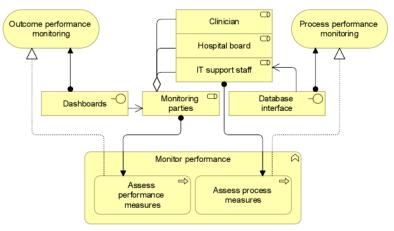
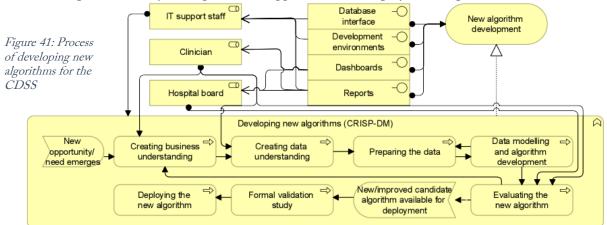


Figure 40: Process of monitoring outcome and process performance of the CDSS

(Figure 40). The actors involved here are the hospital board, clinicians and IT support staff (where only the IT support staff will track the metadata of the system). Outcome performance tracking can best be performed using a dashboard that generates and presents performance measures in an intuitive and understandable way as the hospital board and clinicians might us this interface as well. The process performance tracker can be displayed in an arbitrary manner (depicted here as a simple database interface). Although measuring impact is still difficult, this design at least reserves a space for this.

The third process is a development process (Figure 41). With a dedicated entity for the CDSS in place, development of new algorithms can also take place in this department (in accordance with SYR1b). The results of these new algorithms will not be used in clinical practice until they are validated but can be assessed by developers or clinicians to determine their quality and possible future use in everyday practice. The process of developing these new algorithms relies on the CRISP-DM methodology that was presented in section 3.2. Important to note is that once the hospital is satisfied with the performance of a new or improved algorithm, a formal validation study should take place (SYR9). Since there is a lot of debate on the form that these studies should take, this process cannot be described in detail until the sector has come up with consensus. It is however important to be aware of this and therefore this validation step is stressed by adding another trigger before the deployment step.



### 5.5 Designing the application architecture

In the target situation, the application components of the CDSS will not interact with the environment outside of the CDSS as their sole purpose is to create evidence and insights, create a form of delivery for them, develop new models and manage, govern and monitor this process. The delivery of the analysis is performed in the technology layer (via the transactions) and therefore this section will solely focus on the specification of the internal software components of the CDSS. In this layer, two classes of algorithms can be distinguished: live algorithms that are deployed and validated (SYR1a) and algorithms in development that are used to create new deployed models (SYR1b). The application layer therefore clearly distinguishes between the live environment and the development environment.

The main decision that must be made in this layer is whether the CDSS is implemented internally (inside the environment of the hospital) or externally (inside the environment of the external supplier). The biggest advantage of the former is that data exchange between the environment and the CDSS would be easier and richer. This is because data that leaves the logical or physical walls of the hospital must be deidentified to comply to law. For the live algorithm, the data must be identifiable as otherwise the results cannot be shown in the correct place. Placing the CDSS inside these walls will eliminate this need for deidentification. Also, the government and monitoring effort belongs mostly to the hospital. Despite this extra activity for the hospital, it is vital that they can exert control over this system and process as the algorithms will touch patient care. Finally, the CDSS is free to participate in the current transactions and orchestrations of the hospital without dealing with firewalls and other security mechanisms, making integration easier. The latter option provides possibly quicker iterations for algorithm development and can provide outcomes as a service without the need for governance from the hospital. However, since the benefits of internal deployment outweigh the benefits of external deployment, the live and development environment are deployed internally.

To identify the components in the live environment that can create a pipeline for the creation of intelligence, inspiration is drawn from the CRISP-DM model [58] of section 3.2. Many of the activities described in the CRISP-DM process model must be automated in the live environment. The following components can be derived from this that must be present in the live environment:

- Data acquisition (handled in the technology layer)
- Data processing where data is processed so that it is ready for the deployed model to analyze. This step can also already create evidence that can be presented to the outside environment.
- Model execution where the algorithm is applied to the data in order to create evidence (in the form of new images) or reports (which contain new insights based on the data). Together with the data processing component, this is modelled under the evidence and insights creator.
- Data delivery which is responsible for the delivery of the results of the system to the end user. This is done for performance monitoring (by creating dashboards) as well as delivery in the primary care process (by presenting it to the outside environment). Data delivery can be performed by a standalone application as long as it has access to the data of the CDSS. This also provides space for elaborate explanations of the performed analytics.

This complete workflow of data acquisition, data processing, model execution and data delivery must be governed and monitored in five ways: managing models to ensure that the models work as they should (in terms of for instance compliance), workflow management in order to monitor the entire pipeline and generate process performance and metadata, access management to log activity and restrict access to certain users, worklist management in order to track status and execution of orders, and output management to generate outcome performance data. These functionalities are presented under the model manager component. The live environment of the CDSS is depicted in Figure 42. It depicts five services that are delivered by the application:

- Application management: the ability to exert control over the pipeline, the application and all its components. Also, this provides the ability to track orders (mimicking the current practices in the hospital) (SYR3, SYR6, SYR9, SYR11).
- Performance insights availability: the ability to assess performance data, metadata and logs in raw form (from the model management software) or in process form (from reporting) (SYR8).
- Monitoring and governance capabilities: the ability to monitor and govern the process, models and outcomes and generate performance and metadata (SYR7).
- Evidence and insights creation: the actual outcome of the analysis performed by the CDSS (SYR1).
- Reporting software: the ability to generate data presentations tailored to the users need (SYR2, SYR3, SYR4, SYR8, SYR13).

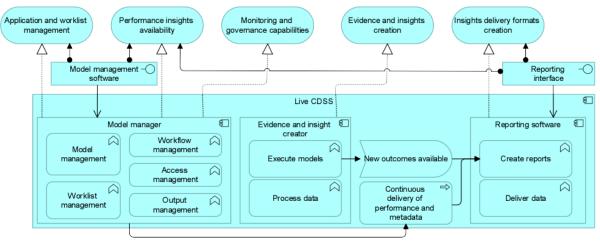
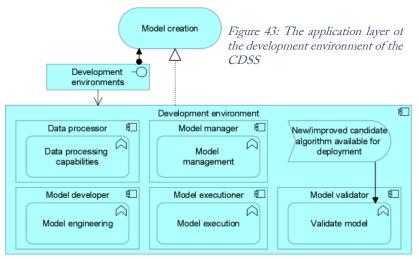


Figure 42: The application layer of the live CDSS

The development environment, since it is used to freely explore new possibility, does not require the same level of governance as the live environment (Figure 43). Also, the outcomes do not have to be placed in a report. The development environment should simply allow for free exploration and development. There is however one new component that should be added. When a model is deemed valuable and reliable, a validation study will be initiated. Whatever



the study may entail, initiation and monitoring of this process can be done in the development environment.

## 5.6 Designing the technology architecture

In the technology layer, two things have to be determined:

- The transactions between the CDSS and the existing actors to ensure automation of the entire pipeline and full integration with the existing infrastructure.
- The types of datasets that can be distinguished within the CDSS.

Since several components are replaced by the CDSS, the transactions between the components needs to be changed. The CDSS will take over most of the transactions that were previously performed by the substituted components (Figure 45) (SYR2, SYR4, SYR5, SYR12) in order to receive orders, query the archive, work on items, retrieve imaging and store results. These transactions are:

- Patient generation (RAD-1) which will notify the CDSS about the creation of a new patient.
- Patient update (RAD-12) which will notify the CDSS about an update of patient information.
- Procedure scheduled (RAD-4) which will notify the CDSS about a scheduled examination (of a "regular" examination).
- Procedure updated (RAD-13) which will notify the CDSS about any changes in the scheduled examination (of a "regular" examination).
- Modality PS completed (RAD-7) will notify the CDSS about the completion of the "regular" imaging examination.
- Image availability query (RAD-11) which allows the CDSS to check whether there are images available that it can use.
- Query images (RAD-14) which allow the CDSS to query the image archive for study, series and image instances for retrieval
- Retrieve images (RAD-16) which allows the CDSS to retrieve images from the image archive.
- Creator images stored (RAD-18) which allows the CDSS to send newly generated images to the image archive for a study. Newly generated images provided by the CDSS do not need a new transaction as the output of the CDSS will be the same as that of the evidence creator and they can thus be sent via the same transaction. Since the evidence creator is absent from the study, the CDSS uses this transaction.
- Storage commitment (RAD-10) which allows the CDSS to receive confirmation of the storage of images. It ensures that the image manager/archive now take responsibility for this image.
- Structured report export (RAD-28) which allows the CDSS to transmit the structured reports.
- Performed work status update (RAD-42) which allows the CDSS to notify the relevant components on the work it has performed.
- Instance availability notifications (RAD-49) that will notify the CDSS when there are new DICOM objects that it can use for its analysis.
- Work item claimed (RAD-38) which is a claim of a work item from the model manager.
- Work item completed (RAD-41) which is an internal notification of a completed work item.
- Query post-processing worklist (RAD-37) and query reporting worklist (RAD-46) which provides orders to the worklist. Both transactions are mentioned as they can contain different instructions and this range of possibilities might be useful during implementation when instructions for the AI can be mapped to the specified instructions of these two transactions.

Numerous types of data are used in the creation of a nonknowledge-based CDSS for treatment evidence analysis. It is clear by now that the main data input in the current scope is image data. However, it comes in various forms depending on the usage of the image. In a development setup, image data can be separated into training data and test data. The former is used to train the algorithm, the latter is used to determine the performance of the algorithm [3]. Both are logically separated datasets. Then, in a live environment, there is a distinction between ad hoc and verified data. Ad hoc data has just entered the CDSS and should be processed first. Verified data is processed and usable data. Furthermore, in this environment, the raw outcomes of each analysis are stored for traceability and possibly for later use in other models. Performance data on the process, models and outcomes is stored here as well. The created evidence and reports (insights) are temporarily stored in this archive as well. However, once a storage commit confirmation has been sent (RAD-10), the data will be deleted as it is good practice to do so (to prevent data contamination and the necessity for data synchronization). The model manager worklist database enables storage of the orders, work items and their status. A model repository holds the different validated models (including their metadata). Finally, a workflow engine allows for the execution of the workflows as specified in the various processes and transactions. The live and development archive are logically separated from each other to prevent data contamination. The entire environment's access managed is orchestrated by an environment manager. The total technology layer is depicted in Figure 44.

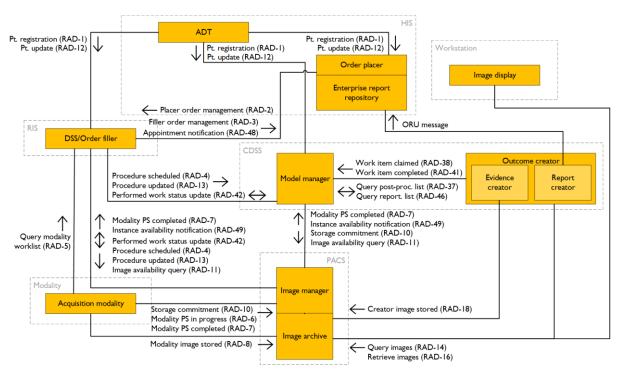


Figure 45: Overview of all transactions in the target situation

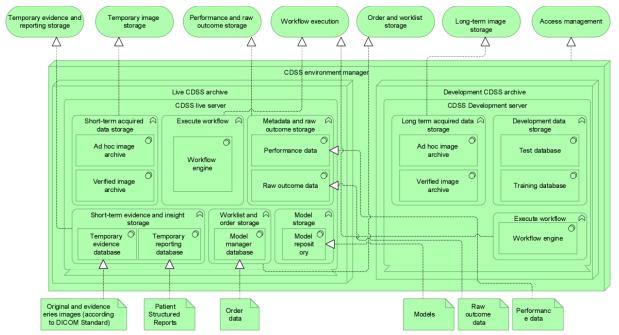


Figure 44: The technology layer of the CDSS

### 5.7 The total view of the reference architecture

The three layers combined generate a reference architecture for the CDSS. First, in Figure 46, a CDSS architecture without connection to its context is presented. This architecture can be implemented in a context that complies to the IHE, DICOM and HL7 standards. To present the way in which it should be integrated into this context, the whole reference architecture consists of the CDSS integrated in a reference context. Figure 47 and Figure 48 depicts the total view of the reference architecture for the integration nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure of the radiology department. The shadow architecture to the left depicts the concepts that are not relevant in the environment of the CDSS, but still do play a vital role in radiology. Figure 49 shows a simplified version of this architecture showing only the business functions, application components and the services they realize. The architecture allows for the ordering, scheduling, creating, storing, presenting and discussing of advanced analytics using radiology imaging with limited disruption to the clinician's workflow.

### 5.8 Assessing workflow and system disruption

The goal of the research was to minimize the workflow and system disruption while integrating the CDSS. From the clinician's perspective, this is achieved as the process models in Figure 22 and Figure 36 show that only two activities have changed. Both these changes occur for the ordering clinician. The first change concerns the additional protocols from which the ordering clinician can choose. This is to ensure that the CDSS examination is ordered. When compared to the original activity, only the list of protocols is larger. The second change concerns the assessment of the results of the CDSS examination. This activity is an additional activity and allows the ordering clinician to absorb the results of the regular radiology study. Also, they can use the results in the same activities as before: an MDO and patient consultation (in the office or at the patient's bed). For the other actors in the workflow (technologist, planner and radiologist) nothing changes.

Regarding system disruption, only minor changes occur as most of the integration can be solved with existing transactions. There are however a few changes that need to be implemented by IT support. Intelligence has to be created to split the order into two ORM messages. The hospital is already used to this setup in other orders. Also, the CDSS should be notified about new and updated patient files, scheduled and updated orders and created and stored images. The responsible system components (the ADT, Order Filler and modality) should be aware of this new destination. In the rest of the transactions, the CDSS sends a message to a system component first and the component can simply respond to the original sender with basic intelligence.

Finally, to setup this solution design, a number of steps need to be taken. First, the hospital board should be convinced about this way of integration. They have to approve the development of an entity that is allowed to add new studies to a patient file. Then, protocols need to be created that depict the procedures that have to be carried out by the systems and actors. Finally, the system integration (with transactions) should be setup according to the designs in this research.

