Design of a Computer-Assisted Anticoagulant Dosing System





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DESIGN OF A COMPUTER-ASSISTED ANTICOAGULANT DOSING SYSTEM

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ABSTRACT

At the moment current anticoagulation dosing computer programs use relatively simple algorithms and provide a useful dose proposal in about half the cases. In the other cases medical staff has to come up with a dose and a return date. This thesis investigates the possibilities of supporting medical staff in anticoagulant dosing by extending current computer programs. Research has been done for improving the current algorithms and incorporating expert knowledge in a computer system. A literature survey showed that a lot of effort already has been made in improving algorithms. The ICAD seems to be the most promising, but still fails in about 20% of the cases to provide a dose or return date, mostly due to special circumstances. My aim was to find out whether the medical expert's knowledge was retrievable and if it was suitable for developing an expert system. Therefore I interviewed dosage doctors and dosage advisors in two Thrombosis Service Departments. The majority of the interviews were held at Star-MDC in Rotterdam, where I work as a Laboratory Manager. A couple of interviews were also held at Saltro, a comparable organization in Utrecht. Knowledge elicitation and representation techniques were applied and a prototype was developed. Further interviews were held, based on the prototype and a OODA-Loop technique. A lot of existing protocols at the Thrombosis Service organizations seemed to be suitable for converting in IF-THEN rules, as a basis for a rule-based expert system. Also the reasoning process of the relative low complex cases are obtainable in an expert system. This is specifically interesting, because the low complex cases are the majority of cases that have to be reviewed by medical staff.

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1 INTRODUCTION



Anticoagulants are used in a wide range of clinical disorders to prevent thromboembolic events. Patients who need to take anticoagulants for a longer period of time often are set on oral anticoagulation therapy by coumarin derivates. In the Netherlands there are about 60 anticoagulation clinics which monitor patients on oral anticoagulation therapy by coumarin derivates.

Inadequate treatment can lead to bleeding or thromboembolic complications. To prevent this, the anticoagulation clinics measure the anticoagulation intensity on a regular basis. This anticoagulation intensity is expressed as the International Normalized Ratio (INR). Depending on the patient's clinical disorder, the INR is kept in a predefined target range. The purpose is to apply or adjust the dosage in such a way, that the INR is in the target range as often as possible.

Computer-assisted oral anticoagulant dosage is available for some years now and has proven to be safe and effective for the cases they can handle. The current computer programs for anticoagulant dosage use simple algorithms. These algorithms are based on the current INR and



usually also former dosages and INR's are taken into account . In part of the cases the computer fails to provide a proposal. And in those cases the computer does provide a dosage, part of the cases may be rejected by medical staff. In both cases medical staff has to assess a dosage themselves. It is therefore interesting to find out whether computer-assisted anticoagulant dosing is extendable in a way that the amount of useful proposals can be increased. This project is aimed at investigating the possibilities of extending current computer-assisted dosing programs.

1.1 SCOPE



FIGURE 1: CLINICAL LABORATORY AT STAR-MDC

The monitoring of patients on anticoagulants is done in cycles of treatment and control. In the Netherlands a major role for this task is reserved by departments called Thrombosis Services. Thrombosis Services are anticoagulation clinics or part of them. Also hospitals and some nursing homes take care of anticoagulation monitoring, but on a smaller scale and most of the time without support of computer-assistance. The cycle of monitoring the patient however is basically the same regardless of computer-assistance. The focus in this project is on improving the computer supported way of working. And thereby hopefully improving the patient's wellness.

1.1.1 PROCESS DESCRIPTION

For regular INR-control in a Thrombosis Service program, a patient is requested to visit a blood collection station or is visited at home. In either case a blood sample is taken from the patient. Changes in medical conditions, medication or other events of interest for the Thrombosis Service are recorded on a form. The blood sample is then transported to a clinical laboratory, together with the requestform. A picture of the clinical laboratory of Star-MDC is shown in Figure 1. In the laboratory a Protrombin Time (PT) test is done and the INR is calculated from the PT on a laboratory analyzer. The INR is an international, normalized and thus comparable unit, indicating the intensity of anticoagulation. The INR is then passed from the lab analyzer to the Thrombosis Service computer system electronically.



In case the phlebotomist (the person who collects a blood sample) has written some notes on the form regarding changes in the patient's clinical condition, these notes are also entered in the Thrombosis Service computer system. This should be done before the INR result, because the INR triggers the computer program to assess a dosage and a return date. And at that point, the changes in clinical condition should be taken into account.



FIGURE 2: MONITORING CYCLE

The main goal of the computer-assisted dosage is supporting the medical staff in determining the dosage of the coumarin derivates and the date of the next INR control. The current computer programs use algorithms, which usually are based on simple rules that try to make a dosage proposal and next date proposal for the INR check. Depending on how well the system is able to provide a proposal and also on the absence of circumstances like bleedings or medication which can interfere with anticoagulation, the system provides a dosage or it queues the case for handling by medical staff. Based on the clinical difficulty of a case, medical staff of different skill and knowledge levels takes care of the case. Simple cases may be automatically handled. In all cases the patients receive a new schedule containing a day to day dose and the next date for INR control. This dosing schedule is often called a calendar and is combined with a requestform for the next INR check. When it is time for the next check, the cycle as illustrated in Figure 2 starts all over again.

1.1.2 CURRENT ISSUES AND DEVELOPMENTS

One issue Thrombosis Services have to deal with is an increasing workload. The number of dosages increase every year, in spite of expectations of new medication which could decrease the



necessity of monitoring a specific group of patients. On the other hand experienced medical staff is hard to get and often hard to keep due to the grayness of the dosing work. One can imagine that at some moment the continuity of the Thrombosis Service may be at stake.

The suppliers of current larger Thrombosis Service systems in the Netherlands are reluctant to apply new technical developments like interaction with webpage's on the internet. Independent companies started initiatives to display dosage and return date on a webpage. So interactive webpages do exist, but they are usually not meant for regular patients, but for so called self management patients. Another new development is making notes by the phlebotomist on a PDA instead of using a form. The data is then online transferred from the PDA to a Thrombosis Service system.

More and more people are transferred to a self monitoring program. These people assess their own INR and in some cases they assess both their own dosage and next control date. Their associated Thrombosis Service keeps responsibility for training and anticoagulation status. However, in the current larger Thrombosis Service programs there are no provisions for monitoring the data these people generate. Separate programs are put in place for that, and so this is creating a barrier between self monitoring and non-self monitoring patients. Especially for patients switching between programs a discontinuity might arise.

The algorithms of the current larger thrombosis systems are relatively simple. This means that about half the cases are provided with an acceptable dosage and return date. At the moment suppliers claim that they put a lot of effort in implementing smarter algorithms, but these are not available yet. Probably because extensive studies are needed to prove there correctness and safety.

When there is a new or renewed submission for a patient to the Thrombosis Service, the requestor has to fill out a form to supply data needed by the Thrombosis Service. The first time a bloodsample is taken there is also a kind of survey, which is filled out by the phlebotomist on a form. For both forms a webpage (or PDA) could be an improvement in communication and efficiency. Some organizations think of making these webpage's, but these are not available yet, partly because of the lag of the Thrombosis Service system supplier.

On the report side the current Thrombosis Service programs use paper reports. Modern communication techniques like email, SMS messages and websites are only sparsely available yet.

Because a lot of paper is coming in, and because not all the items on these papers can be entered into the Thrombosis Service system, a paper archive is still in use. Scanning these papers and incorporating them into the system would be a major improvement.

All the issues mentioned above are each for itself a reason for improving current Thrombosis Service computer programs. It is my intention to create a model that supports the medical staff in providing dosages and return dates in a laborsaving way and that at the same time takes care that each patient is kept in his target range as much as possible, by standardizing the optimum way of working.



1.2 OBJECTIVE AND RESEARCH QUESTIONS

The goal of this research project is:

TO DESIGN A COMPUTER-ASSISTED ANTICOAGULANT DOSING SYSTEM BY ANALYZING THE POSSIBILITIES AND LIMITS OF CURRENT COMPUTER PROGRAMS AND EXTRACTING THE KNOWLEDGE FROM DOCUMENTS AND EXPERT MEDICAL STAFF WHO IS DEALING WITH CASES WHERE CURRENT COMPUTER PROGRAMS FAIL TO DELIVER ACCEPTABLE DOSAGE PROPOSALS.

This goal can be divided into the following research questions:

- 1. Can the knowledge used by medical staff on dosing non-trivial cases be made explicit?
- 2. Can computer-assisted dosing programs be improved by incorporating medical staff knowledge?
- 3. Are current algorithms used by computer-assisted dosing programs extendible to provide a higher acceptable dosage rate?
- 4. Can the interfaces of current computer programs be improved to better support medical staff?

1.3 RESEARCH PROJECT OUTLINE

In order to achieve the goal mentioned in paragraph 1.2 there is some work to be done. The way this is done is illustrated in the scheme in Figure 3. In words this scheme means that a literature survey is done on computer assisted dosage and current developments in this field that may be of interest. Also the current Thrombosis Services' processes and protocols are studied. Special focus here is on the Thrombosis Service of Rotterdam, which is part of Star-MDC, a Medical Diagnostic Center for General Practitioners in the Rotterdam area. Star-MDC contains among others a Clinical Laboratory and an Anticoagulation Clinic. As Laboratory Manager at Star-MDC it is relatively easy for me to access resources at the Thrombosis Service. Also Saltro, a colleague Medical Diagnostic Center in Utrecht has been cooperative in this project.



FIGURE 3: RESEARCH PROJECT SCHEME



Next the theoretical background of expert systems is studied. Based on this theory and on the source survey appropriate techniques for knowledge retrieval and knowledge representation are settled. To get a thoroughly understanding how dosage doctors think and act, there were interviews done with medical staff while they were working, using a computer-assisted anticoagulant dosing program. Based on the outcome and analysis of these interviews, a semantic net is produced for representing knowledge and providing an ontology. Also a first set of IF-THEN rules based on descriptive knowledge is developed. Further investigation is done by using a prototype expert system with ICAD algorithm functionality on real patient data. OODA-Loop techniques are used for analyzing decision making processes on interviews helped by the prototype. Detailed results from these interviews lead to a set of IF-THEN rules representing the reasoning of the medical experts in low complex cases. The joint set of IF-THEN rules are the basis of an expert system design.

METHODOLOGY

	Action	Goal
1	Literature survey	Find out the state of the art in computer-assisted
		anticoagulant dosage.
2	Study tools and methods	Designing an appropriate model to build a decision
	on expert systems	support system
3	Data collection	Make an inventory of papers, items and data sources
		used in the dosage process
4	Interviewing staff and	Knowledge elicitation
	studying protocols	
5	Determining the design	Creating a list of design goals
	goals	
6	Designing a prototype	Use a prototype for introduction to expert staff and as
		support for further knowledge elicitation
7	Testing the prototype	Collecting additional design goals for expert system
		development

In this research project the following actions and goals are planned:

RESEARCH CHALLENGES

This research project eventually leads to a couple of main research challenges, which are:

- Eliciting knowledge from medical experts and documentation.
- Creating new ways and methods for automatic anticoagulant dosage.

1.4 STRUCTURE OF THIS DOCUMENT

This document's structure of this follows in general the research project outline. In chapter 2 the relevant topics of the literature survey are listed. Also a description of the relevant current processes and protocols at the Thrombosis Service is provided. Chapter 3 deals with the theory of expert systems development and with knowledge retrieval techniques, knowledge representation techniques and a brief look at the expert system development process. Based on this theory, the approach of making the knowledge explicit in practice is subject of chapter 4. The first results and findings are summarized in chapter 5. In chapter 6 the results from chapter 5 are leading to recommendations for a global system design. Also a prototype is developed based on these



results. Helped by the prototype further interviews are held, which are described in chapter 7. This is an iterative way of system design, which lead to an extended set of IF-THEN rules. Chapter 8 concludes this thesis with a review on the research questions from paragraph 1.2 and brief suggestions for a follow-up.

1.4.1 ABBREVIATIONS

Throughout this document a number of abbreviations are used. The most common ones are listed below.

- FNTFederatie van Nederlandse TrombosedienstenGPGeneral Practitioner (family physician)
- ICAD Improved Control of Anticoagulation Dosage
- INR International Normalized Ratio
- TIR Time in target INR Range





2 Source survey



This chapter contains an overview of relevant source materials. Paragraph 2.1 discusses articles about computer-assisted anticoagulant dosage. It explains the use and relevance of the TIR as a performance indicator, the safety and effectiveness of the use of computers as opposed to manual dosage, several ways to look at the performance of a computer program, new developments concerning genotypes and finally some insight in computer algorithms. Paragraph 2.2 focuses on processes and protocols in anticoagulation clinics. Because anticoagulation clinics in the Netherlands are bound to standards and certification programs, a lot of information of how these clinics work is contained in process descriptions, protocols and other documents. So, these documents form a rich source of information for this section. Paragraph 2.3 concludes this chapter with an early set of recommendations and a set of reasons for expert system design.

2.1 LITERATURE ON COMPUTER-ASSISTED ANTICOAGULANT DOSAGE

There are a lot of articles about computer-assisted anticoagulant dosage. And many of them have Dutch authors or co-authors. This is probably due to the Dutch way of organizing anticoagulation control in Thrombosis Services and uniting these Thrombosis Services in a national federation



called the FNT. The FNT on its turn has a scientific department called Trombose Stichting Nederland supporting scientific research. In spite of having a lot of information on the subject of computer-assisted anticoagulant dosage, there is very little information on the exact operation of the computer programs. This is probably due to the fact that these programs are commercially available and that the suppliers of these programs regard this information as proprietary business logic. However, articles on trials where computer-assisted dosing is involved, do reveal some information on how these programs work and how well they perform.

An important item for improving computer-assistance on dosing, as mentioned in some articles as something touched on in passing, is the shortage off expert staff in anticoagulation clinics. Besides this point, also other reasons for computer-assisted dosage given. E.g. *Poller et al.* [9] on page 941 asserts as a reason for using computer-assisted dosage outside anticoagulation clinics: 'This is because such centers may be expected to have higher standards of clinical dose control than the average hospital or clinic' and on the same page a reason for using computer-assisted dosage: 'Perhaps more important is the fact that there is no evidence that computer-assistance with anticoagulant dosage puts patients at any added risk of clinical events as compared with dosage by experienced medical staff. This is reassuring to hospitals and community clinics wishing to move to computer assisted dosage to reduce heavy demands on medical staff time and resources.' So shortage off medical staff is a reason for increasing efficiency of computer programs. And making computer-assisted anticoagulant dosage available to others than Thrombosis Services is a reason for making these programs easy and intuitive to use as well as efficient. These two items are in line with this project's research goals.

The next subparagraphs of paragraph 2.1 deals with TIR, safety and effectiveness, performance and algorithms.

2.1.1 TIR

Success in achieving target INR levels is commonly expressed as the Time in target INR Range (TIR). The goal is to keep patients in target INR range, thereby avoiding thrombosis or bleedings. In the vademecum of the FNT [1] it is recommended that depending on the indication for anticoagulation there are two therapeutic ranges, a low range with an intensity of INR 2.0 - 3.5 and a high range with an intensity of INR 2.5 - 4.0. However due to incremental risk on thrombotic events slightly narrower target ranges are used in practice in the Netherlands (2.5 - 3.5 and 3.0 - 4.0 resp.) but for calculation of the TIR the wider ranges may be used.

The TIR is commonly applied to the performance of an anticoagulation clinic, but may also be applied to an individual patient or group of patients in a certain target range. When medical staff use computer-assisted dosing the TIR is the result of the computer dosages combined with the dosages of the medical staff in case the computer dosage was overruled or the computer failed to provide a dosage. So in that respect the TIR cannot simply be applied only to the computer dosage. The calculation of TIR is assessed by the *Rosendaal et al.* method [8]. This method is based on the assumption that the INR between two measurements varies linearly. An example of this calculation is shown in Figure 4: the INR is assessed on January 26th : 2.5 and on February 2nd : 4.9. The subsequent days the INR's are assumed to vary linearly and they are rounded up to 0.1





FIGURE 4: INR BETWEEN ASSESSMENTS

INR point. In this case the therapeutic range is 2.5 - 4.0 and so the INR is 5 out of 8 days in range which means a TIR of 62.5%.

2.1.2 SAFETY AND EFFECTIVENESS

One of the first questions which may arise is how reliable computer programs are in prescribing anticoagulation dosages. To answer that question, many trials have been performed on comparing computer programs to medical expert staff. Recently one of the largest trials was carried out and described by *Poller et al.* [9]. In this trial the safety and effectiveness of computer-assisted dosage was demonstrated in a large multicenter comparison between computer programs and expert medical staff. The main outcome was that the number of clinical events with computer-assisted dosage was lower and the TIR was significantly better then the manual dosage by medical experts. In this very large trial the commercial computer programs PARMA 5 and DAWN AC were compared to manual dosage in 32 centers in 13 countries. Previous versions of PARMA 5 have been used in several centers in Italy, DAWN AC is the most widely used computer-assisted dosage program employed by UK hospitals. Earlier trials demonstrated the safety and effectiveness too in comparison with other computer programs, but this trial was sufficiently large to conclude that computer-assisted dosage has a better performance in comparison to experienced medical staff.

2.1.3 PERFORMANCE

Close related to the reliability question is the performance question. How well does a computer program perform? As mentioned before, widely used indicators are the TIR and the amount of clinical events. When we take a closer look there are other factors involved. The performance of the computer programs PARMA 5 and DWAN AC in the *Poller et al.* [9] trial was expressed as percentage of dosages which were accepted by the expert staff. In the computer-assisted dosage arm the accepted dosage percentage was 78.3, which means that medical staff provided a dosage in 21.7% of the occasions. This was the case because in 10.8% the computer failed to provide a dosage and in the other 10.9% the dose was changed for clinical reasons. So the percentage of acceptable dosages a computer program provides is an indicator too, next to the TIR.

Examples of reasons in the *Poller et al.* [9] trial for overruling computer dosages were: patient not following prescribed medication, about to undergo or had undergone medical or surgical intervention, or experienced a lifestyle change. Current computer assisted anticoagulation dosage programs are developed for the majority of patients on long-term (6 months to lifetime) anticoagulant treatment. This is also one of the reasons, that not all the cases are suitable for



algorithm based dosage proposals. Apart from that, unpredictable factors and special circumstances prevent medical staff to use the current computer programs or their proposals in about 20% of the cases. Among these circumstances: instable patients, due to forgetting to take the pills or not taking the prescribed amount of pills for other reasons (non-compliance), use of interfering medicine, illness, bleedings, very young children, pregnancy, thrombotic events, INR out-of-range, operations, switch of indication and switch of type of anticoagulant medicine. Besides overruling computer dosage proposals, medical staff also can overrule date-proposals for the next visit. In [9] the dates of computer-advised appointments were changed by medical staff in 34.3%. This could be due to the doctor's assessment of the reliability of the recommendation. But also other factors such as convenience to the staff or clinics of follow-up appointments and holidays played a role in this result.

2.1.4 GENOTYPES

The difficulty to get and keep a patient in his INR target range is partly caused by a high inter individual variability as well as intra individual variability, in dose requirement. Known facts by which this variability can be explained are age, drug-drug and drug-food interactions, infections, ingestion of varying quantities of vitamin K, heart failure, impairment of liver function, and difference in genotypes. For some patients initially hard to keep in their INR target range, there is new evidence of a relation between this phenomenon and their genetic expression. Schalenkamp et al. showed in [12] that being a carrier of a combination of polymorphisms of the genotypes VKORC1 and CYP2C9, is associated with severe over-anticoagulation. He also showed in [12] that the time to achieve stability is mainly associated with the CYP2C9 genotype. So when someone's VKORC1 and CYP2C9 genotypes are known prior to anticoagulation therapy, this is beneficial to prevent over-anticoagulation and to improve fast stability. Assessment of genotypes VKORC1 and CYP2C9 is not done on a routine basis at the moment, but might be done in the near future. The current computer programs do not take these genotypes into account. To prevent dosage doctors from extra work due to genotypes, computer programs should be able to handle genotypes.

2.1.5 ALGORITHMS

In general the algorithms used by commercial computer programs are not publicly available. According to the annual report 2007 of the FNT [2] the computer programs used by the Dutch Thrombosis Services are TDAS, Trodis, TROMIS, GLIMS and PORTA VITA. The algorithms used for computer-assisted dosage are private proprietary, however their performance is estimated by the FNT. In the same annual report the TIR of 61 Thrombosis Services are reflected and they vary from 67.1% to 92.0% for the low INR target range and from 62.5% to 85.0% for the high INR target range. In a comparison between the computer programs these Thrombosis Services use, the FNT concluded that the programs scored about equally. But how they do their jobs to reach their performance is still unknown. Fortunately there are articles on algorithms providing some insight.

ICAD

Van Leeuwen et al. [10] compared the Trodis standard computer algorithm with a new developed algorithm called ICAD. ICAD stands for Improved Control of Anticoagulation Dosage. According to *Van Leeuwen,* Trodis uses a complex empiric decision-tree which determines whether the dose has to be adapted and, if so, whether a new dose can be calculated by the algorithm (dose proposal) or whether it has to be determined by the physician. The ICAD model takes physical



circumstances into account and promises to provide a dosage proposal in over 90% of the cases. Trodis as well as ICAD have about the same TIR of 80%. However the Trodis algorithm proposed 60.8% dosages from which 90.9% were accepted where ICAD proposed 97.5% dosages from which 79.3% were accepted by experienced medical staff. This yields to a 77.4% acceptable dosages for ICAD versus 55.3% acceptable dosages for Trodis. The ICAD algorithm is described in detail by *Pasterkamp et al.* in [11]. A summary of ICAD is explained here.



FIGURE 5: SIMPLIFIED ICAD MODEL

Figure 5 shows a simplified model of the ICAD algorithm. The effective dose f(t) is in fact the halflife of the anticoagulant. The INR is calculated as:

$$INR(t) = 1 + s.(f(t))^{\gamma}$$

Where s stands for a sensitivity factor of the patient, f(t) is the half-life function and γ is an E-max parameter descended from a sub model of the extended ICAD algorithm. Both f(t) and γ are dependent on the type of anticoagulant (acenocoumarol or fenprocoumon) and are constant during the treatment. *Pasterkamp et al* assessed these constants retrospectively in [11]. The maintenance dose is calculated as:

$$d = \left(\frac{INR_{target} - 1}{s}\right)^{1/\gamma}$$

Every visit the sensitivity s is calculated. At the k^{th} visit the sensitivity is:

$$s_k = \frac{INR_k - 1}{f_k^{\gamma}}$$

Where with s_k the sensitivity at visit k, INR_k the measured INR at visit k, and f_k the calculated effective dose at visit k.

So this ICAD algorithm is well defined and promises to outperform the not public available standard algorithms. According to *Van Leeuwen et al.* [10] the equations used by the standard algorithm are based on a simple pharmacodynamic model, which implies a linear function between the INR and the dosage.

INDUCTION

According to *Poller et al.* [9] the commercial computer programs PHARMA 5 (Italy) and DAWN AC (UK) use two algorithms. One algorithm for induction of oral anticoagulation therapy, and another for steady-state monitoring. In the Rotterdam and Utrecht Thrombosis Services, starting oral anticoagulation therapy is guided by dosage doctors manually and they use a standard protocol. Induction in Netherlands is standardized by the FNT in its vademecum [1]. This protocol could



easily be incorporated in a computer program as an induction algorithm. Especially when genotype expressions are going to be taken into account, a computer program containing an induction algorithm may be a helpful tool.

ARTIFICIAL NEURAL NETWORK

Algorithms are based on simple equations or they are based on a model that tries to reflect physical mechanisms, like ICAD. The working of the human body seems not so easy to predict in this respect, especially because of inter human differences and differences because of varying conditions of the human itself. Therefore it might be an idea to use an Artificial Neural Network to model the physical processes. The exact functions need not to be known, but there can be a reasonable good correlation between the dose as an input parameter and the target INR as desired output. All input parameters that might be of influence on the result should be taken into account, like age, sex, medication, indication for anticoagulation, inter current diseases, some history of assessed INR's, and when available the genotype. Because the dose is the variable that changes based on difference between target INR and assessed INR, the dose can be modeled as a weight in the network. A simple model could look like the scheme in Figure 6, which is a modification of a picture in the book *Neural and Adaptive Systems: Fundamentals Through Simulations* from *Principe, Euliano, and Lefebvre* [13]. Literature on the use of an ANN in anticoagulant dosing was not retrievable, probably to the inconvenience of training ANN's for individual patients.

2.2 PROCESSES AND PROTOCOLS IN ANTICOAGULATION CLINICS

In the Netherlands outpatient anticoagulation treatment with coumarin derivates is pretty much the exclusive terrain of anticoagulation clinics called Thrombosis Services. These Thrombosis Services are affiliated to a national umbrella organization called FNT which stands for Federatie van Nederlandse Trombosediensten. The FNT provides guidelines for anticoagulation clinics and also monitors and exerts itself to improve the quality of the joined Thrombosis Services. Documents from FNT used here are [1], [2]and [3]. More detailed information is obtained from Quality System documents from Star-MDC: [4], [5] and [6].



FIGURE 6: ANN MODEL



2.2.1 PROCESS FLOW AND PROCESS STEPS

A schematic view of the process flow and the process steps is shown in Figure 7. Now follows a brief description of this process. A medical doctor who is treating a patient sets an indication for oral anticoagulation treatment. Therefore he applies this patient to a Thrombosis Service. This is done by filling out an application form with relevant medical information. Sometimes the doctor makes a start with anticoagulation treatment following a standard protocol. There is an implicit acceptance of the patient by the Thrombosis Service. From that moment the Thrombosis Service takes over the treatment on anticoagulation therapy from the medical doctor. Next the Thrombosis Service starts an intake procedure, by informing the patient on the process and on the critical issues, collecting additional information which wasn't on the application form and



FIGURE 7: PROCESS FLOWCHART



taking a blood sample for an INR assessment. From this point the regular cycle of anticoagulation monitoring is followed. This is illustrated in Figure 2: Monitoring cycle.



FIGURE 8: FRONT AND BACK SIDE FROM DOSE REPORT AND CALENDAR

The cycle of anticoagulation monitoring starts with a visit of the patient to one of the blood collection stations in the area of the Thrombosis Service. On indication of the treating medical doctor the patient can be visited at home. During the visit a blood sample is taken and data which could be relevant for the anticoagulation treatment is recorded. For this data collection a form is used which is combined with the report containing the dosage of the previous period. This form has an A4 format and can easily be split in two A5 format forms by means of a perforated line halfway the form. One part is the request form and the other part is called the calendar. An example of the form which is used by the Rotterdam Thrombosis Service is found in Figure 8. The upper left part of the form is the front of the requestform and the upper right is the back of the requestform. The lower left part of the form is the front of the calendar and the lower right is the back of the calendar. The barcode on the front of the requestform is used as a label for the blood sample. In that way there is a link between the blood sample and the patient. The data and blood samples are gathered at the patient and are next transported to be further processed at the Clinical Laboratory. The data from the request form is handled by the Thrombosis Service and is recorded in the Thrombosis Service information system. The blood samples are processed at the Clinical Laboratory. The Laboratory assesses the INR on one or more analyzers. In the Laboratory of Star-MDC this is done on one of three STA-R Evolution machines. A picture of these an analyzers is shown in Figure 9. Once the INR is assessed, the analyzer sends the INR-barcode number combination electronically to the Thrombosis Service information system. When imported in the Thrombosis Service information system the INR triggers the Thrombosis Service system to set up a dosage advice and a date for the next INR control. How this is done is the





FIGURE 9: 3x STA-RACK EVOLUTION

subject of the next subparagraph. Finally a dosage schedule with a next return date is reported to the patient. This is done by printing forms as shown in Figure 8. These forms are sent by mail to the patients. The patient then knows the amount of pills he has to take every day until the next visit.

2.2.2 CONSTRUCTION OF DOSE AND RETURN DATE

The way a dose is constructed depends not only on the Thrombosis Service system, but also on the way the dosage advisors and dosage doctors organize their workflow. The way Saltro uses the Trodis system in its workflow differs a bit from the way how Star-MDC uses the TDAS system in its workflow. The dose construction flows are reflected in Figure 10 and Figure 11. In both flowcharts, the Thrombosis Service system tries to propose a dosage based on the INR, the historical information already in the system and the new entered data. Because of this there are not well defined terms in the flowcharts like 'stable', 'in range', 'slightly', 'confident' and so on. One might expect that the suppliers of the Thrombosis Service systems take no risk and use tight restrictions. As you can see in Figure 10, Trodis splits up its cases in three different queues. No matter what queue or proposal Trodis supplies, Saltro never accepts a dosage automatically. This is because there may be a proposal in the Good Queue, which has remarks to be taken into account for the dose or the next visit date. The slightly more difficult cases are placed in the Experimental Queue. Both Good- and Experimental Queue take care of about 50% of the 800 cases per day at Saltro and are reviewed by a dosage advisor. She makes her own judgment on accepting a proposal, creating a new dosage herself or leaving the case for a dosage doctor. In case Trodis or an advisor is not able to create a dosage, a doctor has to provide a dosage.

The TDAS/Star-MDC workflow in Figure 11 shows a less complex flow, mainly because Star-MDC has an automatically acceptance of computer proposals. In practice this means that about 45% on a total of 1600 cases per day are automatically settled.

All other cases are first reviewed by a dosage advisor. The advisor has no computer proposal, so she has to make a proposal herself. When she is not confident she leaves the case for a dosage doctor to take care of.



The dose consists of a type of medication and an average number of pills for the next period. The type of medication in the Netherlands is either acenocoumarol or fenprocoumon. The main difference in these medications is that the half-life of fenprocoumon is longer than that from acenocoumarol. At the start of anticoagulation therapy the type of medication is chosen. At relative rare occasions there might be a switch between acenocoumarol and fenprocoumon. The dose is expressed as a daily average amount of pills or as a level, depending on the computer system that is used. In both cases the computer system converts the dosage in a schedule for the patient which contains the amount of pills on each day for a certain period of days. In TDAS the dose is expressed as a level that is called a step and it matches the total amount of pills in 14 days. E.g. an average of 2.5 pills/day matches with a level of 35 and the computer translates this in a day to day schedule of 2, 3, 2, 3, 2, 3 and so on. Together with the dosage the next control date is



FIGURE 10: DOSE CONSTRUCTION AT SALTRO WITH THE TRODIS SYSTEM



constructed. The maximum interval is 42 days. The more stable a patient is, the longer the interval can be. Preferable the interval is kept in multiples of 7 days. This is mainly because it fits in the patients habits and it gives the Thrombosis Service a tool to spread the workload. In case of instability other intervals can be chosen with a minimum of one day.

Additional a remark or message can be printed on the report to the patient. This is done when a doctor likes to have additional information that is not urgent e.g. the name of the patient's family doctor or chemist, which can be retrieved at the next visit of the phlebotomist.



FIGURE 11: DOSE CONSTRUCTION AT STAR-MDC WITH THE TDAS SYSTEM

2.2.3 COMPETENCE FOR PROVIDING A DOSE

Medical doctors are qualified to provide a dosage. Under specific conditions, stated by the FNT [3], paramedical educated people can be declared as qualified to provide a dosage. In that case the term dosage advisor is used instead of dosage doctor. Dosage advisors should work on specific low complex cases and always act under supervision of a dosage doctor. They also need to pass the national exam dosage advisor before they can do their job. In this way dosage advisors fill the gap on the shortage of dosage doctors.

Since a few years point of care devices are available for near patient testing of the INR. Patients who are considered to monitor themselves can be trained to a self-monitoring program. In some



cases patients are educated for self-management programs, which means that besides assessing the INR the patients take care of their oral anticoagulant therapy dosing. Patients in selfmonitoring and self-management programs are under the authority of the local Thrombosis Service. That means that the Thrombosis Service is responsible for education and monitoring the patients in these programs. In the Netherlands at the moment there is very little support from the main Thrombosis Service information systems for self-monitoring and self management programs. Specially developed systems for self-monitoring and self-management do exist, but do not integrate well with the main Thrombosis Service systems. So this calls for a general system that can support self-monitoring patients as well as dosage advisors and dosage doctors.

2.3 CONCLUSION

Computer-assisted dosing has been the exclusive terrain from Thrombosis Services and suppliers of computer-assisted dosing programs for a long time. The current situation shows a lag of development, both in processes at the anticoagulation clinic as well as the development of the computer-assisted dosing programs. Continuing current way of working seems to prevail on fitting to the changing needs of patients now a days. New initiatives are sparse and slow in development. Patients move to self-monitoring programs and want to be in control of their own health as much as possible. Outside anticoagulation clinics there is a lag of knowledge on guiding patients on oral anticoagulation therapy. Inside anticoagulation clinics about 50% of the cases are classified as expert medical staff work, but a preliminary study of protocols and documents indicates that lot of the cases might be standardized. To improve these things the following recommendations are listed:

- Incorporate induction algorithms in computer programs according to FNT protocols.
- Make programs more efficient by incorporating working-methods according protocols. Standardization also may improve the TIR.
- Make dosage knowledge available for a wide variety of medical staff and patients on self management programs, especially outside Thrombosis Services.
- Take genotypes into account in dosing programs. This should lead to faster induction and thereafter to less adjustments of dosages.
- Use more than one algorithm. An INR-dosage relation algorithm can be combined with the ICAD algorithm and perhaps with a dosage that is based on an Artificial Neural Network. Using different algorithms in parallel can improve the performance of a computer program. This could be done by comparing the outcomes of each algorithm and applying weights to them to make a judgment on which outcome to propose.
- Make clear how programs work and make the process tunable by means of parameters. In that way medical staff can get confident with what is automated and what is left for manual handling. In this way a decision on automatically dosage for certain cases can be made.
- Use one integral system for regular patients as well as self-monitoring patients. Only overview of all available data gives clear insight in a patient's status.

Each item on itself is a good reason for extending current computer-assisted dosing programs. Certainly an implementation of more improvements at a time will be of great importance. To accomplish a major improvement, the focus should be on all items that the current computerassisted dosing programs leave to medical experts to deal with. This can be done by incorporating more or better algorithms. But there seems to be also a considerable area where algorithms are



not applicable. This is because several factors may introduce a kind of uncertainty for which algorithms have their shortcomings. Such cases are called ill-structured problems and they are the appropriate domain for an expert system according to *Giarratano* [15]. So the question 'Why designing another current computer programs on anticoagulation dosage' can be positively answered from the next four point of views:

- 1. Efficiency: less people do more work
- 2. Standardization: every case is handled in the same way, less direct involvement of medical staff.
- 3. Optimization: every case is handled in the best way.
- 4. Continuity: medical staff is sparse and hard to bind.

So the challenge for this project is to incorporate dosage knowledge in computer-assisted dosing programs. To do so, this knowledge has to be made explicit and needs to be incorporated in an expert system. Next chapter is about expert system theory and explains knowledge elicitation, knowledge representation and expert system development.





3 EXPERT SYSTEM THEORY



In the previous chapter we saw that current computer programs are only partly capable of providing dosage proposals and next return date proposals. In some cases medical staff is needed for checking on computer proposals. In other cases medical staff is needed to provide a proposal themselves, because of special circumstances which ask for a reasoning about the dosage or return interval. This assumes that an expert system may be helpful to deal with that part of the cases for which there is no acceptable proposal now. This chapter is about the theory on expert system development. Paragraph 3.1 elaborates on expert system theory. For supporting the medical staff with an expert system, there is a need for making their knowledge explicit, before it can be incorporated in a system. Paragraph 3.2 handles the techniques that exists to elicit knowledge and to make a representation of it. Paragraph 3.3 gives a brief overview on expert system development. Paragraph 3.4 concludes with a choice for the application of the techniques used in this thesis.



3.1 IS USING AN EXPERT SYSTEM APPROPRIATE?

To answer this question there is a need for understanding expert systems and their use. Almost all theory in this paragraph is from the book 'Expert Systems: principles and programming' of *Giarratano* and *Riley* [15]. In his book *Giarratano* states that expert systems is a very successful application of artificial intelligence technology. Expert systems use specialized knowledge to solve problems at the level of the human expert. A definition of an expert system of Professor Edward Feigenbaum form the Stanford University is:

AN EXPERT SYSTEM IS A COMPUTER SYSTEM THAT EMULATES, OR ACTS IN ALL RESPECTS, WITH THE DECISION-MAKING CAPABILITIES OF A HUMAN EXPERT. Where a human expert is someone who has expertise in certain area. And where expertise is of a higher level than knowledge. This is best illustrated in Figure 12 where the concept of an expert system is shown. The user supplies facts to the system and the system responds with expert



FIGURE 12: CONCEPT OF AN EXPERT SYSTEM

advice. Internally the system consists of two main components. The knowledge base contains the knowledge from which the inference engine draws the conclusions. These conclusions are the expert system's response to the user's queries for expertise. In rule-based expert systems, the inference engine determines which rule antecedents are satisfied by the facts. When a system only contains a knowledge base and responds with knowledge facts the system should be called a knowledge-based system. However, the terms expert system and knowledge-based system are often used synonymously.

Using expert systems has a number of advantages:

- Increased availability, because expertise can be made available on any suitable computer at any time.
- Reduced cost, because the cost of providing expertise per user is decreased.
- Permanence, in contrary to human experts who may retire or quit, the system's knowledge lasts indefinitely.
- Multiple expertise, by combining the expertise of multiple experts in one system, the system can exceed the expertise of a single human.
- Explanation is an advantage when the system can explain the reasoning that led to the conclusion. This increases the confidence that the correct decision was made.
- Fast response can be a requirement for critical situations (i.e. aircraft landing), but also a good feature for situations which need high capacity on responses.



- Steady, unemotional and complete response at all times may be very important when human experts may not work at optimum because of stress or fatigue.
- Intelligent tutor. The system can act as an intelligent tutor for people running example cases on the system.

The process of developing an expert system delivers an extra advantage, because during the knowledge retrieval the knowledge becomes explicitly known and is subject of examination for consistency, completeness and correctness. Knowledge may then have to be adjusted.

A global view on the development of an expert system is reflected in Figure 13. In the dialog between the knowledge engineer and the expert, the expert's knowledge is elicited. This is more or less analog with discussing the system requirements in conventional program development. Next the knowledge engineer codes the explicit knowledge into the knowledge base of the expert system. The human expert then evaluates the expert system and gives critique to the knowledge engineer. This process iterates until the performance of the expert system is satisfied by the expert. The figure makes clear that the interaction between the human expert and the knowledge engineer is crucial for the development of the system.



FIGURE 13: DEVELOPMENT OF AN EXPERT SYSTEM

An expert system usually has the next design criteria:

- High performance, that means that the quality of the advice of the system has to be equal or better than a human domain expert.
- Adequate response time, which means that the system has to respond equally or preferably faster than a human domain expert.
- Good reliability, which means that the system has almost no downtime and is not prone to crashes.
- Understandable, which means that the system should be able to explain its reasoning's process, rather than just being a black box. Especially when human life may depend on the conclusions of the system this is an important feature. Also during development confirmation of correctness of entered knowledge is traceable and unforeseen interactions may be detected during testing.
- Flexibility, which means that an efficient way of adding, changing or deleting knowledge must be provided.

Developing a rule-based system has the advantage that knowledge can grow incrementally. This facilitates rapid prototyping so that the knowledge engineer can quickly show a working



prototype of the system. Also new rules can be verified in this way when they are added, so checking the validity of the system continually. In case an expert is not able to explain how he solves problems, it is also impossible to make this knowledge explicit and available for a knowledge base. In this case programs that learn by themselves are an option. These programs are based on induction, artificial neural systems or other soft computing methods.

Modern rule-based expert systems are successful because of the convergence of three important factors. First, by the 1970s it became apparent that domain knowledge was the key to building machine problem solvers. Although methods of reasoning are important, studies have shown that reasoning plays a minor role in expert's problem solving most of the time. The current successful expert systems are thus domain knowledge-based expert systems instead of general problem solvers. In fact expert systems is now considered an alternative programming model or paradigm to conventional algorithmic programming. Second, another important development that led to the success of current expert systems was the separation of knowledge base and inference engine. In this way the essential core of the system, the knowledge base, could relative easily be reused or renewed as needed. The third factor is the insight that human understanding can be well expressed as IF-THEN production rules, by Newell and Simon. They also showed that standard reasoning could be done with an inference engine in a way that is looks very much like human reasoning and so is very understandable by humans.

After this short flight over the expert system world, the question whether or not an expert system could be appropriate for this thesis, has to be answered. *Giarratano* [15] states that the appropriate domain for an expert system depends on a number of factors, which follow in the next questions.

- Can the problem be solved effectively by conventional programming? If the answer is yes, an expert system is not the best choice. Because there is no efficient algorithmic solution to all problems in anticoagulant dosing, there is a case here of ill-structured problems and so this is in favor of using an expert system.
- Is the domain well bounded? It is important to have well-defined limits on what the system is expected to know and what its capabilities it should be. The latter is easy to define, because the system should be able to supply a dosage and a return date. The limits to what knowledge should be in the system is hard to answer at this moment and may be known after knowledge retrieval. In any case, the domain limits are well-definable.
- Is there a need and a desire for an expert system? Human experts are scarce to get and hard to keep. On top of that the amount requests for a dosage advice appears to grow and operational managers like to have a high throughput capacity on dosage advices and at the same time want to reduce the costs of staffing. However, from point of view of the current experts there is no real desire for an expert system. So it depends on who you are asking.
- Is there at least one human expert who is willing to cooperate? There are more than enough experts willing to cooperate, so this is no issue.
- Can the expert explain the knowledge so that it is understandable by the knowledge engineer?