### 5.9 Discussion

This solution design provides a way of integrating a nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure according to an extensive list of requirements that was based on literature and interviews with experts in the sector. The solution design proposed to

present the outcomes of the CDSS in a separate study in order to provide the right information to all clinicians, in similar formats as the regular radiology studies, through the central environment of the HIS and presented shortly after the acquisition of the imaging. This separate study environment and workflow supports the clinician in his decision making but does not interrupt it. Some challenges emerge when implementing this solution in the infrastructure of radiology (acquiring images for instance). In most cases, these challenges can be solved using order management. This ensures that the disruption of the current infrastructure is limited as well. This is also achieved by modelling the CDSS components in the image of already existing components in the IHE profile (evidence creator, report creator, model manager). In this manner, existing transactions can be used in the integration of the CDSS. In the presentation of the architecture in section 5.4, 0 and 5.6, design choices are linked to show the requirements they (partially) fulfill. Now that this reference architecture has been presented, the architecture is applied to the case study of CAESAR in order to illustrate its use in practice.

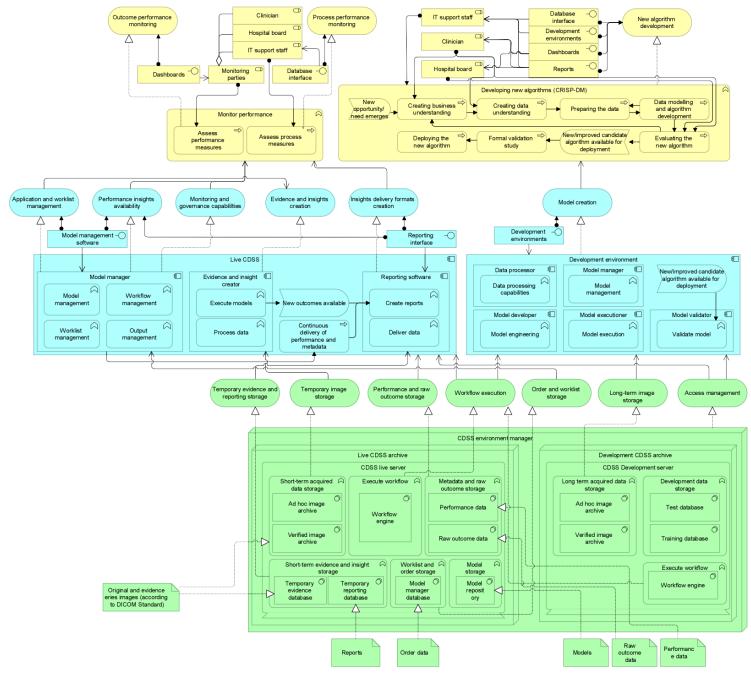


Figure 46: The reference product architecture of a nonknowledge-based CDSS for treatment evidence analysis

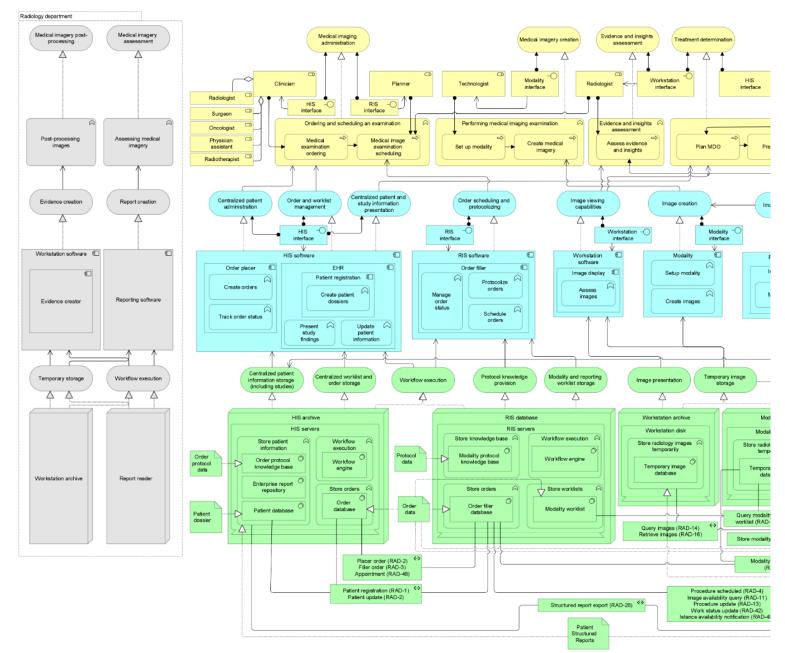


Figure 47: Total view of the reference architecture for nonknowledge-based CDSS for treatment evidence analysis in the radiology department (part 1)

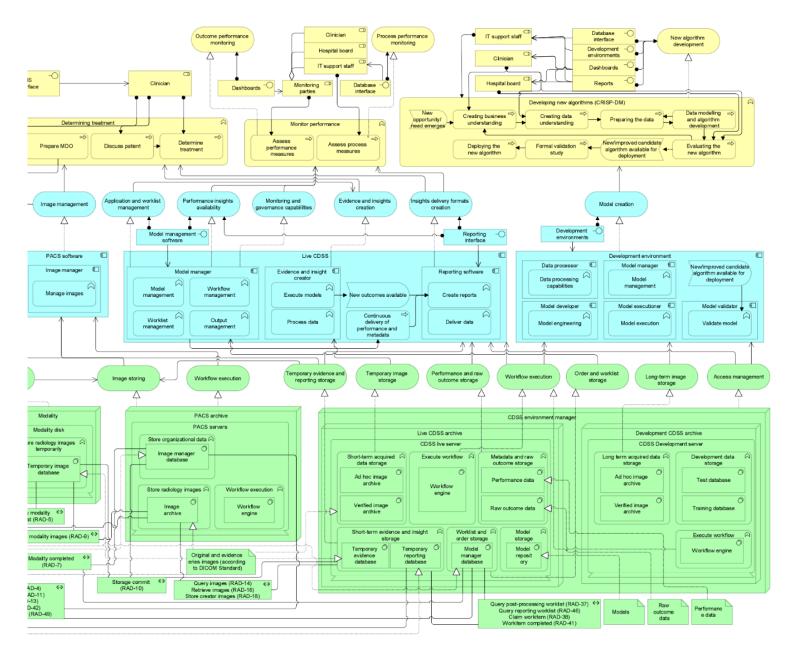


Figure 48: Total view of the reference architecture for nonknowledge-based CDSS for treatment evidence analysis in the radiology department (part 2)

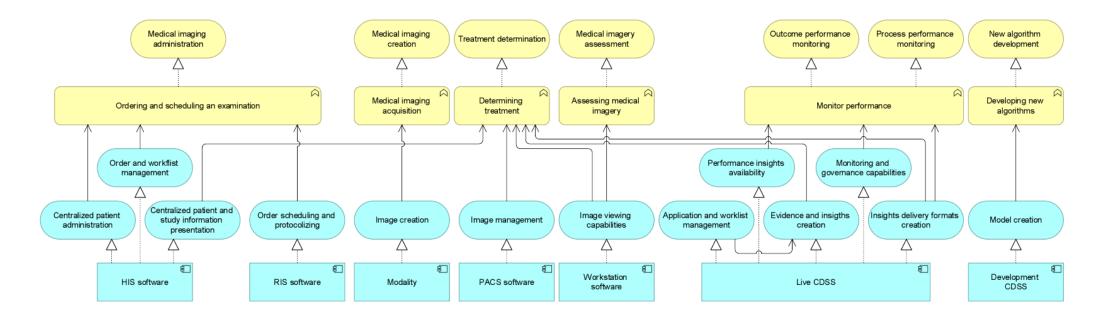


Figure 49: Service realization viewpoint of the reference architecture



# 6 Validation

Validation of the artifacts of the previous chapter is done in two parts. To show the validation of the contents of the models, architectures and overall solution design, three experts were interviewed. Two of them are experts from the Amsterdam UMC who can assess the content of the solution, the final expert can assess the form of the artifacts. One of the experts of the Amsterdam UMC was already involved with the research by iteratively validating the artifacts. Then, the practical use of the architecture is shown by applying it to the real-world case study of CAESAR. This activity is an illustration, rather than a validation as it is not possible to already implement the solution, but it can illustrate how the architecture should be used when implemented.

### 6.1 Validation by expert opinion

Finding experts to validate the artifacts was difficult since there are not many people who have the knowledge about the clinician's perspective, workflows, systems, transactions and standards in radiology. Let alone, what it would mean and take to integrate a nonknowledge-based CDSS into it. Fortunately, three experts were found. Two of these experts work for the Amsterdam UMC. One is the lead IT-coordinator for the radiology and nuclear medicine department. He is an expert in the workflow, infrastructure and standards of the radiology department and has a sense for what it would take to integrate a CDSS into this department. He can validate every artifact and was involved in the iterative development of the solution. The other is a system engineer who is skilled in the radiology standards and systems and can validate the feasibility of the solution design and the infrastructure. He was not involved in the research and was able to look at the results without any prior bias. The final expert works for SAS as a senior solution architect with 20 years of experience in solution design and architecture and can help in the validation of the artifacts in terms of form.

In the interviews with the experts at the Amsterdam UMC, they confirmed that the solution design was technically feasible. They confirmed that the hospital is able to assign the rights to any entity for the ability to create and produce studies (and they were positive that they would do this if the CDSS was validated and certified). The way in which the solution design was translated into the process models and architecture was also deemed correct. The IT-coordinator pointed out that there are two places in the process models where more than one workflow could be used. He stressed that the current way of modelling was definitely not wrong (if anything, it was the right and most automated one), but it is good to be aware of these options when applying the process models to different contexts.

- 1. In some hospitals, the RAD-7 messages are not generated by the modality but require a manual confirmation of the completion of the examination by the technologist. The content of the messages is however the same.
- 2. Receiving raw images can be done via two workflows. One in which the images are retrieved from the image archive after the modality has stored them there (as modelled in the current artifacts). One in which the modality can send the images directly to the post-processor/CDSS. Both workflows are correct, and it depends on the workflow protocol which one is implemented.

The two experts at the Amsterdam UMC specifically valued the fact that the outcomes were easily available during the MDO, consultation and the patient's bed. Furthermore, they valued the lack of disruption into the workflow and current systems. They noted that this solution provides a high-level overview that can be used in communication with stakeholders, as well as a detailed design that can be used in the development and integration of the system. Also, they stated that this design could be used as a basis for an additional integration profile in the IHE standard. A final statement of the IT coordinator stated that he often sees that people develop wonderful algorithms, but that they do not give any thought into the implementation of the outcomes. This often resulted in problems when implementation was considered as the design choices did not match the context. He found it very valuable that in this research, the activities were reversed by assessing the integration of the outcomes before the actual development.

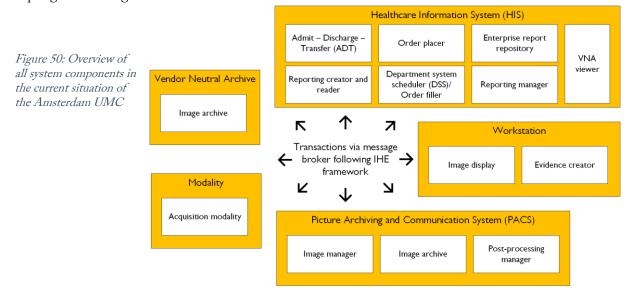
The solution architect was able to confirm that the architecture was an accurate representation of what was depicted in the solution design and the process models.

### 6.2 An illustration of the reference architecture in a real-world case

First, the as-is reference architecture will be instantiated to fit the current situation of the Amsterdam UMC. Then, the target situation will be instantiated to fit the integration of the CDSS into the Amsterdam UMC. This demonstration shows that the architecture of the product of the CDSS, despite some changes in the infrastructure of the Amsterdam UMC, will not change when it is implemented.

#### 6.2.1 INSTANTIATING THE AS-IS ARCHITECTURE FOR THE AMSTERDAM UMC

Instantiating the reference architecture for the Amsterdam UMC starts with mapping their systems and actors to the IHE framework. The Amsterdam UMC complies to the IHE framework and thus depicts the same actors (Figure 50). Yet, their organization of systems is somewhat different from the standard IHE framework. The components that previously constituted the HIS, RIS and reporting software are now embedded into one software package: EPIC. Furthermore, the archiving is performed in a somewhat different manner. The PACS system is indeed used in radiology to store images and present them to a workstation. Yet, the nature of this storage is temporary as the long-term storage is handled in a Vendor Neutral Archive (VNA). This design is chosen since the VNA can store not only radiology images, but imaging from every department of the hospital. Also, given the vendor neutrality of the archive, it is compatible with all other vendor systems in the rest of the hospital. The VNA provides viewer capabilities to EPIC as well. Allowing clinicians to view the images and evidence directly from EPIC. The PACS is however kept since it provides functionalities for image processing that is not provided by the VNA. Finally, a message broker is placed in between these systems to facilitate loose coupling and message orchestration.



Feeding these changes through in the transaction model, it is noted that there are now some extra transactions between the PACS and the VNA that transcribe the forwarding and archiving om images from the PACS to the VNA. Moreover, some transactions have a different destination now given the long-term storage nature of the VNA. Instance availability notifications (for the presentation of links to images in EPIC (the former RIS) and the storage of evidence images are send or received directly by the VNA instead of PACS as this system is now just used for temporary storage and evidence creation. The message broker is not explicitly modelled in the transaction model. This is done on purpose as this would only simplify the diagram to the point where almost every message is send to and originates from the message broker. Although a message broker is a valid design option and good practice for loose coupling, modelling it here would oversimplify the transactions and would still require to model the intelligence and rerouting of the message broker (which would in turn again resemble the transaction model as described in Figure 51). Therefore, this message broker is not modelled in the coming models.