It is hard to tell upfront if the knowledge can be made explicit. The medical terminology and the jargon are familiar to the knowledge engineer, so this should not be a problem.


• Is the problem-solving knowledge mainly heuristic and uncertain? The knowledge of the experts in this case is largely based on experience and the problems they deal with that are left by the current computer programs are not simply solvable with logic and algorithms. So this question can be positively answered.

So using an expert system appears to be appropriate for this project.

3.2 TECHNIQUES FOR KNOWLEDGE ELICITATION AND REPRESENTATION

The process of building an expert system as described in previous paragraph consists of a three step cycle:

- Elicit knowledge from the human expert in a dialog.
- Code the knowledge explicitly in the knowledge base.
- The expert evaluates the expert system and gives a critique.

So there is a need for making knowledge explicit, before it can be coded in an expert system. This is also called knowledge retrieval and can be roughly split in two phases:

- Knowledge elicitation from sources.
- Representation of this knowledge.

The sources used for knowledge elicitation is not restricted to human experts, but also very convenient is documented information like books, reports, drawings, visual inspection, databases and internet. Documented information is useful for retrieving declarative knowledge, where interhuman contacts are useful for procedural as well as declarative knowledge. It is common to take the next steps in the process of knowledge retrieval, also called knowledge acquisition:

- Application of a technique to make the way of working of an expert explicit.
- Interpreting and analyzing the way of working to gain insight in the way of thinking and reasoning of the expert, and which knowledge is used for which situation.
- Use this insight to construct a model as a simplified view on reality.
- Verify the model to see if it is a correct interpretation of way of working of the expert.
- Make the model available for coding in the knowledge base.

Knowledge acquisition and knowledge model development is an iterative process that cycles through above steps until a satisfied model exists. An overview of common knowledge elicitation methods is given in subparagraph 3.2.1. Methods of knowledge representation are summarized in subparagraph 3.2.2.

3.2.1 KNOWLEDGE ELICITATION TECHNIQUES

To find out what a human domain expert is doing and thinking to assess his conclusion, is the goal of the knowledge retrieval. From developments on artificial intelligence (AI) and knowledge base systems (KBS) there is insight on how to acquire and represent knowledge from experts. The most common knowledge acquisition techniques are summarized in this paragraph. For all these techniques more or less the same problems might arise during knowledge acquisition. The most relevant are:

- The domain expert knows more than he says, often stated with the term 'expert knowledge is tacit'.
- The knowledge engineer often has to be a specialist too in the domain.



- The expert thinks in his own patterns, typical cases, objects and events.
- It is very difficult to find a knowledge representation that is understandable for the expert and at the same time suitable for the knowledge engineer.
- Validation of the elicitated knowledge is not easy.
- How to merge the knowledge of several experts, how to resolve conflicts?

The methods for knowledge acquisition can be split in direct methods and indirect methods. Where direct methods on its turn can be split in structured and unstructured methods. Direct methods refer to knowledge that can be directly expressed by an expert. To the unstructured techniques belong:

- Unstructured interview.
- Observations.
- Thinking aloud and protocol analysis.

Structured techniques are supposed to apply structure to knowledge, including knowledge acquired with unstructured techniques. This implies that it is common to start with unstructured techniques before using the structured ones. To the structured techniques belong:

- Structured interview / questionnaires.
- Goal decomposition: twenty questions technique and laddered grid.
- Relation elicitation: drawing closed curves and inferential flow analysis.

Indirect methods track down a specific structure in the knowledge. They are suitable for knowledge that is hard to express. Examples of indirect methods are: sorting cards, repertory grid, Multi-Dimensional Scaling, cluster analysis, network analysis and automated methods (induction principle).

For each technique there is a danger for knowledge deformation on three occasions, that is:

- While posing questions by the knowledge engineer.
- Expressing himself by the expert.
- Interpretation by the interviewer.

One has to bear in mind these risks during knowledge elicitation. Next follows a brief description with pro's and con's of some of the above summarized techniques.

UNSTRUCTURED INTERVIEW

The unstructured interview is suitable for the first phase of knowledge elicitation. It is done by recording the interview on tape and asking questions on all aspects of the working terrain. The conversation should be directed by the interviewer as little as possible and questions should be thought up on site. The advantages of an unstructured interview are:

- Provision of a very extensive and diverse knowledge.
- It is a good way to get a coarse view on the domain.

Disadvantages of the unstructured interview are:

- Hard to perform, because the interviewer has to pay attention to many things at the same time.
- There is a big danger of deformation by thinking up the questions on the spot.



• It is messy and time consuming.

OBSERVATIONS

The expert is observed during daily practice while handling cases that are subject of knowledge modeling. Everything is recorded on (video) tape, and when possible, the expert is thinking aloud. The advantages of observing are:

- It gives a truthful reproduction of the method of working of the expert.
- When the expert is thinking aloud, insight in the way of thinking on the moment of acting.

Disadvantages of observations are:

- No direct influence from the interviewer on the problem that is solved. So not the complete problem area might be covered.
- The interviewer can't intervene and ask for an explanation.
- Especially common problems will be examined.

THINKING ALOUD AND PROTOCOL ANALYSIS

The expert is performing tasks, while he has to think aloud. Everything is recorded on tape. Everything is written out and the protocol is analyzed. The advantages of thinking aloud and protocol analysis are:

- There is almost no deformation of the acquired data by interpretations, expectations or memory mistakes.
- Delivers the richest and most direct data about the thinking processes.

Disadvantages:

- High costs in time consuming, processing and analyzing.
- Can be troublesome to expose the problem solving method, because there is no good picture of it.

STRUCTURED INTERVIEW / QUESTIONNAIRES

A structured interview or questionnaire is used for clarifying a specific part of the knowledge domain. It asks for a thorough preparation, and the interview has to be done on the basis of prepared questions. Based on the answers the expert gives, a method called probing can be applied to reveal additional information. With probes standard questions are meant like 'why/how/when do you do that'. Advantages are:

- The interview passes smoothly and that way efficiently.
- There is room for elaboration on relevant issues.
- All desired information is acquired, because there is less change on forgetting parts.

A disadvantage could be that the interviewer asks the wrong questions because he doesn't have a right picture of the domain.

GOAL DECOMPOSITION: TWENTY QUESTIONS TECHNIQUE

The twenty questions technique is used to retrieve information on how the expert tackles certain problems. A couple of problems from the domain are prepared and presented to the expert. The expert has to retrieve the underlying problem by posing questions. Advantages of this method are:



- Delivers a very good insight in the problem solving process of the expert.
- Delivers some structure for the system that has to be built.
- Delivers some insight in the sequence of rules.

Disadvantage of this method is that this method is very difficult for a knowledge engineer.

GOAL DECOMPOSITION: LADDERED GRID

This method is interesting when a hierarchical structure in the knowledge is presumed. An arbitrary concept in the domain is chosen. By way of questioning more insight in the rest of the domain is acquired, e.g. questions like 'give examples of ...' or 'what have ... and ... in common' or 'what alternatives are there for ...'. Advantages are:

- Useful for declarative hierarchical knowledge.
- Useful for procedural knowledge, when there is a hierarchy of actions.
- It gives insight in the structure and in the way a knowledge base could be set up.

Disadvantage: when the knowledge is not hierarchical, this method is very difficult to handle.

RELATION ELICITATION: DRAWING CLOSED CURVES

This method traces concepts in the domain. The assumption is, that concepts have a spatial representation. Concepts are displayed graphical to the expert. Groups of concepts are bundled by drawing lines around them. The advantage of this method is, that it delivers a spatial representation of the knowledge domain.

RELATION ELICITATION: INFERENTIAL FLOW ANALYSIS

This method also traces concepts in the domain. The assumption here is, that there are quantitative relations between concepts. A list of concepts is set up. A structured questionnaire is made, and the expert has to relate each time two concepts. This method is suitable for follow-up interviews. It also forms a good basis for formulating production rules for quantitative relations between concepts.

INDIRECT METHODS

Indirect methods can be helpful in the retrieval of knowledge that is hard to express. They are also very useful in visualizing structure in knowledge. Advantages of indirect methods are:

- It is more formal
- The chance for completeness of the data is bigger.
- Experts like to see representation of their knowledge in a new way. It can be a motivator.
- The results are very useful as a basis for follow-up knowledge acquisition sessions.

The disadvantages of indirect methods are:

- They are context sensitive, the results are dependable of the used objects.
- Some experts feel aversion to indirect methods.
- The sessions can be very time-consuming.
- The methods are subjective, so one must be careful.

3.2.2 REPRESENTATION OF THE ACQUIRED KNOWLEDGE.

Next to the elicitation of knowledge, it has to be represented in some way. Knowledge representation is very important for expert systems for two reasons. First, an experts system



reasons by the way of making inferences, which is drawing conclusions based on formal logic. So these systems are designed for a certain type of knowledge representation on rules of logic. Second, knowledge representation is important because it affects the development, efficiency, speed and maintenance of the system. This is analog to good program design and choosing the right data structures for conventional programming.

Knowledge can be classified into procedural knowledge, declarative knowledge and tacit knowledge. Procedural knowledge is about knowing how to do something, declarative knowledge is about knowing that something is true or false. Tacit knowledge is sometimes called unconscious knowledge and cannot be expressed in a language. In computer systems ANN's are related to tacit knowledge because a neural net also cannot explain its knowledge directly.

Knowledge is also part of a hierarchy, as illustrated in Figure 14. For developing expert systems it is important to have a notice of the differences in the levels of this hierarchy. Because expert systems draw inferences using facts and a fact is information that is considered true. Sometimes an expert system has to separate data from noise, transform data into information or transform information into knowledge. But it is extremely dangerous to use raw data in an expert system that expects facts. Expertise is a specialized type of knowledge and skills that experts have. It is in the knowledge, metaknowledge and wisdom levels of Figure 14. Expertise is the implicit knowledge and skills of the expert that must be extracted and made explicit so that it can be encoded in an expert system. Metaknowledge is knowledge about knowledge and expertise. In expert systems an ontology is the metaknowledge that describes everything known about the problem domain. In artificial intelligence (AI) and expert systems ontology means the explicit formal specification of the terms in the domain and the relations among them.





Common forms of knowledge representation are production rules, objects, semantic nets, schemata, frames and logic. A brief overview of some representation methods is summarized next.

PRODUCTION RULES

Rules are commonly used as the knowledge base in expert systems, since their advantages greatly outweigh their disadvantages. *Post* created production systems which gained popularity over the years since production rules could be used for representing major classes of knowledge.



Computer languages like CLIPS are commonly defined using the Backus-Naur Form (BNF) of production rules. This BNF notation is a metalanguage for defining the syntax of a language. The idea behind production rules is, that given an input string, a production rules provides an output string. I.e. the input string 'INR is too high' could produce the output string 'decrease dosage'. In that way familiar IF-THEN rules can be interpreted like:

IF INR is too high THEN decrease dosage

In this production rule the term 'INR is too high' is called the antecedent and the term 'decrease dosage' is called a consequent. A production rule may have multiple antecedents like:

IF INR is too high AND INR is greater than 8.0 THEN prescribe vitamin K

A *Post* production system consists of a group of production rules like:

- R1: If ... Then ...
- R2: If ... Then ...
- ...
- Rn: If ... Then ...

When data become available, the rule-base is passed through for assessing the target conclusion. The Rete algorithm was developed for finding an efficient way to match antecedents without having to try each rule sequentially. This is especially important when the production system consists of many rules. Another drawback of a big rule-base is that it is hard to interpret, verify and validate. For this reason and for the ease of discussing rules with experts decision tables may be helpful.

DECISION TABLES

A decision table consists of four quadrants, as shown in Figure 15:

- condition subjects: relevant decision criteria.
- action subjects: possible decision outcomes.
- condition entries: (subranges of) values that the condition subjects may take ('-' : irrelevant in the context of that column).
- action entries: action values to be assigned under the corresponding condition combination ('x' : execute).

Decision Table dosage for Acen	ocoumarol							
INR N			-	<	1,6			
Anticoagulation Level	2,0-	2,5	2,5-	3,5	3,0-	4,0 🖌	3,5-4,5	
Sex (Female/Male/Unknown)	F	M or U						
Morning/Afternoon sample	-	-	-	-	-	-	М	-
Dosage level adjustment	+0,21	+0,21	+0,42	+0,42	+0,42	+0,42	+0,42	+0,42
Dosage High/Low start	н	Н	Н	н	н	Н	н	н
Deviate dose day 1	2x average		2x average		2x average		2x average	
Deviate dose day 2								
Deviate dose day 3 🥢								
Return after days	<=7	<=7	<=7	<=7	<=7	<=7	<=7	<=7

FIGURE 15: EXAMPLE OF A DECISION TABLE



The condition subjects should represent a complete set of decision rules, also called the exhaustivity criterion and where columns are mutually exclusive, called the exclusivity criterion.

Advantages of decision tables are:

- Intuitive also to non-IT people, which means that it facilitates communication between business user, analyst and programmer, it is easy to validate and it is assumed faster and less prone to human mistakes than if-then rules.
- Provides a range of implementation options like automatic export to other target representation as well as program code (nested if-else statement) as in a if-then rules & rule inference engine or relational database table.
- Easy to maintain, even by business user directly, because it provides a level of abstraction from implementation issues and implementing changes requires little effort.

SEMANTIC NETWORK

A semantic network or net, is a classic AI representation technique used for propositional information. Propositions are a form of declarative knowledge because they state facts. The structure of a semantic net is shown in Figure 16 where the nodes or objects are connected with arcs called links or edges. The links are used to show the relationships and the nodes are used to represent physical objects, concepts or situations. Although many different types of relations exists, it is convenient to use common types as much as possible for clear understanding, like IS-A and A-KIND-OF (AKO), where IS-A means 'is an instance of' and refers to a specific member of a class. AKO relates generic nodes and the AKO arrow point to its superclass. AKO is the opposite of the HAS-A relation which relates a class to a subclass. Inheritance is a useful tool in knowledge representation because it eliminates the need to repeat common characteristics. A semantic net is also an efficient representation technique since many complex relationships can be shown with a few nodes and links. Modern expert system software has object-oriented capabilities next to rule-based features.



FIGURE 16: EXAMPLE OF A SEMANTIC NET

UML

Unified Modeling Language (UML) has been accepted as a standard notation in industry and is used in a broad range of applications on software engineering and system design. However UML



is used only lately as an modeling tool for knowledge representation. Although above mentioned representation techniques are developed for the specific area of AI technologies, there exist a number of obstacles for acceptance of these techniques. The integration of development and maintenance of knowledge based systems with industrial software development processes is an important prerequisite for a broader application of AI technologies, such as knowledge based systems. Since knowledge base system development and maintenance is only feasible with the support of knowledge engineers who can handle the formal representation language of the underlying system, UML has become an important tool used in modeling knowledge.

BAYESIAN NETWORKS

The deductive method of reasoning in which conclusions must follow from their premises, is called exact reasoning, because it deals with exact facts from which exact conclusions follow. With inductive reasoning, an inference is made from a specific case to a general case. The premises of an inductive argument give support to a conclusion, but are no guarantee. One of the main strengths of expert systems is the ability of reasoning under uncertainty. Important methods for reasoning under uncertainty use probability theory and fuzzy logic. Probability is a quantitative way of dealing with uncertainty. The conditional probability P(A|B), states the probability of event A given that event B occurred. The inverse probability states the probability of an earlier event given that a later event occurred. The solution to this problem is Bayes' theorem. Bayesian networks are graphical structures for representing the probabilistic relationships among a large number of variables and doing probabilistic inference with those variables. The inference is done according Bayes' theorem. An example is shown in Figure 17 and Figure 18. Suppose that the outcome of the INR of an old patient is (too) low. A prior subjective opinion may exist that the patent has forgotten to take his tablets. Assume the probability F for forgetting the tablets as:

P(F) = 0.6 and thus P(F') = 0.4.

To check for forgetting tablets, often a call is made to the patient or his supporter. We can consider this call as a test and we can indicate its outcome with a + for confirmation of forgetting the tablets and a – as a result for not forgetting the tablets. However, what people tell and what happens in reality is not always the same. So in this test we have also false negative and false positive results. The results can be expressed as conditional probabilities, because the cause



FIGURE 17: INITIAL PROBABILITY TREE



(forgetting the tablets) must have occurred before the effect (test result). Assume the next probabilities:

P(+|F) = 0.8 P(-|F) = 0.2 (false -) P(+|F') = 0.1 (false +) P(-|F') = 0.9

As shown in Figure 17 we can now calculate the probabilities for

$$P(- \cap F') = P(F')*P(-|F') = 0.4 * 0.9 = 0.36$$
$$P(+ \cap F') = P(F')*P(+|F') = 0.4 * 0.1 = 0.04$$
$$P(- \cap F) = P(F)*P(-|F) = 0.6 * 0.2 = 0.12$$
$$P(+ \cap F) = P(F)*P(+|F) = 0.6 * 0.8 = 0.48$$

From this the total probability of a + and – test is calculated as:

 $P(+) = P(+ \cap F) + P(+ \cap F') = 0.48 + 0.04 = 0.52$

$$P(-) = P(- \cap F) + P(- \cap F') = 0.12 + 0.36 = 0.48$$

Next based on the outcome of the test, the probability of forgetting the tablets can be calculated according Bayes theorem:

$$P(H|E) = \frac{P(E|H)P(H)}{P(E)}$$

where H it the hypothesis (in our case forgetting tablets) and E is the event (in our case the test call). This is illustrated in Figure 18.



FIGURE 18: BAYESIAN DECISION TREE

3.3 EXPERT SYSTEM DEVELOPMENT

The development of an expert system has some aspects of interest. A software engineering methodology is the usual way to build an expert system, so that it can be a quality product developed in a cost-effective and timely manner.

The software project management concerns of conventional programs are also applicable to the development of expert systems. The requirements however should be customized for expert systems. In his book [19] Software Project Management, *Hughes* provides the stages in a typical life cycle for a software project, as illustrated in Figure 19. In general, these stages are valid for an expert system development project as well. It is important to follow the standards in the



development of a product to accomplish a good quality product. This is especially important for expert systems, because they are generally mission-critical applications supplying expertise in situations where human life and property is at stake. This is of course also the situation in providing dosages for Thrombosis Service patients, where human life may be jeopardized.



FIGURE 19: TYPICAL PROJECT LIFE CYCLE

One of the key concepts of software engineering is the software life cycle. The life cycle starts with the initial software concept and ends with its retirement of use. The life cycle concept provides a continuity that connects all stages of the cycle. By planning maintenance and evolution early in the life cycle, the costs of these stages are reduced later in the life cycle. There are several models for software life cycles. The classic model is the waterfall model, where each stages is verified and validated before entering the next stage. A modification on this model is the incremental model, in which the software is developing according the waterfall model in increments of functional capability. The spiral model is a way of visualizing the incremental model. According to Giarratano [15], the linear model is very successful in the development of expert system projects. This model is illustrated in Figure 20. The idea is, that the life cycle runs through all the stages from planning to system evaluation. Next, the life cycle repeats the same sequence until the system is delivered for routine use. The life cycle is then used for maintenance and evolution of the system. In a way, this life cycle can be interpreted as a circuit of the spiral model.



FIGURE 20: LINEAR MODEL OF EXPERT SYSTEM DEVELOPMENT LIFE CYCLE

The knowledge definition main task and the knowledge design main task can be split into a subtask structure. For the purpose of this thesis, only a brief first acquaintance is accomplished of the first steps in the development lifecycle.



3.4 CONCLUSION

In subparagraph 3.1 we saw that an expert system most likely is appropriate for decision support for the medical staff. The current computer system then may take care of the regular cases based on internal algorithms. This leaves the cases with special circumstances for an expert system. At this moment it is not completely clear if the expert system has to be of the rule-based type or based on another type like an artificial neural network or perhaps a combination of these types. This depends on whether or not the knowledge can be made explicit or not. This is the main subject of the next chapter. Closely connected to this subject is the way of knowledge representation. Of course if there is no explicit knowledge, there is no way of making a representation for it. However, there is a lot of information documented in the Document Management Systems (DMS) of the Thrombosis Services from Star-MDC and Saltro. These DMS's support the knowledge management of Thrombosis Services and may be an important source for knowledge retrieval. The exact relevance of these documents should be checked with the domain experts.

The knowledge acquisition by dialog between knowledge engineer and domain expert is an obvious first step. An important factor is that there are dosage doctors and dosage advisors willing to help on this subject. Next to that, the author of this thesis is playing the role of a knowledge engineer, but is a bit of a domain expert himself. Nevertheless it is better to start doing things by the book with global sessions before getting into details. Based on the outcome of paragraph 3.2 it makes sense to start with an unstructured interview followed by observation sessions. In this case the unstructured interview serves as an introduction to the expert system development as well as getting a global idea of how the observation sessions could be well organized. After these general knowledge gathering sessions more specific problem-solving knowledge-gathering sessions can be arranged based on the outcome of the first sessions. The decision on the type of knowledge representation can be made after acquiring more insight in the domain.





4 HOW TO MAKE KNOWLEDGE EXPLICIT



This chapter is about the way the knowledge from the dosage doctors and the dosage advisors is retrieved. Interviews are an important part of the knowledge retrieval. During these interviews it became clear that the doctors and advisors often use documented knowledge. The documents they use are incorporated in a Document Management System, which is the company's way of knowledge management for securing the organizational knowledge. In a certain way, part of the knowledge of the dosage doctors and dosage advisors is captured in these documents. The only thing that seems to be needed here is to make the relevant knowledge from these documents available for an expert system. But for knowing what is relevant and what isn't, the opinion of the experts is needed. During interviews with the medical staff this would become clear. Paragraph 4.1 deals with the way the experiments are set up and gives a brief overview of the first results. From these results a list of concepts could be retrieved. These concepts are important for the ontology used in the domain. In paragraph 4.2 is explained how these concepts and their relations contribute to a semantic net. Paragraph 4.3 focuses on the documented knowledge and especially on the dosage schemes they contain. Paragraph 4.4 concludes this chapter with a summary.



4.1 DESIGN OF THE EXPERIMENT

To get a broad view on the knowledge domain it is common to use multiple knowledge sources and multiple methods of knowledge acquisition. In this case the scope of the domain is the work of the dosage advisors and dosage doctors when constructing a dose and a return date. The knowledge elicitation from the experts is done with a couple of interviewing methods and in subsequent phases. The idea behind the phasing of knowledge elicitation is, that every next phase gives a more detailed view on the knowledge that is used. When making a start with exploring the domain a coarse overview is acquired. This is done with the participant observations technique and is explained in subparagraph 4.1.1. In subparagraph 4.1.2 the thinking aloud protocol analyses is illustrated as a follow up on the participant observations. In every next phase refinement is achieved by using a more structured technique. Finally, in subparagraph 4.1.3, the OODA-Loop is explained as the preferred method.

4.1.1 PARTICIPANT OBSERVATIONS

For the first phase the technique of participant observations is used, as described at Wikipedia [20]. Participant observations is a kind of observation technique that was described in previous chapter. Participant observation is a widely used methodology in many disciplines, particularly, cultural anthropology, but also sociology, communication studies, and social psychology. Its aim is to gain a close and intimate familiarity with a given group of individuals and their practices through an intensive involvement with people in their natural environment. A strength of participant observation is that researchers can discover discrepancies between what participants say (and often believe) and what actually does happen. An unstructured interview also might be applicable, but because there was already some knowledge of the domain present and because a lot of procedural information is well documented, an unstructured interview would deliver too coarse information, especially in respect to the amount of work an interview takes. To deal with the major disadvantages of the observations as: 'there should be no direct influence from the interviewer on the problem that is solved' and 'the interviewer can't intervene and ask for an explanation', there was participation in the observations by asking for explanations. Audio recording is preferable if there is only one expert and there is no pertinent visual information to record. In this case the only essential visual information was the screens the experts work on. So the observation sessions were recorded on an audio device while the relevant screens were captured. Afterwards the audio recordings were typed out in a transcript report. The captured screens were placed on the applicable places in the transcript report. While typing and reading the report new questions and need for clarifications raised. These questions were placed in the right margin of the report. Next the reports were sent to the experts to verify the text and to make a second appointment for answering the questions in the margin.

There were two participant observation sessions in the first phase. The first session took place at the Thrombosis Service of Star-MDC in Rotterdam with a longtime experienced dosage doctor. The second session took place at the Thrombosis Service of Saltro in Utrecht also with a dosage doctor. For both sessions appointments were made upfront and a small document was send with a brief explanation of the observation session. So the experts knew upfront that it would take no more than 1 hour, the session was going to be recorded and they were asked to perform some of their most common tasks, while explaining what they were doing and thinking. On the start of



each session there was an introduction and a brief explanation of the purpose of the observation session. Permission for recording the session on an audio device was asked. At the end of the session the expert is acknowledged and asked for a review of the text once it has been typed out. This was approved in both cases.

The output of the participant observation sessions is a report for each session with global information on how dosage doctors perform their most common tasks. The report also contains the screens and documents they used. Based on these reports a list of concepts was made which is subject of paragraph 4.2. The reports also lead to the most interesting cases for protocol analysis in the second phase.

4.1.2 THINKING ALOUD AND PROTOCOL ANALYSIS

The outcome of the participant observations formed the basis for a more detailed way of knowledge retrieval. This was because the impression arose that the work of the experts could be classified in a limited number of types of cases. So the next interviews were focused on how the experts were dealing with cases. This was done with the technique of the thinking aloud and protocol analysis method. One of the reasons that the method of protocol analysis was chosen for follow up of the participant observations is that it is hard to provide fake cases for finding out detailed procedural knowledge at this point of knowledge retrieval. Also there is a need of confirmation on the outcome of the participant observation sessions. This was done by having protocol analysis sessions with a other dosage doctors and a dosage advisor. The cases were chosen at random because the current systems provided them more or less at random during daily work. The way of working was likewise the participant observation technique, because there was participation by asking questions for clarifications as like their job was learned. The experts were explicitly asked to think aloud while performing their work. The protocol analysis sessions were recorded on an audio device while relevant screens were captured. Afterwards the audio recordings were typed out in a transcript file. Each session contained several cases. For each case that was resolved by the expert a document was made. The captured screens were placed on the applicable places in the transcript files. Questions for clarification that came up afterwards were placed in the right margin of the report. At the end of each reports a flowchart was inserted indicating the assumed evolving of their process. Next the reports were sent to the experts to verify the text and the flowcharts. And at the same time to make a second appointment for answering the questions in the margin and for discussing the flowcharts. Additional clarifications on the cases were edited in the reports afterwards, so the final documents contain the actual procedural way of the work of the experts on the specific cases.

There were four protocol analysis sessions in this second phase. All sessions took place at the Thrombosis Service of Star-MDC in Rotterdam. Three of them with experienced dosage doctors and the fourth with an experienced dosage advisor. The same procedure of making appointments upfront as for the participant observations was followed. So at the start of each session there was an introduction and a brief explanation of the purpose of the protocol analysis session. Also there was a request for recording the session on an audio device. At the end of the session the expert is acknowledged and asked for a review of the text once it is typed out. This was approved in all cases.



The output of the thinking aloud and protocol analysis sessions is a set of reports. For each case a report was made. Next these reports were analyzed with the OODA technique that is explained in the next subparagraph. A graph and summary for each type of case was produced using OODA. These cases form the bases for a detailed knowledge representation and are a means to converge to a design of an expert system.

4.1.3 FURTHER KNOWLEDGE RETRIEVAL AND THE OODA-LOOP

The outcome of the participant observation sessions and the thinking aloud sessions are still to coarse for the design of an expert system. Further investigations were necessary to reveal more specific information. The common structured technique of a questionnaire was not very convenient, because the experts find it hard to express their knowledge based on an imaginary case. So that is why the next phase was based on working with real cases. The technique however was structured and based on the OODA-loop which is explained next. Typical questions were: what do you observe, what items are part of the orientation, how do you decide on the information you gathered and what actions are involved. Depending on the outcome of the answers on the standard questions follow up questions like 'why/how/when do you do that' were posed to gain detailed results.

Analysis was performed during the interviews and afterwards with the OODA method. OODA [16] stands for Observation, Orientation, Decision, Action. The OODA-loop was created by a military strategist Colonel John Boyd. The OODA-loop is a decision cycle that refers to the continual use of mental and physical processes by an entity to reach and implement decisions. Boyd viewed the enemy as a system that is acting through a decision making process. This decision making process is based on observations of the world around it. Boyd states that the orientation phase of the loop is the most important step, because if the enemy perceives the wrong threats, or misunderstands what is happening in the environment around him, then he will orient his thinking (and forces) in wrong directions and ultimately make incorrect decisions. The goal should be to complete your OODA Loop process at a faster tempo than the enemy's, and to take action to lengthen the enemy's loop. While it was developed for military purposes OODA has also been applied frequently in other sectors because of its common-sense approach to making decisions. In a way OODA is shorthand for what practitioners of business intelligence know as: gather your data, analyze it, make your decision and execute it. So in this way OODA is of practical use to analyze the decision process of the medical experts. The cases of the protocol analysis sessions in paragraph 5.3 were analyzed using the OODA phases.

4.2 ONTOLOGY

In AI and expert systems jargon, an ontology is defined as the explicit formal specifications of the terms in the domain and relations among them. Basically an ontology is a standard, agreed upon set of terms used to describe a domain. An ontology is in that way helpful in designing an expert system without having to worry about ambiguities. From the first interviews a list of domain concepts was made. These concepts are reflected in semantic net graphs like in Figure 21, which is a copy of a graph from the next chapter, where the graphs will be explained. The concepts are interconnected by an arrow which is indicating the relationship between these concepts. The AKO relationship stands for A-Kind-Of. The graphs were verified and validated by the dosage doctors





FIGURE 21: SEMANTIC NET

from Star-MDC and Saltro. In this way the terms are not explicitly defined, but their meaning and relationships are graphically reflected and so their use is clear enough for the design process. A semantic net of relationships form the basis of a rule-based expert system, so creating a good semantic net of the domain is an important step in the design process.

4.3 DOCUMENTED KNOWLEDGE

The documentation of the two anticoagulation clinics from Star-MDC and Saltro give guidelines for dosages for new patients, patients who had their first treatment and patients who are on therapy for a longer time and need to be adjusted. Also special circumstances as additional medication, bleedings and operations are described in protocols. These guidelines are a form of documented knowledge. An important part of the documented knowledge is the way how dosages have to be adjusted depending on anticoagulation level, the former dose and the current INR outcome. This is reflected in so called dosage schemes.

4.3.1 DOSAGE SCHEMES

When the INR is out of target range, the expert may decide to adjust the dose. The expert staff of the Thrombosis Service of Star-MDC use a protocol [7] to guide themselves in assessing the new dose. The expert staff of the Thrombosis Service of Saltro have a similar protocol. Examples of a small part of the dosage schemes in both protocols are illustrated in Figure 22 and in Figure 23. The schemes in these protocols are helpful in supplying a dosage for most of the INR outcomes and they also contain information on when to call a patient back for the next INR check.

stre	efgebied INR	3,0-4,0 (acenocou	marol of fenpr	ocoumon)
Gemeten INR	Dosis dag controle	Voorloopdosis	Verhoging Dosis	Max. controle interval
1,0-1,7*	1½-2x dosis		10%	1 week
1,8-2,0*		1½-2x dosis	8%	2 weken
2,1-2,4*		evt 11/2x dosis	6%	3 weken
2,5-2,9			2-5%	6 weken

FIGURE 22: PART OF THE SALTRO DOSAGE TABLES



INR	Stap		Indruk		Begin	Controle
		V	М	0		
< 1,6	4-6 meer	2d	-	-	Н	max. 1 week
1.6 – 2.0	2-4 meer	-	1½-2d	-	Н	1 week
2.0 – 2.8	2 meer	-	-	-	Н	1 week korter/max 2 weken
2.8 – 3.0	1 meer	-	-	-	Н	zelfde/max 28dagen
3.0 – 3.9	Zelfde	-	-	-	-	1 week langer/ max 42 dagen
3.9 – 4.4	1 minder	-	-	-	L	zelfde/ max 28 dagen
4.5 – 5.5	2 minder	-	-	-	L	1 week korter/ max 21 dagen
5.5 – 6.5	2-4 minder	-	1⁄₂ d	-	L	1 week
6.5 - 8.0	4 minder	0 -1/2 d	-	-	L	1 week

FIGURE 23: PART OF THE STAR-MDC DOSAGE TABLES

There is a difference in the dosage schemes between Star-MDC and Saltro. This is because the TDAS system at Star-MDC works with a step wise adjustment and in this way introduces a fixed incremental or decrement change, where as Saltro uses the Trodis system which can make use of a percentage change. The schemes in both protocols were constructed by dosage doctors who captured their longtime experience in dosage adjustments in a table form guideline. It is obvious that these tables can be incorporated in a computer program. I.e. the dosage tables can relative easily be converted to a decision table or IF-THEN rules. Table 1shows the IF-THEN rules derived from the Saltro document in Figure 22. Figure 15 on page 32 shows a decision table based on a part of the Star-MDC dosage schemes. An alternative would be a calculated dosage. This could i.e. be done by implementing the ICAD method as state of the art algorithm. To compare the dose adjustments calculated by the ICAD method to the dose schemes of Saltro and Star-MDC two graphs are presented in Figure 24. This is done for two target ranges. As one can see the ICAD and percentage adjustments are similar, the step wise adjustment differs especially in the low and high INR levels.

Based on the adjustments inferred from the IF-THEN rules, the expert system may make other adjustments based on special circumstances. For most cases there are a lot of standardized protocols that can support dosage doctors for assessing the dosage and the return date.

1	IF	INR between 1.0 AND 1.7
	THEN	The loading dose for today is 1.75 times the average dose
2	IF	INR between 1.0 AND 1.7
	THEN	Increase the average dose with 10%
3	IF	INR between 1.0 AND 1.7
	THEN	The return interval is in max 7 days
4	IF	INR between 1.8 AND 2.0
	THEN	The loading dose for tomorrow is 1.75 times the average dose
5	IF	INR between 1.8 AND 2.0
	THEN	Increase the average dose with 8%
6	IF	INR between 1.8 AND 2.0
	THEN	The return interval is in max 14 days
7	IF	INR between 2.1 AND 2.4
	THEN	The loading dose for tomorrow is 1.25 times the average dose

TABLE 1: IF-THEN RULES FOR INR TARGET RANGE 3.0 - 4.0, FROM THE SALTRO PROTOCOL



8	IF	INR between 2.1 AND 2.4
	THEN	Increase the average dose with 6%
9	IF	INR between 2.1 AND 2.4
	THEN	The return interval is in max 21 days
10	IF	INR between 2.5 AND 2.9
	THEN	Increase the average dose with 3.5%
11	IF	INR between 2.5 AND 2.9
	THEN	The return interval is in max 42 days

The TDAS and Trodis systems however very sparsely use these protocols, so the expert staff has to learn this knowledge by experience or by looking up the tables in the protocols. The doctors themselves do not think of this as a big problem, because the majority of the time they are busy in getting the right information to base their decisions on. For learning, standardization and optimization purposes however, using an expert system with all documented knowledge online would be a great improvement. So this is one more reason of implementing knowledge in an expert system.



FIGURE 24: DIFFERENCE IN ABSOLUTE AND RELATIVE DOSAGE ADJUSTMENTS

4.4 CONCLUSION

The knowledge retrieval experiment is a process of starting at the overview level followed by fine tuning till there is a thorough understanding of the knowledge of the medical experts and how it is used in the decision making process. The selected techniques used for the knowledge retrieval process are participant observations, thinking aloud and protocol analysis. The OODA-Loop phases are used for analyzing the decision making process in detail. Concepts from interviews are used to build an ontology. The documented knowledge from the Star-MDC and Saltro organizations contains useful items that are convertible to IF-THEN rules and as such could feed an expert system. The next chapter handles the outcome of the first sessions.





5 FIRST RESULTS AND EXPERIENCES



This chapter contains the results of the knowledge retrieval procedures. There is an introduction on how the doctor is doing her work in paragraph 5.1. This paragraph starts with an overview of the system's interface. The main dosage window of TDAS system is explained in detail, the main window of the Trodis system is briefly mentioned, because of the similarity. The items on the main window that get the focus of attention are subject of this paragraph. Next paragraph 5.2 demonstrates the concepts that were distilled from the first interviews. Semantic net graphs are made to show the relations between the concepts. In paragraph 5.3 cases that advisors and doctors work on are examined more closely, using the OODA approach. The items that are involved in the decisions of doctor and advisor are subject of interest here. Paragraph 5.4 concludes this chapter and answers on these additional research topics:

- 1. Are the doctors comparable?
- 2. Which data in this phase is suitable for automating?
- 3. To what level is the knowledge retrievable?



5.1 DESCRIPTION OF THE SETTING

The unstructured interviews were based on participated observation techniques while recording all speech and capturing screens and relevant documents. This resulted in multiple documents with lots of raw information. From these documents follows a description of what happens when dosage doctors are performing their jobs. But before starting with the normal work processes, an explanation of the used screens in these work processes is given. This was also the first thing the experts started with, when performing the first interviews. A description of the TDAS main screen and its relevant parts is provided in subparagraph 5.1.1. This is followed by a very brief view on the Trodis main screen in subparagraph 5.1.2. In subparagraph 5.1.3 the actions involved by working with the TDAS system are described.

5.1.1 DOSING WITH THE TDAS SYSTEM

The situation during the interview is that the doctor sits at her desk behind a computer monitor and the knowledge engineer sits next to her. On the monitor the TDAS program is running and it supplies the doctor with patients, one at a time. An example of the most used computer screen is in Figure 25. The screen is composed from parts which each have a special purpose. The top left of the dosage window consists of textboxes which are meant for entry of result data. This part is in more detail illustrated in Figure 26. The three grayed out textboxes on the top are fixed and disabled because of earlier chosen entries. They are standing for the dosage doctor's code (in this case 001), the area code (in this case 00, meaning no particular area) and the queue of cases a

Openene Paierken Resultaten invoeren Afspraken/Statisteken Window SELTOETEN Poiseren voor 0 0 1 2 Voorkeursdagen Print Ratzong Apatheek Hatzen Fauer Paier Maarz Fauer Paier Paier Paier Paier Paier Paier Paier<	🗽 Softwarebureau DIMASYS in applicatie TDAS do	or gebruik	er M				in gro	ep AD\	/I op	TR04	67 Releas	e:TDA9	510803 <	<d< th=""><th>>></th><th>- 8 ×</th></d<>	>>	- 8 ×
Description Description <thdescription< th=""> <thdescription< th=""></thdescription<></thdescription<>	Algemeen Patiënten Resultaten invoeren Afspraken/S	tatistieken	<u>W</u> indow	SNELTOET	ISEN											
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15-01-09 L 01.4 10 04 013 H 2.00 003 210 T 00 N 19 12-01-09 L 03.5 10 03 013 L 012 210 T 00 N 08-01-09 28-12-08 07-01-09 ARTS: ONBEKEND TELEFOON PERM: N ZHOPN: J REDEN: SFG PNEUMONIE	19-01-09 L 02.8	10 03 0	13 H					0	04	210	T 00	N				
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FIGURE 25: EXAMPLE OF THE TDAS DOSAGE MAIN WINDOW



Doseren voor I 001 00 2 Antistollingspreparaat 10 Acenocoumarol Doseerdagen 0 Doseerstap 18 0 Hoog/Laag H Indrukker Vitamine K Code/Tekst	

FIGURE 26: DATA-ENTRY PART OF THE DOSAGE SCREEN

doctor wants to take care of (in this case queue 2). Every dosage doctor or dosage advisor has its own unique code which is stored with the results. The area code is not used in Rotterdam.

For the queue type selection there is a choice out of 9 options. Every option stands for a subset of the total of patients who need a dosage. In Figure 27 is illustrated how TDAS gives you an overview of the possibilities in selecting queues. Selection 1 stands for checking all dosages automatically provided by TDAS. In Rotterdam the checking of the automatically provided dosages is not performed, since it was demonstrated in a small research project that there is no improvement in patient care (TIR) by doing this. Selection 2 stands for the queue in which TDAS did not provide a dosage and so this queue is the complementary queue of selection 1. This is the most common selection. With selection 3 one can directly select a specific patient. Selection 4 is for the queue with the cases that were skipped by others. In general this queue contains cases that dosage advisors considered out of their capabilities and are to be handled by a dosage doctor. Selection 5 is a subset from selection 2, starting from a specific patient number. In the same way is selection 6 a subset of selection 1 starting from a specific patient number. Both selection 5 and 6 are not used generally in Rotterdam. Selection 7 lets you handle the queue for a doctor and hasn't any practical use at the Rotterdam Thrombosis Service. Selection 8 is a subset of selection 2 and deals with all cases without dosage and having an INR outside the 2.0 - 6.0range. Selection 9 is also a subset of selection 2 and deals with all cases without dosage and having an INR inside the 2.0 – 6.0 range. This queue is suitable for beginning dosage advisors, because it is supposed to contain the easier cases.