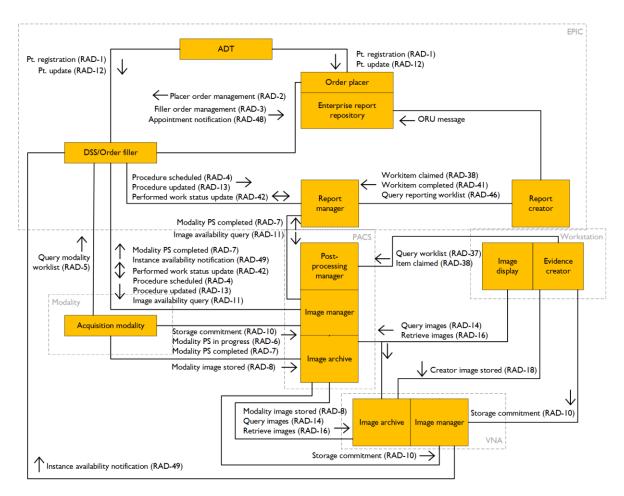
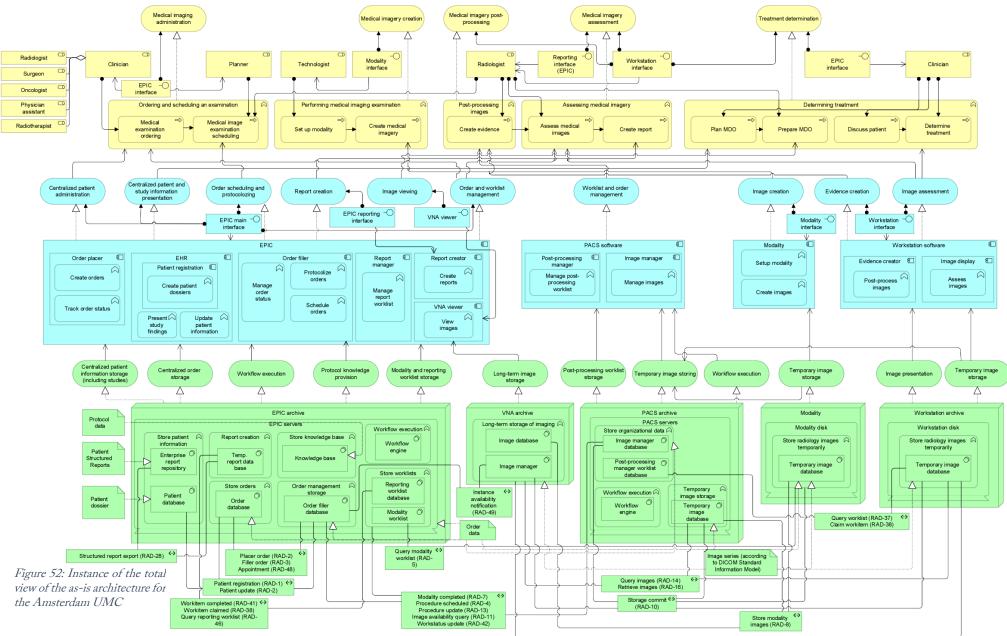


Figure 51: Overview of all transactions between system components in radiology at the Amsterdam UMC

The workflow that is supported by these system components is no different from the workflow that was depicted in the reference architecture. In the process models as well as the architecture no changes are necessary to describe the processes. In terms of the application layer, the components of the RIS, reporting software and HIS are now merged into one EPIC software component. This software also includes a component and interface that allows for the viewing of images in the VNA. Notice that the VNA itself does not have any application component in this layer since it does not provide value to the workflow of medical image examination and treatment determination. The technology layer merges the components of the beforementioned systems as well in order to create an EPIC archive. Transactions within this system, although not concerned with the outside environment, are still modeled for completion. Here, a dedicated VNA archive is modelled to show the separate environment where the images and evidence are stored long term. The total instantiation of the as-is situation for the Amsterdam UMC is shown in Figure 52.



Store creator images (RAD-18)

71

#### 6.2.2 INSTANTIATING THE TO-BE SITUATION FOR THE AMSTERDAM UMC

The instance of the as-is architecture for the Amsterdam UMC is now transformed in order to incorporate the changes and additions that emerge from the integration of the CDSS. This results in an instance of the to-be architecture for the Amsterdam UMC. If correctly designed, the CDSS product architecture will not have to change to be integrated in this target situation.

Figure 53 depicts all components that are present in the target situation of the Amsterdam UMC. The same components are replaced as in the reference architecture and no changes are necessary further.

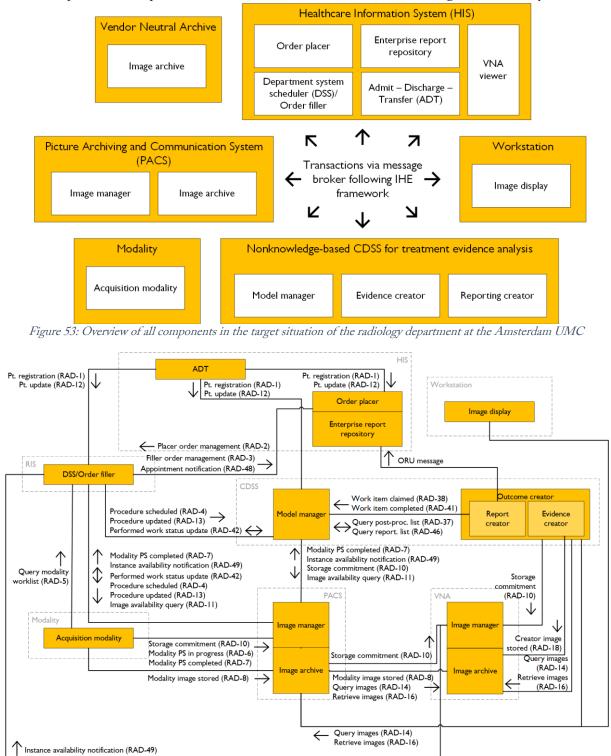


Figure 54: Transaction model of the target situation at the Amsterdam UMC

Then, the transaction model of the reference architecture is instantiated to fit the situation at the Amsterdam UMC (Figure 54). The same connections are made as in the reference architecture. However, the CDSS can now query and retrieve images from the PACS and VNA archive and instead of committing the creator images to the PACS archive, it is archived to the VNA archive. Finally, the reference architecture can be instantiated for the Amsterdam UMC (Figure 55 and Figure 56).

This demonstration shows that the as-is and to-be reference architectures can be instantiated to fit a practical case. Every case will present deviations from the reference (depicted here with the addition of a VNA) but it is shown that with little effort, the architecture can represent that situation. The CDSS product architecture does not have to change for this situation. This shows that, at least in this case, the architecture of the CDSS itself is not dependent on changes in the environment as long as this environment complies to the standards and follows the DICOM information model.

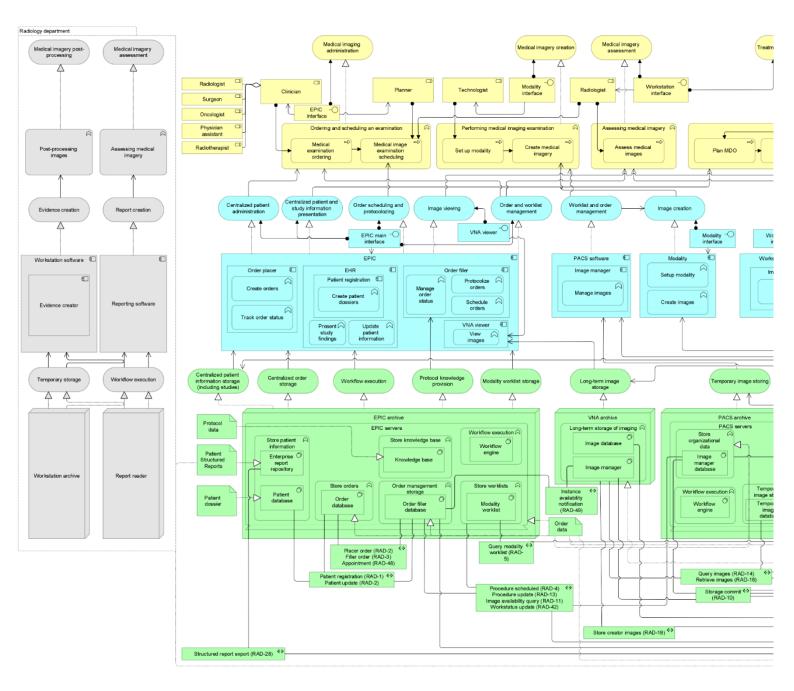


Figure 55: Total view of the architecture for nonknowledge-based CDSS for treatment evidence analysis in the radiology department of the Amsterdam UMC (part 1)

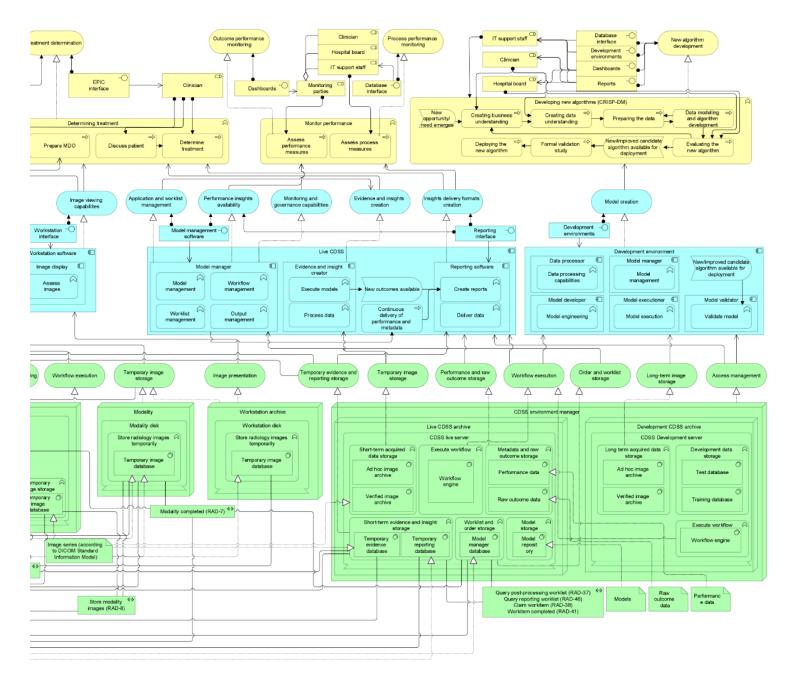


Figure 56: Total view of the architecture for nonknowledge-based CDSS for treatment evidence analysis in the radiology department of the Amsterdam UMC (part 2)



# 7 Discussion &

# recommendations

The discussion provides an explanation of all results that were obtained during the research. It presents answers to the main research question and supporting knowledge questions and discusses the main outputs of the research: a typology for CDSS in the therapeutic cycle, a reference architecture for the integration of nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure of radiology (with supporting process and transaction models) and an illustration of the practical use of this architecture using the CAESAR case study. Furthermore, this section discusses more general aspects that touch the research and relate it to other critical issues and opportunities that were noticed in the field of healthcare informatics. The section is closed with several recommendations and opportunities for further research.

#### 7.1 DISCUSSION

The main objective of the research was to solve two of the major implementation challenges of CDSS: integration into the clinician's workflow without disrupting it and integration into the infrastructure of radiology. The main research question that was posed at the beginning of the research was:

How to integrate a nonknowledge-based CDSS for treatment evidence analysis into the workflow and infrastructure of the radiology department of Dutch hospitals whilst minimizing disruption in the clinician's workflow and systems in order to improve the implementation of these types of systems?

To support the search for a solution to this question, several knowledge questions were answered.

#### What is CDSS and AI and how can we classify types of CDSS?

The field of CDSS is a very broad one. There are many different forms that a CDSS can take as long as it shows the following functionalities [30]:

- 1. The general aim of CDSS can be one or both of the following:
  - a. To make data more readily available for, or easier to asses by a human.
  - b. To create optimal problem-solving, decision-making and action capabilities for a human.
- 2. The decision support is provided to a user who can be any stakeholder in the clinical environment (from clinician to patient).
- 3. A primary task of the system is to select knowledge that is pertinent, or to process data to create pertinent knowledge.
- 4. The selection of knowledge and processing of data requires the carrying out of some inferencing process, algorithm or association method.
- 5. The result of the CDSS is to perform some action, usually to make a recommendation.

The research produced a list of 26 challenges that describe the implementation challenges of CDSS that show these functionalities. Challenges regarding the integration of a CDSS into the workflow and infrastructure were the most frequently mentioned. Finding a design for integration for all CDSS would be unachievable since there is much diversity in the systems. Despite this, there are a very limited number of typologies available that can be used to classify them. None of these typologies were deemed extensive enough to provide an ideal type. Taxonomies on the other hand are better represented, yet, they do not provide the ability to define an ideal type of CDSS. Given that the research wants to provide a reference solution for a type of CDSS instead of a point solution, a typology was needed. Therefore, this research set out to create one. It was hypothesized that a typology for CDSS should be able to specify the inner mechanisms of the CDSS itself (such as data input and analysis technique) as well as the impact that the system has on the context in which it is placed.

To specify the inner mechanisms of the CDSS an already existing typology was used [12]. It describes the division of CDSS into nonknowledge-based (using AI and (non)structured data) and knowledge-based (using a rule engine and structured data) CDSS. To specify the impact of the CDSS on the context, the primary care process and decision-making process were analyzed next.

#### What does the care process look like and how can CDSS support this process?

The research found that there are two process perspectives on what the impact of a CDSS is: one regarding the improvement of a step in the decision-making process and one regarding the improvement of a decision in the primary care process. Both processes have been extensively researched and as such, they can accurately be modelled [61] (ZiRA). What strikes is that these processes can be mapped on top of each other: the decisions in the primary care process describe an iteration of multiple cycli of the decision-making process. Together with the earlier mentioned dimension, the typology was finalized (Figure 57).

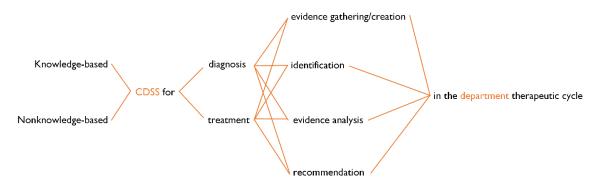


Figure 57: A typology for the classification of CDSS in the therapeutic cycle

Using this typology, it was determined that the focus of this research was on the integration of a nonknowledge-based CDSS for treatment evidence analysis in the radiology department (the CDSS of SAS). It was noted here that this means that the CDSS will primarily use data from the radiology department but can provide value in many different departments.

# What are the requirements for the integration of this CDSS into the clinician's workflow and infrastructure?

The main input for requirements for this type of CDSS were interviews with stakeholders at the Amsterdam UMC and the list of challenges in literature. A list of 13 system requirements was proposed and used when designing the reference architecture.

#### Main question

Using the provided background information, the new typology and the list of requirements, a design effort was made to create a reference architecture for the integration of a nonknowledge-based CDSS for treatment evidence analysis in the radiology department. A reference architecture was chosen as it provides a holistic overview of the end-to-end integration of value, processes, application and technology that can be used to model a current and target situation [24]. The TOGAF ADM [29] method was used to structure the creation of this architecture. Using three standards that are internationally used in radiology, a current situation of the workflow and infrastructure was designed. These standards were DICOM (a medical imaging standard) [65], HL7 (a message standard) [66] and IHE (an integration standard) [67]. The standards were used to design an as-is situation consisting of process models (showing chronology of activities), transaction models (showing the transactions between system components) and an as-is architecture that provides a holistic overview of the entire context. This showed the entire workflow and infrastructure regarding the ordering, scheduling, creating, storing, processing, assessing, presenting and discussing a medical image examination.

To develop a target situation, a solution design was introduced. This design concept provides structure to the solution that is presented in the target situation as it describes how and where the integration of the CDSS in the workflow will be handled. Using the Osheroff et al. [32] "Five Rights" framework, the candidate solution designs were assessed by determining whether they allow for the provision of the right information, to the right actors, in the right format, through the right channels and at the right point in the workflow. It was noted that an examination performed by a nonknowledge-based CDSS for treatment analysis will present the same outcomes as a regular radiology examination: it creates and uses raw data to generate evidence and insights in the form of images and reports. Therefore, the final solution design states that for a CDSS to become effective, it should be allowed to present its outcomes in a separate study (next to the regular radiology study) in the centralized information systems of the hospital (the healthcare information system (HIS) or electronic health record (EHR)). In this manner, the CDSS can provide outcomes to all clinicians, in the formats that they are used to (images and reports), through the centralized environment of the hospital (the HIS), right after a modality has acquired the images. More importantly, allowing it to create a separate supporting study ensures that no clinician will experience any disruption in workflow and work environment.

To integrate the CDSS in the infrastructure of radiology according to this solution design, the CDSS can be modelled as a substitution for the system components that are normally responsible for the creation of outcomes in a regular imaging examination. These components are the evidence creator, report creator, post-processing manager and report manager. Challenges regarding data interoperability were solved using order management. This resulted in the creation of a reference architecture for the integration of nonknowledge-based CDSS for treatment evidence analysis in the clinician's workflow and infrastructure of the radiology department without disrupting the workflow (Figure 47 and 48). The architecture was supported by process models and a transaction model. It was concluded that from a clinician's perspective, the only two changes in the workflow are 1) the addition of new protocols in the predefined list at the order placer and 2) an additional study in the patient file in which the clinician can assess the results of the CDSS. From an infrastructure perspective, integration is handled via the IHE transactions and it only requires minor changes to the configuration of message destination to integrate the CDSS. All the while the clinician can use the results in the places where it is needed: an MDO, patient consultation and bed-side consultation.

The architecture was validated by expert opinion. Also, its practical use was illustrated by applying it to the case study of CAESAR. The illustration showed that although the context and adoption of standards might differ slightly for every hospital, as long as it complies to the general structure of the IHE integration profiles, the reference architecture can be instantiated to create a valuable blueprint for the integration of CDSS (Figure 55 and 56).

The major contributions of this research are:

- A new typology that allows for the classification of CDSS in the therapeutic cycle. It can be used to determine the impact that the system will have on its environment and the inner mechanisms. This will result in the fact that implementation and integration efforts will be more focused, since different types will require different solutions. Also, it can be used in communications with stakeholders to clarify any ambiguities surrounding the goals and means of these systems.
- A first of its kind reference architecture for the integration of a nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure of the radiology department. In the field of healthcare informatics, this is the first time that an extensive analysis of the current workflows and infrastructures has resulted in a solution for these integration challenges. This brings implementation of these systems into clinical practice one step closer. Also, the architecture can be used as a basis for integration designs of other types of CDSS in other departments.
- Since the architecture uses the international standard of IHE, the architecture could be used as a basis for a new integration profile in the IHE standard that depicts the integration of CDSS providing advanced analytics.
- A valuable and concrete design for integration that SAS can use in their efforts of implementing CDSS in healthcare. They can use the findings in their communication with partners as well as in the integration of their systems. Furthermore, from the wider perspective of operationalization of analytics, SAS was shown the importance of domain knowledge when attempting to introduce innovative analytics. The approach that was taken in this research will also be generalized to form a reference approach to operationalization of AI.

To close this discussion, a number of reflecting remarks are made that surpass the scope of the research and reach beyond it to discuss more general research-related concepts.

#### Regarding the challenges surrounding the implementation of CDSS...

This research demonstrates why it is hard for CDSS to be implemented into clinical practice. This research shows that in order to provide a useful and concrete reference architecture for integration the fields of healthcare and IT have to converge into one solution. Merging these fields is hard as few people understand both domains. Especially when some of the domains are relatively new (or have sparked new attention lately). Working with a confined dataset in one's own development environment allows for the creation of great analysis with major implications if it were to be implemented. However, it is in this implementation that efforts are often seized. If real clinical impact is the goal of someone's analysis, then implementation is vital. This reference architecture for nonknowledge-based CDSS for treatment evidence analysis provides a valuable blueprint for this effort and combines many different aspects from the fields that were described here.

#### Regarding implementation of CDSS as a whole...

This research provides valuable information on how to integrate CDSS without disrupting the workflow of the clinician. However, this is not the only aspect that needs to be discussed before it can be implemented. There are three large debates that I would like to point out as aspects that will also need to progress (among many others). One of these debates is an ethical one where people ask themselves what the ethical impact of a CDSS will be. The typology can already help in this discussion, since it clearly shows that a CDSS will only make a decision if it is placed in the most mature step of the decision-making process. All other CDSS are supporting the clinician. The clinicians will always be in the lead but can now use the CDSS outcome as another diagnostic tool. People will have to realize for themselves whether they think that it is acceptable if a machine has an impact on the decision of a clinician. One clinician, in favor of CDSS, that was spoken to in this research pointed out his disagreement by stating: "would it not be more unethical to leave machines out of our medical decisions?". Another debate is a methodological one where the main issue relates to the way in which we will validate, certify and approve the CDSS (or any algorithm). Certainly, the normal procedure for medicine is too long given the speed with which analytics improve. Yet, it is undesirable to certify an algorithm too quickly. Also, and this leads to the final debate, there is no consensus on the way in which validation data can be collected and interpreted as human behavior and impact on human behavior is very hard to determine. This final debate concerns the measurement of impact of the outcomes of a CDSS. In a live environment, it is very hard to measure, whether the clinician actually uses the outcomes of the CDSS and whether this has led to a better outcome (since the other outcomes are non-existent). Smart ways of measuring this impact have to designed. The architecture already supports in this need since it allows for an advanced way of presenting outcomes (that could include active or passive measurement of impact).

Another important remark to make is that the standards that are present in the healthcare sector will play a critical role in the uptake of the system. They have provided this research with a means of creating a general as-is and to-be situation that holds for every hospital that complies for this standard. In future endeavors, they will function as a lifeline in bringing together people from other sectors. This enabled the creation of a general solution instead of multiple point solutions. Hospitals should conform to these standards as much as possible in order to speed up the integration process. On top of that, integration solutions for CDSS or AI should be incorporated in the standards. The artifacts created in this research could be a part of this standard.

#### Regarding CDSS as a whole...

CDSS is a very broad field with many different characteristics that can call themselves a CDSS. The term CDSS is used as an umbrella term that describe many different systems, in many different departments, providing very different functionality. It was thus unexpected to find out that many researchers, when talking about the implementation of these systems, spoke of the implementation of CDSS in general terms instead of for specific types (which made the proposed typology an unexpected result of the research). This was also shown by the absence of usable typologies. All implementation

efforts that have been assessed for this research focus solely on the implementation of one (real-world) system. Although this might be fine for some systems, the disregard of the larger picture and the process on which these systems have an effect lead to implementation challenges. The fifth most mentioned implementation challenge described a lack of deep knowledge of the domain which leads to faulty/imperfect system. Different kinds of domain knowledge are needed. Where clinical domain knowledge plays a vital part in developing a valuable analysis, domain knowledge about the workflows, infrastructure and decisions are vital for its implementation in daily care.

#### 7.2 LIMITATIONS OF THE RESEARCH

The research is subject to a number of limitations. One limitation is that the solution design was not validated via the hospital board. The solution requires the hospital board to approve a new entity that is allows to add studies to a patient. The research showed that this solution is technically feasible, however, it should also be organizationally feasible (the experts did however provide an indication for this). Another limitation is the fact that real world demonstration was not yet possible given the resource-consuming undertaking that this would require. Future efforts should therefore prove that the solution can be used in the real world. A final important limitation is the fact that the current reference architecture is built around an always correctly functioning workflow. In reality, workflows fail, and mechanisms should be placed in order to correct these failures.

#### 7.3 RECOMMENDATIONS AND FUTURE RESEARCH

Based on the findings in this research, the following recommendations are made:

- Recommendation 1: use this architecture in integration efforts of nonknowledge-based CDSS for treatment evidence analysis. The architecture, together with the process and transaction models depict a target situation that follows international standards and fulfill an extensive list of requirements for these types of system. Also, the main solution design allows for expanding the architecture to also fit other applications and data inputs.
- Recommendation 2: use the typology in communication with stakeholders and development of systems.
- Recommendation 3: convince the hospital boards of the design concept. Since the solution prescribes the AI as a new logical department at the hospital, it is vital that the hospital board agrees to this plan. Therefore, it is recommended to speak and convince the hospital board about this solution when starting an actual implementation process.
- Recommendation 4: use the approach that was taken in this research when creating an integration design in other departments or sectors.

Future research should focus on:

- The incorporation of imperfect workflows. IHE workflows like patient reconciliation and encounter-based imaging should be incorporated into the architecture. Other failure handling mechanisms will differ for each project and should be researched for particular cases.
- The expansion of the architecture by solving other implementation challenges (like validation and explanation of results).
- The continuation of the validation effort by applying it to more case studies and actual usage in an implementation project.
- The validation of the typology so that it can be used as a standard in the classification of CDSS to further crystalize implementation efforts for other types of CDSS.

# 8 Conclusion

#### The conclusion provides a short summary and key findings of the research.

Clinical decision support systems (CDSS) aid in the decision making of clinicians regarding the care of individual patients at the time and place that these decisions are made. These systems have proven that they can improve practitioner performance and indicate an improvement in patient outcome [8] [10] [7] [11]. The rise of artificial intelligence techniques in these systems has strengthened this [59] [36]. AI allows for the analysis of big (and unstructured) data and allows for the creation of insights at a patient level, rather than on a population level. These insights on an individual patient level aid in the development of personalized medicine: a practice in which care and treatment needs are tailored to the individual rather than the masses [1]. SAS, a data analytics company, together with the Amsterdam UMC are developing a CDSS called CAESAR. The goal is to use CT-images to assess and determine treatments for patients with colorectal liver metastases. Despite the potential of these systems, successful implementation into clinical practice is rare [12]. Numerous challenges arise when implementing these systems and thus many of the systems never live up to their potential of improving patient care. In order to improve this uptake, this research set out to find a solution to two of the major implementation challenges: 1) integration of the CDSS into a clinician's workflow without disrupting it and 2) integration of the CDSS into the current infrastructure.

An analysis into CDSS implementation generated a list of 26 challenges that arise when attempting this implementation. Also, it was found that current research treats CDSS implementation as a whole instead of focusing on specific types of CDSS. This was also demonstrated due to the lack of typologies. With the research goal of developing a reference architecture instead of a point solution, a typology was created. The created typology consists of two dimensions. One dimension allows for the specification of the data input and analysis technique that the CDSS uses, the other allows for the determination of the impact that the CDSS has on the context in which it is integrated. Using the typology, CAESAR was identified as a nonknowledge-based CDSS for treatment evidence analysis in the radiology department.

Next, the context in which this CDSS will be placed was analyzed. Using the international standards in radiology (DICOM, HL7 and IHE), it was possible to design the current workflow and infrastructure. With an extensive list of system requirements elicited from stakeholders and literature, solution designs for the integration of CDSS were assessed. The final solution design proposes that a nonknowledge-based CDSS for treatment evidence analysis can best be integrated by allowing it to present its findings in a separate study in the centralized information environment of the clinician. This will allow every clinician to access the outcomes in a form that they recognize (the same images and reports as in radiology) through a centralized access point. This ensures that the system can support the clinician without disruption in the workflow or work environment. With the solution design and radiology standards in mind, the workflow and infrastructure of the target situation was designed. The resulting process models, transaction model and reference architecture for the integration of a nonknowledge-based CDSS for treatment evidence analysis into the clinician's workflow and infrastructure of the radiology department was then validated by expert opinion and its practical use was illustrated by applying it to the case of CAESAR.

This research presented a first of its kind integration design for nonknowledge-based CDSS for treatment evidence analysis. Together with the typology and supporting models and architectures, the research provided a solution to the integration challenges that arise when implementing a CDSS and with this, brought the widespread implementation of CDSS a step closer.

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# Appendices

This chapter includes all appendices relevant to the research.

# Appendix A: SAS

SAS is a company specialized in the delivery of analytics software and solutions originally from Cary, North Carolina. SAS develops and markets a suite of analytics software, which helps access, manage, analyze and report on data to aid in decision-making. The company is the world's largest privately held software business (14,052 employees and \$3.2 billion in revenue as of 2016) and its software is used by most of the Fortune 500.³

Their vision is to transform a world of data into a world of intelligence. They envision a world where everyone can make better decisions, grounded in trusted data and assisted by the power and scale of SAS analytics. When decisions happen at just the right moment, advancements are set in motion and the world moves forward. Their mission is to empower and inspire with the most trusted analytics. To make it easier for more people to use powerful analytics every data, to shorten the path from data to insight – and to inspire bold new discoveries that drive progress. The result is analytics that breaks down barriers, fuels ambitions and gets results.⁴

# Appendix B: colorectal cancer (CRC)

The CAESAR-case focuses on optimizing decision making in the process of colorectal liver metastases treatment. These metastases emerge after or synchronous to a form of colorectal cancer. Colorectal cancer (or bowel cancer/rectal cancer/colon cancer) is any cancer that affects the colon and the rectum. It can be benign, or non-cancerous, or malignant. Malignant forms of cancer can spread to other parts of the body. Since this case is the main motivation for this research, understanding of these diseases upon which it focuses is essential for the creation of domain knowledge. This appendix discusses the anatomical and pathological characteristics of the diseases including diagnosis, disease development and treatment options. This appendix shows the complex assessments that clinicians have to make in order to treat a patient with colorectal cancer or liver metastases.