So once the doctor's code, the area code and the queue number are entered, the textboxes are grayed out indicating that they are disabled during the further processing of the selected queue. As a response the system shows the first case from the selected queue. At that moment the screen looks like Figure 25. The doctor has to fill out the textboxes as shown in detail in Figure 26. Default the textbox for anticoagulation medication type has the focus and is prefilled with the current anticoagulation medication the patient is using. This does not make sense because it is relatively rare for patients to change their medication during treatment. So the doctor almost always has to hit the enter button to set the focus to the next textbox as a first action. This textbox is for the amount of days for which the dosage is valid. At the same time the return date





FIGURE 27: TDAS QUEUE SELECTION

for the next blood collection is fixed. It is common to enter a 7-fold, so that the patient has a blood collection on the same days of the week every time. The next two textboxes that have to be filled out are the dosage step and the difference in dosage step. TDAS uses a step mechanism. For acenocoumarol a step is equivalent to 1 tablet every 14 days (till step 84). The red 18 in Figure 25 and Figure 26 indicates that the patient currently is on step 18, meaning that he has to take 18 tablets distributed over 14 days. So when i.e. the doctor decides to increase the dose with 2 tablets per 14 days, the new dosage is step 20 and the difference is 2. In that case the doctor enters the 20 and 2 figures she has calculated in the two textboxes and TDAS performs the same computation to check for consistency. This is a bit of a peculiar way for the TDAS system to perform a kind of 'are you sure' feedback to the doctor. Next the High/Low textbox has to be filled out. High or Low is a way of indicating the distribution of the tablets over 14 days in case there is a different amount of tablets over the days. For instance step 3 can have a 1-0-1-0-1-0-0 distribution over the week and is called a High (starting) distribution, where a 0-0-1-0-1-0-1 distribution is called a Low (starting) distribution. So default the H or L is filled out (note that other controls, like radio buttons, are more suitable for a two-way selection) and the doctor may change this. The next 9 textboxes are optional and can be used for dosing a specific amount of tablets the first 1 till 3 days, for recording vitamin K supplement, or for making comments on the report to the patient.

The remainder of the window in Figure 25 contains information on which the doctor makes her decisions. There are other windows that may be accessed to give additional information on historical data, but the most recent information is shown here. At the right of the textboxes in Figure 25 the calendars and dosage information is placed. This is illustrated in more detail in Figure 28. The top calendar shows the current calendar which is in use by the patient. The numbers on top are the week numbers. The numbers in the raster correspond with the amount of tablet the patient has to take that day (note that the two decimal digits do not make sense and suggest an unrealistic accuracy). The blue cell is highlighting the current day. So in this example the patient still has a dose for the next two days. The calendar on the bottom shows the new dose scheme. Because there is no new dose scheme settled yet, the calendar is empty. At the right of the top calendar there are some details shown of the last dosage: date of INR assessment (19-02-





FIGURE 28: CALENDAR PART OF THE TDAS DOSAGE SCREEN

2009), INR outcome on that date (1.8), return date (26-02-2009) Average amount of tablets per day (1.28) and the last dosage (10.07.018 H). The code 10.07.018 H means: 10 = medication code for acenocoumarol, 07 = return after 7 days, 018 = step 18 (18 tablets in 14 days) and H = High distribution scheme. Once the dosage and return date are assessed for this case, the fields at the right of the bottom calendar are filled too.

At the most right part of the window in Figure 25 there is a space for additional text information that may be relevant. This is illustrated in Figure 29. It contains items as cell phone number or telephone number at work, name and phone number of the family doctor, name, address, phone number and fax number of the chemist.



FIGURE 29: ADDITIONAL INFO PART OF THE TDAS DOSAGE SCREEN

The middle part of Figure 25 is shown in Figure 30 and contains the patient's name and address, and information on the patient's treatment and visit preferences. The first four items on the left are name, address, ZIP-code + phone number and city. The next four items are area code, start date of the treatment, presumed stop date of the treatment, where ' - - ' indicates that there is no stop date and age in years. The third column contains sex, blood collection place, where P means at a collection station and T means at home, the maximum interval in days between two visits is reflected, with 42 days default for all patients and the anticoagulation level, in this case L. The next column contains the preferred days of the week for blood collection. The 6th column contains the diagnoses for the anticoagulation treatment (note that it is called diag. codes, but actually



contains the diagnose descriptions). In this case 210 is the diagnose code for atrial fibrillation. The most right column may contain contra indications, which are indications why a patient should not be on anticoagulation therapy. In this case CA stands for cancer related diseases.



FIGURE 30: PATIENT, TREATMENT AND VISIT INFORMATION PART OF THE TDAS DOSAGE SCREEN

The bottom part of the dosage window in Figure 25 contains the last 12 entries of the patient's records. This part is illustrated in Figure 31. There are several types of entries, the most common one is the INR-dosage entry. The type of the other entries is indicated with a small icon in front of the entry. The heading of this part of the screen is intended for the INR-dosage entries. However the first column is used for every type of entry. And the second and third columns are intended for all non INR-dosage entry types. The first column is the date of entry, the second and third are the date from which an entry is valid and date till which an entry is valid. These two columns may indicate the period for which a patient gets additional medication or has a hospital submission. Examples of non INR-dosage entries are on the bottom three rows of Figure 31. Examples of INR-dosage entries are on the top 9 rows of Figure 31. Next to the three date columns is a H/L column, indicating the anticoagulation level. L means Low and has an target INR range of 2.5 – 3.5. The next column is the INR. The values that are out-of-range are in red. The next 4 columns have the same meaning as the last dosage code (10.07.018 H) from Figure 28. The column GEM is meant for the average dosage, but for unknown reasons the average dosage is not shown by TDAS.

The IN1, IN2 and IN3 columns may indicate daily loading or stopping doses. This means an amount of tablets for the first 1 till 3 days, used for fast increasing or decreasing an INR without increasing or decreasing the maintenance anticoagulation dosage. The column ARTS contains the code of the doctor who provided the dosage, where code '000' is for system dosage. DIAG contains the main diagnose code, where 210 indicates atrial fibrillation. PT is for the blood collection location, with

In Van	T/M H/LINR	ASP DG STP	H/L GEM	IN1 IN2	IN3 ARTS	DIAG PT	VB BEL K	V KM KO KG
26-02-09	L 01.7	10 00 000	L 0.00		000	210 T	N	
19-02-09	L 01.8	10 07 018	H		002	210 T	00 N	
12-02-09	L 02.0	10 07 016	н		003	210 T	00 N	
05-02-09	L 01.4	10 07 015	H		001	210 T	00 N	
29-01-09	L 02.5	10 07 014	H		003	210 T	00 N	
22-01-09	L 02.2	10 07 014	H		005	210 T	00 N	
19-01-09	L 02.8	10 03 013	н		004	210 T	00 N	
15-01-09	L 01.4	10 04 013	H	2.00	003	210 T	00 N	19
12-01-09	L 03.5	10 03 013	L		012	210 T	00 N	
🔀 08-01-09 28-12-08 (07-01-09 ARTS :	ONBEKEND T	ELEFOON	PERM: N ZI	HOPN: J RED	EN: SFG	PNEUMON	IE
🔗 08-01-09 01-01-09	PREDNI	SOLON						
08-01-09 08-01-09	08-01-09 non-ho	dgkin l yn f	oor vv j	palliatieve	e behandeli	ng		

FIGURE 31: LAST PATIENT RECORD ENTRIES PART OF THE TDAS DOSAGE SCREEN



the same meaning as in Figure 30. The meaning of the columns UB till KG is unknown to the doctors in Rotterdam.

TDAS also may provide other screens with information of the patient like his medical history, his INR-dosage entries and all other entries. In spite of this, the Thrombosis Service in Rotterdam also keeps track of records on a paper status archive. This is because some historical changes are not recorded in TDAS. I.e. changes in diagnose codes over time are not recorded in TDAS. It is not clear at this moment whether this is due to the fact that TDAS does not show former entries because they are overwritten or that the former entries are not recorded in the right way in TDAS. Next to the patients paper status there are also all kinds of letters from hospitals and other doctors that are kept within the paper status archive of the patient. TDAS has no facilities of recording scanned papers. So this is a major reason of keeping a paper status archive. In practice, this is an uncomfortable situation, because new hospital admission papers have to be merged with the paper status and they both have to be at the doctor's desk when she is dealing with the patient. She also needs to record items in the TDAS screen as well as on the paper status. Afterwards the paper status has to be archived again for possible future use. The main incoming papers are the (hospital) admission forms, which ideally would be entered via a website or web service, and the data the phlebotomist collects during her visit at the patient. These data are recorded on the request form and are manually entered by administrative people in TDAS. It is known that the Amsterdam Thrombosis Service uses PDA's for phlebotomists to enter data online in TDAS during their patient visits. This feature is on the Rotterdam wish list also.

The dosage doctors also have to make letters to patients (i.e. for other Thrombosis Services during holidays), to chemists (i.e. a vitamin K prescription) and to hospitals, family doctors or dentists (i.e. an update of the anticoagulation status prior to treatment). For unknown reasons the TDAS facilities are not used for these letters and in the Rotterdam practice the letters are partly preprinted and partly filled out by hand. This is also an uncomfortable way of working, because there is a lot of administrative actions involved moving the letters from desk to desk and finally posting or faxing the letter. And there also has to be a copy in the paper status archive for traceability reasons.

So, based on the items on the screen the doctor may look for additional data in other screens, or she may call the patient, his chemists or his family doctor for additional information. The dosage doctor makes a lot of calls every day and she has to read the phone number from the screen and next pushes the phone buttons to make the call. In practice this may lead to entering a wrong number in the phone from time to time. The expert's work process would be greatly improved by automatically making a call when a phone number on the screen is (double) clicked.

The doctor also may consult documents like a submission form, a patient's paper status, or a Standard Operating Procedure (SOP). The SOP's contain information on processes and declarative knowledge on how to deal in certain situations. After collecting the information she makes a decision on the dosage and return date for this patient. The dosage and return date are entered in the computer screen. This concludes the case and a next case from the selected queue is shown on the screen, when available. Of course the declarative knowledge from the SOP's should preferably be incorporated in the expert system.



5.1.2 DOSING WITH THE TRODIS SYSTEM

The information in the Trodis main screen is very similar to that of the TDAS main screen as illustrated in Figure 32. Trodis does not use a step system like TDAS does, so there is no step related information in the Trodis screens. Trodis allows to increase or decrease of the average dose by entering a percentage, which is especially convenient for patients on a very low or very high amount of tablets per day. In contrary to TDAS, Trodis also allows a repetitive scheme like 2-2-3 tablets, which would not fit in the TDAS 14 day step schedule. The Trodis main window has in the left upper corner the last patient record entries, the oldest at the top of the screen and the last entry below the dotted line. The current calendar is in the right top of the screen and the area below that shows the latest medication. The bottom of the screen contains tabbed items. The tab that is active in Figure 32 shows the entry text boxes for the dose. Because the functionality of both systems is very similar, the Trodis overview is intentionally kept short here.

F K [M] 82251235 *ATRFI [2,5-3,5] 315DB/17-12-2008 Dagpa	atient/YoorstelGegenereerd Doseren 📃 🗗 🗙
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Dossier	Bestaande kalender
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29-11-2006 V 341/DOS SCHEMA VA 20-11: 3-3-2-3-2-3-2 ACENO,	2350 Ma 2 2 2 2
V INR VA 20-11:2.2-X-X-2.4 V DHR NEEMT VA 3 TABL ACENO	2350 Di 3 3 3 3
V VANNACHT SPUGEN EN DIARREE + VERHOGING	2350 Wo 2 2 2 2
08-12-2006 VB 3 2 3	5183 Do 3 3 3 3
30-08-2007 V KUUR IS VERLENGD T/M 2/9	2034 Vr 2 2 2 2 2 2
10-09-2007 V KUUR IS VERLENGD TOT 15/9	2220 Za 2 2 2 2 2
11-10-2007 V 352/SOMS KOORTS,ALGEHELE MALAISE NA GRIEPPRIK 9/10	6625 Zo 3 3 3 3 3
17-01-2008 315DB 2,7 2,50 ACENO 34 1 23 661	2192
21-02-2008 315DB 3,0 2,50 ACENO 41 1 23 G61	4501 Medicijnen
02-04-2008 315DB 3,2 2,50 ACENO 42 23 G61 15-05-2008 315DB 3,4 2,50 ACENO 41 1 23 G61	5166 05-09-2005 V DICLOFENAC 5/9-15/9
25-06-2008 315DB 3,4 2,50 ACENO 42 23 G61	4501 06-10-2006 V ERBIJ:DICLOFENAC
07-08-2008 315DB 3,2 2,50 ACENO 48 1 23 G61	6516 27-10-2006 V ERAF: CABAPENTINE
125-09-2008 31508 3,8 2,43 ACENU 20 1 2232323 E22 16-10-2008 31508 3,4 2,43 ACENU 27 1 2232323 662	2192 27-10-2006 V ERBIJ:MORFINE-PLEISTERS
	29-11-2006 V DUROGESIC, SLOW-K, GABAPENTINE
13-11-2008 315DB 3,4 2,43 ACENO 34 1 G62	14-09-2007 V ERBIJ:FLUCLOXACILINNE
[Einde dossier]	20-12-2007 V ERAF:SLOW-K. ERBIJ:INSPRA
0. Naw 1. Extra-1 2. Behandelperiode 3. Extra-2 4. Afspraak 5. Medicijnen 6. Indicaties 7	, Contra Indicaties 8. Opmerkingen 9. Doseren
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5.1.3 GLOBAL DESCRIPTION OF THE ACTIONS

In addition of the description of the setting above, a description of the actions follows here. The actions are a bit different for the dosage advisor and the dosage doctor. This is because the advisor selects a queue with INR's within the 2.0 - 6.0 range or the advisor selects all not automatically dosed patients, but she skips the difficult cases. The doctor may select the skipped cases but she also deals with cases related to hospital admissions and other planned surgeries and so on. These latter cases are not triggered by an INR measurement but by a notification of a current or future event that may affect the anticoagulation status. These cases may lead to a



modification of former provided dosages. So two triggers exists on providing an advice: a new INR measurement and a notification of a current or upcoming event.

An INR entry is electronically entered in the system by a lab analyzer. The TDAS system then tries to provide a dosage and return date itself. When this is successful TDAS places the case in the automatically dosed queue. In Rotterdam this means that there is no check on this outcome performed anymore. There is no description on the criteria TDAS uses in the decision for automatically dosing, but overtime it is shown that TDAS most of the time provides dosages on trivial cases. All other cases are placed in non-automatically queues and they are not provided with a proposal. So the dosage advisor enters her code, selects a queue and gets the first patient from that queue presented in her screen. Because the queue insertion criteria of a case are considered as TDAS proprietary information, the advisor may wonder why she gets a case and why it was not dealt with automatically. On the other hand it is known by experience, that when the INR is far out of target range or when there is a recent entry other than an INR-dosage or when there is no stable INR history, TDAS does not provide an automatic dosage. This does not mean that the expert staff always agrees with an automatic TDAS proposal. Because there is no direct check on TDAS automatically provided dosages and return dates, a disagreement is most of the time detected afterwards when a next visit may put a patient in a queue for an advisor or doctor.

So when the dosage window shows a new case, the advisor or doctor first tries to get a picture of what is going on. Most of the time the INR is out of target range. The advisor or doctor screens the latest INR-dosage combinations and other entries in the bottom part of the screen. This may lead to a preliminary conclusion of the type of case that she is dealing with. Based on this first impression she might try to support her thoughts by scrolling through historical data or making a call to the patient or his family doctor. During a phone call with the patient the advisor or doctor may decide to give advice on the phone on the amount of tablets for this day or the next day. Based on the total of information that is available, she makes a decision. When the advisor is not sure she has to skip the case and leave it for a doctor. This certainly is the case when there should be vitamin K prescribed in case of a very high INR. Paragraph 5.3 elaborates in more detail about the types of cases and how they are handled. When the case isn't skipped, the dosage and the number of days until next visit are entered as shown in Figure 26 on page 49. In some cases loading or stopping doses are entered or sometimes a vitamin K supply for fast initial changes of the INR level. After entering the dosage results the TDAS system shows a new case from the chosen queue.

5.2 SEMANTICS AND OBJECTS

As stated in paragraph 4.2 a list of concepts is made from the interviews and the list was verified by dosage doctors. Besides interviews, also the fields of the most frequently used forms provide additional concepts. The two of the most frequently used forms are the hospital admission form and the phlebotomist intake form. The paper status of a patient does not contain additional information, but is used mainly to match with changes for treatment requests. The concepts are useful for ontology purposes. For expert system development, the concepts terms are placed in a





semantic net. Because there are too many concepts for a single graph, the semantic net is split in a few graphs. An overview of the main objects and their relation are shown in Figure 33.

FIGURE 33: SEMANTIC NET, MAIN CONCEPTS

The concepts which belong to these main objects are shown in Figure 34 till Figure 39. The importance of every concept for the dosage construction was verified by a dosage doctor. Important concepts are indicated by a green color. In Figure 34 the concepts related to the patient are illustrated. When someone is pregnant she is set on a maximum interval of 14 days between two visits. The assumed delivery date is important because 1 month before delivery the oral anticoagulation has to be stopped and a switch to heparin is indicated. A bad clinical condition is an indicator for a lower dose level and shorter intervals.





The treatment is one of the main objects for managing a patient in the expert system design. The concepts 'different anticoagulation level', 'risk increasing factors', and 'reason for different level' in Figure 35 are items from the hospital admission form. When a patient enters the Thrombosis Service program for the first time or for a renewal there may be a change in anticoagulation level needed. Once a new treatment policy is settled, these items are less relevant for common dosage practice.





FIGURE 35: SEMANTIC NET, TREATMENT CONCEPTS

In Figure 36 the items related to the visit concept are shown. The importance of the concepts INR, anamnesis and extra medication may be obvious. The 1st and 2nd preferred day of the week are however also items which are taken into account for assessing the next return date to be preferably on one of these days.





All items related to the entry concept are of importance as is illustrated by the green concepts in Figure 37. This may be obvious from the fact that when something is worth wile to make an entry, it should be is of relevance for the patient's treatment.

The items in Figure 38 related to a hospital admission are almost all derived from the hospital admission form and the phlebotomist intake form. Although not labeled green, the admission date and discharge date may be of importance to find out if the last dosages are start dosages or ongoing dosages. This may be of importance to the new dosage.



FIGURE 37: SEMANTIC NET, ENTRY AND NOTIFICATION CONCEPTS





FIGURE 38: SEMANTIC NET, HOSPITAL ADMISSION

Figure 39 illustrates the concepts related to the dosage advice. Because all these items are part of the advice itself or derived from the advice, it does not contain green objects.



FIGURE 39: SEMANTIC NET, DOSAGE ADVICE

For object modeling, the concepts Patient, Treatment and Entry may be identified as the main objects. The Visit concept may be modeled as an important subclass of the Entry class. The representation of the semantic net as objects is very helpful for constructing a data model.

5.3 TYPICAL CASES

During the interviews it became more and more clear, that there are a relatively small amount of different types of cases that appear to be the majority of the cases that dosage doctors and advisors work on. Therefore an inventory of the cases that dosage experts deal with was made. These cases involve computer-assisted dosage cases that are overruled and cases the computer fails to provide a dosage. These cases were grouped so that similar cases were placed together. For each group of cases, protocols and flowcharts were made of the reasoning process. Next to that these protocols and flowcharts were verified by the experts. The similarity is best typed as the cases having the same observation in the OODA-Loop. In that respect the trigger of each case is the same.

These cases are

- New applications.
- Reapplication after discharge from a hospital.
- Stopping and starting for a temporary interruption.
- INR below target range.



- INR in target range.
- INR above target range.

There may be other triggers for a patient to get in contact with the Thrombosis Service, like notifications of changes in physical condition or bleedings. When it concerns a relevant notification, the patient is requested to have his INR measured as soon as possible. Next this patient is classified and treated according one of the INR below, in or above target range cases.

5.3.1 NEW APPLICATIONS

Most of the time new patients are submitted by a hospital or a family doctor. The hospital or family doctor may have started the anticoagulation treatment before submitting the patient. When this is not the case the Thrombosis Service deals with the starting phase. Because there is no INR that triggers the dosage system and there are no historical records, the Thrombosis Services of Star-MDC and Saltro use declarative knowledge from SOP's for the initial dosage. The initial dose is based upon the type of anticoagulation medication and may be based on the age of the patient too. The FNT provides guidelines in their vademecum [1] for initial dose schemes: patients using acenocoumarol the dosage of the first three days is 6-4-2 tablets, patients using fenprocoumon the dosage of the first three days is 4-2-1 tables. Note that the patient's genotype as described in subparagraph 2.1.4 should be taken into account in this phase, when known.

Contrary to the FNT, Saltro and Star-MDC use their own initial schemes. Saltro uses the next schemes:

for patients using acenocoumarol the dosage of the first three days is 6-4-2 tablets, for patients using fenprocoumon the dosage of the first three days is 3-2-1 tablets. For people with relative contra-indications or people older than 80 years, Saltro uses the schemes:

for patients using acenocoumarol the dosage of the first three days is 4-4-2 tablets, for patients using fenprocoumon the dosage of the first three days is 2-2-1 tablets. For people with elevated risk on bleedings, Saltro uses:

for patients using acenocoumarol the dosage of the first three days is 4-2-2 tablets, for patients using fenprocoumon the dosage of the first three days is 2-1-1 tablets.