#### **B.I STATISTICS**

Colorectal cancer is an important health issue. More than 14.000 new patients are diagnosed with CRC in the Netherlands, 4000 people pass away⁵. Numbers show that there was a peak of newly diagnosed patients in 2015 (see Figure 58⁶). The decrease probably occurred due to better screening in a national research that started in 2014. According to the American Cancer Society, it is estimated that 1 in 21 men and 1 and 23 women in the United States will develop colorectal cancer during their lifetime⁷. It is thus slightly more prevalent in males. It is the second leading cause of cancer death in women, and the

³ https://en.wikipedia.org/wiki/SAS_Institute

⁴ https://www.sas.com/en_us/company-information/vision-mission.html

⁵ https://www.oncoline.nl/colorectaalcarcinoom

⁶ https://www.cijfersoverkanker.nl/

⁷ https://www.medicalnewstoday.com/articles/155598.php

third in men. Also, the disease is very common in Western countries, but rather infrequent in Africa and some Asian countries. In terms of distribution within the organ, carcinomas in the left bowel are most prevalent (70%). Colorectal liver metastases appear in 50% of all cases with CRC [6]. The survival rate among those afflicted is (only) 20%. Being able to diagnose early-stage forms of CRC greatly increases the prognosis for recovery or containment. Later-stage diagnosis on the other hand results in slim chances at recovery.

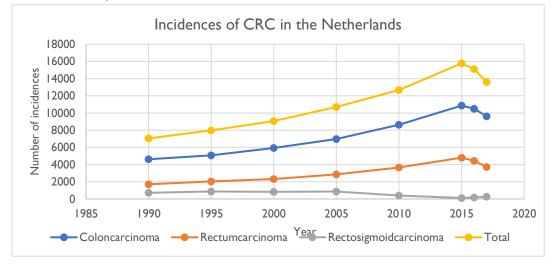


Figure 58: Incidences of invasive CRC in the Netherlands throughout the years for men and women

#### **B.3 ANATOMY AND FUNCTION OF THE COLON**

The colon is situated in the lower torso and surrounds the small intestine. Relevant parts of the colon are the appendix, cecum, ascending colon, transverse colon, sigmoid colon and rectum (Figure 59). The colon is the last organ in the digestive tract and its main function is thus concerned with digesting. Before the waste enters the colon, it has first passed the esophagus before entering the stomach. Then, it passes through the duodenum. When food arrives in the colon, it is almost fully digested. In the colon, the remaining waste is reduced by extracting water and salt. This is transported via mucous membrane and blood. It starts at the end of the small intestine and ends with the anus. The length is in the order of 100 to 150 cm. The

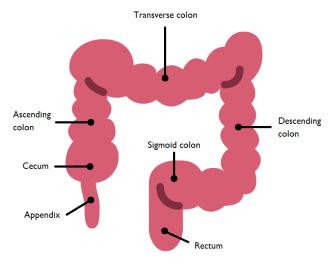
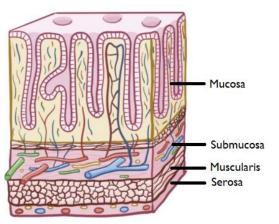


Figure 59: Anatomy of the colon

walls of the colon can be divided into four layers: serosa (outermost layer), muscularis (containing muscles), submucosa (containing blood vessels and lymphatic flow) and the mucosa (Figure 60). The mucosa has invaginations called intestinal glands or colonic crypts. The muscularis layer is covered by two layers of circular and longitudinal smooth muscle cells. Contraction of the external longitudinal muscle layer accounts for the appearance of the characteristic haustrations (pouches that give the colon a segmented appearance). The blood supply to the colon (in the submucosa) is provided from the superior mesenteric artery (artery branched off from the aorta) and the inferior mesenteric artery. The



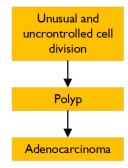
large majority of venous blood (blood that will return to the heart and lungs) leaves the colon through the portal system and, thus, reaches the liver. It is important to mention this blood flow as metastasis are often found in the liver due to this flow. Lymphatic flow takes place through channels that parallel the blood vessels and is drained by lymph nodes. Colon cancer emerges most often in one of several areas of the colon: right colon (ascending, and transverse), left colon (descending colon and sigmoid), and the rectum.

Figure 60: Colon wall layered structure

#### **B.4 PAHTOLOGY OF COLORECTAL CANCER**

All cancers have one characteristic in common: it concerns the uncontrolled cell proliferation resulting in abnormal growth of cells that have the ability to invade or spread to other parts of the body. This is no different for colorectal cancer. The earliest phases of colorectal tumorigenesis (the process of tumor

development) starts in the normal mucosa, with a generalized disorder of cell replication [74]. This appears in clusters of enlarged colonic crypts that show biochemical and biomolecular abnormalities. The large majority of colorectal malignancies (something evil in nature) develop from adenomatous polyps that grow in the intestinal glands. A polyp is a growth of tissue from the inner lining of the colon in the lumen (hollow center) of the colon. Adenomatous polyps are a type of polyp who appear in intestinal glands that look much like the normal lining but with an abnormal growth pattern. An adenoma can be considered malignant when the tumor cells (who proliferate uncontrollably or do not die) pass through the muscularis mucosa and infiltrate the submucosa. At that point,



it is often called an adenocarcinoma. To summarize, adenocarcinomas are malignant polyps who have emerged due to unusual and uncontrolled cell division in the inner layer of the colon wall (the intestinal glands). Colorectal carcinoma

*Figure 62: Adenocarcinoma development* 

can be graded into well, moderately and poorly differentiated lesions: there is little evidence, however that grading may be of help in evaluating prognosis of affected patients [74]. In a normal healthy colon, part of the mucosa is an actively proliferating and self-renewing system. In these conditions, replication

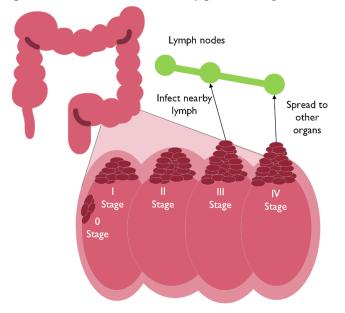


Figure 61: Colorectal cancer disease development (Berkel)

takes place in the lower three quarters of the colonic crypts. In the upper quarter and on the surface of the crypts, it is absent. This ensures that cells move upwards into the most superficial part of the glands and are then extruded from the mucosal surface. Now, an adenomatous polyp appears, before evidence suggests that other alterations can be detected first [74]. For instance, the process of tumorigenesis may begin with a generalized disorder of cell replication and differentiation which results in cells becoming unable to repress DNA synthesis during migration from the lower portion to the upper portion of the crypt. Since, in normal conditions, this ability is repressed, the proliferation area in these glands expands. Another indication of early tumorigenesis is the vast increase of abberant crypt foci (ACF).

Once a carcinoma has been developed, Dukes' staging is used to describe its growth (Figure 61). In stage 0, the carcinoma has not grown beyond the inner layer (the mucosa) of the colon or the rectum. In stage I, the carcinoma has grown through the submucosa (T1) or muscularis (T2). It has however not yet spread to nearby lymph nodes or to distant sites in this stage. In stage II, tumors have invaded through the muscularis into the subserosa and pericolic tissues (T3), or infiltrate the visceral peritoneum invading other organs (T4). In stage III, there is a metastasic involvement of lymph nodes (N1 for 1 to 3 nodes; N2 for more than 3 nodes). Finally, stage IV tumors metastasize to the liver, lung or other organs.

#### **B.5 PROTOCOLS AND GUIDELINES FOR CRC IN THE NETHERLANDS**

#### Diagnostics

Colonoscopy is the standard for the detection of colorectal carcinomas because of the combination of high sensitivity and high specificity. Sensitivity describes the percentage of correct positive results among ill patients. Specificity describes the percentage of correct negative results among non-ill patients. CT-colography, MR-colography or X-colon can be considered as alternatives for a full colonoscopy. During a colonoscope, clinician can use routine tattooing to mark the polyp. This tattooing is essential for a planned laparoscopic resection and for endoscopic removal of a clinically malignant looking polyp.

There are four important moments where imagery of liver metastases plays a role:

- During the diagnostics and treatment of a colorectal tumor (detection of synchronous liver metastases)
- In the follow-up (for metachronous liver metastases). It is recommended here to make a scan of the entire abdomen.
- During determination of resectability (the ability to remove by surgery) of liver metastases
- During evaluation and follow-up after or during treatment of liver metastases.

In case of doubt about the presence or nature of liver metastases, repeat the examination every three months. MRI has the preference over CT when it comes to treatment of patients with colorectal liver metastases. This is due to the better detection of lesions under 10mm. An FDG PET(-CT) can be used as a supplementary examination. It is not recommended to perform puncture in the liver.

#### Primary treatment colon carcinoma (Stage I and II)

When treating a (moderately) well differentiated T1 invasive carcinoma in a polyp (one of the earliest stages) with a radical resection (resection margin of less than 1mm) and without (lymph)angioinvasion (infiltration in blood vessels or lymph nodes), polypectomy suffices. In a polypectomy, the polyp is removed from the colon. This is often done during a coloscopy. Radical resection refers to the removal of blood supply, lymph nodes and sometimes adjacent structures of a diseases organ or tumor. In all other cases, additional surgery is to be considered. This is the case for carcinoma's that are badly differentiated, and/or are (lymph)angioinvasive and/or have a resection margin equal to or larger than 1mm.

In a sessile malignant polyp (not moving) where the resection margin cannot be assessed or where the polyp is removed using piecemeal resection (gradual resection), a surgical resection needs to be considered.

In case of clinical suspicion of a malignant polyp the location of the polypectomy needs to be marked with two to three markings. This is done for potential additional resections. These markings can also be used to relocate scars tissue in order to check for residue or local relapse.

When this additional surgery is actually needed, a formal oncological colon resection needs to be performed. This includes an adequate mesocolon lymphadenectomy (removal of the lymph nodes close to the colon).

When surgical resection is considered after endoscopic (using a coloscopy) removal of a malignant polyp, the decision should always be a weighted decision where the patient is fully informed about the oncological advantages on the one hand and the possible complications (perforation and bleeding) on the other hand.

If endoscopic removal of a malignant polyp has taken place, staging and follow-up needs to be performed according to the advices regarding T1 colon carcinomas. Endoscopic follow-up of the polypectomy scars is recommended to take place after three and six months. In this follow-up, the clinician can check for local radicality (full removal of the tumor).

When treating a T4 colon carcinoma, the aim should be to perform a R0 resection (radical resection). In this case, preoperative imaging and discussion in an MDO is essential for the decision regarding possible referral to an expertise center, neoadjuvant treatment and planning of the resection. Neoadjuvant therapy (chemotherapy or chemoradiation) are to be considered when the CT-scan of the abdomen initially shows that a radical resection cannot be performed. During the MDO, the decision between chemotherapy and chemoradiation has to be made. When there appears to be a fixed tumor process with risk of non-radical resection, the tumor should remain in-situ (in the place where it originally formed).

#### Adjuvant systemic therapy (Stage III and IV)

Adjuvant systemic therapy is needed for patients with stage III and IV colon carcinoma. As said before, stage III colon carcinoma can be identified when metastases in the resection specimen of the lymph nodes are located, but not in the surrounding organs. Stage IV concerns the development of metastases in distant organs. On top of that, a risk group of Stage II patients is identified by assessing the following histopathological features: presence of T4 carcinoma(s), less than 10 lymph nodes examined, obstruction/perforation during presentation, vascular invasion, bad and undifferentiated tumors. In assessing metastases in the lymph nodes, tumors of max 0,2 mm are to be treated as negative glands.

For these stage III patients, it is recommended to start a chemotherapy consisting of fluoropyrimidine (capecitabine or 5-fluorouracil/leucovorin) plus oxaliplatin (CAPOX or FOLFOX). In case of a contraindication for oxaliplatin, the treatment should consist of capecitabine monotherapy or possible 5FU/LV. If the patient has an MSI carcinoma, only supply the oxaliplatin containing chemotherapy with fluoropyrimidine as it is unclear what the effect of fluoropyrimidine monotherapy is on these patients. For stage II patients in the high-risk group, adjuvant chemotherapy consisting of oxaliplatin can be considered. If these patients however have an MSI carcinoma, then it is recommended to abandon this treatment. Older age (above 70) should in itself not be a reason to not supply adjuvant treatment. Adjuvant treatment has a duration of 6 months and should ideally start within 6-8 weeks after the resection of the colon carcinoma. However, it should start within 12 weeks of the operation the latest.

#### Metastatic diseases

Every patient with colorectal liver metastases should be discussed by a center with expertise regarding liver surgery, local treatment techniques of the liver and the (metastasized) colorectal carcinoma. In general, partial liver resection has the preference above all else if the patient meets the criteria for resectability. These criteria are:

- In case of normal liver parenchyma and no neoadjuvant systemic therapy, at least 20% of the liver should remain after the resection.
  - In case of too little remaining liver parenchyma after resection, induction systemic therapy, and/or vena-portae embolization, and/or 'two-stage' resections should be considered.
- No absolute contra-indications. This is assessed based on number of metastases, size of metastases, synchronicity, extra-hepatic metastases, stage of primary tumor, age and value of the CEA serum.

Simultaneous surgery of both the primary tumor and synchronous metastases is no standard. If a patient develops new liver metastases after a previous surgery, re-resection is advised if the patient meets the criteria for resectability. If patients do have extra-hepatic metastases, a resection can still be considered.

If a patient does not meet these criteria but has liver metastases with a relatively low circumference (up until 3 cm), local thermal ablation is an important treatment. It is important to note that this treatment is not a replacement for patients with resectable metastases. Other treatments are isolated liver perfusion, trans arterial chemoembolization, yttrium-90-radio-embolisation and stereo tactical radiotherapy.

Systemic treatment can also be applied to treat metastatic diseases. The type of treatment is determined by a classification in patients:

- Patients with primary resectable metastases (goal: curing the disease)
- Patients with primary irresectable, but potentially resectable metastases when response to the systemic therapy is substantial (goal: curing the disease).
- Patients with permanently irresectable metastases (goal: extending life with preservation or improvement in quality of life).

#### Aftercare

In general, for every hospital and every patient, it has to be clear who is coordinating the follow-up. Also, in the first two to three years, a biannual check-up has to take place. Then, up until five years after the operation, an annual check-up is required.

In terms of imagery and CEA in stage I – III patients. Echography of the liver or a CT-abdomen is recommended biannually for the first two years. Then again, up until five years, an annual scan is recommended. A CEA test is recommended to be performed every three to six months in the first three years. Then biannually up until five years after treatment. It is also recommended to perform a colonoscopy one year after the treatment (or after three months if this was no possible pre-operation). If this is not possible, a CT-colography is good alternative.

## Organization of care

Care for patients with CRC or colorectal liver metastases should be carried out by a specialized team. This team has to have an MDO every week. In the diagnostics phase, findings are to be discussed collectively. During these talks, a surgeon, gastro-enterologist, internist-oncologist, radiologist, radiotherapist, pathologist, case manager and possibly other nurses like a stoma nurse are present. The goal of this pre-treatment MDO is to draw up an effective as possible treatment plan, if this is necessary, determine whether other diagnostics are necessary.

#### **B.6 CAREPATHS FOR CRC AND COLORECTAL LIVER METASTASES**

The guidelines as described in B5 can be summarized in a flow diagram to show the carepath of patients with colorectal carcinoma and colorectal liver metastases. This flow diagram is provided by the Integraal Kankercentrum Nederland (IKNL; Integral Cancer Center Netherlands) and shows a template of a carepath for hospitals.

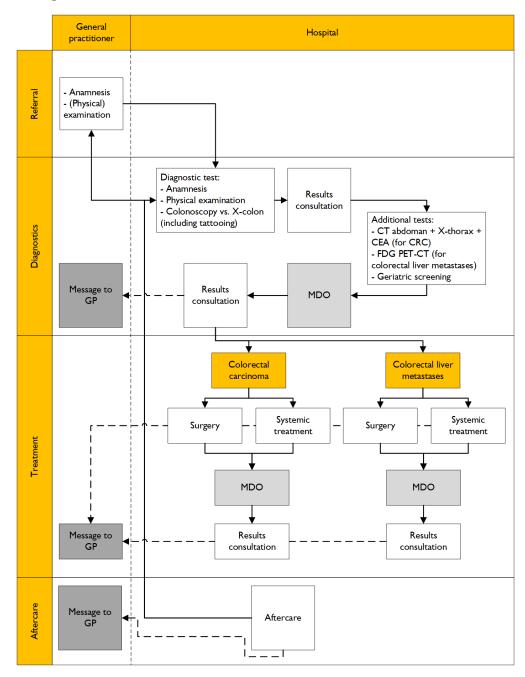


Figure 63: Schematic carepath for CRC and colorectal liver metastases

# Appendix C: determining the architecture design methodology

This appendix depicts the way in which the methodology for architecture design was determined.

# C.I STATE-OF-THE-ART IN ARCHITECTURE DESIGN

A general approach to the modelling process consists of five generic steps [24].

- *Establishing the purpose, scope and focus of the architecture.* Since modelling is a goal-driven activity, the stakeholders, purpose and the relation between these should be accurately determined. The scope and focus describe which parts of reality will be described in the model and with which detail.
- Selecting one or more viewpoints. Viewpoints define abstractions on the set of models representing the enterprise architecture, each aimed at a particular type of stakeholder and addressing a particular set of concerns [24]. This allows a stakeholder to look at the architecture from their point of view. Defining these viewpoints provides a guide in determining what information should be included in the model, given the stakeholder.
- *Creating and structuring the model.* In this stage the required information is gathered and used to create, structure and visualize the architecture.
- *Visualizing the model.* Depending on the viewpoints and needs of stakeholders, one or more appropriate ways for visualization are selected.
- *Maintaining the model.* Modelling is an iterative approach and appropriate care is therefore necessary to keep it relevant.

To add to these steps and describe them in more detail, several enterprise architecture frameworks are considered (as they show the layered structure that the research is trying to achieve). These frameworks structure architecture description techniques by identifying and relating different architectural viewpoints and the modelling techniques associated with them. The Zachman framework [75] for information systems architecture was introduced in 1987 as the first and best-known enterprise architecture framework. It provides a taxonomy for relating the concepts that describe the real world to the concepts that describe an information system and its implementation [75]. Although this framework is very well-known and easy to understand, the number of cells in the framework (views) limit the practical applicability [24]. Also, there is no specific method for the development of these architectures. Another very well-known framework is The Open Group Architecture Framework (or TOGAF) [29]. This framework provides numerous concepts that can be used in the design, development, implementation and maintenance of enterprise architectures. One concept related to development is the architecture development method (ADM). This method provides 'a way of working' for architects. It is considered as the core of TOGAF and consists of a stepwise cyclic approach for the development of the overall enterprise architecture [29]. Since the TOGAF ADM is a well-known and complete method for the development of architectures, this framework is used.

As of version 9.2, the TOGAF ADM consists of the following phases (Figure 64).

- A. Architecture vision: the cycle starts with efforts to develop a high-level vision of the value that has to be delivered as a result of the proposed architectures. It includes the identification of purpose, stakeholders, scope and current business landscape and together forms an architecture vision for the project.
- B. Business architecture: to develop a target business architecture that describes how the enterprise needs to operate to achieve its goals. It shows the processes that support the architecture vision.
- C. Information systems architecture: to develop a target information systems architecture (divided into a data architecture and an applications architecture) that describes how it will Figure 64: The TOO enable the business architecture and the architecture vision.

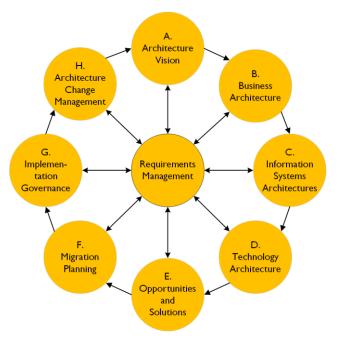


Figure 64: The TOGAF Architectural Development Method

- D. Technology architecture: to develop a target technology architecture that enables the business, data and application architecture and the architecture vision.
- E. Opportunities and solutions: to generate the initial complete version of an architecture roadmap, based upon a gap analysis. This is then used to determine whether an incremental approach the target architecture is required. If this is the case, transition architectures that will deliver continuous business value are developed. This means that the target architecture is this phase will be finalized as well.
- F. Migration planning: to finalize the architecture roadmap and a supporting implementation and migration plan. In this phase, communication of business value, work packages and transition architectures to key stakeholders is vital for a common understanding
- G. Implementation governance: to ensure conformance with the target architecture by implementation project.
- H. Architecture change management: to ensure that the architecture lifecycle and architecture governance is well executed and to monitor that the architecture keeps meeting the requirements
- I. Requirements management: the continuous process of managing architecture requirements that were identified during any execution of the ADM cycle are managed and readily available in each phase.

# Appendix D: process results of the systematic literature review

This appendix shows the systematic execution of the literature review into the object of study. The literature on other subjects was found using a set of high quality papers and applying snowballing and backwards reading techniques [76].

# D.I A METHODOLOGY FOR SYSTEMATIC LITERATURE REVIEWS

To acquire background knowledge on the subject, a literature review is executed in a systematic way [77]. This means that first, search assignments are determined. Secondly, inclusion and exclusion criteria are stated. These criteria create a scope and are used to shorten the list of references that are obtained using the search assignments. Thirdly, the search assignments are executed, and duplicates are removed from the results. Fourthly, the articles are examined using the inclusion and exclusion criteria. Fifthly, the shortened list is read and articles that are not valuable are removed. Also, using backwards reading and snowballing [76], other interesting articles are added. The concepts are then merged and used in the discussion below. The results of the review are discussed in the next sections.

## **D.2 AI POWERED CDSS**

The knowledge that has to be acquired is on AI powered CDSS as this will create a basic understanding of the object of study. In the first step of the literature review, search assignments are determined that are going to be used in the literature databases (Table 3). These search assignments are created based on questions that have to be answered in the study. These questions were:

- What are CDSS?
- Which types of CDSS exist? What are their differences?
- What is AI for image analysis?
- Which types of AI exist for image recognition? What are the differences?
- What are the characteristics of an AI powered CDSS for image analysis?
- Which challenges are present when implementing AI powered CDSS?

The search assignments are executed in Google Scholar⁸, LISA⁹ and Web of Science¹⁰. They are exported to Endnote¹¹ using the export function where they are managed properly.

Search term	Purpose
Clinical Decision Support Systems	To learn about CDSS and the different types of
	CDSS in general
CDSS literature review	To learn about CDSS in general
CDSS image recognition	To learn about a specific type of CDSS
CDSS implementation challenges/barriers/	To learn about CDSS challenges
problems/issues/obstacles	
AI image recognition	To learn about AI for image recognition
AI image recognition typology/classification	To learn about types of AI for image recognition

Table 3: Search assignments used in the literature	review
----------------------------------------------------	--------

A summary in Table 4 shows the results of these search assignments. Since the search terms for some of the assignments are rather broadly defined, many assignments yielded a large number of results. In the table, the exclusion criteria of the exclusion of the 31st hit is already implemented.

⁸ https://scholar.google.nl/

⁹ https://www.utwente.nl/nl/lisa/bibliotheek/

¹⁰ http://apps.webofknowledge.com

¹¹ https://endnote.com/

Search term	Google Scholar	Web of Science	LISA
Clinical Decision Support Systems	30	30	30
CDSS literature review	30	28	30
CDSS image recognition	30	1	4
CDSS implementation challenges	30	30	30
AI image recognition	30	30	30
AI image recognition typology/classification	30	0	4

Table 4: Results of the search assignments in the different databases

In total, 427 references were found. After removing duplicates, 312 remained. Then, the results (stored in Endnote) were assessed based on their title and abstract (or even more if these two parts do not make it clear) using a number of inclusion and exclusion criteria (Table 5).

Inclusion criteria	Exclusion criteria
The paper discusses CDSS in general,	The paper discusses a specific type of CDSS that is not
without focusing on one specific type	AI powered or focused on image recognition
An exception to the criterium above is	The paper discusses a typology that does not include AI
when the focus is AI powered CDSS	powered CDSS
and/or medical image recognition CDSS	
The paper discusses a CDSS typology for	The paper discusses challenges that do not apply to AI
all CDSS or for AI powered CDSS	powered CDSS
The paper discusses challenges that emerge	The paper discusses forms of AI that are not relevant to
when CDSS are implemented	the type of CDSS present in this research
The paper explains how AI can be used for	The paper discusses a typology where AI for image
image recognition	recognition is not present
The paper presents a classification of AI	When there are a lot of results for a search assignment,
powered image recognition or AI in	papers on rank 31 and below are not taken into account
general (that includes image recognition)	
	When there are a lot of book in the search results, the
	most cited books are used, the rest is discarded.
	The paper discusses a specific instance of a CDSS or AI
	that is not of the same type as the CDSS or AI in this
	research
	The paper discusses the acceptance of new technology
	(including CDSS)
	The paper is not written in English or Dutch
	Citations and patents are excluded from the research
	The paper is not peer-reviewed

Table 5: Inclusion and exclusion criteria used to assess literature

The result of this assessment was that 106 articles remained for further analysis. In total 38 were included in the related work. 15 more articles were added using snowballing and backwards reading. This resulted in a total 52 of included articles in this part of the background.

# Appendix E: artificial neural networks (ANN)

This appendix covers the basic artificial neural network understand by using the 'hello world'-equivalent for machine learning: recognizing the integers of 0-9 from handwritten numbers. This is done to provide a background into the inner mechanics of the CDSS that is the topic of this research. This case is presented many times and written down in detail by Nielsen [78]. The artificial neural network is a multi-layer perceptron (MLP), one of the earlier ANNs. Despite its age, decreased use and superior competitors, it is still a very useful network to discuss in order to show the inner workings of an ANN. The section starts by addressing the basic concepts and structure of an ANN. Then, the way in which the structure learns is discussed. After that, the backpropagation algorithm is presented in conceptual form and then in mathematical form. The section is concluded with differences between an MLP and a convolutional neural network (CNN).

#### **E.I THE CHALLENGE**

People are, often without realizing enough, the most extreme wonders in the world. Our visual system is one of those wonders as well. Take for instance the sequence of written digits in. Without any effort, we are able to recognize this as 504192. This lack of effort is deceptive however. What happens in our brains is that millions of neurons and billions of connections

504192

*Figure 65: Hand-written number sequence* 

are ready to fire whenever we see something. This is the results of millions of years of evolution and therefore, for a machine, this task is not so trivial. Hard coding machines into recognizing numbers is hard. Writing a statement that says "an 8 are two loops on top of each other" is already hard. Adding in the fact that handwriting has lots of variations and you end up drowning in exceptions and special cases. Neural networks however do not use hard coding, but instead, uses a set of training data (labeled handwritten numbers) and learns from this training set to infer rules for recognizing handwritten digits [78].

#### **E.2 THE STRUCTURE: ARTIFICIAL NEURONS AND LAYERS**

To understand how they do this, the concept of an artificial neuron is explained. An artificial neuron takes several numerical inputs, say  $x_1, x_2, x_3$  and produces a single output. These inputs all have a respective importance when determining the output of the artificial neurons. These weights are expressed as  $w_1, w_2, w_3$ . The output of such a neuron would just be the weighted summation of all the inputs  $= \sum_j w_j x_j$ . For notation purposes, we can notate this as a dot product where w and x are vectors whose components are the weights and inputs so that  $\sum_j w_j x_j = w \cdot x$ . On top of that, a bias can be introduced to push the neuron into being likely to be active (positive bias) or likely to be inactive (negative bias). It can be seen as a threshold statement. We call this bias b. So, to indicate the output of an artificial neuron  $= w \cdot x + b$ . There is however one problem with this statement, the outputs of the neuron using this function can be really large or small numbers. We want to normalize these values to

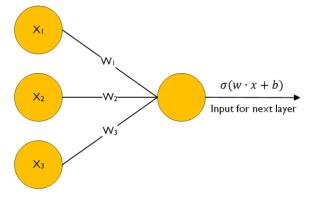


Figure 66: Basic structure of an artificial sigmoid neuron

produce outputs between 0 and 1. To do this, we use a sigmoid function where  $\sigma(z) = \frac{1}{1+e^{-z}}$ , so that the output of an artificial neuron is  $\sigma(w \cdot x + b)$ . The sigmoid function has two asymptotes for y=0 and y=1 and therefore it is very effective for normalization here. This type of neuron is called a sigmoid neuron (Figure 66). By tweaking the bias and the weights of the connections between neurons, we can change the outcome of an artificial neuron to ensure that we get the result that we are looking for. This property is very useful for learning. For example, the network classifies a "3" as an "8". By altering the weights and biases minimally, we can incrementally correct the network. Doing this over an over will eventually produce better outputs. The network would be learning.

The output of one neuron can then be used as the input for another neuron to create a layered structure (Figure 67). The first layer that inputs the data into the network is called the input layer. The layer producing the eventual output is the output layer. The neurons in the layers in the middle are called hidden layers as they are neither input nor output neurons.