Star-MDC uses a 5 day scheme for new applications. This is for convenience when the end of a three day schedule falls in a weekend. The target for a return date is preferably three days. For people younger than 70 years Star-MDC uses:

for patients using acenocoumarol the dosage of the first five days is 6- 4-2-3-3 tablets, for patients using fenprocoumon the dosage of the first three days is 4-2-1-1-0.5 tablets. For people between 70 and 80 years, Star-MDC uses:

for patients using acenocoumarol the dosage of the first five days is 4-4-2-2-2 tablets, for patients using fenprocoumon the dosage of the first three days is 3-2-1-0.5-0.5 tablets. For people older than 80 years, Star-MDC uses:

for patients using acenocoumarol the dosage of the first five days is 4-2-1-1-1 tablets, for patients using fenprocoumon the dosage of the first three days is 2-1-0.5-0.5-0.5 tablets. The return date is after 3 days at Saltro and 3-5 days at Star-MDC. The policies for initial dosage



and return dates may be relative easily implemented in a computer program. Even in a way, that every Thrombosis Service may use their self assessed schemes. The follow up of this initial phase is described in both Thrombosis Service SOP's, but is very dependent on the first INR and other circumstances of the patient. Further research to this more complicated situation is needed. Based on the next measurement of the INR, the patient's case falls into one of the groups listed above.

Based on the input of anticoagulation medication and the age of the patient the rules from Table 2 may be applied:

1	IF	(age < 70) AND (anticoagulation medication = acenocoumarol)
	THEN	Use scheme A
2	IF	(age BETWEEN 70 AND 79) AND (anticoagulation medication =
		acenocoumarol)
	THEN	Use scheme B
3	IF	(age > 80) AND (anticoagulation medication = acenocoumarol)
	THEN	Use scheme C
4	IF	(age < 70) AND (anticoagulation medication = fenprocoumon)
	THEN	Use scheme D
5	IF	(age BETWEEN 70 AND 79) AND (anticoagulation medication =
		fenprocoumon)
	THEN	Use scheme E
6	IF	(age > 80) AND (anticoagulation medication = fenprocoumon)
	THEN	Use scheme F

TABLE 2: IF-THEN RULES FOR NEW APPLICATIONS

Where scheme A till F is definable by each Thrombosis Service suitable for its own experiences.

Could information on a former treatment help to speed up the initial phase? The situation may get a bit more complex when a patient has been on a former treatment. In that case the way the patient responded to anticoagulation medication could be taken into account too. Especially, when this former treatment was not a long time ago. Recent average dosage schemes which were right for a patient may influence the initial target, especially when a patient was on a very low dose scheme. However when there was a long time between the former treatment and the startup phase, historical data are of little meaning. Start-up programs are dealt with by the doctors only and should be skipped by the advisors.

5.3.2 REAPPLICATION AFTER DISCHARGE FROM A HOSPITAL

Sometimes a patient may undergo an operation. Or a hospital admission for a longer time, that is more than one or two days. The difference between a hospital admission and an operation is the responsibility for the guidance of the patient regarding the anticoagulation therapy. In case of an operation the patient goes to a hospital for no longer than one day and the Thrombosis Service stays responsible for monitoring the patient. In case of a hospital admission the hospital has responsibility for monitoring. During hospital admission the dosage and INR assessment is out of scope for the Thrombosis Service in most cases. After discharge from the hospital the patient may be reapplied to the Thrombosis Service. This is done by filling out a form and sending this form to



the Thrombosis Service. From that moment the cycle at the Thrombosis Service (re)starts and the patient is visited for an INR assessment. The phlebotomist fills out an intake form at the patient. Figure 40 shows the scheme that applies to this situation.



FIGURE 40: REAPPLICATION AFTER DISCHARGE FROM HOSPITAL

These cases typically are for doctors only. Besides the dosage screen with the INR and the historical data from before the hospital admission, the doctor has an application form from the hospital and an intake form from the phlebotomist and the paper archive status of the patient on her desk. The hospital application form and the phlebotomist form contain a lot of items for administrative purposes. The items that are relevant for changes in treatment or that may influence the next dosage or return date are part of the semantic nets shown in paragraph 5.2. Because there is an INR as trigger to this type of case, it may be considered as a special case of INR below target range, INR in target range or INR above target range. The main difference is that special attention is needed for possible changes in clinical conditions that may lead to other treatment targets. This is the main reason why these types of cases are for doctors only. Assessing new treatment targets is not in the scope of developing an expert system for dosage purposes. So these types of cases are not explored for further modeling in this thesis.

5.3.3 STOPPING AND STARTING FOR A TEMPORARY INTERRUPTION

There are all kinds of relative small medical operations that do not require a hospital admission, but which increase the risk for bleedings. Examples of such operations are endoscopic operations, molar extractions and pacemaker implantations. To prevent complications due to injury caused by these operations the anticoagulation therapy is stopped a couple of days before the operation. After the operation, the anticoagulation therapy is started as soon as possible. Both Saltro and Star-MDC have similar protocols for guiding the anticoagulation control around these operations. The main difference is that Saltro starts therapy the day after the operation with 1.5 times the average dosage and Star-MDC starts on the evening of the operation with 2 times the lowest amount of tablets in the scheme. The Saltro protocol refers to *Van Geest-Daalderop* [17] and the Star-MDC protocol is based on own experiences. In OODA terms, the trigger in these cases is not the Observation of an INR result, but a notification from the patient, that he or she has to



undergo an operation. Also the OODA-Action is not the output of a calendar, but a specific letter to the patient with stop and start-instructions and in some cases a vitamin K prescription for the chemist. Figure 41 illustrates the OODA phases Observing, Orienting and Deciding. The letter with stop and start instructions and the possible vitamin K prescription is dealt with by administrative people and checked and signed by a doctor. These type of cases are also for doctors only. This is because of possible prescription of vitamin K and taking into account special circumstances that may be of influence to the stopping or starting policy. Also there may be interactions necessary with medical specialists on the treatment of the patient during an operation.

The decisions based upon the protocol as shown in Figure 41 can be supported by a rule-based expert system. Table 3 shows a set of rules that were derived of the Star-MDC protocols.



FIGURE 41: TEMPORARY INTERRUPTION OF THE ANTICOAGULATION PROGRAM


TABLE 3: IF-THEN RULES FOR A TEMPORARY INTERRUPTION

1	IF	(endoscopic type of operation on day X) AND (anticoagulation medication
		= acenocoumarol)
	THEN	Dose for day X-1 is 0
	THEN	On day X-1 supply 5 mg vitamin K
	THEN	Dose for day X is highest amount of tablets per day
	THEN	Dose for day X+1 is regular scheme
2	IF	(endoscopic type of operation on day X) AND (anticoagulation medication
		= fenprocoumon)
	THEN	Dose for day X-4 is 0
	THEN	Dose for day X-3 is 0
	THEN	Dose for day X-2 is 0
	THEN	Dose for day X-1 is 0
	THEN	On day X-1 supply 5 mg vitamin K
	THEN	Dose for day X is highest amount of tablets per day
	THEN	Dose for day X+1 is regular scheme
3	IF	(non-endoscopic type of operation on day X) AND (anticoagulation
		medication = acenocoumarol)
	THEN	Dose for day X-2 is 0
	THEN	Dose for day X-1 is 0
	THEN	Dose for day X is 2 times lowest amount of tablets per day
	THEN	Dose for day X+1 is regular scheme
4	IF	(non-endoscopic type of operation on day X) AND (anticoagulation
		medication = fenprocoumon)
	THEN	Dose for day X-2 is 0
	THEN	Dose for day X-1 is 0
	THEN	On day X-1 supply 5 mg vitamin K
	THEN	Dose for day X is 2 times lowest amount of tablets per day
	THEN	Dose for day X+1 is regular scheme

Based upon the type of operation, the anticoagulation medication a patient uses and the presence of a heart valve, a schedule can be produced for the stopping and starting schemes. On top of that the letters could be assembled and printed automatically. TDAS seems to have templates for all kind of letters, but the Rotterdam Thrombosis Service does not use it. This may be due to unfamiliarity with this possibility or it may not fit in the department's business processes.

The advantage of automating the process around the stopping and starting anticoagulation in case of an operation is clearly the standardization and optimization of this process. The decision making seems not very hard under normal circumstances. It may be the interactions with patients, chemists, family doctors or medical specialists that consumes most of the time of the dosage doctor. The temporary interruption cases themselves form a small percentage of the daily workload, but are generally more time consuming than INR triggered cases.

5.3.4 INR BELOW TARGET RANGE

When the INR drops below the lower boundary of the target range, the patient's risk for thrombosis increases above an acceptable limit. From management point of view the policy is to increase the anticoagulant medication to accomplish an increase of the INR next time. However



we have to deal with patients acting like humans, so they do not always act in a predictable way. So, besides a too low dose last time, there are other factors that can cause a too low INR. It is important to find out the reasons causing the drop below target range to respond in a correct way.

One of the common reasons that can cause an INR below target range, is when a patient doesn't take his medicine conscientiously. Non compliance to the therapy might first be suspected, but is only certain after confirmation by the patient or his doctor. There are some operational actions to make sure which way to follow up the treatment as shown in Figure 42. Close to the low INR caused by not taking medication is the low INR caused by changes in clinical condition or other circumstances of the patient. In some cases there is a persistent low INR in spite of increasing the dosage. The actions for the dosage doctor are on the level of trying to recover the truth about the reasons of the instability or low INR's. This asks for contacting patients or other related persons. These actions are not directly related to the dosage advice construction, but are part of the orient phase of the OODA-Loop to accomplish a good decision. An expert system may support in suggesting the orientation actions as well as the decision actions. Guidelines for the decisions are part of the documented knowledge. As we saw in Table 1 on page 44, this knowledge may be well captured in a set of IF-THEN rules. When the expert is convinced that a patient is not regular taking his tablets, the protocol prescribes not to increase the average dose, but to increase the dose for the same day or for the next day. Saltro and Star-MDC differ a bit in the way they make this loading dose. Also there is no Dutch naming convention for this phenomenon. Saltro increases the dose for one day with 1.5 times the average dose and call this increase a precursor. Star-MDC increases the dose for one day with 2 times the lowest amount of tablets in the scheme of the patient and calls this increase an impression. The effect of the one day increase has no meaning for the effective dose after a week because of the half-life of a few hours till a few days. Also knowing that a patient does not take his tablets according to his scheme makes it difficult to give a meaningful interpretation of the difference between the Saltro and Star-MDC approach. A low INR may be a measurement in a range of INR's that are varying between too low and too high. This situation is called instability, and it is often hard to keep an instable patient in his target range. There is no exact definition of instability, but there is a relation with the amount of outliers in a period as well as the quantity of which the outliers are out of range. The ICAD method uses a sensitivity index based upon the INR and dose values. Changes in this index over time could be an indicator for instability.

The policy for dealing with instable patients is differs between the experts. Most of them change the dose and make the patient come back in a short time. Some experts think that targeting for a good average dose over a longer period of time give better results. Because of the stabilizing effect of the ICAD method, which uses an exponential average of the sensitivity index over a longer period of time, the ICAD method may be a good guide in these cases.

The flowchart in Figure 42 was verified by a dosage doctor, but it is still too coarse to convert it into a decision tree or decision table or into a set of IF-THEN rules. This holds for all flowcharts in the subparagraphs 5.3.4, 5.3.5 and 5.3.6. Therefore interviews are planned with another technique to gather more details. At this point it is clear that an expert system could be helpful in supporting the orientation actions, giving an alternative dosage with the ICAD method and





FIGURE 42: INR BELOW TARGET RANGE

provide a set of tools that may help to discriminate between non compliance and other factors. These tools may give an indication of the probability of non compliance. Based on this probability the expert system could suggest further steps to be taken.

5.3.5 INR IN TARGET RANGE

One could wonder why an INR in target range could be an issue: apparently the former dosage was leading to an INR in target range and the best thing to do seem to be using the same dose scheme again. Besides the fact of aiming for the exact target INR in the middle of the target range, there are a few cases that may interfere with this straight forward decision making. When taking a closer look at these specific cases, one can see that there are special circumstances leading to a expert judgment request. These circumstances are not specific for INR in range cases, but they hold for all cases, regardless of the outcome of the INR. I.e. the system does not provide a proposal or makes a decision on the return date when this falls in the patient's vacation or on a national holiday. The TDAS system should be able to provide a dosage when INR is in range. In



practice TDAS makes even decisions on cases having the INR out of range. These automatically dosed cases are not reviewed because of the large amount of work involved and there is no overall improvement for the TIR when these cases are reviewed. Still the experts may disagree with the systems decisions in the past when they are looking back in history. There are two things to mention here. One is that experts sometimes even may disagree with each other when they are looking at former decisions. The other is that it is easier to disagree with a historical decision knowing the result. Still it may be a good idea to provide an expert system with an alternative proposal to compare with, i.e. to provide a proposal based on the ICAD method. This proposal could support the decision making of the experts as well as the decision making of the current TDAS system. Large discrepancies between automatically provided TDAS dosages and ICAD dosages are candidate for having a closer look by an expert. This way the quality of the automatically made decisions increases with only little extra effort of the experts.

Next to the fact that TDAS makes decisions that may be doubted in some occasions, it is also not always clear why TDAS does not make a proposal. The experts don't mind that there is no obvious reason why they have to deal with the case, and make a decision themselves. Time spent on obvious cases is a waste, especially when one knows, that experts should like to spend more time on complex cases, preferably by discussing these cases with colleagues. Also, in the Rotterdam situation there may be over 2000 cases per day. With a small team of experts, this workload can lead to fatigue at the end of the day. So a good support for the less complex cases and helpful suggestions for not obvious cases is an important design goal for the expert system.

There are other reasons that cases do not get a proposal besides vacation. From experience it is known that when a notification is made recently, this notification is not interpreted by the TDAS system, but is left for the expert. Examples of these notifications are remarks made by the administration or the expert, about phone calls and changes in medication. There is a list of medicine outside the TDAS system that is updated regularly by the doctors. This list contains the influence that these medicine may have on the anticoagulation therapy. This list is printed and copied to all workplaces of the experts for lookup support. An obvious better support could be achieved by keeping such a list updated in TDAS. A requirement for an expert system is to keep such a list maintained inside the system by the experts, where each medicine has an indication of the influence on the anticoagulation therapy. One has to bear in mind, that administrative staff may not have sufficient knowledge to select the right medicine from a list based on the way the name of the medicine is spelled. On the other hand, the names of the medication are currently entered in the TDAS system in a free text form. This may induce typos and lead to misinterpretation. A coded list with synonyms might overcome this problem. Preferably this list is maintained or derived from a national maintained by the FNT or perhaps a global list. Once the list is in a coded form available for an expert system, it is possible to support the decision making process based on the influence of the medicine.

What holds for the medicine also holds for other types of notifications and remarks. Using coded notifications, where each type of notification gets an indication of its influence on the dosage or return date decision, is an important requirement for designing an expert system.



5.3.6 INR ABOVE TARGET RANGE

Cases of INR > 6 are placed in queue 8 of the TDAS system for patients with INR outside the 2 - 6 range. This queue contains also cases with INR < 2, but there is an agreement that dosage advisors do not deal with the high INR cases, these are for doctors only. This is because of the high risk on bleedings and because there may be non trivial reasons for having a high INR. Because all target ranges have an upper boundary that is below the INR = 6 level, there are also lots of INR above target range cases dealt with by the advisors. The Observation according the OODA systematic is an INR above the high boundary of the target range, as illustrated in Figure 43. The Act phase is not part of this graph, because in this case as in all other cases the calendar report to the patient with the dosage and next return date is the automatically performed action. In the Orient phase the expert is checking for changes in medication, for inter current diseases and for other reasons that might have effect on the INR. And lastly perhaps concluding that there are no obvious demonstrable reasons for the high INR. For supporting the decisions, the doctors can look up the standard way of dealing in a documented protocol. As we saw before in Table 1 on page 44, the



FIGURE 43: INR ABOVE TARGET RANGE



documented guidelines are suitable for applying IF-THEN rules in an expert system.

The risk on bleedings increases as the INR rises above target range. Bleedings are complications that need to be reported by patients to the Thrombosis Service. There is a difference in treatment between serious and not serious bleedings. There is a clear definition in the protocols to which category a bleeding belongs. When the phlebotomist notes bleedings, there is always an INR result. When the patient notifies the Thrombosis Service in between visits of a bleeding, there is scheduled an INR assessment as soon as possible. In both circumstances there is a protocol with guidelines on how to deal with dosages in case of bleedings. Because there are a lot of subjects that may have influence on the decision making process, bleedings seem to belong to the most complex cases to automate. There is also strict tuning between dosage doctor and family doctor or hospital specialist and between dosage doctor and the patient. Besides a temporary decrease of the dose a long term adjustment of the dosage level may be the result of a consult between doctors. Because bleeding management is very complex and bleedings are relatively rare, the dealing with bleedings is not modeled as part of this thesis.

However when for a temporary stop of anticoagulation is decided, it is commonly followed by a restart of the anticoagulation program. The restart is something that is supportable by an expert system as shown in subparagraph 5.3.3 Stopping and starting for a temporary interruption.

5.4 CONCLUSION

The first interviews resulted in many items that are candidate for improvement of the dosing process. Not all these improvements are specific for the development of an expert system. However, the success of the development and the use of an expert system depends strongly on the way the expert system is embedded in or connected to a general system. Therefore the next chapter contains a general recommendations paragraph with a listing of possible improvements and a view of an overall system design addressing these improvements and how an expert system could be interfaced or embedded.

Until now the results from the interviews gave a coarse impression of the cases the experts work on. It turns out, that in practice about 50% of the workload is handled by implicitly accepting the automatic proposals from TDAS, so no work is done on this part of the cases at Star-MDC. The next big chunk of work is dealing with the cases that TDAS does not provide a dosage for and these cases are primarily handled by the dosage advisors. A relatively small amount of cases which are more complex and commonly need more investigation are left for the dosage doctors. They deal with the majority of the workload and the cases are less complex than the doctor's cases. Expert system support for the low complex cases yields the most profit and leaves more time for the advisors to discuss less obvious cases. A logical next step is to research the work of the advisors more closely. This is the subject of the next two chapters.

The first results of the unstructured interviews showed that the cases where experts work on can be generalized in a few groups of cases, based on the way these cases are triggered. These cases are:

- 1. New applications.
- 2. Reapplication after discharge from a hospital.



- 3. Stopping and starting for a temporary interruption.
- 4. INR below target range.
- 5. INR in target range.
- 6. INR above target range.

We saw that the documented protocols for new applications and stopping and starting for a temporary interruption could be very well defined with a set of IF-THEN rules. The reapplication after discharge from hospital cases are the most complex ones, because the outcome of these cases is primary not aimed at providing a dose or return interval, but at providing a good basis for follow up treatment. These type of cases are a minority of the total of cases and are high complex, so they are left as candidate for further research. The majority of the cases that experts work on are the ones triggered by INR below, in or above target range. There is a lot of documented protocols for these types of cases too, but there is more to it. A general way of reasoning here is the observation of the INR, looking back to the former dose that 'caused this INR', and reasoning on the circumstances that may have caused other outcome than expected or are possibly going to cause an unwanted outcome. The idea is that the experts are introduced to a prototype of an expert system, containing two algorithms for dose proposal, a short term simple proposal and a long term ICAD proposal. Based upon these proposals, the current INR and the former dose, the experts are asked to reason according the OODA-Loop method. The next chapter contains the design of the prototype application, chapter 7 deals with the results of the interviews based on the OODA-Loop and the use of the prototype application.

Lastly a reflection on the additional research topics stated at the beginning of this chapter:

1. Are the doctors comparable?

Doctors are generally working based on the standards and protocol of the organization they work for. There are some small differences in the Star-MDC and Saltro protocols. Also in some occasions a doctor thinks that she may have acted different then a colleague did when looking back on a former decision. When fine tuning on rules for an enhanced expert system, these small differences may lead to further standardization and optimization.

- Which data in this phase is suitable for automating?
 In this phase the accent lies on building rules on descriptive knowledge.
- To what level is the knowledge retrievable? The descriptive knowledge is very good retrievable. The next phase is on finding out how the knowledge of the expert exceeds the documented knowledge. And to what extend it is to catch in IF-THEN rules.





6 РRОТОТУРЕ



This chapter starts with a motivation on the design of a general system. Based on a list of recommendations in paragraph 6.1 a global overview of the design of a general system is provided in paragraph 6.2. The design of a prototype called DoseAssistant and a small helper application called PrepareDataTables is subject of paragraph 6.3. This chapter is concluded in paragraph 6.4.

6.1 Recommendations

The experts mentioned opportunities for improvement on the current computer programs and the way they support the total process of patient care. Much of the paperwork can be automated. Digital imaging of documents and making them available on the fly would be very helpful as is making automatic phone calls by clicking on a phone number. Especially when there is an automatic logging entry of the phone call in the history.

• Make programs user friendly by improving user-interfaces. The user-interface of the Trodis system seems to be better constructed than the TDAS interface. Further



improvements are possible by using docking windows and sliding windows. With these controls additional information can be hided and made visible in an easy and convenient way.