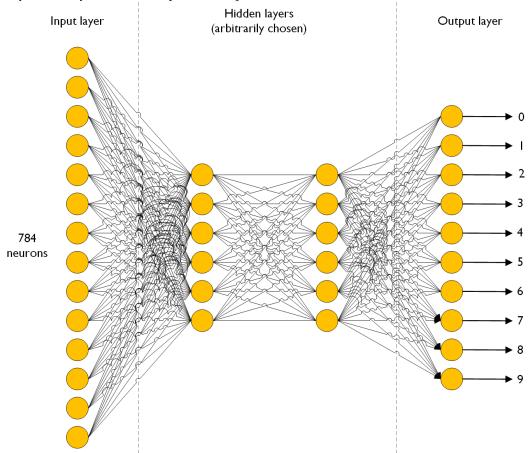


Figure 67: The structure of an artificial neural network able to recognize hand writing

With this structure, we can build an architecture for a simple network that is able to classify handwritten digits. In this example, the network is fed images with a 28x28 pixel measurement. Each pixel is an input value depending on its greyscale value between 0 (white) and 1 (black). In total, there are 28 x 28 = 784 input neurons. The output neurons in turn represent the digits that the network is supposed to classify (0-9). The network will output the number corresponding to the neuron with an output of  $\approx 1$ . Figure 67 shows these layers. For esthetical reasons, this figure also shows two hidden layers. However, for this example we only need on hidden layer with n = 15 neurons. This number is arbitrarily chosen and can be experimented with. Before diving into the math behind a neural network, the outputs of the hidden layers are explained conceptually by comparing it to how humans recognize digits. After all, the artificial neural network is based upon our biological neural network. This will help in creating an understanding of what the neural network might be doing later. Take for example the number 9. To recognize this, humans break down the image into smaller segments. For instance, a circle at the top and an edge at the bottom right. This might be the output of the second to last layer. But these subcomponents can be dissected even further. A circle can be dissected into four arcs in four corners. The edge might consist of two short edges at the right side, making sure that it is not an 8 for instance. Now, when these neurons spike in a particular fashion, as shown in Figure 68, they will in turn activate neurons in the next layer which group these subcomponents into bigger subcomponents. Doing this iteratively, will eventually allow the network to recognize the number that it is shown.

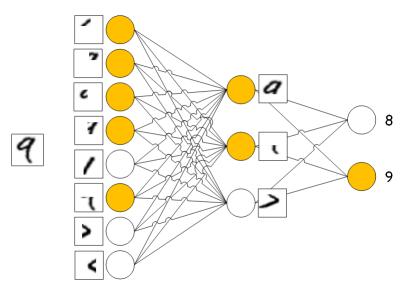


Figure 68: Example of an artificial neural network (orange = 1, white = 0).

#### **E.3 LEARNING WITH GRADIENT DESCENT AND BACKPROPAGATION**

We start with a large amount of training data. Let's denote x as a training input (this is a  $28 \times 28 = 784$ dimensional vector) and the desired output as y = y(x). For example, if a training image x represents a "3", then  $y(x) = (0,0,1,0,0,0,0,0,0)^T$ . Where T is the transpose operation, turning a row vector into an ordinary (column) vector. What we want to achieve is to have an algorithm that adjusts the weights and biases in such a way that the output from the network approximates y(x) for all training inputs x. To quantify how well the system is performing, we define a cost function. This cost function shows the mean squared error of the network

$$C(w,b) = \frac{1}{2n} \sum_{x} ||y(x) - a||^2$$

Where a is the vector of output from the network when x is the input. The goal for C is to approximate 0. To do this, the algorithm of gradient descent is used. Picture the cost function as a function with for instance 3 variables. Plotting this function will result in a graph spanning three planes (x, y, z). To minimize *C*, the global minimum has to be found. Finding this for a three-variable function can be done with derivatives, but it is impossible when working with the large amount of variables that is common to a neural network. What can be done however, is to start from an arbitrary point in the function and determine where the slope in that point decreases the most and then move in that direction. Doing this iteratively will results in landing on a point where there is no decrease and where thus a minimum is found. This can be done by calculating the gradient  $\nabla C$  (which shows the most positive slope) and then moving in the opposite direction. Note that there is no prove that it will find a global minimum. It does however certainly find a local minimum. Feeding an entire large dataset to the model would make an iteration very slow as the process of finding the negative gradient descent for every training can take a long time. To make the algorithm computationally cheap, the set of training data is fed to the network in batches. This is because the cost function requires the average of all differences between the output (a) and the truth (y(x)). Being that the training set is very large, this can take a long time. Therefore, stochastic gradient descent is introduced that feeds the data in batches so that the network can optimize after each subset of data.

One very important thing has not been discussed yet. How does the network compute all gradients and ultimately change the weights and biases to improve performance? The answer is via the backpropagation algorithm; the workhorse of learning in neural networks. At the heart of backpropagation is an expression for the partial derivative  $\partial C/\partial w$  of the cost function with respect to w (or bias b) in the network. It shows how quickly the cost changes when one changes the weights and biases and gives us an indication into how much the impact of change will be.

To explain it, first some notations. We'll use  $w_{jk}^l$  to denote the weight for the connection from the kth neuron in the (l-1)-th layer to the *j*-th neuron in the *l*-th layer. The same type of notations is used for the bias  $(b_j^l)$  and the activation  $(a_j^l)$ . The activation of  $a_j^l$  of the *j*-th neuron in the *l*-th layer is related to the activations in the (l-1)-th layer by the equation where the sum is over all neurons k in the (l-1)-th layer. (Note that this equation shows a lot of resemblance with the earlier equation of  $w \cdot x + b$ ).

$$a_j^l = \sigma(\sum_k w_{jk}^l a_j^{l-1} + b_j^l)$$

Transforming this into a matrix form gives

$$a^l = \sigma(w^l a^{l-1} + b^l)$$

This equation gives a global way (instead of neuron by neuron) of thinking about how the activations in one layer relate to activations in the previous layer. By introducing  $z^{l} = w^{l}a^{l-1} + b^{l}$  (the weighted input to the neurons in layer l) we can shorten the equation even further and receive a useful quantity for further use.

$$a^l = \sigma(z^l)$$

To compute  $\partial C/\partial w_{jk}^{l}$  and  $\partial C/\partial b_{j}^{l}$ , we need to introduce one final quantity: the error in the *j*-th neuron in the *l*-th layer  $\delta_{j}^{l}$ . With backpropagation, this error can be computed, and this will then be related to the partial derivative. To understand this error, imagine changing the output of the *j*-th neuron in the *l*-th layer with  $\Delta z_{j}^{l}$ . The output of this neuron will thus not be  $\sigma(z^{l})$  but  $\sigma(z^{l} + \Delta z_{j}^{l})$ . Translating this through the layers in the network will cause the overall cost to change by an amount of  $\frac{\partial C}{\partial z_{j}^{l}} \Delta z_{j}^{l}$ . Now remember,  $\partial C/\partial z_{j}^{l}$  shows how quickly the weighted input to neuron *j* in layer *l* will change. We want this number to be close to zero, as the cost then cannot be improved much (or at all) by changing the weighted input of  $z_{j}^{l}$ . This shows that  $\frac{\partial C}{\partial z_{i}^{l}}$  is a good measure of the error of the neuron, so

$$\delta_j^l = \frac{\partial C}{\partial z_j^l}$$

Now, with all notations and elements explained, the four fundamental equations of backpropagation can be introduced. Together, those equations provide a way of computing the error and the gradient of the cost function. With a basic understanding of what we are looking for, the equations are just listed below with their function.

An equation for the error in the output layer  $\delta^{L}$ .

$$\delta^L = \frac{\partial C}{\partial a_j^L} \sigma'(z_j^L)$$

An equation for the error  $\delta^{l}$  in terms of the error in the next layer,  $\delta^{l+1}$ ,

$$\delta^{l} = \left( \left( w^{l+1} \right)^{T} \delta^{l+1} \odot \sigma' \left( z^{l} \right) \right)$$

where  $\odot$  is the Hadamard product (the elementwise product of two vectors). An equation for the rate of change of the cost with respect to any bias in the network.

$$\frac{\delta C}{\delta b_j^l} = \delta_j^l$$

And an equation for the rate of change of the cost with respect to any weight in the network.

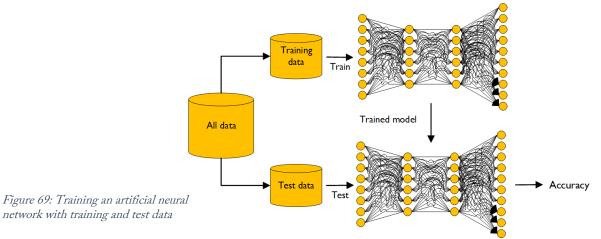
$$\frac{\delta C}{\delta w_{jk}^l} = a_k^{l-1} \delta_j^l$$

Putting everything that is discussed in section B.3, the backpropagation algorithm looks like this:

- 1. Input *x*: set the corresponding activation  $a^1$  for the input layer.
- 2. Feedforward: for each l = 2,3, ..., L compute  $z^{l} = w^{l}a^{l-1} + b^{l}$  and  $a^{l} = \sigma(z_{l})$ .
- 3. Output error  $\delta^l$ : compute the vector  $\delta^L = \nabla_a C \odot \sigma'(z^l)$ .
- 4. Backpropagate the error: for each l = L 1, L 2, ..., 2 compute  $\delta^{l} = ((w^{l+1})^{T} \delta^{l+1} \odot \sigma'(z^{l}).$
- 5. Output: the gradient of the cost function is given by  $\frac{\delta C}{\delta w_{jk}^l} = a_k^{l-1} \delta_j^l$  and  $\frac{\delta C}{\delta b_j^l} = \delta_j^l$

#### **E.4 TRAINING A BASIC ARTIFICIAL NEURAL NETWORK**

To train a model (feed the learning algorithm), data is fed to the model in two sets. A training set that contains examples of digits that are used to set the weights and biases and a test set that shows, once the model is done training, how accurate it is when recognizing new examples (Figure 69).



When a model is trained on training data, the accuracy on the test data will (hopefully) increase every iteration. However, this learning stagnates up to the point where it stops improving. The cost function can however still improve, this improvement however is an illusion and it doesn't generalize to new examples. When this property appears, we call the model overfitted [78]. Learning in this manner from a general function or rule from specific input-output pairs is called inductive learning [3] and is very useful when all possible cases are known (for instance with recognizing digits). Another version of learning is deductive learning: going from a known general rule to a new rule that is logically entailed given the newly presented data. This is a useful approach when not every possible case is known beforehand [3].

These types of training are supported by specific types of feedback to the network: supervised or unsupervised [3]. ANNs often learn using supervised learning. This means that the data that is fed to the model comes in input-output pairs where the system in the end knows whether it was correct or incorrect (labeled data). The network aims to learn a function that maps the input to output. In unsupervised learning, the network learns patterns in the input even though no explicit feedback is supplied (concerning what it actually is). This type of learning is often seen in clustering tasks. Often though, the distinction between supervised or unsupervised learning is not so clear. For instance, when classifying handwritten digits, the human eye might also misclassify a digit if the handwriting is that bad. In this case, the input-output pair is incorrectly labeled. We speak of semi-supervised learning as the network is given a few labeled examples and must make what it can of a large collection of unlabeled or wrongly labeled examples [3]. It is therefore wise, in practice, to speak of a continuum between supervised learning.

#### **D.5 A CONVOLUTIONAL NEURAL NETWORK**

Convolutional neural networks (CNNs) are good at image recognition and are an advanced technique building on top of the basic ANN as discussed previously. CNNs are a family of multi-layer neural networks particularly designed for the use on two-dimensional data, such as images and videos [79]. These networks add many more powerful techniques to ANN like convolutions, pooling, the algorithmic expansion of training data (to reduce overfitting) the use of dropout technique (again to reduce overfitting) and the use of ensembles of networks [78]. An essential addition for convolutional networks is the inclusion of spatial structures in an image [79] [80] [78]. Simple neural networks treat input pixels which are far apart and close together exactly the same, however, understandably, this should not happen. Neurons spiking close together hold more info than ones spiking far from each other. A CNN uses three basic ideas: local receptive fields, shared weights and pooling [80] [78]

In the basic neural network, every layer was fully-connected to the other layer. However, in a CNN, the hidden neurons are only connected to a small surrounding region of input neurons (or pixels in images). This region in the input image is called the local receptive field. In other words, each hidden neuron is specialized in analyzing its particular local receptive field. This greatly reduces the connections.

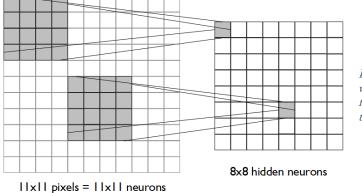


Figure 70: The connection of hidden neurons with their local receptive field. The 4x4 receptive field moves around the 11x11 grid one pixel at a time in order to connect to 8x8 hidden neurons.

Not only are the amount of connections limited, also the weights are reduced significantly by introducing shared weights. Each of hidden neurons are going to use the same weights and biases. Each neuron can thus detect exactly the same feature. This seems strange, but it rests upon the fact that it is useful that every hidden neuron in a layer should be able to extract the same feature as it might have value in every part of the image. If for instance, a picture of a number moves to the right, it is still a picture of a number with the same relevant feature. For this reason, the map from the input layer to the hidden layer is called the feature map (or filters, or kernels) [78]. Of course, this means that we will need lots of feature maps as just one feature will not be enough to recognize something. In addition to these convolutional layers, the network also contains pooling layers. Pooling layers simplify the information in the output from the convolutional layer [78]. They take each feature map output from the convolutional layer and prepare a condensed feature map. The final layer of connections in the network is then a fully-connected one and produces the output of the network (Figure 71).

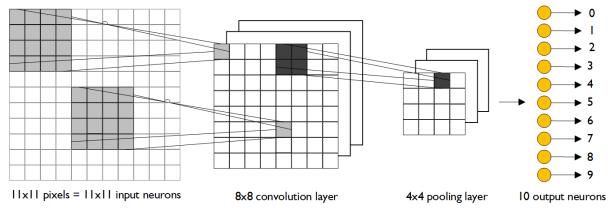
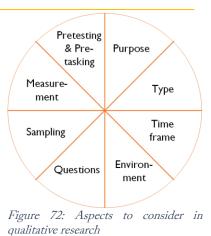


Figure 71: A convolutional neural network with one convolutional layer and one pooling layer

# Appendix F: methodological approach to interviews

Interviews were performed in a structured way by addressing eight aspects before conducting them [81]. Each segment specifies a certain aspect of the way in which the interviews will be performed and together they form the research design for the qualitative part of this research. The segments are: purpose (why is this necessary and what is the goal?), type (which method will be used?), time frame (when will the data be gathered?), environment (where will the data be gathered?), sampling (from whom will the data be gathered?), questions (what will be asked?) and measurement (how are the answers measured?).



# **F.I PURPOSE**

The purpose of the interviews is to acquire information on a couple of areas and therefore it has multiple goals. These qualitative research goals (QG) are:

- G1 To acquire information on the process of medical image examination in Dutch hospitals. This concerns information about all steps required from making the CT-scan to the communication of the diagnosis with the patient including the underlying supporting systems, data formats (and flows), stakeholders and protocols. This information will be used to design the process layer of the architecture.
- G2 To acquire a validation of the system requirements. Literature has provided an extensive list of barriers and critical success factors that were used in the creation of list of requirements. The interviews are used to confirm these findings (and possibly, add to them).

G3 To acquire information on the CAESAR project that will be used to validate the architecture. These goals provide information for different parts of the research.

# F.2 TYPE

Since the goal of the interviews is to acquire detailed information on processes, requirements and projects, a descriptive qualitative research is used. More specifically, Individual Depth Interviews (IDI) will be carried out [81]. This method calls for an interaction between one interviewer and one interviewee. The interview will be carried out face-to-face (with a duration of up to two hours). Using IDI's, topics can be discussed in detail and follow-up questions can be asked immediately when interesting things come up.

## F.3 TIME FRAME

The interviews are carried out over a time span of approximately four weeks. This gives flexibility to the interviewees as to when they have time to sit down and talk.

#### **F.4 ENVIRONMENT**

In order to get the most valuable and honest data, interviewees must feel safe and comfortable [81]. That is why the interviews will take place in the workplaces of the interviewees. The interview will, if possible, start off with a small tour and an introduction to the hospital and an introduction to my research. If the interviewee is Dutch, then this language will be used. In any other event, the language will be English. If the language is in Dutch, the transcripts will be translated and transcribed into English. However, this translating can again pose challenges in vocabulary, so translation will be done very literally and meticulously.

#### **F.5 SAMPLING**

To obtain the information that is needed to create a valuable architecture, the appropriate people (holding this information) need to be sampled. To draw this sample, personas are created. These personas describe groups of people that share characteristics who can provide valuable information to

the research. Describing what such a person looks like helps to identify people suitable for interviews. In total, four personas were created. One person can satisfy the characteristics of multiple personas. For instance, a radiologist might be a process operator and a future user.

# PROCESS OPERATOR

The process operator is any person involved with medical image assessment process. He/she knows from start to finish what needs to happen when a patient is recommended to take medical images. He/she can describe in detail how this process works and what kind of systems and protocols have to be used to support this process. Examples of process operators are radiologists or technical operators. Their knowledge will be used to develop the process layer.



Figure 73: Process operator persona



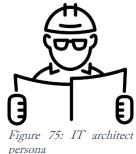
# FUTURE USER

The future user is anyone who is going to use the CDSS once it is implemented. He/she knows what these systems can do, and he knows what he wants these systems to do. He/she knows several obstacles that limit the uptake of these systems. He/she doesn't necessarily have to like the systems. He/she works in an academic hospital. This knowledge will be used to determine requirements (probably functional) for the architecture.

persona

# IT ARCHITECT

The IT architect is involved with the organization and maintenance of the systems that support the medical image assessment process. He/she is knowledgeable on the architectures of (a part of) the hospital and can speak about the ins and outs of system integration, data formats, standards, protocols etc. Their knowledge will be used to determine requirements (probably a lot of non-functional ones) for the technology and application layer.



# **F.6 QUESTIONS**

The questions that will be asked to the interviewee depend on the persona that they fit, involvement with the CAESAR project. The different combinations of these characteristics result in different sets of questions that can be asked to the interviewee. Each person will thus receive a tailored interview. Lists of questions are roughly defined for the following characteristics (together with the goals they support):

- All people (G2)
- People who are process operators and/or IT architects (G1, G2 & G3)
- People who are involved in CAESAR (G3)

In Table 8 through 13, the questions for each group are described.

Table 6: Questions asked to all interviewees	1
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Purpose	Question
General information	In which department do you work?
(beginning of interview)	What is your function there?
Establishing knowledge	Do you know the process of medical image examination?
(beginning of interview)	Do you have a role in the process of medical image examination?
	Do you know what a clinical decision support system is? Do you know
	what an image-based CDSS is?
	*Explain the type of CDSS in this research*
	Do you use a CDSS? Do you use an image-based CDSS?
	Would you like to use a CDSS? And an image-based CDSS?

	Are you, in any way or form, involved in the research or implementation of CDSS?
Establishing	For each of the requirement, do you agree or disagree
requirements (end of the interview)	Do you have any requirements that were not mentioned during this interview?

Table 7: Questions asked to	process operators and/or IT architects
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Purpose	Question
Medical image	Can you describe the process of medical image assessment in terms of
assessment process	steps from start (when a person walks into the hospital) to finish (patients
	receiving the results)?
	Who is involved with these steps?
	Which systems are involved with these steps?
	Which protocols are involved with these steps? Are they comparable to
	other protocols used in the hospital?
	What are the data formats and data flows in the process? Are these similar
	to the rest of the hospital?
	Does this process differ among departments? How?
	Does this process differ among hospitals? How?
Implementation of	Do you know details of any CDSS implementation in this process (at the
Image-based CDSS	person's workplace)?
	What would be the impact of CDSS implementation on the process,
	systems, protocols and data flows? What changes would occur?
	What would you want to see in an architecture that will support this
	implementation?

#### Table 8: Questions asked to people involved with CAESAR

Purpose	Question
CAESAR process	Can you describe the process supported by CAESAR when this system is
	not implemented?
	Who is involved with these steps?
	Which systems are involved with these steps and how are they linked?
	Which protocols are involved with these steps?
	What are the data formats and data flows in the process?
Implementation of CAESAR CDSS	How would CAESAR be implemented in this process?
	Do you think this is comparable to other CDSS of this kind?
	What would be the impact of CDSS implementation on the process,
	systems, protocols and data flows? What changes would occur?
	What would you want to see in an architecture that will support this
	implementation?

In summary, the questions provide the research with the ability to design the following aspects:

- The as-is and to-be situation of the medical image assessment process with and without the implementation of a CDSS with supporting systems, protocols, stakeholders and dataflows in hospitals (the focus lies more on the as-is situation because the to-be situation will be designed in the research in combination with literature). This includes confirmation (and possible addition) of the requirements posed in literature. This information is vital to the design of the reference architecture.

- The as-is and to-be situation of the medical image assessment process with and without CAESAR with supporting systems, protocols, stakeholders and dataflows in non-academic hospitals. This information is vital for the validation of the treatment.

# **F.7 MEASUREMENT**

For G1, G2 & G4, no specific measurement is needed as information related to this goal concerns facts. If major differences in answers occur, this probably means that we are either dealing with different processes, different contexts or wrong information.

# F.8 PRETESTING & PRETASKING

To fine-tune the interview, it was tested on two people of SAS. Using their feedback, the final question list was specified. To prepare the interviewee, an information sheet was sent to the interviewee. This document contained information on the nature of the research, benefits and risks of partaking in it, procedures for withdrawal, collected personal information, the retention period of the data and contact details (see Appendix G). This allowed the interviewee to be well-prepared but most of all, provided an honest look at the nature of the interview and rights of the interviewee. During the interview, the first task was to review an informed consent form (Appendix G) that again showed the rights of the interviewee and the setup of the interview.

# Appendix G: information sheet and informed consent form

Author:Antonie Berkel in cooperation with the Ethics Committee of the faculty of EEMCSLast edited:16-10-2018

This information sheet provides details on the interviews that the researcher, Antonie Berkel, will conduct for the purpose of his Master thesis research on the implementation of clinical decision support systems (CDSS) in academic hospitals. This document will provide the interviewee with the purpose of the research, benefits and risk of participating, procedures for withdrawal, collected personal information, usage of data in the research, retention period of data and contact details.

## G.I PURPOSE OF THE RESEARCH

Decision support systems have the potential to improve patient care and practitioner performance, reduce cost and increase efficiency. Although these systems are used often in a research environment, the translation and implementation to the clinical practice is mostly absent. The goal of this research is to create a reference architecture for the implementation of a CDSS in academic hospitals so that these systems can be implemented more easily. More specifically, we are building a reference architecture for CDSS that is capable of image analysis in CT-scans with the purpose of tumor recognition and classification. The purpose of this interview is to receive information on the current process of image analysis and the position and impact of CDSS in this process. In addition, requirements for successful CDSS usage are inquired. This information can be used to accurately model the process and goals and desires of stakeholders and in turn to develop the reference architecture.

#### **G.2 BENEFITS AND RISKS OF PARTICIPATING**

The interviewee benefits from partaking in the research in the following manners:

- Contributing to science
- Contributing to the implementation of new innovative technology that could impact the interviewee in his/her professional and/or private life

A very minor risk is that if interviewees do not provide accurate information, the outcome of the research might not be an optimal outcome which might lead to the less effective and valuable implementation of this new technology. To assure the interviewee about the absence of any other risk, it is stated that this research is reviewed by the ethics committee of the University of Twente.

#### **G.3 PROCEDURES FOR WITHDRAWAL**

If the interviewee would want to withdraw from the research, then this can easily be done by contacting the researcher (Antonie Berkel). Contact details are placed at the end of the document.

#### **G.4 COLLECTED PERSONAL INFORMATION**

Since the goal of the interviews is to acquire knowledge on the process of image assessment in general (and not practitioner specific) the only personal information that will be collected is the name of the participant, his/her role in the hospital and his/her affinity and knowledge of CDSS. This is done for reference only. This information will be available to the UT, SAS and visitors of the essay library of the UT (see "Retention period of data"). If the interviewee requests to remain anonymous, then this request will be accepted under all circumstances. When the research will be published in any journal or conference, the interviewee is asked again whether he/she wants to be anonymous.

In addition to this, the interviews will be audio recorded and later transcribed. When transcribing is finalized, the interviewee will receive a copy of the interview so that he might be able to rectify some of the things that he has said. However, rectifications do not always have to be accepted by the researcher. If this is the case, rectifications will be accepted in a mutual discussion.

# G.5 RETENTION PERIOD OF DATA

The data that is provided by the interviewee will, in principal, be available for as long as essay.utwente.nl is online. This site shows all master theses of the University of Twente. The data that is used in the theses will thus be available on this site as well.

# **G.6 CONTACT DETAILS**

Information	Researcher	Ethics Committee	Client
Name	Antonie Berkel	Ethics Committee BIT	SAS Institute BV
E-mail	antonie.berkel@sas.com	ethics-comm-	alfredo.iglesias.rey@sas.com
		ewi@utwente.nl	
Phone	+31 620750684	+31 534896719	+31 208085228

# Informed consent form

<u>Author:</u> Antonie Berkel in cooperation with the Ethics Committee of the faculty EEMCS <u>Last edited</u> : 16-10-2018		
Consent Form for CDSS Implementation Research YOU WILL BE GIVEN A COPY OF THIS INFORMED CONSENT FORM		
Please tick the appropriate boxes	Yes	No
Taking part in the study		
I have read and understood the study information dated (16-10-2018), or it has been read to me. I have been able to ask questions about the study and my questions have been answered to my satisfaction.	0	0
I consent voluntarily to be a participant in this study and understand that I can refuse to answer questions and I can withdraw from the study at any time, without having to give a reason.	0	0
I understand that taking part in the study involves answering questions in a face-to-face or online (Skype) interview about the process of image analysis in radiology, the impact of CDSS on this process and the requirements for successful CDSS usage. I understand that the interviews will be audio recorded and transcribed.	0	0
Use of the information in the study		
I understand that information I provide will be used for the contents of a master theses which will be published in an essay library. My information will also be available to SAS Institute. I know that my name and anything that can identify me can be made anonymous if I request so.	0	0
I understand that personal information collected about me that can identify me, such as ([e.g. my name), will not be shared beyond the study team if I wish so.	0	0
I agree that my information can be quoted in research outputs.	0	0
I agree that my real name can be used in the research (check "no" if you want to be anonymous).	0	0
I agree to be audio/video recorded.	0	0

#### Future use and reuse of the information by others

I give permission for the information on the image analysis process, impact of CDSS on this OOO process and requirement for successful CDSS usage that I provide to be archived in essay.utwente.nl so it can be used for future research and learning. This archive has no access restrictions. This information will be recorded using transcripts. It can still be anonymized by blurring out my name.

I give the researchers and SAS permission to keep my contact information and to contact me O O for future research projects.

Signatures

Name of participant

Signature

Date

Date

I have accurately read out the information sheet to the potential participant and, to the best of my ability, ensured that the participant understands to what they are freely consenting.

Antonie Berkel_____Researcher nameSignature

Study contact details for further information:

Antonie Berkel antonie.berkel@sas.com +31 620750684

## Contact Information for Questions about Your Rights as a Research Participant

If you have questions about your rights as a research participant, or wish to obtain information, ask questions, or discuss any concerns about this study with someone other than the researcher(s), please contact the Secretary of the Ethics Committee of the Faculty of Electrical Engineering, Mathematics and Computer Science at the University of Twente by <u>ethics-comm-ewi@utwente.nl</u>

# Appendix H: background on the ArchiMate language

The enterprise architecture modelling language called ArchiMate is used to design the architecture of the CDSS. ArchiMate provides a graphical language that can be used for the representation of enterprise architectures. ArchiMate is a lightweight and scalable language in several aspects [71]:

- Its architecture framework is simple but comprehensive enough to provide a good structuring mechanism for architecture domains, layers and aspects.
- The language incorporates the concepts of the "service orientation" paradigm that promotes a new organizing principle in terms of (business, application and infrastructure) services for organizations, with far-reaching consequences for their enterprise architecture. It is thus very valuable to be able to implement the service aspect in this architecture.

The ArchiMate language exists of an architectural framework consisting of three layers [71]:

- Business layer. This layer offers products and services to external customers, which are realized in the organization by business processes performed by business actors.
- Applications layer. This layer supports the business layer with application services. These services are realized by (software) application.
- Technology layer. This layer offers infrastructure services (such as processing, storage and communication services) needed to run applications. These services are realized by computer and communication hardware and software.

In this language, services are described as the following: a unit of functionality that a system exposes to its environment, which provides a certain value (monetary or otherwise). It does this while hiding internal operations.