- Apply new patients and reentering patients with the help of a web-interface. Give feedback by email that the patient application is OK and that he is accepted.
- Give patients control over their anticoagulation therapy, by setting up a
 'MyThrombosisService' webpage for each patient. Besides the day-to-day dosage and INR
 outcomes (in Rotterdam already available) a patient should be able to report all relevant
 items as they are on the requestform at the moment. Forgotten or overruled dosages,
 upcoming clinical events, changes in medication or medical condition can be reported at
 this webpage. Changes in chemist or family doctor can be submitted online, request for
 setting up SMS services for dosage and remarks can switched on and off, and changes in
 visit day can be requested. And self-monitoring patients can submit their INR's and
 dosages or dosage requests online.

Because there is most of the time no feedback from patients on changes in the amount of tablets a patient takes, the doctor may build her decision on a wrong assumption that the measured INR is a reflection of a compliant patient. The truths however may be that the effective dose on the day of INR measurement is different from the assumed dosage. When a patient is able to modify his dosage according the reality, and when he is also able to see what difference this makes on the effective dose, two goals may be served: the patient is more involved in his wellness and the doctor is able to give a better advice.

• Supply TIR management information to the patient. This can be done on the patient's calendar or on his personal website. For each patient his TIR over last year as opposed to the target and mean of population could stimulate the patient. Also the mean TIR for the periods a patients gets a dosage for each dosage advisor and dosage doctor. The goal of this feedback to patients and medical staff is, to help themselves to improve their TIR over time. Another reason for this is that there is a tradeoff between the responsibility of the anticoagulation clinics for a regular control of the INR in a relative high frequency and the convenience for a patient to have a low frequency on control moments. Involving the patient in some way, e.g. by giving feedback on his stability, might contribute to a lower control frequency.

Besides the TIR the sensitivity index used in the ICAD calculation seems to be a promising parameter for monitoring stability. The CV of this sensitivity index could be an performance indicator. The targets of this indicator are not know at this moment and still have to be established.

- The Rotterdam Thrombosis Service has about 2000 dosages per day. The experts remark that quality of decisions may decrease at the end of a busy work day. Some more complicated cases deserve more attention preferably in a team discussion. Because of time constraints and workload there is too little attention for these cases which may lead to suboptimal decisions. Support for the more easy cases by help of an expert system may increase work speed and leave more time for complex cases.
- The experts sometimes disagree with the automated cases from TDAS in the past. An expert system with a second algorithm could check on these cases and filter out the cases with significant difference in dosage.
- I noticed that the experts make a lot of telephone calls and have to dial a lot of numbers which leads to making mistakes now and again. Supporting dialing by a computer system should be not too difficult and improve the work of the expert. I.e. clicking on a phone number on a screen or on an icon next to a number should ease the calling process a lot. Next, for traceability reasons it would be of help if the system would not only assist in automatically making calls but also support logging of calls and possible outcome.



6.2 GLOBAL SYSTEM DESIGN

The expert system is preferably part of a total Thrombosis Service system or has to interact with such a system. Ideally, the global system is at least composed of the subsystems shown in Figure 44. When developing a total Thrombosis Service system, it should contain multiple interfaces which can interact with the environment based upon messages.



FIGURE 44: THROMBOSIS SERVICE SUBSYSTEMS

LABORATORY SUBSYSTEM

The interaction with the Laboratory analyzers and TDAS is now based on file I/O. Once a batch of INR results is ready, a file is created by the LIS and it is read from time to time by TDAS. For Laboratory analyzers it is common to send each validated INR result to the LIS. Batching and file I/O slows down the process, especially when there are not enough results to complete a batch. The Laboratory Subsystem should deal with online incoming INR messages.

PDA SUBSYSTEM

The PDA subsystem is interacting with the PDA devices from the phlebotomists. During visit of the patient at home or at a collection station, date, time, phlebotomist code and location of the bloodsample collection is entered in the system, together with the sample ID. Also additional items like changes in medication and clinical condition are entered in a coded way. In this way, the relevant items are placed in the system in a coded format and is as such interpretable by the Expert Subsystem when applicable. Also the data entry process of the administrative people is strongly simplified.

HOSPITAL WEB CLIENT

The hospital web client subsystem processes the submissions of new or reentering patients. This system is also used by family physicians who want their patients on anticoagulation therapy. Problems with unreadable forms and not filling in required fields belong to the past. Information can be entered in a coded and unambiguous manner. The subsystem could also provide a printed copy of the submission as a form that can be signed by the doctor. After receiving the printed and



signed form the administrative people can confirm the reception of the submission in the system and scan the form for digitally reviewing purposes. Besides entering data, the hospital may want to know how a patient is kept in control by the Thrombosis Service at the moment he is admitted to the hospital. Information on the patient's anticoagulation history records could be of benefit for his stay in the hospital.

PATIENT WEB CLIENT

A very important subsystem is the patient web client. Although at this moment Star-MDC provides a calendar to its patients on the company website, a web client should contain much more functionality. First there is the need to process the self management patients and the regular patients is the same manner by the Thrombosis Service staff. At the moment two applications with very different interfaces are used. Learning two interfaces is a burden, but an more important drawback is the splitting of the patient's data between two applications. Especially when someone is switching between self management and regular control or vice versa, this leads to discontinuities in the patient's history. Which is clearly not good for patient care. The other improvement a patient's web interface would make, is the structured interaction between patient and the Thrombosis Service system. This way, a lot of registration actions of the phlebotomist could be skipped, the number of phone calls could be reduced, and thus increasing the attainment of the Thrombosis Service department. The web client should be able to provide letters in various languages to accompany the patient on holidays in foreign countries, the patient should be able to pass through vacations, changes in medication, request for SMS alarms or SMS dose reminders, get copies of calendars, see management information like TIR and pass through removals. Important for assessing the effective dose with ICAD are the actual taken amount of tablets every day. A possibility to adjust the provided scheme by a patient to the really applied scheme would highly increase the dosage quality. In short all requests and messages that are dealt with through the web client , increase the quality of the requests and patient care, reduces the work for the administrative staff and improves traceability by logging the actions. A simple example of a web client from the virtueletrombosedienst.nl [21] is illustrated in Figure 45.

Datum en tijdstip					
Datum (dd/mm/jjjj)	6 /	r jur	un 🖌 j 2006		
Uur (hh:mm)	16	24			
INR					
INR waarde 2.8					
Meettijd (sec) 20.6	6	1			
Complicaties					
Blauwe plekken				Spierbloeding	
Bloedneus				Gewrichtsbloe	ding
Bloed in urine				Rooddoorlope	in ogen
Bloed bij ontlasting				🔲 Gezichtsverlie	s
Zwarte ontlasting				Thrombose/er	nbolieen
					-
					ingeven
					argeven

FIGURE 45: WEB CLIENT EXAMPLE

ADMINISTRATIVE CLIENT

The administrative client subsystem takes care of the administrative tasks, like patient management, billing, reporting calendars, setting reporting ways as mail, email and SMS, digitally archiving scanned documents. This subsystem is already part of the current Thrombosis Service



systems, but could be enhanced with items like digitally archiving. Also the interaction could be reduced by providing the services in the subsystems mentioned above.

EXPERT SUBSYSTEM

The expert subsystem is responsible for providing dosages and return dates. The server subsystem keeps track of cases that need a dosage and return date proposal. The server sends a request to the subsystem, together with the appropriate data, and receives a proposal from the expert subsystem. Based upon criteria that are tunable by the company, the expert system labels its proposal with at least one of the next three labels: No review needed, to be reviewed by an advisor or to be reviewed by a doctor. Also the reason for reviewing is provided, so that the expert client users do not need to wonder why they are dealing with a case.

EXPERT USER CLIENT

The current interface for the experts using the dosage window has to be renewed, so that experts may use the expert system facilities. Next paragraph is discussing the expert system design more closely and shows an interface of the prototype.

SERVER SUBSYSTEM

The heart of the Thrombosis Service system is the Server subsystem. The server provides services for all subsystem calls. It keeps track of the queues for the dosing cases and all the requests from the subsystems like patient's requests, hospital submission requests and Laboratory INR messages. Splitting up the system in subsystems makes it possible to divide the workload over multiple CPU's. When performance issues occur, the services of the central server system could be spread over multiple CPU's too. In this way scalability is guaranteed.

DATABASE SUBSYSTEM

Because the Thrombosis Service system relies heavily on the performance of the database subsystem, this subsystem should be constructed with care. The clustering and indexing of tables should be tailored to the insert and retrieval traffic of the system, to avoid performance issues. Also the way concurrency is dealt with needs careful application. A database management system that provides scalability options and tuning and monitoring possibilities is required. The data model should provide tracking facilities of the treatment settings.

6.3 EXPERT SYSTEM PROTOTYPE

Before setting up an expert system design, it is a good thing to think over again whether an expert system is the right thing to develop to address computer assisted dosing. George Rudolph, assistant professor of Computer Science has put some guidelines for deciding whether to use a rules engine on the internet [18]. These guidelines state that a rule-based expert system is the most suitable solution when:

- 1. There significant decision-making capability involved.
- 2. Decisions that need to be made are based on multiple conditions.
- 3. The rules are likely to change over time.
- 4. The code needs maintaining over time.

More or less all four conditions mentioned here are in favor of developing a rule-based expert system. A reason not to use a rule-based expert system according Rudolph, may be that high-end



performance is needed, because the system needs to respond to a lot of cases in a relatively small time frame. On the other hand, a rule-based system is suitable for software development reasons, simulation and prototyping. When performance of a rule-based expert system is too low, a hard-coded system may be considered afterwards. For now, the expert system design is suitable.

A helpful step in the design of a complete expert system, is the development of a prototype of an expert system. The idea of a prototype is to present a possible interface of the system, on which the expert user can give feedback. The main advantage of prototyping in this case is, that the prototype can be instrumented to collect detailed data for knowledge elicitation. Another good reason for prototyping is the cyclic way of software development. By providing a prototype interface, a revisit of the knowledge acquisition phase and the knowledge representation phase is lifting these phases to a next higher level. The interface of the prototype is the most important part. However, to obtain additional rules there has to be some functionality in the prototype. The next subparagraph describes the functionality of the prototype.

6.3.1 DOSEASSISTANT

The prototype application is called DoseAssistant. For comparison reasons and for the cases TDAS has no proposal, a second algorithm, the ICAD algorithm is incorporated in the DoseAssistant. Because the ICAD method takes into account the effective dose at the day of INR measurement and an exponential average of the sensitivity of a patient for the recent dosages, it is tuned for the patient and therefore superior to a set of IF-THEN rules just based on the most recent available values. Therefore the ICAD method is chosen to form a basis for the maintenance dose proposal. Based upon the TDAS and ICAD proposals, the current INR and the former dose, the experts are asked to reason according the OODA-Loop method. An example of the DoseAssistant interface is in Figure 46.

The prototype expert system development has to deal with the fact, that there is already a running dosage application. Although the best thing to do is to build a whole new global system from scratch, this may not be realistic, because this will very likely lead to high costs and there may be only a small amount of companies willing to invest in such a project. So the DoseAssistant should run in parallel with a current system, possibly in the background to pop up when there has a decision to be made in the current client. A drawback is, that the data model is not suited for the expert systems rules and facts. A separate database is needed.

The interface window of DoseAssistant has on the left a tabcontrol for quickly retrieving additional information on Patient, Treatment, Visits, Medication, Notifications, former calendars and scanned documents. In the prototype this control did not work. Next to the tabcontrol, a patient can be selected by entering the patient's ID. In a normal situation the application lets you select a queue of patients in which the patients are showed sequentially. After entering a patient ID, the patient information, treatment information and visit information is retrieved from the database. The visit information consists of a list of the last 10 visits, but also aggregated information on these last visits, as a CV of the sensitivity index (used for ICAD), average INR, the % of time in range, below range and above range.



🔜 Do	🖬 DoseAssistant									
Patient	Patien Nr: P	t ATI30041955	Se	earch P. Pati	ent - NeedDose 30-0	Dose Previous value Simple calcula	a: 1.79 tion: 1.79	Review Reason(s): medication change		
Treatment	Treatm Diagnos Contra i	n ent sis: 219 indication: No)-ATR. FIB ne	R + CVA/TIA 240	PACEMAKER / ICD		ICAD proposal Eff. dose: Rules: decreas Proposal: 1.74	l: 1,63 = step 22 1,87 se 3%	Current INR: 3.3 calc	
Medication Visit	Target level: L = 2,5 - 3,5 Anticoag. med.: 10-Acenocoumarol Visits CV Sensivity Index: 56 % Average INR: 2.8						Interval Previous value: 28 days Rules: increase 7 days Proposal: 35 days		Dose: 1.74 Interval: 35 days accept skip	
ations	Time Below Range: 59 % Time In Range: 55 % Time Above Range: 12 % Visit date INR TDAS dose Average dose Effective dos						ICAD dose Sensitivity index			
otific	•	9-6-2009	3,3	10.28.025.L	1,79	1,82	1,60	0,56	OSE 7	
Z		26-5-2009	3,4	10.21.025.L	1,79	1,82	1,58	0,58	8	
ndars		12-5-2009	3,5	10.14.025.L	1,79	1,82	1,56	0,61	ㅋ	
Caler		28-4-2009	2,4	10.14.025.L	1,79	1,61	1,54	0,45		
<u> </u>		21-4-2009	2,5	10.07.023.L	1,64	1,56	1,48	0,52		
		14-4-2009	2,0	10.07.023.L	1,64	1,73	1,43	0.27		
		7-4-2009	2,4	10.07.021.L	1,50	1,61	1,34	0.45		
		3-4-2009	1,5	10.04.020.H	1,43	1,50	1,27	0,19		
		31-3-2009	5,9	10.03.020.H	1,43	1,36	1,17	2,36	<u></u>	
		27-3-2009	4,5	10.04.025.L	1,79	1,61	1,27	1,14		

FIGURE 46: DOSEASSISTANT INTERFACE

Next four groupboxes are placed on the window. The Dose groupbox contains four dose values: the previous, the simple calculated (not working in the prototype, it should be supplied by TDAS), the ICAD calculated dose, and the effective dose (used for ICAD). Next an increase or decrease is suggested based on the expert systems rule-base inference engine. This is of course not working in the prototype. For the same reason the proposal is not functioning. The interval groupbox contains the previous interval, and fake rules and proposal labels. The review groupbox should contain the reason why the case is selected by the system for review. The shown reason is a fake reason for example purposes only. The current INR is online retrieved from a TDAS table. If this is not working, the INR could be entered by hand and clicking the calc-button recalculates the relevant values. The decision groupbox contains dose and interval textboxes, which are already filled out with the suggested values. This part of the application is not working either. Finally, on the bottom-right side there is a tabcontrol for reviewing the rules and conditions that caused the system to provide its proposal. And this tabcontrol is also not functioning.

The preliminary data model for the database is constructed from the objects in the semantic net. It is suitable for supporting the DoseAssistant application. The data model is shown in Figure 47. The Patient and Treatment tables are 1-to-n related on the External_ID field.

The Patient and Visit tables also have a 1-to-n relation on the External_ID field, because during a treatment there are usually more than 1 visits involved. The bold fieldnames are not allowed to have NULL values. The main challenge for the prototype is to retrieve and calculate the data. A brief overview of this database filling job is subject of the next subparagraph.





FIGURE 47: DOSEASSISTANT DATA MODEL

6.3.2 PREPAREDATATABLES

TDAS is an application that is build with Microsoft Visual FoxPro. It is a Microsoft Windows based client-server application. TDAS uses a Visual FoxPro database, which is accessible through ODBC connection(s). After some research on the tables in the TDAS database, the tables that contain the data that are necessary for the DoseAssistant database and the ICAD method calculations were found. Accessing these tables directly through ODBC is very time-consuming and therefore not suitable for online accessing by the DoseAssistant. This is the reason that an extra data retrieval application was designed. This application is called PrepareDataTables.

PrepareDataTables selects the appropriate data from the TDAS tables via ODBC overnight, computes ICAD data and places the new created data in a separate database. For this database MS SQL Server Express 2008 is chosen, because of familiarity with the SQL Server database application. Also the scalability and speed of this application is well known. But any other fast and reliable database application would have been OK too. The same goes for the development language. PrepareDataTables as well as DoseAssistant were developed with Microsoft Visual Studio 2008 in the C# language, where languages like Java, Visual Basic or C++ would have done the job too.

PrepareDataTables is a console application, running a couple of queries for retrieving data from the TDAS database and for making some calculations to retrieve ICAD related data. When a field has to be calculated for ICAD parameters, this is done according the formulas as reflected in paragraph 2.1.5 Algorithms and as described by Van Leeuwen and Pasterkamp in [10] and [11]. An overview of the tables and fields involved in the querying process is illustrated in Figure 48.



Table	Field	Origin
Patiënt	External_ID	dimasys.patienten.patienten_cextern_patientnummer
	Name	dimasys.patienten.patienten_crapportnaam
	BirthDate	dimasys.patienten.patienten_dgeboortedatum
	Sex	dimasys.patienten.cgeslacht
	ReturnDate	tdas.historie.herkdatum
Treatment	External_ID	tdas.nawtdas.cexpatnr
	TreamentStart	tdas.nawtdas.daanmeld
	ControlType	tdas.nawtdas.csrt_pat
	Diagnose1	tdas.nawtdas.cdiagnose1 - tdas.diagnoses.ckddiag + tdas.diagnoses.comschrijv
	Diagnose2	tdas.nawtdas.cdiagnose2 - tdas.diagnoses.ckddiag + tdas.diagnoses.comschrijv
	Diagnose3	tdas.nawtdas.cdiagnose3 - tdas.diagnoses.ckddiag + tdas.diagnoses.comschrijv
	ContraIndication1	tdas.nawtdas.ckon_ind1 - tdas.contra_ind.nkdkntrind + tdas.contra_ind.comschrijv
	ContraIndication2	tdas.nawtdas.ckon_ind2 - tdas.contra_ind.nkdkntrind + tdas.contra_ind.comschrijv
	ContraIndication3	tdas.nawtdas.ckon_ind3 - tdas.contra_ind.nkdkntrind + tdas.contra_ind.comschrijv
	AntiCoagMedication	tdas.nawtdas.cantist_pr - tdas.anti_stol_prep.prep_nr + tdas.anti_stol_prep.prep_naam
	AntiCoagLevel	tdas.nawtdas.cantist_nv
	RangeLowBoundary	tdas.nawtdas.cantist_nv
	RangeTarget	tdas.nawtdas.cantist_nv
	RangeHighBoundary	tdas.nawtdas.cantist_nv
	CV_SensitivityIndex	Calculated from Visit.SensitivityIndex
	TIR	Calculated from Visit.DaysInRange, Visit.DaysBetweenVisits & Visit.INR
Visit	External_ID	tdas.historie.expatnumme
	VisitDate	tdas.historie.ddatumuits
	History_ID	tdas.historie.nwi
	INR	Calculated from tdas.historie.nuitslag
	TDAS_Dose	Calculated from tdas.historie.casprep, tdas.historie.dosstap, tdas.historie.dosdagen,
		tdas.historie.kdhooglaag
	AverageDose	tdas.historie.ngem
	EffectiveDose	Calculated from Visit.AverageDose, Visit.VisitDate, Visit.SchemeStartDay,
		tdas.nawtdas.cindva, tdas.nawtdas.cindmo, tdas.nawtdas.cindov, Visit.HighLow,
		Treatment.AntiCoagMedication
	SensitivityIndex	Calculated from Visit.INR, Visit.EffectiveDose, Visit.AntiCoagMedication
	SI_ExponentialAverage	Calculated from Visit.SensitivityIndex
	ICAD_Dose	Calculated from Treatment.Target, Visit.SI_ExponentialAverage, Visit.SensitivityIndex
	DoseDoctor	tdas.historie.kddosarts
	SchemeStartDay	tdas.historie.ndosdagnr
	HighLow	tdas.historie.kdhooglaag
	DaysBetweenVisits	Calculated from Visit.VisitDate
	DaysInRange	Calculated from Visit.VisitDate, Visit.INR

FIGURE 48: DOSEASSISTANT DATA ORIGIN

After every task the PrepareDataTables application has performed, it echoes the completion of a task to the screen. This is demonstrated in Figure 49. The PrepareDataTables application is scheduled to run at 02.00h Monday till Friday.

DoseAssistant needs to have new measured INR results available. These are not available overnight, but are released during daytime by the laboratory analyzers. TDAS places the INR results, together with other items in a table called TDAS.ttbestand.

The INR and External_ID are retrievable from this table through ODBC. Because it is a relative small table (about 2000 entries at the end of the day), it is relative fast accessible compared to other tables of TDAS. So, in this way it is possible to let the DoseAssistant application run together with the TDAS application that the expert is working on.



📼 file:///C:/Users/Jan/Documents/Visual Studio 2008/Projects/PrepareDataTables/PrepareDat... 🗕 🗖 🗙 PrepareDataTables start... Retrieving from tdas.historie: active patients (returndate >= 2009-06-14) ... Done. Retrieving all patients from AntiCoag.Patient ... Done. Matching AntiCoag.Patient with tdas.history ... Updating patient demography from dimasys.patienten ... Done. Updating AntiCoag.Patient Done. Deleting all AntiCoag.Treatment ... Done. Retrieving all patients from AntiCoag.Patient for treatments ... Done. Updating treatments from tdas.nawtdas ... Dône. Retrieving last visits from AntiCoag.Visit for NeedVisitUpdate list ... Done. Greating delete list: visits without active patients ... Done. Removing delete list from NeedVisitUpdate list ... Done. Deleting delete list from AntiCoag.Visit ... Done. Appending new patients to NeedVisitUpdate list ... Done. Match NeedVisitUpdate list with tdas.historie ... Done. Retrieving visits from tdas.history from 11*42 days ago (2008-04-08) ... Done. Removing visits which do not need an update Done. Trimming Visits to 11 per patient Done. Updating and inserting Visits Done. Inserting treatments in AntiCoag.Treatment ... Done. PrepareDataTables completed!

FIGURE 49: PREPAREDATATABLES CONSOLE WINDOW

6.4 CONCLUSION

This chapter started with recommendations on a global system design. Next a prototype was introduced called DoseAssistant. The main purpose of this application is to try to retrieve additional IF-THEN rules for in a detailed knowledge acquisition phase of the expert system design. The next chapter is about the results from interviews with the help of the prototype application.



7 DESIGN OF AN EXPERT SYSTEM



The goal of the next set of interviews with support of the DoseAssistant application, is to acquire a set of rules for the design of a rule-based expert system. First the setting of the interview is described, together with an introduction of the DoseAssistant application to the experts. Special attention was given to the explanation of the ICAD algorithm. This is subject of paragraph 7.1. In paragraph 7.2 the outcome of the interviews are presented. The OODA approach was used for investigating the reasoning process of the experts. Again the starting point were the INR below target range, INR in target range and INR above target range observations. Next a new set of IF-THEN rules was derived. Paragraph 7.3 concludes this chapter.

7.1 DESCRIPTION OF THE SETTING

The setting of the interviews was very much like the unstructured interviews at the beginning of the knowledge extraction phase. The difference was, that the interviews were not recorded and written out. Instead of that notes were made of the reasoning, especially the OODA orientation and decision making areas. For this, many 'why do you make this decision ' and 'on what condition



do you make this decision' questions were asked. The expert was working on her desktop in the usual way. Another difference to the first interviews was the extra laptop on which the DoseAssistant prototype application was running. The night before each interview, the PrepareDataTables application took care of providing all relevant data in the database of the DoseAssistant application. In that way TDAS and DoseAssistant had the same patients at their disposal without interfering each other. When a dosage advisor or a dosage doctor gets a new patient from the queue she is working on, (part of) the TDAS External_ID was typed in the patient number textbox of DoseAssistant followed by a click on the search button. DoseAssistant responds to this event with the execution of three consecutive queries in the tables Patient, Treatment and Visit in the local SQL Server Express database, and displays the retrieved data. Next a query is done in the TDAS.ttbestand table to retrieve the new INR result. If there was a result available, the effective dose, the exponential average of the sensitivity index, the ICAD dose and the TIR were calculated and displayed. If for some reason (only the patients that have a return date in the near future are selected from TDAS) there is no data available, the INR can be entered in the textbox and after clicking on the calc button, the ICAD is calculated, based on the entered INR value. So in this way there were two monitors on the desktop of the expert, with the TDAS and the DoseAssistant screens, providing information on the same case.

Before starting the interviews, the experts had to become familiar with the DoseAssistant purpose and its interface. The interface explanation was similar as in previous chapter and was straight forward. The explanation of the ICAD algorithm was a bit more complex and provided some insight in the human physiologic processes. First of all there was the effective dose concept. The experts know that there is a half-life for the anticoagulant medication. This phenomenon is noticed regularly when a patient stops taking medication: his INR decreases in a few days, depending on which type of anticoagulant he is taking. According to the FNT in [1], the half-life of acenocoumarol is about 8-11 hours and the half-life of fenprocoumon is about 160 hours. Pasterkamp estimated in [11], that the effective half-life is longer, when the clotting factor production was taking into account. A drawing of an alternating daily dose with the half-life of the acenocoumarol anticoagulant and the effective dose makes this clear, as illustrated in Figure 50. It makes a big difference in INR depending on the effective dose of the patient on that moment. Especially the lower graph in Figure 50, which shows the effect of TDAS step 15H, where one can see that the extra tablet on day 1, is almost not traceable on day 3 and it has little effect from day 4 and has no effect from day 7 anymore. The importance of the effective dose on the INR measurement day is clear for the experts and it is something that TDAS does not take into account. The next concept that needs some understanding is the sensitivity index. It is a factor that reflects the effective dose – INR relationship and takes the anticoagulation medication type into account. Every visit the sensitivity index is assessed. From a history of sensitivity indexes an exponential average is calculated. This exponential average reflects the sensitivity index over time, where the last assessed sensitivity index has the most weight in the average. An example of the influence of the exponential average on the sensitivity index is shown in Figure 51. It is clear that the exponential average has an equalizing effect and as such this is reflected in the ICAD dose proposal. The ICAD method then calculates the next dose from the inverse effective dose - INR relationship, based on the target INR and the exponential average of the sensitivity index. In that way a dose is created that reflects the average maintenance dose for that is specific for a patient.





FIGURE 50: DOSE, HALF-LIFE AND EFFECTIVE DOSE RELATIONS

With the DoseAssistant application giving the ICAD dose for the patient that is subject of the regular decision making process, it should provide a basis for reasoning from this dose, the former dose and possibly the TDAS dose.

As a kind of management information on the patient's history, the DoseAssistant displays the TIR of the last 10 visits of a patient, indicating the amount of time the patient was in range. Also the CV of the sensitivity index is shown, what could be an indicator for stability.

7.2 DETAILED RESULTS

The idea is that the experts are asked which items they consider while achieving their decision. From the first set of interviews it became clear, that there are two interventions on the dosage. The first is to get a patient back in range as fast as possible when he is out of range. The second is to set a suitable maintenance dose for the patient that leads to a good INR for the next visit. The reasoning for both interventions is based on documented guidelines. In practice the experts do not always follow these guidelines, so the situations in which not to follow the guidelines are



FIGURE 51: SENSITIVITY INDEX



points of interest. The guidelines themselves are relative easily convertible in a computer program, as we have seen yet. The most used guideline is, that the current INR is related to the former dose and based on this combination the next dose is assessed. Special circumstances may influence the expert to increase or decrease a dose more or less than the dose suggested by the guidelines. It is one of the major tasks, to make an inventory of these circumstances and how they have their impact on the change of the suggested dose from the guidelines. And of course to convert them into a rule set. As mentioned, the current INR and former dose were the main orientation factors to take into account, and when available a proposal of the TDAS system. The TDAS system does not provide a proposal when there are special circumstances. Even when these circumstances have no influence on the dosage or return date. So there was almost never a TDAS proposal for the cases that were examined. Because the experts had the DoseAssistant program to their disposal, there was an ICAD dose for every case. The ICAD dose was taken into account too, but the experts need to get accustomed to the change in dose even when a patient is in range. This is because the ICAD targets for the exact middle of the range. Also the change in dose suggested by ICAD was most of the time a bit bigger than the change the experts were used to.

Based on the OODA-Observation of a case being of a INR below target range, INR in target range or INR above target range type, the OODA-Orient and OODA-Decision items were captured in a set of IF-THEN rules. The TDAS queues do not separate the INR in range, below range or above range cases, so they appeared mixed. But grouping the rules by observation leads to the rules in the next subparagraphs.

7.2.1 INR BELOW RANGE

TABLE 4: IF-THEN RULES FOR INR BELOW RANGE OBSERVATIONS

1	IF	There was a period with INR in range recently
	THEN	The dose in this period is probably (p=H) a good dose
2	IF	The current dose is >= 4 tablets acenocoumarol per day
	THEN	The probability the dose needs to increase is low (p=L)
3	IF	The patient recently stopped an antibiotic therapy
	THEN	The probability the dose needs to increase is high (p=H)
4	IF	The patient is recently discharged from hospital
	THEN	The return date is in max 7 days
5	IF	There are INR values above range recently
	THEN	Do not increase more than the minimum increase
6	IF	Age > 80
	THEN	The probability of non compliance is high (p=H)
7	IF	There is alcoholism
	THEN	The probability of non compliance is high (p=H)
8	IF	There is diabetic disease
	THEN	Do not increase more than the minimum increase
9	IF	There are psychic complaints
	THEN	The probability of non compliance is high (p=H)
10	IF	The patient stays in a hot country
	THEN	The probability the dose needs to increase is high (p=H)



11	IF	The INR changes between above range and below range on a constant
	THEN	The probability of non compliance is high (p=H)
12	IF	History shows notifications of forgotten tablets
	THEN	The probability of non compliance is high (p=H)
13	IF	History shows loading doses to correct low INR's
	THEN	The probability of non compliance is high (p=H)
14	IF	INR > 1.7
	THEN	Do not use a loading dose
15	IF	INR >= 1.7 after a period of INR in range
	THEN	Call patient to verify compliance
16	IF	INR <= 1.7
	THEN	The return date is in max 7 days
17	IF	INR <= 1.2
	THEN	Non compliance is almost sure
18	IF	There is diarrhea
	THEN	The probability the dose needs to increase is high (p=H)
19	IF	INR <= 1.7 AND probability of non compliance is high
	THEN	Give a loading dose of 2x the lowest amount of tablets in the last scheme.
		Do not increase the average dose
19	IF	INR > 1.7 AND probability of non compliance is high
	THEN	Do not give a loading dose AND do not increase the average dose.
20	IF	The probability the dose needs to increase is high
	THEN	Increase average dose according protocol
21	IF	INR is max 0.2 below lower boundary incidentally
	THEN	Do not increase dose.
		The return interval is max 28 days

Some rules came up while dealing with INR below range cases, but they are also applicable when dealing with the INR in range or INR above range cases. Examples of these rules are rule 1, 3 and 4. An alternative for rule 6 is increasing the probability of non compliance with the age, instead of using a fixed age. Rules 5 and 8 are based on instability. Diabetic people appear often to be hard to keep stable. So the policy is to be cautious with changes in dose in these cases.

A lot of rules are meant to detect the probability of non compliance. This is because there is a difference in policy between low INR due to non compliance and low INR due to physical reasons. In this way the rules aimed at detecting a probability e.g. for non compliance should have a higher priority than rules based on the (highly probable) condition of non compliance. The follow up of the non compliance cases is, that they keep their average dose and may get a loading dose. The other cases increase the average dose according a protocol. When no rules were applicable and the expert was asked to accept the ICAD proposal, the expert would agree with the ICAD proposal, in spite of the fact that ICAD almost always gave a higher suggestion than the protocol. Because only a very small amount of these types of cases were compared, it is too early to draw conclusions here.



7.2.2 INR IN RANGE

TABLE 5: IF-THEN RULES FOR INR IN RANGE OBSERVATIONS

1	IF	The system does a proposal AND there are no notifications
	THEN	Accept the proposal
2	IF	The former INR was below range AND the patient stays in a hot country
	THEN	Do not change the average dose
		The return interval is max 14 days
3	IF	There are no notifications
	THEN	Do not change the average dose
		The return interval is 7 days longer with a maximum of 42 days
4	IF	The patient is recently discharged from hospital
	THEN	Do not change the average dose
		The return interval is max 7 days
5	IF	The patient is recently started with anticoagulation therapy
	THEN	The return interval is 3 - 5 days
6	IF	Next return date is in vacation AND patient is stable
	THEN	The return date is shifted to before or after the vacation
7	IF	Next return date is in vacation AND patient is not stable
	THEN	The patient is requested to get an INR measurement during vacation
8	IF	Next return date is in on a national holiday
	THEN	The return date is shifted to before or after the national holiday

There are a few occasions in which a patient has standard a label indicating not to be automatically dosed. This is for instance the case when the patient is ordered to an INR range other than the standard ranges that TDAS uses. Also when a patient gets a cardioversion (abnormally fast heart rate correction or cardiac arrhythmia correction) the patient is labeled for manual dosage. There is however no signal by the TDAS system (i.e. indicated by a timeframe), that the manual dosage label could be stopped. This can introduce longtime unnecessary manual dosing. As was noticed in practice, this happened a few times. Regular screening for the need to manual dose a patient would increase the automatically dosed patients.

7.2.3 INR ABOVE RANGE

TABLE 6: IF-THEN RULES FOR INR ABOVE RANGE OBSERVATIONS

1	IF	There is disease
	THEN	There is a physical cause for high INR
2	IF	There is diarrhea
	THEN	There is a physical cause for high INR
3	IF	There is antibiotic therapy
	THEN	There is a physical cause for high INR
4	IF	The patient is on prednisone medication
	THEN	The return interval is 7 days
5	IF	The INR keeps increasing AND the dose keeps decreasing AND the patient
		is on fenprocoumon
	THEN	Give a 3 days stop dose and 5 mg vitamin K
		Return after 7 days
6	IF	The dose is low ()</td
	THEN	Do not decrease more than the minimum decrease



7	IF THEN	There is a serious indication (like returning thrombosis) Do not use vitamin K
8	IF	The patient is recently discharged from hospital
	THEN	The return interval is max 7 days
9	IF	The patient has Turkish or Marrakech background
	THEN	The probability of non compliance increases
10	IF	The dose decreases AND the INR stays above range
	THEN	There is probably (p=H) a physical cause for high INR
11	IF	The INR changes between above range and below range
	THEN	The probability of non compliance is high (p=H)
12	IF	The probability of non compliance is high
	THEN	Do not decrease more than the minimum decrease
13	IF	There is a physical cause for high INR
	THEN	Decrease the dose according protocol
		The return interval is 7 days shorter with a minimum of 7 days

7.3 CONCLUSION

This detailed results chapter started with a description of the setting. Next the experts were introduced to the DoseAssistant prototype and the ICAD method was explained. The experts were not fully aware of the effective dose at the INR measurement date. The fact that the half-life of a dose means that every day has a different effective dose level which may lead to different INR results was an eye-opener for some of them. Even more impressive in this connection was the fact that the Rotterdam Thrombosis Service works with the TDAS step system, which increases or decreases the dose with 1 tablet per 14 days. The half-life of 1 tablet acenocoumarol is such that after three days there is almost no effect demonstrable of this tablet. Yet, the long term dose is conducted on assumed INR changes after 7 of 14 days based upon this 1 tablet change! For this reason the ICAD method should provide better long term advice in these cases. Another idea from one of the experts was to use the ICAD proposal to perform a check on the automatically by TDAS dosed patients. The ones with a big difference between the proposals could be reviewed by the experts. In this way the problem of not reviewing a lot of cases will probably lead to an increase of quality that is expressed in a higher overall TIR. A simple rule could check the difference between both proposals and put the outliers in a special queue.

In order to draw a conclusion in an IF-THEN rule, the premises have to be interpretable by the expert system. Most of the premises are in the current system in a form of free text. Trying to interpret the sometimes ambiguous texts makes is almost impossible to retrieve good premises. So there is a need for standardizing comments, i.e. by means of coding. And this holds of course also for the registration of medicine.

Regular screening for the need to manual dose a patient would increase the automatically dosed patients. A good start would be to set a timeframe for manual intervention. Another solution is to provide a rule in the expert system that checks for the condition of a consecutive range of manual provided dosages without firing a rule.

The interview sessions with the DoseAssistant prototype expert system has delivered an extension on the rules that were derived from the descriptive knowledge. The joined set of IF-



THEN rules from all the tables in this thesis should provide a basis for a light version of an expert system. By extending the rule-base for new types of cases, the expert system is potentially developing to an imitation of a dosage advisor and to some extend even a dosage doctor. A quick win could be achieved by introducing a relative simple expert system for the low complex cases, in order to reduce time spent on these types of cases. Also for training new staff, the expert system would be a good partner, especially when a surveyable explanation facility is provided. Reviewing of expert system proposals will be necessary until the expert staff is certain about the interpretation of the expert system. Automatically acceptance of expert system proposals should be tunable for selectable rule sets. For now is the question whether this point is going to be achieved. During daily practice it may become the question when this point is going to be achieved.



8 CONCLUSION



At this moment the computer proposals of the main Dutch Thrombosis Service system suppliers are able to provide an acceptable dose in about 50% of the cases. New algorithms are developed, like ICAD, which promise to provide a dose in about 80% of the cases. There is an opinion among medical staff and dosage experts that it is very hard, if not impossible, to build computer programs that deal with more than 80% of cases. This thesis shows that by using an expert system, the amount of dose proposals may increase beyond the algorithm only based systems. Besides dose proposals, interval proposals play an important role too in the decision making process of the experts. Interval proposals are strongly dependent to the protocols of each organization. These protocols are a form of declarative knowledge, that is very good convertible into IF-THEN rules. And as such these rules are relatively easy to implement in an expert system. In that way the amount of proposals for an interval may increase too.

8.1 RESEARCH QUESTIONS

The research questions from chapter 1 are now to be answered.



1. CAN THE KNOWLEDGE USED BY MEDICAL STAFF ON DOSING NON-TRIVIAL CASES BE MADE EXPLICIT?

Yes. In this thesis it is shown, that a lot of knowledge that is used by medical staff is declarative knowledge. This type of knowledge is documented in protocols which are part of a document management system of the organization. The organization uses this document management system as a way of knowledge management. The declarative knowledge is very suitable for converting into a set of IF-THEN rules. This thesis also illustrates, that part of the knowledge of the reasoning process of the expert can also be captured and made explicit. This is shown by extending the set of IF-THEN rules from the declarative knowledge. Also a semantic net was retrieved from the knowledge elicitation sessions. The semantic net provides a basis for an ontology as well as a graphical representation of the domain objects and their relations.

2. CAN COMPUTER-ASSISTED DOSING PROGRAMS BE IMPROVED BY INCORPORATING MEDICAL STAFF KNOWLEDGE?

Yes they can. As we saw, especially the low complex and also most common cases that medical staff work on, are the most suitable for handling by an expert system. Using expert system technology on top of basic algorithm programs will improve current computer-assisted dosing programs. There may even be a better result achievable by using more than one algorithm in combination with an expert system. By comparing the result of a simple short term dose algorithm with the result of a more complex long term algorithm like ICAD, an expert system may provide the best of calculated proposals in combination with rule-based inferences.

3. Are current algorithms used by computer-assisted dosing programs extendible to provide a higher acceptable dosage rate?

This is very like the case. Although only a small amount of cases were researched for the use of a second algorithm based on the ICAD method, a first impression was suggesting that the experts were positive for accepting the ICAD proposals, at least for the cases that had no obvious reasons for intervention. Because the standard TDAS algorithm does not provide a dosage in about 50% of the cases, and first surveys suggest about 80% acceptable dosages for ICAD, it is very likely that a higher acceptable dosage rate is achievable. To assess the difference in acceptable dosage rate, prolonged research is needed.

4. CAN THE INTERFACES OF CURRENT COMPUTER PROGRAMS BE IMPROVED TO BETTER SUPPORT MEDICAL STAFF?

Yes, they can. Although the interface of the Trodis system makes a more clear impression than the TDAS interface, both interfaces can be improved by using modern windows controls. This is because the dosage advisors and doctors use a limited amount of information to make a first observation and orientation. Only for further research other information sources are consulted. The interface would improve when taking this approach into account, by hiding all consultable information one click away behind auto hiding tabs and using controls like the Microsoft Outlook 2007 interface. Another improvement could be achieved by supplying important management information like TIR on the patient's treatments. This should be easily available for supporting the decision



making process. Also a brief reason for providing a specific case to be reviewed in a certain queue could remove the question 'why has this case to be reviewed' and gain some time in the decision making process by the expert. And of course when using expert system facilities, a view on the conditions, rules and inferences should be available.

8.2 WHAT'S NEXT?

This thesis gives a glimpse on the improvements that could be made on the current computerassisted dosing programs. A convenient follow up would be to extend the current programs with an expert system facility. There is probably a lot of effort involved in developing a good expert system that is embedded in a Thrombosis Service system. On the other hand, organizations may gain a lot in continuity, standardization and optimization by implementing such a system. Shortage on expert medical staff problems may become less severe. Also placing high standard expert clinical dosage control support at the proposal of other small organizations or individual medical's is interesting from wellness point of view as well as from economic point of view.

As we saw the declarative knowledge in an expert system could be immediately applied in practice, so by using this way knowledge management, the document management system knowledge management is out performed. Also steady, unemotional and complete response at all times may be very important when human experts may not work at optimum because of stress or fatigue. From the organization's point of view these are major advantages. From the experts point of view the advantage may be that automated support for the low complex cases leaves room for the attention the more complex cases need.

The next thing to do is building an expert system with the rues from this thesis, extended with rules for management of return dates dealing with holidays and vacations. This should be put on a trial to compare its performance with expert medical staff and other computer programs. It is clear that this is beyond the scope of a one person - working in the evening hours on his attic- job. I would be happy to work on such a project in a team with a partner organization.





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